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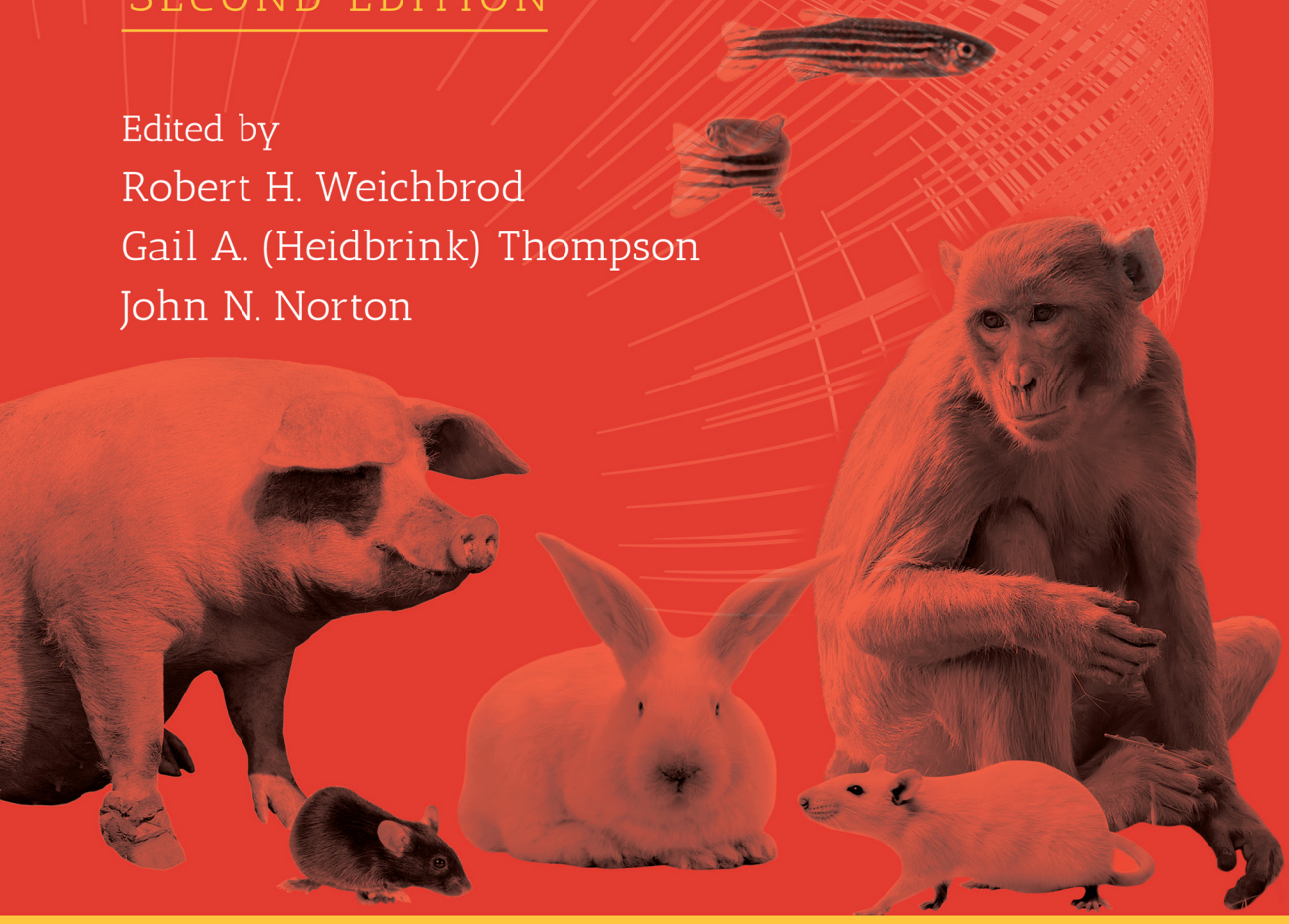
Management of Animal Care and Use Programs in Research, Education, and Testing

SECOND EDITION

Edited by
Robert H. Weichbrod
Gail A. (Heidbrink) Thompson
John N. Norton



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Contents

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Foreword

I am pleased and honored to have been asked to write the Foreword to the second edition of *Management of Animal Care and Use Programs in Research, Education, and Testing.* I am especially grateful to Dr. Weichbrod, Dr. Norton, and Ms. Thompson for allowing me to convey my personal views on the importance and value of providing exceptional laboratory animal care and management and its vital link to performing outstanding biomedical science.

Today, in 2017, science in general, and biomedical science in particular, is under attack from those who believe that science and the funding of science should not be a federal, state, or local priority. There are those who believe that breakthroughs in health care come merely from studies that solely use computer models, cell-based studies, bioinformatics, and device engineering. The scientific community and the lay public have discussed these issues for many years. The reality is that no advances in health care can be achieved with just the use of these adjuncts; the use of animals and animal models of disease remains imperative, lest we do great harm to humans and animals. The competition for research funding is at its highest level in over 20 years. Everyone is aware, and most would agree, that science is synonymous with a search for truth. Acquiring believable facts is the only way biomedical science will provide therapies that work and cures to both human and animal diseases. Importantly, federal agencies, universities, industry, and journal publishers have increased their emphasis on issues related to rigor and reproducibility in science so that more science can be trusted and will contribute to understanding basic biological processes that lead to new therapies and cures. As part of the animal kingdom, the quality of our lives, however, matters. The quality of laboratory animals' lives and human lives is indelibly intertwined. In many ways, it is within this context that *Management of Animal Care and Use Programs in Research, Education, and Testing* is such an important body of work.

When I started my career as a graduate student in 1966, the guidelines for carrying out experiments on large and small animals were generally left to the discretion of the investigator. Even laboratory animal facilities were rather lax in both oversight of investigators and their own husbandry practices. Certainly, this was an era well before the advent of Institutional Animal Care and Use Committees (IACUCs) and/or oversight bodies. It is now clear that the evolution of governmental, local, and institutional guidelines has changed the landscape and certainly the quality of the science produced. In 1976, I became the chair of the University of Nebraska Medical Center's (UNMC) advisory committee on animal resources, a precursor to the UNMC's IACUC formed in 1985, a position I held until 1988 when I became chair of the Department of Physiology. I became a student member of the American Physiological Society (APS) in 1968, and in 1985, I served and was the chair of the APS's Animal Care and Experimentation Committee until 1988. I became chair of the APS Public Affairs Committee in 2001. I then went on to be elected councilor and the president of the APS in 2008. I also served on the council of the Society for Experimental Biology and Medicine from 1998 to 2002. I bring these service appointments up because in every discussion as well as on every scientific review panel, the issue of animal care and associated regulations was discussed and continues to this day. It's appropriate to discuss these issues because without continual refinement, the science may suffer.

Given that the readers of this book agree that animal models of human disease are necessary and given that there are no perfect animal models of human disease, it behooves investigators to maximize the science that is acquired from these models. Unless a study is proposed to evaluate the mechanisms of stress per se, it is not beneficial to perform studies on stressed animals, either under anesthesia or in the conscious state. I'm confident that potential life-saving information has been lost in experiments carried out on animals where optimal husbandry, maintenance of consistent and appropriate environment conditions, and the successful alleviation of stress were not maximized effectively.

The community of biomedical science is vast and includes principal investigators, administrators, laboratory facility managers, animal caregivers, veterinarians, physicians, and allied trade representatives.

It cannot be emphasized enough that individual science is a thing of the past. Today, team science is the norm. We need to all recognize that working and using animals in biomedical research or testing is a privilege, not a right. This concept comes out loud and clear in this book. The editors have put together a text that is not only for those directly involved in the care and use of experimental animals but also for all of us that need the support of the animal care team to do good and believable science. The book focuses on every issue and concern from the culture of caring to technical issues related to animal husbandry. Importantly, it also reviews issues related to compliance and regulation. How much regulation is too much? What is reasonable and how to comply with federal guidelines without impairing the ability of investigators to carry out good science are just some of the important topics covered in this text. The book makes it clear that as new techniques are developed, issues relating to animal welfare change accordingly. Finally, the future of animal oversight and the impact of pending legislation are discussed.

The editors and contributors have taken the second edition to a new level. Compiling the second edition was a real *tour de force* and I congratulate the editors for this outstanding text. This book should be used by anyone who cares about biomedical science: principal investigators, members of IACUCs or other oversight bodies, institutional administrators, policy makers (including legislators), as well as animal facility personnel. I would also recommend that trainees make this book part of their library, as important as a text on physiology, biochemistry, genetics, or any other biomedical discipline. It is important that only well-trained individuals carry out procedures on animals for the benefit of science. Those of us who have worked with animals for many years have an obligation to pass on high-quality practices to those who will do science in years to come. The culture of science will be changed by this edition, which should be a required reading for all those contemplating a career in biomedical science.

Irving H. Zucker, PhD, FAHA, FAPS
Omaha, Nebraska

Preface to the Second Edition

Since the publication of the first edition, there have been many notable advances in biomedical research that have resulted in a better understanding of complex biological systems. This has led to the development of new therapeutic modalities that have improved the quality of life for people and animals across the world.

The importance of continuing biomedical research with animals remains critical to these developments. Therefore, it is important for administrators, managers, and scientists working with and responsible for laboratory animal resources to have the practical experience, knowledge, and understanding of the topics concerning humane animal care and use.

The *Management of Animal Care and Use Programs in Research, Education, and Testing*, Second Edition, is an expanded and revised edition to the original text published in 2001. Like the first edition, this book is meant to serve as a first-line management resource, provide a strong advocacy reference for advancing quality animal welfare and science worldwide, and continue as a valuable seminal reference for those engaged in all types of programs involving animal care and use. The book has been greatly expanded to provide a more thorough overview of the current breadth and depth of the field, with applicability to an international audience.

Over the 16 years since the publication of the first edition of the book, *Management of Laboratory Animal Care and Use Programs*, a multitude of critical regulatory guidance documents have been updated and expanded. Among these are the

- *Guide for the Care and Use of Laboratory Animals*, Eighth Edition (National Research Council 2011)
- *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (Federation of Animal Science Societies 2010)
- European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (European Treaty Series 123)
- *Biosafety in Microbiological and Biomedical Laboratories*, Fifth Edition (U.S. Department of Health and Human Services 2009)
- AVMA Guidelines on Euthanasia of Animals (American Veterinary Medical Association 2013)

Additionally, there have been updated regulatory and policy guidelines and direction from the

- Office of Laboratory Animal Welfare, the NIH office overseeing compliance with
  - U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals
  - Animal welfare assurances
  - Statements of compliance
- U.S. Department of Agriculture (USDA), with policy directives on
  - Animal Welfare Act of 1966 (Public Law 89-544) and subsequent amendments, as promulgated in USDA regulations 9 CFR Chapter 1, Subchapter A, Animal Welfare, Parts 1–3
- AAALAC International, with
  - More than 980 accredited units in 44 countries
  - Applicable position statements and reference resources
  - Relevant governmental legislation and regulatory updates

This second edition has been broadly expanded to address changes and provide a more thorough overview of the current complexity and extensiveness of the field. It is timely that the material in the

second edition be expanded and updated to reflect the advancements and new information both within and outside the United States.

The new features and expanded scope of the book will be highly beneficial to readers and practitioners as well as provide strong rationale for advancing the quality of animal welfare and science worldwide. The editors intend this book to be of the highest quality and surpass the much-deserved reputation of the first edition as a first-line management resource, and to continue to be a valuable seminal work for those engaged in all types of programs involving the management and administration of animal care and use programs.

The book consists of 36 chapters written by individuals with notable experience and expertise in the pertinent topical areas. They bring insights into emerging technologies and an appreciation for the needs of an international audience. Each chapter has been peer-reviewed and contains the latest information, resources, and reference materials from the scientific literature. Key revisions to the book include a new section on environment and housing, which contains chapters focused on the management considerations of housing and enrichment delineated by species; an enhanced narrative throughout the book of critical topics in program management, physical plant, animal health, and husbandry; and expanded coverage of regulatory compliance, assessment, and assurance processes. These topics are addressed and information is provided about the impact of globalization and efforts to harmonize and build on cultural awareness initiatives around the world. Emphasis is given in new chapters on the development of a collaborative "culture of care" within an animal care and use program, and how behavioral management through animal training can play an integral role in a veterinary health program.

The overall goal of the book is to improve the reader's ability to recognize, interpret, and adapt in a more complex and dynamically changing environment, as well as to provide a better understanding of engineering principles, the application of performance-based standards, and the valuable use of professional judgment. Ultimately, the book represents foundational information for managers and administrators to bridge the connection between quality science and quality animal care to the international audience. While the application of the information and principles contained within this book may vary among different managers, organizations, or specific countries, the editors hope the book provides strong advocacy for advancing and connecting animal welfare and science of the highest quality worldwide.

The editors acknowledge and thank all the contributing authors and reviewers of the chapters for sharing their time and expertise. We offer our sincerest thanks to Bonnie Hamalainen, MFA, for contributing her superb art design talents in creating the second edition text cover.

And a special tribute is given to Tim Allen who worked with the USDA's Animal Welfare Information Center in Beltsville, MD for many years. Tim, who passed away suddenly at the end of 2016, was a remarkable human being and he will be truly missed. He thoroughly embraced and gave valuable sage advice in the development of the second edition text. Tim provided the tools and expertise in providing high-quality comprehensive literature searches for many of our second edition authors. Over the course of his career, he provided valuable information on improved animal welfare practices to numerous individuals on an international basis. Tim left an indelible mark on many people in the way they approached their research in the field of animal care and use.

Royalties due the editors of *Management of Animal Care and Use Programs in Research, Education, and Testing*, Second Edition, will be donated to the following professional societies who have agreed to copublish the book:

American College of Laboratory Animal Medicine (ACLAM)
Canadian Association for Laboratory Animal Science (CALAS)
European College of Laboratory Animal Medicine (ECLAM)
International Association of Colleges of Laboratory Animal Medicine (IACLAM)
Institute for Animal Technology (IAT)
Japanese College of Laboratory Animal Medicine (JCLAM)
Korean College of Laboratory Animal Medicine (KCLAM)
Laboratory Animal Management Association (LAMA)

Editors

Robert H. Weichbrod is the chief animal program administrator with the National Eye Institute of the National Institutes of Health in Bethesda, Maryland. Before this position, Dr. Weichbrod was responsible for managing laboratory animal resources for the U.S. Department of Defense's Uniformed Services University of the Health Sciences. Dr. Weichbrod received his bachelor of science in zoology from the University of Maryland, master of business administration from Marymount University, and doctor of philosophy in public administration and policy from Walden University. His dissertation, providing an analysis of the care and use of laboratory animals in Department of Defense activities, is a seminal work that has been frequently cited during congressional hearings. Dr. Weichbrod earned his laboratory animal technologist certification from the American Association for Laboratory Animal Science (AALAS) and was a charter class graduate of AALAS's Institute for Laboratory Animal Management.

Dr. Weichbrod's distinguished career in animal care and use spans over 35 years. He has worked in positions ranging from an entry-level animal care technician (age 24) to animal program administrator. Dr. Weichbrod has served in a wide variety of leadership roles during his career, including AALAS president in 2000, member of the American Association for Accreditation of Laboratory Animal Care (AAALAC) International's Council on Accreditation from 1997 to 2009, on its board of trustees from 2010 to 2016, and currently as a member organization delegate for AAALAC International. Dr. Weichbrod has served as a vice president for the Institute of Animal Technology in England since 2002.

Dr. Weichbrod has authored more than 70 scientific, managerial, and technical articles pertaining to programs involving the effective care and use of animals in biomedical research, training, and education. He was the founding editor in chief and publisher of the Laboratory Animal Management Association's (LAMA) journal the *LAMA Review* and coeditor of the book *Management of Laboratory Animal Care and Use Programs* (CRC Press 2001). He has served on numerous scientific advisory review committees and journal editorial boards. Dr. Weichbrod is an experienced and dedicated advocate for the welfare and responsible use of animals in research. He is committed to maximizing the outcomes of the biomedical research team, enabling increased knowledge of complex biological systems, resulting in health benefits for animals and people.

Among Dr. Weichbrod's awards are AALAS's Joseph J. Garvey Award and George R. Collins Award; LAMA's William O. Umiker Memorial Award, U. Kristina Stephens Award, and Charles River Medallion; the Purina LabDiet Animal Technician of the Year Award; and the Award of Excellence from the U.S. Secretary of Defense.

Gail A. (Heidbrink) Thompson has been active in the laboratory animal science community since beginning her career at the University of Minnesota in 1966. She has held research positions at the University of Minnesota, at Emory University/Yerkes Regional Research Primate Center, and as director of animal resources at National Jewish Health in Denver, Colorado. She was a principal and cofounder of Britz-Heidbrink, Inc. (a manufacturing company for animal research facilities and zoological parks). She was the founder, owner, and president of Peak Animal Resources+, Inc. until her retirement in December 2014.

Along with her long career in laboratory animal science and zoological park facilities, Gail has been a dedicated volunteer in several associations that strive for the humane care of laboratory and captive animals through facility and housing improvement, education and training, and oversight and management. The associations include but are not limited to AAALAC International, trustee (2000–2016), delegate and board of directors (current); the American Association for Laboratory Animal Science (AALAS) since 1973; the Laboratory Animal Management Association (LAMA), formed in 1983, founding member; the Institute of Animal Technology United Kingdom since 1989; and the Mile High Branch of AALAS since 1977, founding member. Additional organizations in which she has participated include the American

Society of Primatologists, Canadian Association for Laboratory Animal Science, Scientists Center for Animal Welfare, Scandinavian Society for Laboratory Animal Science, International Conference on Environmental Enrichment, Association of Zoos and Aquariums, American Association of Zoo Keepers, and several branches of AALAS.

Significant activities or positions held include the honor of serving as president of AALAS in 2004 and holding committee appointments and leadership roles on most AALAS committees over the years. In 1991, Gail initiated and developed the Institute for Laboratory Animal Management as a joint program for AALAS and LAMA. She served as a director and chair of the board of regents of the Institute for Laboratory Animal Management for 6 years and also as the editor of *Tech Talk*. Gail has been involved in the formation and continuation of the AAALAC International Fellowship Award since its conception in 2005. She has served as chair of the award selection committee since 2005. Additionally, she serves as a vice president of the Institute of Animal Technology and member of the President's Advisory Group. She has served as president, treasurer, and program chair for LAMA.

Gail has authored, coauthored, or presented in more than 100 publications, platform presentations, and workshops. Several have been international, with presentations in the United Kingdom, Denmark, Brazil, Canada, and Australia, and for the Federation of European Laboratory Animal Science Associations.

She is a recipient of several awards, including Ralston Purina Animal Technician of the Year, George Collins Award (AALAS), Joseph Garvey Award (AALAS), Ulla Kristina Stephens Award (LAMA), Charles River Medallion, Wm. O. Umiker Award (LAMA), Roland Tibbetts Award (U.S. Small Business Administration), Manufacturing Legacy of the Year (University of Wyoming), and life memberships for AALAS, LAMA, and the Mile High Branch of AALAS.

Beyond her career activities, she has been active in community events, including serving as a mentor for science fair students; a board member on Wyoming's Science, Technology and Energy Authority; and a distinguished lieutenant governor and club president for the Rocky Mountain District of Kiwanis International.

John N. Norton is the director of the Division of Laboratory Animal Resources, is a professor of pathology, and serves as the attending veterinarian for all animal care and use activities at Duke University in Durham, North Carolina. He also serves as an adjunct professor of clinical sciences at North Carolina State University College of Veterinary Medicine. Prior to returning to academia, Dr. Norton served as a toxicologist and directed a laboratory animal resources organization in the private sector.

Dr. Norton received his bachelor of science degrees and doctor of veterinary medicine degree from North Carolina State University and his doctor of philosophy in pharmacology from Vanderbilt University. He is board certified through the American College of Laboratory Animal Medicine and the American Board of Toxicology.

Dr. Norton's distinguished career in both toxicology and laboratory animal medicine spans over 25 years. He has managed preclinical discovery and development projects, prepared regulatory dossiers for both domestic and international submissions, designed and managed complex animal facilities, and strived to optimize research outcomes while ensuring regulatory compliance of animal programs. In his roles in drug and biomedical device development, he has served as study director and/or manager in more than 150 preclinical pharmacology and safety studies in both the academic and private sectors. In his current position, he has developed a preclinical core capable of performing a wide variety of discovery and developmental studies, including those requiring performance under good laboratory practice regulations.

Dr. Norton has served on numerous committees of professional organizations, such as the American College of Laboratory Animal Medicine, and he currently serves as a board member for the National Association for Biomedical Research. In addition, he serves on the board of directors for the North Carolina Association for Biomedical Research, including current service as the chair, and formerly served on the board of directors for the Texas Society for Biomedical Research. In addition, Dr. Norton served as a member of AAALAC International's Council on Accreditation from 2004 to 2016, and as its president during 2013 to 2015. He currently serves as a council member emeritus for AAALAC International.

Dr. Norton's collaborative research focuses on extrinsic factors that may influence the animal research model, specifically in the area of noise and vibration. He has published via scientific, managerial, and technical articles and book chapters on a variety of topics, and he is a frequent reviewer of scientific articles and grant proposals. Dr. Norton is an advocate of ensuring animal welfare while focusing on quality research outcomes and translational research involving novel therapeutics and biomedical devices.

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Section I

Introduction/Historical Overview

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1

Evolution of Laboratory Animal Program Management

James F. Taylor

The use of animals for research and teaching began many hundreds of years ago, wherein animal dissection provided education and training for scientists, medical students, and physicians. Such animal use coupled with human's ownership and subsequent treatment of domesticated species eventually led to the creation of societies for the prevention of cruelty to animals; the Royal Society for the Prevention of Cruelty to Animals was the first one, created in the United Kingdom in 1824. The first national law addressing animal experimentation, the Cruelty to Animals Act, was passed in Britain in 1876.

Since that time, the presence of those societies and antivivisection and animal welfare organizations, and the passage of associated animal anticruelty laws throughout the hemispheres eventually formed the societal posture upon which laws, regulations, and standards evolved that now form the regulatory and oversight environment we now work under in our pursuit of knowledge through the humane and responsible care and use of animals in biomedical research, education, and testing.

In 1947, the Laboratory Animal Bureau was formed in the United Kingdom. The initial directors were R. E. Glover and W. Lane-Petter. They recognized that there was no standardized education system for laboratory animal care providers, and without a standard education and training program, the quality of animal care and research studies would be inconsistent and variable. The bureau organized the first of several conferences for animal care personnel on April 20, 1948, at the Royal Veterinary College of London. Subsequent conferences were held all around the United Kingdom. The organizational meeting for the new Animal Technician Association (ATA) was held on August 27, 1949 (renamed the Institute of Animal Technology [IAT] in 1965). Under the chairmanship of Dr. W. Lane-Petter, the association was ratified on March 30, 1950. The actions to establish a certification program and branches, appoint journal editors, and elect officers were also ratified.

In the meantime, in the United States, the Animal Care Panel (ACP) was formed in the late 1950s by a group of veterinarians to facilitate the sharing of information regarding the management of research animal colonies. The ACP published several species standards, and in 1963 published the *Guide for Laboratory Animal Facilities and Care* (the first *Guide*). In conjunction with that publication, revised in 1965, the ACP's Animal Facilities Certification Committee, later renamed the Animal Facilities Accreditation Board, became the American Association for Accreditation of Laboratory Animal Care (AAALAC) International. The ACP later became the American Association for Laboratory Animal Science (AALAS) in 1966. Thus, by 1965 we had in place the seminal nonregulatory entities (the *Guide*, AAALAC International, and AALAS) that continue to set the majority of the standards that are followed in the United States in pursuit of using animals in biomedical research, teaching, and testing.

Internationally, the United Kingdom passed the Medicines Act in 1968, largely in response to the thalidomide tragedy. Subsequently, the Animals (Scientific Procedures) Act (ASPA) was passed in 1986, and revised to comply with EU Directive 2010/63/E2 in 2012. The ASPA is enforced by the Home Office, which must issue specific licenses to individuals who design and perform animal procedures. Enforcement is based on establishment, project, and individual licenses; training requirements; ethical review of projects; and annual or more frequent inspections. Each establishment must also have at least one Named Animal Care and Welfare Officer (NACWO). The NACWO acts as an advocate for and provides advice on the welfare of animals being used under the project licenses.

The theft of pet dogs from backyards by animal dealers for sale to research laboratories led to startling articles in *Sports Illustrated* and *Life* magazines in 1965 and 1966, respectively, that served as the final stimulus for the U.S. Congress to vote on the Animal Welfare Act (AWA). Congressional hearings on the humane treatment of animals in experiments were first held in 1962, subsequent hearings were held in 1965 and 1966, and the legislation passed in August 1966. The AWA was the first U.S. federal law that specifically regulates the care and use of animals in research; enforcement of the AWA was assigned to the U.S. Department of Agriculture (USDA).

The original law covered dogs and cats, nonhuman primates, rabbits, guinea pigs, and hamsters held by dealers or by research facilities prior to the conduct of studies. Animal dealers delivering dogs or cats across state lines to research facilities had to be registered. Research facilities were required to register only if they received federal funding.

The 1970 amendment to the AWA expanded species coverage to all warm-blooded animals, removed the requirement for interstate transport of the animals, added the need for the appropriate use of anesthetics and tranquilizers in experiments, and added minimal standards of care for research animals. The 1976 amendment revised the standards for the transport of animals and expanded the definition of a carrier. Also, the U.S. Freedom of Information Act (FOIA), passed in 1966, received major amendments in 1974.

The next major amendment occurred in 1985. The USDA's jurisdiction was enlarged to cover animal testing, as well as animals used in teaching. Regulations were established for exercising dogs and providing for the psychological well-being of nonhuman primates, designing studies to minimize pain and distress, and requiring scientists to consider alternatives to procedures causing pain or distress. Practices that were considered to be painful were defined, and animals could not be used in more than one recoverable operative procedure; however, exceptions were presented. The amendment mandated the creation of Institutional Animal Care and Use Committees (IACUCs) and listed their roles, composition, and responsibilities. The amendment also created the Animal Welfare Information Center (AWIC).

The 1990s' amendments created a minimum holding period for dogs and cats in animal shelters destined for sale to dealers and further required dealers to provide written background information about those animals to the buyers. Space and environmental condition requirements were also revised for guinea pigs, hamsters, rabbits, horses and other farm animals, and elephants, and dealers selling pocket pets were brought under the Animal and Plant Health Inspection Service's (APHIS) jurisdiction.

Amendments since the 1990s have added housing and care requirements for marine mammals held in captivity, and have specified that only birds bred for research were to be covered under the AWA. The National Institutes of Health (NIH) adopted standards for housing chimpanzees held in federally funded sanctuaries and placed restrictions on the importation of dogs destined for research to only dogs with import permits.

USDA Animal Care (AC), a component of APHIS of the USDA, administers the AWA, and its inspectors are required to inspect registered research facilities on an annual basis. They base their findings on the Animal Welfare Regulations (AWR). Per the AWA, the secretary (USDA) shall promulgate standards (AWR) to govern the humane handling, care, treatment, and transportation of animals by research facilities (as well as exhibitors and dealers). AC also publishes the *Animal Care Policy Manual* and the *Animal Welfare Inspection Guide*, which augment and specify how the AWR shall be enforced. Inspectors make unannounced visits to research facilities and inspect and review facilities, practices, and documentation regarding all regulated aspects of animal care and use at those facilities. The results of those visits, as well as facility annual reports, are now posted on the USDA website. AC also operates the Center for Animal Welfare and the Animal Care Emergency Programs, as well as enforces the Horse Protection Act.

The U.S. Public Health Service (PHS), a component of the Department of Health and Human Services (DHHS), through the NIH, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC), provides the largest U.S. investment in biomedical research through the award of grants and contracts. In 1971, the NIH issued a policy on the humane care of laboratory animals. That policy required institutions using warm-blooded animals in NIH-funded projects to evaluate their facilities regarding the acceptable standards for the care, use, and treatment of those animals. In 1985, the Health Research Extension Act (HREA) provided the statutory mandate for the publication

of the PHS Policy on Humane Care and Use of Laboratory Animals (PHS Policy). The secretary of the Department of Health, Education, and Welfare (now the DHHS), through the director of the NIH, via the NIH Office for Protection from Research Risks (OPRR) (now the NIH Office of Laboratory Animal Welfare [OLAW]), implemented the HREA. The act requires the proper care and treatment of the research animals, directing the appointment of an IACUC to semiannually review and document the institution's program of animal care and treatment, identify any violations, and report those findings annually to the OPRR.

During that same year, in parallel with the release of the International Guiding Principles for Biomedical Research Involving Animals, the U.S. government adopted the Interagency Research Animal Committee publication "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training" (U.S. Government Principles). The PHS Policy, published in 1986, endorses the U.S. Government Principles and requires institutions receiving PHS funding for animal activities to use the *Guide* (last revised by the National Research Council [NRC] of the U.S. National Academy of Sciences in 2011; *Guide for the Care and Use of Laboratory Animals* [NRC Guide]) in developing and implementing their animal care and use program. The PHS Policy describes the assurance process; defines the roles and responsibilities of the IACUC, to include animal program and scientific protocol reviews; and requires proper training and access to a health program for personnel having animal contact. It also requires compliance with applicable USDA regulations, and describes the annual reporting requirements. Compliance with PHS Policy is administered by OLAW through a self-reporting, self-correcting program, with a minimum of for-cause inspections by OLAW staff. Institutions are required to inform the OLAW of noncompliant issues, with subsequent written reports when the institution has implemented corrective actions that are designed to preclude such incidents from occurring in the future.

The *Guide for Laboratory Animal Facilities and Care*, published by the ACP in 1963, was first revised in 1965 and renamed the *Guide for the Care and Use of Laboratory Animals* (NRC Guide). The 1965 revision, and subsequent editions, was published by the Institute for Laboratory Animal Resources (ILAR) (now known as the Institute for Laboratory Animal Research), a component of the NRC of the National Academy of Sciences, in conjunction with the NIH. Pursuant to National Academy practices, panels of laboratory animal science experts were appointed to committees to create revisions to the NRC Guide. In 1985, the ILAR published the sixth edition of the *Guide*. That particular edition reflected the significant regulatory changes that were brought about by the 1985 AWR amendments and the newly published PHS Policy. The *Guide* was last revised in 2011, resulting in the eighth edition of that publication. The last two editions reflected the growing practice of the application of performance standards (in comparison with the previous use of engineering standards), as well as recognition of professional judgment by providers and users to achieve compliance with the recommendations enunciated in the *Guide*. The *Guide* has become an internationally recognized reference on the care and use of animals in biomedical research.

AAALAC International is a private, nonprofit accrediting organization that provides peer-reviewed assessments of institutional animal care and use programs. AAALAC International was founded in 1965. Accreditation by AAALAC International is voluntary and thus is not a regulated endeavor. AAALAC International began as the American Association for Accreditation of Laboratory Animal Care and became international in the mid-1990s. There are now more than 980 institutions accredited in greater than 44 countries. AAALAC International uses the NRC Guide, the Federation of Animal Science Societies' *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (Ag Guide), and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Council of Europe (European Treaty Series 123) as its three primary standards to evaluate animal care and use programs. The PHS Policy recognizes AAALAC International accreditation as evidence that an assured institution is in compliance with the recommendations enunciated in the NRC Guide. AAALAC International performs site visits to accredited units every 3 years to reevaluate their programs and reassure their compliance with the standards, as applicable, mentioned above.

Training of research, veterinary, and animal care staff members is a requirement of the regulations and standards. The USDA AWR require training programs that, at a minimum, include instruction on humane animal care and experimentation; research and testing methods that minimize or eliminate the

use of animals or limit animal pain or distress; use of the information service at the National Agricultural Library (AWIC), established under a subsection of the regulations; and methods wherein deficiencies in animal care and treatment should be reported.

The *Guide* calls for personnel to receive training or have the experience to complete the tasks for which they are responsible, as well as to regularly participate in continuing education activities. AALAS provides the AALAS Learning Library (ALL), an online educational resource with curriculum topics for technicians, veterinarians, IACUC members, and research personnel. AALAS, in conjunction with the Laboratory Animal Management Association (LAMA), has offered laboratory animal management education through the Institute for Laboratory Animal Management (ILAM) since 1992. The LAMA is an international membership organization "… dedicated to advancing the quality of management and care of laboratory animals throughout the world." LAMA provides a quarterly management publication and training sessions, and holds an annual meeting. Laboratory Animal Welfare Training Exchange (LAWTE) is a membership organization that generates training materials for use by trainers and sponsors seminars and webinars for animal care and use staff members. In addition, there are a number of college-level programs that offer 2-year associate of science degrees or 4-year bachelor of science degrees in veterinary technology. The Scientists Center for Animal Welfare (SCAW) is a membership organization that provides educational resources in support of humane animal care and use in the research environment. Those resources include conferences, workshops, publications, and training materials.

AALAS has developed certification programs for laboratory animal technicians that confer recognition of an individual's experience and knowledge: the three levels of certification include the assistant laboratory animal technician, laboratory animal technician, and laboratory animal technologist. AALAS sponsors a voluntary registry continuing education program wherein certified technicians or technologists are recognized as having stayed current in the field of animal science. AALAS also sponsors (in conjunction with the Institute for Certified Professional Managers) a certification program for managers in laboratory animal science positions, wherein they can become a Certified Manager of Animal Resources. In addition, AALAS and LAMA sponsor an on-site educational program for technicians, technologists, and managers entitled the Institute for Laboratory Animal Management. That program offers instruction in management concepts and provides communications, team building, and networking opportunities for attendees.

Internationally, the oldest (founded in 1950) education and training program offered for animal care and/or technical personnel is provided by the IAT. The IAT offers programs, certifications, and registry for several levels of technicians, technologists, and NACWO licensees. Additionally, they offer a government-recognized 4-year college education program. The IAT education and certification programs are used and recognized by several European and Scandinavian countries and India.

The American Veterinary Medical Association (AVMA) is a professional membership organization for veterinarians engaged in private, corporate, government, academic, and uniformed services practices. The AVMA is governed by a house of delegates, which includes 70 members from state, territorial, and allied veterinary organizations. Among those allied organizations is the American Society of Laboratory Animal Practitioners (ASLAP). ASLAP is the only organization that represents laboratory animal veterinarians within the AVMA. ASLAP provides support for educational activities and advocacy for veterinary involvement in humane animal care and use in research endeavors. The AVMA's American Board of Veterinary Specialties (ABVS) recognizes specialty organizations that meet ABVS standards for board certification of veterinarians (diplomates) in a specialized field of veterinary medicine. Among the 22 AVMA-recognized specialties is the American College of Laboratory Animal Medicine (ACLAM). ACLAM currently has greater than 975 active diplomates engaged in support of the responsible and appropriate care and use of animals in research. Those diplomates provide clinical and management expertise to the myriad species used in research, participate in IACUC deliberations of research protocols, and serve as subject matter experts to both institutional officials and research investigators.

In the United Kingdom, the Laboratory Animals Veterinary Association (LAVA), founded in 1963, formerly the British Laboratory Animal Veterinary Association, is made up of veterinary surgeons and students from the United Kingdom and elsewhere who are interested in laboratory animal medicine and

science. Many members act as named veterinary surgeons under ASPA in a full- or part-time capacity. Vets working in academic, drug discovery, commercial, and contract research environments are represented as clinicians or in other aspects of the care and use of animals in biomedical research. LAVA promotes best practice and the dissemination of new technologies through its biannual meetings and other avenues. It represents laboratory animal veterinarians at the national and international level when needed for discussions and decision making on laboratory animal law, welfare, ethics, transport, techniques, and disease.

Internationally, the Japanese College of Laboratory Animal Medicine was formed in 1999; the European Society of Laboratory Animal Veterinarians and the European College of Laboratory Animal Medicine were formed in 1996 and 2000, respectively; and in 2006, the Korean College of Laboratory Animal Medicine was formed. Their missions and functions are similar to those described above for ASLAP and ACLAM. The International Association of Colleges of Laboratory Animal Medicine provides a communication platform for those colleges and promotes the responsible use of laboratory animals through the certification of veterinary specialists.

In 1959 in the United Kingdom, W. M. S. Russell and R. L. Burch published *The Principles of Humane Experimental Technique*. That publication arose from an initiative generated in the mid-1950s by the Universities Federation for Animal Welfare (UFAW). That book espoused the principles of replacement, reduction, and refinement (the 3Rs) as steps scientists could apply to improve the welfare of research animals.

The creation of IACUCs brought a regulatory and oversight presence down to the local (institutional) level. The IACUCs are empowered by both regulatory (AWR and PHS Policy) and standards-driven (*Guide*) requirements to proactively oversee the care and use of animals in research, testing, and education on a continuing basis. The members, to include (at a minimum) an individual not affiliated with the institution, a scientist involved in animal studies, and a veterinarian with delegated program authority, have defined responsibilities: review and approval of research protocols (prior to the conduct of studies); assessment of the training and occupational safety and health of personnel involved in animal activities; at least semiannual review of the institutions' animal care and use program components, as well as physical inspection of the animal facilities and animal activity areas where animal procedures are performed; investigation of alleged noncompliant actions by staff involved in animal activities; and communication of their activities to institutional officials. The presence of the IACUC brought oversight and implementation of compliance monitoring and enforcement to the very local level. Such IACUC oversight and review activities permitted assessment and judgment to be applied by individuals with direct familiarity and understanding of the animal activities performed by the research staff, enabling the application of professional judgment and performance standards enunciated in the *Guide*.

There are a few international organizations that have maintained prominence in global laboratory animal science.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, nonprofit organization established jointly by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization in 1949. Starting in the early 1980s, the CIOMS developed the International Guiding Principles for Biomedical Research Involving Animals. In 1985, the executive secretary of CIOMS stated, "In elaborating and publishing the International Guiding Principles the objective of CIOMS is not to duplicate such national regulations or voluntary codes as already exist but to provide a conceptual and ethical framework, acceptable both to the international biomedical community and to moderate animal welfare groups, for whatever regulatory measure each country or scientific body chooses to adopt in respect of the animals used for scientific purposes." At the time of their release in 1985, those principles were fully endorsed by the European Medical Research Councils and the WHO Advisory Committee on Medical Research.

The International Council for Laboratory Animal Science (ICLAS) is a scientific membership organization promoting the ethical care and use of laboratory animals. Membership categories include national (countries), scientific and union, institutional, associate, and affiliate members. ICLAS was formed in 1956 (initially known as the International Committee on Laboratory Animals; renamed ICLAS in 1979). ICLAS collects and disseminates information on laboratory animal science, fosters harmonization of policies and practices, and promotes international collaboration of animal care and use.

In 2012, an ad hoc committee cochaired by CIOMS and ICLAS revised the International Guiding Principles. In 2013, the OLAW ruled that institutions outside the United States that receive PHS funding are required to have a foreign assurance that commits the institutions to following the revised guiding principles.

The Federation of European Laboratory Animal Science Associations (FELASA) is a membership organization open to laboratory animal science organizations of Europe and beyond. FELASA has published numerous internationally recognized guidelines, recommendations, and position statements and continues to host triennial international congresses. FELASA also sponsors an accreditation program for education and training programs for individuals who perform any of the four functions (animal care, carrying out animal procedures, designing animal procedures and projects, and killing animals) outlined in EU Directive 2010/63.

While the practices and equipment related to animal care and use have become extremely sophisticated and significantly refined, there remain detractors to the animal research enterprise. Those organizations continue to voice their opposition to the use of animals in research through public demonstrations, lobbying efforts to support legislation opposing or limiting the scope of animal research, antivivisection advertisements, and attempting to use internal institutional document material (obtained through FOIA requests for federally funded organizations or state sunshine laws) to embarrass or demand regulatory investigations at institutions where noncompliant activities were alleged to have occurred. Members of a small number of these organizations conduct illegal acts of violence or terrorism against institutional facilities or individuals to demonstrate their objections to the use of animals in research. Several arrests of individuals committing acts objecting to the use of animals in research have been made, in accordance with the 2006 amendment to the 1992 U.S. Animal Enterprise Terrorism Act. Among the more active detractors are the Animal Legal Defense Fund (ALDF), the Animal Liberation Front (ALF), Cruelty Free International (previously called the British Union for the Abolition of Vivisection [BUAV]), the Humane Society of the United States (HSUS), In Defense of Animals (IDA), the National Anti-Vivisection Society (NAVS), the New England Anti-Vivisection Society (NEAVS), People for the Ethical Treatment of Animals (PETA), the Physicians Committee for Responsible Medicine (PCRM), and Stop Animal Exploitation Now (SAEN).

The relative explosion of electronic technology over the past couple decades has amplified and made possible almost instantaneous communications and data sharing among individuals and organizations. The Internet, and the associated hardware and software supporting it, has literally erased international borders and brought knowledge and social interchange to practically all the world's population. While the overwhelming majority of that interchange is positive and productive, persons or organizations that either disagree with or oppose the use of animals in research can easily reach a practically unlimited number of recipients. Posting information and opinions and/or photo and video on the Internet (or unsolicited e-mails) is a practically unhindered activity, as there are essentially no "filters" or *a priori* reviews of that information, other than establishing a log-in name and password. The social media websites enjoying the greatest popularity at present include Facebook, Google, Instagram, Twitter, and YouTube.

Conclusion

As noted above, the care and use of animals in biomedical research has a long and somewhat complex and involved history. The training and experience of animal care staff and the veterinary specialists engaged in supporting these research endeavors has grown in leaps and bounds to keep up with the explosive growth of sophistication in the technology of facilities and equipment paralleling the advancement of scientific techniques and procedures. The remaining chapters of this book will greatly expand on the management and implementation of the myriad activities carried out on behalf of the biomedical research enterprise.

Section II

Developing a Collaborative Culture of Caring

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Culture of Care: Organizational Responsibilities

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CONTENTS

Introduction

Animal use in research has contributed significantly to advances in science and medicine, and the role of laboratory animal professionals in this process is pivotal (AALAS 2001; Medina 2008). While it is desirable to use alternatives to live animals for this process, the use of animals continues to be necessary to protect human and animal health and the environment (EU 2010). To preserve the privilege to use animals in research, a strong program of animal care and use becomes important for several reasons: regulatory compliance, quality of scientific results, addressing public sensitivities, managing staff sensitivities, and moral obligations to the animals themselves. Regulations impacting on the care and use of research animals are covered in greater detail elsewhere in this text. The most commonly referenced regulatory standards include the *Guide for the Care and Use of Laboratory Animals* (*Guide*) (recognized internationally as setting standards for animal care and use), European Union (EU) Directive 2010/63/EU, and the World Organization for Animal Health (OIE). The *Guide* states that "all who care for, use, or produce animals for research, testing or teaching must assume responsibility for their well-being," and that "both researchers and institutions have affirmative duties of humane care and use" of research animals, which is later defined as "those actions taken to ensure that laboratory animals are treated according to high ethical and scientific standards" (NRC 2011). The *Guide* further states that "it is the institution's responsibility to put into place policies, procedures, standards, organizational structure, staffing, facilities, and practices to ensure the humane care and use of laboratory animals throughout the institution" (NRC 2011). The EU Directive states that animals

have intrinsic value that must be respected and that "animal welfare considerations should be given the highest priority … that each use is carefully evaluated," and that principles of replacement, reduction, and refinement (the 3Rs) should be considered systematically when using animals in research (EU 2010). The OIE, comprised of more than 170 member countries, has eight guiding principles on animal welfare outlined in its Animal Health Code. These principles also support incorporation of the 3Rs and state "that the use of animals carries with it an ethical responsibility to ensure their welfare to the greatest extent practicable" (OIE 2008).

Biomedical progress depends, fundamentally, on scientific excellence, which is dependent on quality animal care (Ad Hoc Committee to Revise the International Guiding Principles 2012; Friese 2013). The provision of excellent care also addresses some of the ethical and moral concerns of the general public regarding the use of animals in research. Animal care and use carries with it the responsibility to ensure that high ethical and scientific standards (NRC 2011) are met, and the public is reassured by knowing how much effort is expended by animal caregiving staff on behalf of the animals, to adhere to the intent as well as the scope of the laws that protect research animals (Medina 2008; EU 2010; Coleman 2011). Strong animal care and use programs also address the sensitivities of staff, who often choose careers in animal research because of their love and compassion for animals (Coleman 2011; Davies and Horst 2015).

Institutional culture influences the productivity and performance of many enterprises (Simone 2009; Ng'ang'a and Nyongesa 2012; Uddin et al. 2013), and cultures that promote caring for the animals and people supporting animal care and use programs can provide a basis for an exceptional animal care and use program. This culture, often referred to as the "culture of caring" or "culture of care," promotes compassion and respect for laboratory animals and the people who work with them. In discussing a "strong culture" at a successful large technology company, Kunda focuses on the "self-conscious and tireless celebration of the company's strong culture—one in which employees are creative, committed, entrepreneurial, independent, and moral." This involves not only employees' intellectual skills and physical presence, but also their emotions, moral sense, and personal loyalties (Kunda 2006). Care is less something to be rigidly defined than a style of thinking. It "directs attention to what was once rendered invisible within scientific research … as opposed to the calculable and controllable" (Mol et al. 2010). Davies and Horst (2015) write about the relationship between "craft" (or skills) and "care" and reflect on the potential implications of the promotion of a culture of care in a research setting. They propose a model of craft as a caring practice "which brings together skill, a focus on utility or purpose and a particular emotional orientation (care, passion and commitment)." In their analysis of numerous research labs globally, they found that "a happy group was understood as a productive one," and the strongest leaders accommodated different individuals and viewed treating people well as vital, "both because it is the right thing to do and because it is, ultimately, good for science."

A culture of care goes beyond being compliant with applicable rules and regulations and strives to meet the full intent of established rules and regulations—excellent animal welfare and reproducible scientific results. Many of the laws and guidelines surrounding animal care and use allow for the use of professional judgment (Klein and Bayne 2007). This should not be interpreted to support a minimalistic approach that just meets the letter of the law, but instead should be applied to working with animals in a manner that strives to provide the best possible care for the animals, thus producing the highest-quality scientific results (Medina 2008). A culture of care often starts with an institutional mission and value statement that clearly states the institution's commitment to the humane care and use of animals (Phanuel Kofi Darbi 2012). This mission statement frequently refers to the advancement of knowledge, the development of life-saving procedures and drugs, improving the quality of life for humans and animals, or some similar goal. The corresponding value statement, often referred to as "core values," articulates the institution's commitment to animal welfare, the humane care and use of laboratory animals, and/or the implementation of the 3Rs. Examples include

- "[Our Institution] is committed to the humane care of the research animals we produce and work with in all of our activities" (http://www.criver.com/about-us/humane-care/best-practices).
- "We are committed to reducing our reliance on animal testing methods, and promoting the development, validation and use of non-animal testing models. [The Institution] requires

that where animals have been or may be used for research or testing, that we abide by the principles of the 3Rs of animal research" (http://www.bms.com/sustainability/environmental_performance/Pages/product_stewardship.aspx).

- "[Our Institution] is committed to ensuring the humane care and use of laboratory animals in the company's research and development programs. We recognize that high quality science and humane animal care are inseparable. In addition to complying with applicable legislation and regulations, [Our Institution's] laboratory animal research programs and facilities aim to exceed regulatory agency standards" (http://www.abbvie.com/responsibility/transparency-policies/home.html#).

A culture of care usually includes

- Strong institutional commitment to provide the resources and leadership necessary, such as ongoing communication from management that reinforces the commitment to animal welfare for all institutional stakeholders (scientists, technicians, shareholders, and the public)
- Creation of an environment where staff feel empowered to come forward with any concerns or suggestions they have to improve the animal care and use program and that respects and nurtures staff compassion
- Mechanisms to support open communications on all aspects of the program
- A well-defined program of training on aspects of animal care and use, including ethics for all employees (from animal care technicians to top research scientists) and mechanisms to ensure competency
- Programs that recognize excellence in animal care and use
- Empowerment of animal welfare oversight committees, such as the Institutional Animal Care and Use Committee (IACUC), Ethics Committees (ECs), and Animal Welfare Bodies (AWBs)
- Commitment to, and proactive implementation of, the 3Rs

The productivity of any enterprise is, ultimately, dependent on the culture established to drive its success (Kunda 2006). Biomedical advances in a research culture are a significant aspect of their measure of productivity, and as a result, these advances continue to improve and save human and animal lives. There are still many unmet medical needs for both people and animals. Therapeutic discoveries are necessary to address these various diseases and disorders. The research community cannot provide the cures and treatments needed without collecting scientific data in both preclinical animal studies and human clinical trials, which both must adhere to high scientific and ethical standards as described in good laboratory practice (GLP) and good clinical practice (GCP) regulations, respectively (FDA 2001). The miracles of tomorrow depend on ongoing innovations in biomedical research progress today (Brouwers et al. 2011). Caring for research animals can present a variety of emotional challenges for research and laboratory animal professionals (AALAS 2013); however, a strong culture of care that supports the overall well-being of all the animals and people involved in biomedical discovery may drive productivity in unprecedented ways.

This chapter elaborates on the important components described above, providing examples and suggestions for how a culture of care can be incorporated into any animal care and use program, regardless of size or scientific mission.

Organizational Commitment

A commitment to animal welfare starts with the institutional leadership. Institutional leaders include officers of a company, academic administrators, managers, faculty, and any others having organizational leadership responsibilities. Leaders of programs in which animals are used must be able to articulate the commitment to animal welfare and be able to discuss it with both internal and external stakeholders. Institutional leaders should also seek opportunities to reinforce the messages supportive of a culture of

care, for example, through staff meetings, "all hands" meetings, and video messaging. If institutional leaders stress the importance of animal welfare as part of the overall institutional culture they support, other employees, be they management or technicians, will understand the importance of demonstrating this commitment in their work at the institution. Institutional leaders should also convey that activities that are not in keeping with the institution's values and culture of care will not be tolerated (Albanese et al. 2015). Based on relevant animal care and use job responsibilities, it is good management practice for an employee's commitment to animal welfare to be assessed as part of his or her performance review, so the importance of this commitment is emphasized and formally recognized as part of the institutional culture (Meehan et al. 2008; Phanuel Kofi Darbi 2012).

A commitment to animal welfare should be applied to all species of animals, regardless of their intended use for research, teaching, testing, or production or inclusion in regulations and standards. This commitment is often articulated in a short value statement, mentioned earlier, which should be something that resonates with all employees (including management) involved in animal work, as well as those employees who may be involved in other aspects of the institution's work (ancillary support staff such as receptionists, administrative assistants, janitorial and grounds staff, and facilities engineers). This value statement should be something that all employees can refer to when discussing their employment with others. The message of the value statement can be reinforced by displaying it prominently in areas, such as the institutional website, institutional handbooks, and facilities where animals are housed. This display makes the institution's commitment clear not only to employees but also to visitors and regulators.

An institution can demonstrate its commitment to animal welfare and a culture of care in a variety of ways, depending on the size and scope of the institution. Some large institutions employ staff specifically dedicated to the ongoing support and enhancement of the culture of care (Albanese et al. 2015; Bratcher and Reinhard 2015). Support for committees that work to enhance environmental enrichment and normal animal behavior is another way institutions can demonstrate their commitment to animal welfare. Committees, dedicated personnel, or other initiatives that foster implementation of alternatives, also known as the 3Rs (covered later in this chapter), are also important aspects of a culture of care (James et al. 1995; Medina 2008). Strong support for training initiatives, including the recruitment and development of highly competent trainers and providing adequate time for initial training and reinforcement training, is another key aspect of institutional support. Institutional support for training should include not only internal training but also support for continuing education at professional meetings for various stakeholders, such as technicians, veterinarians, IACUC members, and managers.

The IACUC, EC, AWB, or comparable internal animal welfare oversight body can also influence the culture of care and help ensure animal welfare, sound science, implementation of the 3Rs, and regulatory compliance (Coleman 2011). As such, this committee should be strongly supported by the institution. Other ways an institution can show its support for a quality animal care program and a culture of care include involvement in professional organizations such as the American Association for Laboratory Animal Science (AALAS) or similar organizations in the institution's country, involvement in AAALAC International, and supporting internal research efforts and publications in the areas of animal welfare and the 3Rs. Support for recognition programs can also be powerful and should start at the top and include all levels of management.

Having key institutional leaders involved in recognition events is just one way of demonstrating an institutional commitment to a culture of care (Saunderson 2004). In addition, institutions should provide support for staff experiencing difficulty, which can be inherent when compassionate individuals are involved in tasks such as euthanasia (Herzog 2002). Management should ensure that staff who work with animals are given high regard in the institutional framework, to acknowledge the importance of the challenging work they do in support of ethical biomedical research. Last, since senior leaders (institutional officials, IACUC chairs, and others) play critical roles in establishing organizational culture, consideration should be given to succession planning that will help ensure future leaders who will maintain a culture of care (Valentine 2012).

There are several internationally accepted guidelines and principles that can serve as a foundation when developing or assessing an organization's culture of care. One example is the CIOMS-ICLAS International Guiding Principles (Table 2.1) (Ad Hoc Committee to Revise the International Guiding Principles 2012). Another reference is the Five Freedoms (Table 2.2) created by the Bramble Commission in the United Kingdom in 1955 (Mellor 2016).

TABLE 2.1

CIOMS-ICLAS Principles: International Guiding Principles for Biomedical Research Involving Animals, December 2012

The following principles should be used by the international scientific community to guide the responsible use of vertebrate animals in scientific and/or educational activities.

I. The advancement of scientific knowledge is important for improvement of human and animal health and welfare, conservation of the environment, and the good of society. Animals play a vital role in these scientific activities and good animal welfare is integral to achieving scientific and educational goals. Decisions regarding the welfare, care, and use of animals should be guided by scientific knowledge and professional judgment, reflect ethical and societal values, and consider the potential benefits and the impact on the well-being of the animals involved.

II. The use of animals for scientific and/or educational purposes is a privilege that carries with it moral obligations and responsibilities for institutions and individuals to ensure the welfare of these animals to the greatest extent possible. This is best achieved in an institution with a culture of care and conscience in which individuals working with animals willingly, deliberately, and consistently act in an ethical, humane and compliant way. Institutions and individuals using animals have an obligation to demonstrate respect for animals, to be responsible and accountable for their decisions and actions pertaining to animal welfare, care and use, and to ensure that the highest standards of scientific integrity prevail.

III. Animals should be used only when necessary and only when their use is scientifically and ethically justified. The principles of the Three Rs—Replacement, Reduction and Refinement—should be incorporated into the design and conduct of scientific and/or educational activities that involve animals. Scientifically sound results and avoidance of unnecessary duplication of animal-based activities are achieved through study and understanding of the scientific literature and proper experimental design. When no alternative methods, such as mathematical models, computer simulation, *in vitro* biological systems, or other nonanimal (adjunct) approaches, are available to replace the use of live animals, the minimum number of animals should be used to achieve the scientific or educational goals. Cost and convenience must not take precedence over these principles.

IV. Animals selected for the activity should be suitable for the purpose and of an appropriate species and genetic background to ensure scientific validity and reproducibility. The nutritional, microbiological, and general health status as well as the physiological and behavioral characteristics of the animals should be appropriate to the planned use as determined by scientific and veterinary medical experts and/or the scientific literature.

V. The health and welfare of animals should be primary considerations in decisions regarding the program of veterinary medical care to include animal acquisition and/or production, transportation, husbandry and management, housing, restraint, and final disposition of animals, whether euthanasia, rehoming, or release. Measures should be taken to ensure that the animals' environment and management are appropriate for the species and contribute to the animals' well-being.

VI. The welfare, care, and use of animals should be under the supervision of a veterinarian or scientist trained and experienced in the health, welfare, proper handling, and use of the species being maintained or studied. The individual or team responsible for animal welfare, care and use should be involved in the development and maintenance of all aspects of the program. Animal health and welfare should be continuously monitored and assessed with measures to ensure that indicators of potential suffering are promptly detected and managed. Appropriate veterinary care should always be available and provided as necessary by a veterinarian.

VII. Investigators should assume that procedures that would cause pain or distress in human beings cause pain or distress in animals, unless there is evidence to the contrary. Thus, there is a moral imperative to prevent or minimize stress, distress, discomfort, and pain in animals, consistent with sound scientific or veterinary medical practice. Taking into account the research and educational goals, more than momentary or minimal pain and/or distress in animals should be managed and mitigated by refinement of experimental techniques and/or appropriate sedation, analgesia, anesthesia, nonpharmacological interventions, and/or other palliative measures developed in consultation with a qualified veterinarian or scientist. Surgical or other painful procedures should not be performed on unanesthetized animals.

VIII. Endpoints and timely interventions should be established for both humane and experimental reasons. Humane endpoints and/or interventions should be established before animal use begins, should be assessed throughout the course of the study, and should be applied as early as possible to prevent, ameliorate, or minimize unnecessary and/or unintended pain and/or distress. Animals that would otherwise suffer severe or chronic pain, distress, or discomfort that cannot be relieved and is not part of the experimental design, should be removed from the study and/or euthanized using a procedure appropriate for the species and condition of the animal.

(*Continued*)

TABLE 2.1 (CONTINUED)

CIOMS-ICLAS Principles: International Guiding Principles for Biomedical Research Involving Animals, December 2012

IX.	It is the responsibility of the institution to ensure that personnel responsible for the welfare, care, and use of animals are appropriately qualified and competent through training and experience for the procedures they perform. Adequate opportunities should be provided for ongoing training and education in the humane and responsible treatment of animals. Institutions also are responsible for supervision of personnel to ensure proficiency and the use of appropriate procedures.
X.	While implementation of these Principles may vary from country to country according to cultural, economic, religious, and social factors, a system of animal use oversight that verifies commitment to the Principles should be implemented in each country. This system should include a mechanism for authorization (such as licensing or registering of institutions, scientist, and/or projects) and oversight which may be assessed at the institutional, regional, and/or national level. The oversight framework should encompass both ethical review of animal use as well as considerations related to animal welfare and care. It should promote a harm–benefit analysis for animal use, balancing the benefits derived from the research or educational activity with the potential for pain and/or distress experienced by the animal. Accurate records should be maintained to document a system of sound program management, research oversight, and adequate veterinary medical care.

Source: Ad Hoc Committee to Revise the International Guiding Principles, CIOMS International Guiding Principles for Biomedical Research Involving Animals, 2012, retrieved April 4, 2016, from https://grants.nih.gov/grants/olaw/Guiding_Principles_2012.pdf.

TABLE 2.2

Five Freedoms, December 1979

1. Freedom from thirst, hunger and malnutrition—by providing ready access to fresh water and a diet to maintain full health and vigour.
2. Freedom from discomfort and exposure—by providing an appropriate environment including shelter and a comfortable resting area.
3. Freedom from pain, injury or disease—by prevention or rapid diagnosis and treatment.
4. Freedom from fear and distress—by ensuring conditions and treatment which avoid mental suffering.
5. Freedom to express normal behaviour—by providing sufficient space, proper facilities and company of the animal's own kind.

Source: Mellor, D.J., *Animals (Basel)*, 6(10): (Article 59) 1–7, 2016.

Designing a Culture of Care

In addition to a succinct institutional value statement, how an institution embraces the importance of animal-based research, embodies a commitment to compassion and respect, and shares this both within the organization and outside the organization also defines its culture of care. The structure of a program helps define responsibility and expectations and can create an environment where teamwork toward a common goal—that of animal welfare and quality science—can thrive. This environment creates a supportive workplace where compassion, recognition of the importance of the human–animal bond, and respect are a focus. Caring environments support open communication about all aspects of the culture of care, and ensure that all staff are appropriately trained and competent, and that excellence is recognized and rewarded. In this way, the core values of the culture are reinforced continually, ensuring ongoing assessment of activities and supporting improvements, including opportunities for more fully implementing the principles of the 3Rs.

Key Characteristics of a Culture of Care

Structure

Many individuals contribute to the creation of a culture of care. As previously stated, it is very useful to have informed, engaged senior leadership set the tone for the commitment to animal welfare (Albanese et al. 2015). Additional key staff include managers, veterinary staff, husbandry caregivers, research technicians, scientists, and the local animal welfare oversight body (IACUC, ECs, AWBs, etc.). These positions have unique and shared responsibilities for ensuring animal welfare. Clearly understood expectations, open communication, and teamwork are key to functionality. For example, the establishment and implementation of setting humane endpoints illustrates how this can work. During review of a protocol, the animal welfare oversight body discusses the impacts of the proposed study on animal welfare, including strategies that will be used to minimize pain and/or distress. Through interaction with site veterinary staff and the scientist, plans of action are developed. Including research and husbandry technicians as part of the team in this discussion, since they are often at the forefront of identifying adverse effects on animals and also often the ones who will carry out many of the treatment and supportive care strategies, helps promote a robust plan. Team meetings, prior to the start of a study, help ensure that the plan is well understood by all who will be involved in the study. Intervention points, be they treatment, supportive care, or euthanasia, can be discussed and understood so as to avoid unnecessary delays in the implementation of the intervention plan. Committees may also be used to establish policies and procedures relating to animal welfare since different perspectives can lead to a more informed process and encourage buy-in by the various people involved in the success of the project.

Developing, growing, and fostering a culture of care program can be enhanced through committees and working groups, dedicated positions, and volunteer programs—all of which can be adapted to any research setting. Internal committees and working groups, such as alternatives committees, enrichment committees, and other welfare or project-focused working groups, bring together expertise, potentially globally, with varied influence and experience (Bratcher et al. 2012; Albanese et al. 2015). Working together as a team, across areas of primary responsibility, fosters a sense of the common goal of animal welfare. In addition to internal committees and working groups, staff can be encouraged to be involved in external consortia aimed at welfare advances (https://iqconsortium.org/initiatives/leadership-groups/3rs; https://www.nc3rs.org.uk/). Such involvement can provide dividends to an institution as it speaks well of the institution's commitment to animal welfare and may also result in staff bringing learned ideas for improvement back to the home institution.

Human–Animal Bond and Staff Empowerment

The key attributes of a culture of care are compassion and respect for both the animals and the people who work with them (Buckmaster 2012; Brown 2014; Albanese et al. 2015). The majority of caregivers in research laboratories have chosen the field because of a strong interest in animals (Chang and Hart 2002; Coleman 2011). Caregivers work closely with animals and often develop strong relationships with them. These relationships can bring joy to caregivers, referred to as compassion satisfaction (Figley and Roop 2006; Mehelich 2011; Neff 2012). These positive relationships can minimize the impacts of stressors on animals, such as alterations of the hypothalamic–pituitary–adrenal axis, cardiovascular function (Von Holst 1998; Gerber et al. 2002), and reproductive and immunological functions (Rogers et al. 1999; Bethea et al. 2008). Stress also increases experimental variability (Schapiro et al. 2000; Weed and Raber 2005). Positive interactions with caregivers can reduce abnormal behavior, increase species-appropriate behavior, and promote coping skills that help mitigate stress reactivity toward novel objects or situations (Rennie and Buchanan-Smith 2006). Engaging in positive interactions with the animals leads to increased morale and job satisfaction in caregivers, which leads to better care and improved animal well-being (Waitt et al. 2002). Positive human–animal relationships facilitate

research by allowing human observers to approach the animals easily and safely, thereby facilitating daily observations and health checks (Lehman 1992). Training animals using positive reinforcement training (PRT) can create situations where the animals cooperate for common husbandry, health care, and research procedures. Although this training requires an investment in time and a level of skill on the part of the caregiver, PRT can reduce fear and stress in the animal and reduce the need for pharmacological restraint, thus reducing stress- and drug-associated variability in the data (Crockett et al. 2000; Bassett et al. 2003; Laule et al. 2003; Lambeth et al. 2006). PRT can also decrease potential animal or human injury that can result from struggling and can also decrease the technician time needed to perform husbandry and research procedures. One potential complication of the positive human–animal bond can be the development of favoritism—when one or more select, favorite animals receive extra attention and perhaps treats. This can have unintended consequences, such as weight gain or disruption of normal conspecific social relationships (Coleman 2011). Researchers and caregivers should be mindful of the impact of their interactions and how their relationships may be perceived by the animals in their care (Shyan-Norwalt 2009).

In a strong culture of care, an institution develops mechanisms to celebrate the compassion, caring, and respect their staff exhibit toward animals, and will be prepared with resources to address issues if such care creates personal conflict. This conflict can result in a condition known as compassion fatigue. This condition has been recognized in various health care fields (Carmack and Becker 1988; Baran et al. 2009). Because of the emotional investment on the part of research staff, illness and death of research animals may lead to compassion fatigue in caregivers (Coleman 2011). The "cost of caring" in the animal research setting has been recognized since the 1980s and has resulted in numerous publications and guides (Herzog 2002; Overhulse 2002; Russow 2002; Kelly 2015). The AALAS publication "The Cost of Caring" provides an introduction to this topic (AALAS 2013). It stresses that "close contact with animals affords personnel intense feelings of satisfaction in knowing they are not only providing essential needs such as food, water, and clean bedding but also affection" (AALAS 2013). It also recognizes that personnel may experience grief and mourning with the death of an animal and describes the steps that may be experienced in the grieving process (AALAS 2013).

Moral and emotional consequences of caring for animals should not be ignored or minimized (Coleman 2011). "Institutions and caregivers benefit when grief associated with the loss of animals is acknowledged and supported" (Coleman 2011). An institution can develop strategies to reduce the moral conflict that may be present in research staff. This can start by acknowledging that these moral conflicts exist. Scientists can explain the importance of their studies and the reasons for the procedures used and provide caregivers with a voice in the ethical decisions (e.g., "brown bag" lunches, staff training, and service on the IACUC) so they can feel that their opinions and moral concerns are being considered (Herzog 2002). Engaging individuals at all levels of animal use in the review process for animal activities (IACUC, ECs, and AWBs) so different perspectives are heard, and staff feel an ownership of decisions made about animal care and use, can enhance staff empowerment. Helping staff understand the nature of the research, expected clinical signs, and humane endpoints (and the rationale for those endpoints) can help them to cope with animal illness and death. Consideration should be given to allow staff to opt out of situations that cause angst, such as euthanasia of an animal to which they have become particularly attached. Having programs for rehoming animals, when euthanasia is not a necessary part of the study, is also a proactive way to help staff cope. Such programs can also utilize employees who are not caregivers to assist in socialization and other steps that must be taken before adoption, thus making such a program a high-profile aspect of an institution's animal care and use program (Bratcher 2014; Albanese et al. 2015). Individuals who cannot cope with the loss of animal life that is inherent in most animal research programs may need professional support. Access to professional grief counselors is a benefit offered by many institutions. Their guidance and support can be invaluable in individual and group settings. However, informal gatherings that allow caregivers to share their emotional experiences with each other are often just as powerful for healing. Discussing feelings about the loss of animals and celebrating their lives and contributions can also be deeply comforting and strengthen the caregivers' connections with one another (Coleman 2011; AALAS 2013). An increasing number of institutions have developed programs of remembrance or paying tribute to laboratory animals to help staff handle the emotional consequences of their compassion (James et al. 1995; Herzog 2002; Iliff 2002). Such activities

may include a plaque, organized "ceremonies," or creation of a dedicated quiet place, such as a garden, where staff can go to reflect. Such activities allow staff a way to recognize the loss, as well as the important contributions animals have made to research. This may also give people an opportunity to discuss and share their feelings in a supportive environment (Lynch and Slaughter 2001; Iliff 2002; Coleman 2011; Nishikawa and Morishita 2012; Dickens 2013; Wenting 2016).

Every animal research institution should create an environment where staff feel empowered to raise concerns about animal welfare. In fact, reporting animal welfare issues should be an expectation of all employees. The *Guide* clearly states that "the institution must develop methods for reporting and investigating animal welfare concerns, and employees should be aware of the importance of and the mechanisms for reporting animal welfare concerns.… Mechanisms for reporting concerns should be posted in prominent locations.… Multiple points of contact, including senior leadership are recommended.… The process should include a mechanism to report anonymously and nondiscrimination against the concerned/reporting party" (NRC 2011).

Individuals involved in the mechanisms for reporting, such as veterinary staff, supervisors, or IACUC, EC, and AWB members, should know how to receive such concerns. They should also know how to initiate the review process, which should highlight root causes and the development of sustainable corrective and preventive actions. The last step of the review process should include a method that provides feedback to staff members sharing a concern. Without this last step, staff may become bitter and disengaged because they feel their concerns and suggestions are not being heard (Albanese et al. 2015). When concerns are raised, an opportunity is created for employees to collaborate on solutions to a situation that results in better animal welfare, better understanding among stakeholders of the issues and goals, and improved staff morale. This proactive approach can minimize the potential for reactive responses to whistle-blower concerns.

Communication

Communication begins with ensuring the visibility of the culture of care program throughout the institution. As previously noted, the value statement should be prominently displayed. Another option is to post signs in or near the animal facility that recognize the purpose of animal research. For example, if cancer research is being conducted, a sign could note, "We Are Curing Cancer Here." The concept and goals of a culture of care can be shared throughout the organization. Nonanimal users may be asked about their place of work, and having an understanding of the value placed on animal welfare may help this employee speak proudly about the organization's commitment. The institution should develop multiple mechanisms to communicate details of the culture of care both internally and externally. This is most often done via meetings, newsletters, websites, bulletin boards, and e-mail announcements. Involvement by human resources and communications professionals in preparing these communications tools is an excellent way to engage management and to increase management awareness of these issues. Posters, particularly those that have a visual feature, such as a logo, to clearly link them to the culture of care, are another way of getting the word out. Of course, the mechanisms to report concerns and suggestions for improvement and the program's commitment to recognize excellence are also key opportunities for open sharing of information.

Communication that promotes a culture of care at every level of an organization is necessary for ensuring a consistent approach to facilitating the sharing of best practices in large, multisite, and global organizations. Larger organizations may benefit from having dedicated personnel, such as a central coordinator or overarching senior management champion, for the culture of care. However, activities are often overseen locally by the IACUC, EC, and AWB (Brown 2014). It is desirable to have some type of mechanism to ensure communication between these bodies throughout the organization (often organized by the group of dedicated personnel or champion mentioned earlier). Such communication can occur through telecommunications and face-to-face meetings. These should occur on a regular basis and often enough that ideas and momentum are not lost.

An additional opportunity for enhancing communication about the culture of care is to hold a "Culture of Care Day" where researchers present the work that they are doing and how the care for the animals is integral to the success of their work. Participation by all employees in the Culture of Care Day

celebration will help them gain insight for the work that is accomplished and meet the people who take care of the animals. A Culture of Care Day is also an opportunity to recognize the animals who have enabled discoveries (the idea of remembrance tributes is covered in more detail elsewhere in this chapter). An invitation to attend this celebration can be sent to all employees involved in the animal care and use program and also be extended to the facilities staff who are responsible for the animal environment and repairs. It is important for them to understand their role in ensuring optimal animal care and use. Engaging others in the culture of care program, and having consistent reminders of the program until it matures and is embedded in the work culture, will help to ensure the success of the program.

Public outreach and educational opportunities help to gain public trust in the care and use of research animals. The research and laboratory animal care staff will benefit from instruction that helps them to talk about the work that they do and the impact that it has on both human and animal life. Various organizations provide resource materials to help with public outreach efforts. Although it is not possible to provide an exhaustive list, some examples include the Foundation for Biomedical Research (http://fbresearch.org/), Americans for Medical Progress (www.amprogress.org), Understanding Animal Research (www.understandinganimalresearch.org.uk), Speaking of Research (speakingofresearch.com/), and States United for Biomedical Research (www.statesforbiomed.org/).

Training

Training, and the topics that must be covered, is mandatory in most countries (EU 2010; NRC 2011; USDA 2013) and is covered in greater detail elsewhere in this text. Therefore, this section highlights the aspects of training that directly support a culture of care. There are two major categories of training for individuals involved in an animal care and use program. The first is technical training. Ensuring that staff have adequate technical training to perform necessary tasks with animals prior to actually working with animals is paramount and mandatory for a successful program (EU 2010; NRC 2011; USDA 2013). Such training should include an assessment of each person's technical competency (NRC 1991, 2011; EU 2010; Brown et al. 2013). Refresher training and periodic confirmation of competency is also part of a strong training program. During technical training, gentle handling, careful observation, and recognition of abnormalities (both physical and behavioral) are topics that will support a culture of care. The second part of a training program should include topics central to a culture of care that impact attitudes, such as understanding why animals are used in research, the ethics of such use, and animal welfare (Brown 2013). Training must take into consideration different local cultural characteristics. This training must also include the mechanism to report concerns or suggestions for improvement in animal welfare and inform employees of their protection from retribution for coming forward with a concern. This training should be required for all employees who have animal handling responsibilities (EU 2010; NRC 2011; USDA 2013) and can be either mandatory or optional for ancillary staff who provide support for the animal care and use staff. Human resources staff should have a good understanding of the purpose of animal research and the need for the animal care and use staff to perform their jobs with technical proficiency, as well as compassion and sensitivity. Every employee is a representative of the institution in the public sphere and is thus in a position to convey the institution's strong commitment to animal welfare and a culture of care. Since the use of animals in research can be a sensitive topic, training can be provided to help them talk with their friends, family, and neighbors about the job that they do. Such training helps them better understand the issues, encouraging pride in their contributions to biomedical research.

Training on why animals are necessary in research and teaching, how we work with them, and the importance of animal welfare can be delivered easily in lectures or self-learning materials. Training that instills compassion, respect, and sensitivity may be done most effectively face-to-face, allowing staff to gain a comfort level for these discussions. Training on the availability of support programs for employees who are having problems related to the nature of their work should also be considered.

Recognition

Programs of recognition help demonstrate that an organization or group values individuals and teams who have exhibited excellence or made exceptional contributions in areas of importance to that organization

or group. Recognition can be an extremely powerful employee motivational tool (McConnell 1997). Awards have been shown to encourage higher standards of performance (Shuaib et al. 2015). Recognition can be both internal and external to an organization. A program of recognition within an organization that has a strong culture of care may recognize staff who demonstrate caring by providing ideas for improvements to animal care and use, creating solutions to problems, going "above and beyond" their job description to enhance animal welfare, advancing the implementation of the 3Rs, or serving as role models in exemplifying the behaviors and characteristics consistent with a culture of care. While some employees may be motivated by tangible rewards, others may find the act of being recognized and appreciated, particularly when done in a group setting by someone high up in the organization, to be even more rewarding (Saunderson 2004). Examples of tangible awards that have been used by some research organizations include special pins or mugs, gift cards, certificates for time off, a special parking spot, certificates of achievement, and monetary awards. In addition to rewarding employees who have achieved something particularly special, such a program can also serve to motivate others who would like to be recognized "next time" (Shuaib et al. 2015).

Internal recognition programs may have an "open nominating process" wherein any employee may nominate a deserving individual. Other programs may limit who can submit a nomination to individuals in more senior positions. Some programs may have both types of nomination processes. To help foster a team approach and the idea that caring values are shared by all employees, an organization may choose to have the winners selected by an awards committee, consisting of individuals who represent various types of positions—caregivers, research technicians, scientists, veterinary staff, and others. Generally, a recognition event is held at least annually, but some organizations have found that smaller, quarterly events help keep the momentum going and keep the values of their culture front and center in everyone's thinking.

As mentioned previously, there are also external awards that recognize excellence in animal welfare, laboratory animal science and medicine, and the 3Rs. Creating a strong nomination packet for an employee or colleague, even if they are not selected for the actual award, is a form of recognition in itself. Examples of just some of the organizations having such awards include AALAS, AAALAC International, the American Veterinary Medical Association (AVMA), the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs), Charles River Laboratories, F. Hoffmann La Roche, and the World Congress on Alternatives and Animals in the Life Sciences. Information on these awards can be found on the organizations' websites.

Auditing and Continuous Improvement

An effective culture of care program requires the commitment of employees at all levels of the organization. Broadly distributed institutional policies or statements that codify the importance and priority of animal care and welfare in research are a powerful way to promote this commitment. Compliance with the relevant federal, state, and local regulatory requirements is just the starting point for a culture of care. Compliance with established industry standards, such as those described in the eighth edition of the *Guide* (NRC 2011), the *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (*Ag Guide*) (FASS 2010), the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS 123) (Council of Europe 1986), and the AVMA Guidelines for the Euthanasia of Animals (AVMA Panel on Euthanasia 2013), as well as clearly defined internal performance standards and operating procedures, is also central to a culture of care. In addition, there are several journals and online resources available that feature successful strategies for improving animal welfare in research settings. Some of the most popular include AALAS's *Laboratory Animal Science Professional*, the *AALAS Journal* and *Comparative Medicine*, Nature's *Lab Animal* magazine, the *ILAR Journal*, the Institute of Animal Technology's *Animal Technology and Welfare*, and NC3Rs' website. Making time to review these and related resources regularly is an excellent way to stay current on the latest developments for improving animal welfare, an important component for maintaining a strong and progressive culture of care.

Internal Audits and AAALAC Accreditation

Regular assessments or audits of the animal care and use program are a critical feature of a culture of care. Required IACUC audits can be combined with additional internal audits conducted by researchers, study directors, members of the husbandry and veterinary teams, and others that have a professional investment in the program, to measure its success. Soliciting feedback in this manner also encourages involvement and suggestions for improvement that foster alignment with the culture of care that supports established animal care and use policies. A variety of performance measures and trends can be tracked and evaluated to inform and guide programmatic adjustments. Some examples include the number and types of substantiated compliance concerns reported, rodent breeding performance, success rates for socially housed animals, number and types of abnormal animal behaviors documented, technical proficiency measures, and employee retention rates.

Programmatic reviews by external consultants or inspectors are also helpful, and some are required by federal law, for example, the Animal Welfare Act and Animal Welfare Regulations (USDA 2013). In addition, many organizations voluntarily request assessment every 3 years by AAALAC International (www.aaalac.org). AAALAC's mission is to enhance the "quality of research, teaching, and testing by promoting humane, responsible animal care and use." AAALAC site visits involve an intense and detailed programmatic review by a variety of industry experts from all over the world. Animal care and use programs are evaluated using the three standards mentioned earlier (*Guide*, *Ag Guide*, and ETS 123), and formal accreditation is only granted to programs that meet or exceed them. AAALAC has been assessing and accrediting animal care and use programs for more than 50 years and has accredited more than 950 research institutions in 41 countries. Suggestions offered by the collective wisdom and global expertise of AAALAC site visitors are unique and unparalleled. As such, triennial AAALAC reviews can be especially powerful for improving a culture of care, providing continual guidance and opportunities to raise the bar for animal care and well-being in research settings.

Reinforcement

Having a variety of mechanisms in place to reinforce the culture of care across the various stakeholder groups is helpful to continuously highlight the institutional commitment to provide excellent care for research animals. One element is to create a written "commitment to humane care and use of animals" that all employees who work with animals read and sign upon initial employment and on an ongoing basis thereafter, for example, after regularly scheduled animal welfare training (Albanese et al. 2015). In addition to reminding employees of their personal commitment to animal welfare, the use of a written pledge to the culture of care enables the IACUC, EC, AWB, and managers to reinforce the institutional commitment to uphold high standards for research animal welfare. Another way to reinforce this culture of care is for the IACUC, EC, and AWB members, including the committee chair, to attend research department and animal support staff meetings. They can then provide updates regarding the culture of care, including the need to maintain sensitivity when working with living animals and the need to respond quickly when animal welfare issues are identified. These visits from the animal welfare oversight body leadership help to reinforce one of the reasons the IACUC, EC, or AWB exists: to provide oversight to ensure that all individuals within a program do their part to maintain a high-quality animal care and use program (EU 2010; NRC 2011; USDA 2013; Brown 2014). Visual features, such as a logo that represents the culture of care, that convey the commitment to animal welfare can be placed on training materials, name badges, lanyards, awards certificates, and posters and be posted throughout the animal facilities and beyond (Brown 2003; Albanese et al. 2015). Such posters can be created internally or can be obtained from a variety of sources, such as http://www.criver.com/aboutus/humane-care/humane-care-posters, http://www.aalasfoundation.org/outreach/resources/posters, https://www.aaalac.org/commerce/bookstore.cfm, and http://oacu.od.nih.gov/posters/index.htm. Finally, creating animal welfare–focused programs that reach out beyond the research community to employees who are not involved in the animal program can greatly enhance a culture of care. An example of this is establishing

a program where employees from around the institution can be trained to interact with research dogs through play, exercise, and caring attention (Bratcher et al. 2012).

The 3Rs

The 3Rs, as stated by Russell and Burch in *The Principles of Humane Experimental Technique*, are supported by laboratory animal research institutions in various ways (Russell and Burch 1959). Concepts of the 3Rs are stated in the Animal Welfare Act, the Public Health Service Policy on Humane Care and Use of Laboratory Animals, the *Guide*, the EU Directive, and various other national and regional guidelines. Institutions can further enhance their commitment by defining the expectations of the 3Rs in institutional policies and guidance documents (Bratcher and Reinhard 2015). By incorporating the 3Rs into the company culture, many other aspects of an optimal animal welfare program will fall into place. The regulations and guidelines help programs to build a foundation of animal care and use that is based on the 3Rs, but each institution can have a variety of different approaches for furthering its culture of the 3Rs based on specific program needs and resource availability. There are many approaches to promoting a culture of care. One example is the establishment of an alternatives committee that draws support from a broad base of scientists, veterinarians, animal care technicians, and the IACUC, ECs, and AWBs.

This broad-based approach to the 3Rs, with ideally one or more key leaders to coordinate efforts, ensures that champions of alternatives are empowered to advance the most ethical science and animal welfare through the development of annual goals and coordinated cross-institutional initiatives—which are a mutually beneficial and sustainable way to promote a culture of care (James et al. 1995; Bratcher and Reinhard 2015). The IACUC, ECs, and AWBs or alternatives committee can also send out a regular newsletter, for example, quarterly or semiannually, that highlights advances in the 3Rs to help reinforce the message that we are continuously seeking ways to refine, reduce, and replace animals as part of our culture of care. Hosting a journal club for the 3Rs or "lunch-n-learns" on hot topics about animal welfare can also strengthen a culture of care.

Conclusion

A strong culture of care supports the humane care of animals, which in turn supports quality research, compliance with regulatory requirements, improved public trust in the process of biomedical discovery, and our moral obligations to the staff and animals. A culture of care requires strong and visible commitment from organizational leadership, clearly defined responsibilities, and open communication fostering a team approach to animal welfare. The program recognizes and, indeed, celebrates compassion and respect for animals and the people who work with them. The organization ensures that all staff working with animals are appropriately trained and competent and has programs for recognition of excellence to encourage continued employee commitment to a culture of care. Implementation of the 3Rs of animal use is found throughout the program.

Achieving a culture of care is not the end—this program will require ongoing support and enhancement as conditions change, new scientific information is available, and new technologies arise. A culture of care is served by embracing innovation and evolution. Advances in alternatives will require the reassessment of current practices and an openness to incorporate new technologies, be they *in vitro* opportunities; new animal models, such as fish or invertebrates; or new genetically engineered models that may present their own challenges with creation and maintenance. As new information becomes available in the area of animal welfare science, an institution may need to reassess its practices of animal care and use to ensure the highest standard of animal welfare.

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3

Fostering Collaborative Roles and Responsibilities for Members of an IACUC or Oversight Body

Ernest D. Prentice, M. Elizabeth Blackburn, and Robert S. Dixon

CONTENTS

Introduction

One of the key components of an animal care and use program (hereafter referred to as the "Program") is the Institutional Animal Care and Use Committee (IACUC). In the United States, the establishment of an IACUC is mandated by the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Office of Laboratory Animal Welfare 2015) and the Animal Welfare Regulations, which apply to U.S. Department of Agriculture (USDA)–regulated species (APHIS 2013). The overall purpose of an IACUC is to provide assessment and oversight of the Program. The eighth edition of the *Guide for the Care and Use of Laboratory Animals* (hereafter referred to as the *Guide*) also uses the term *IACUC*. The *Guide*, which is an internationally recognized reference, describes the IACUC as being "responsible for assessment and oversight of the institution's Program, components and facilities" (NRC 2011). In the international setting, there are other equivalent oversight bodies (OBs) that serve the same function as an IACUC but have a different label. However, in order to ensure both consistency and clarity in this chapter, the term *IACUC* is used to designate any committee or OB responsible for the Program as described above. The term *institution* refers to a university, medical center, corporation, or other organization that has a Program, and *researcher* means a person who uses animals for research, testing, or teaching.

The primary purpose of this chapter is to address how best to foster collaborative roles and responsibilities for members of the IACUC, with particular emphasis on the IACUC chair, IACUC administrator, and attending veterinarian (AV). In addition, the position of the institutional official (IO) will be addressed, although the IO is usually not a member of the committee. There is, however, no intent to address in any detail the roles and responsibilities of any of the above. Indeed, much has been written about IACUC functions, such as review of protocols that propose to use animals for research, testing, and teaching (hereafter referred to as "activities" when textually appropriate); semiannual program evaluations; and postapproval monitoring. Much has also been written about the AV's responsibility

for providing adequate veterinary care for animals. Therefore, the focus will instead be on a "fostering process" and desirable management skills related to enhancing the functionality of the committee within the Program.

We believe our ideas about fostering collaborative roles and responsibilities for members of IACUCs that are presented in this chapter will help an institution develop and sustain a successful Program that necessarily requires an effective committee. This is a committee that is structured and resourced and operates in a way that best serves the institution, its researchers, and the animals. Furthermore, it is our hope that both institutions and their IACUCs will recognize that while animal well-being and compliance go hand in hand, undue regulatory burden is widely viewed as a major problem (this topic is covered in Chapter 10 of this text). Clearly, a bureaucratically driven overemphasis on compliance does not help the animals, the institution, or its researchers, and is, in effect, tantamount to compliance micromanagement. The IACUC should not lose sight of its charge and obligation to ensure humane animal care and use while facilitating valuable research. This charge is reinforced by the congressional findings for the 1985 amendment of the Animal Welfare Act, where Congress stated "the use of animals is instrumental in certain research and education for advancing knowledge of cures and treatment for diseases and injuries which afflict both humans and animals" (Agriculture 2011). Indeed, the core of the Program is the committee's review and approval of worthwhile research and other activities involving animals for societal benefit.

The Program

The *Guide* provides the following insight related to the Program: "The primary oversight responsibilities in the Program rest with the IO, the AV, and the IACUC. Their roles fit in a defined organizational structure where the reporting relationships, authorities, and responsibilities of each are clearly defined and transparent. Together they establish policies and procedures, ensure regulatory compliance, monitor Program performance, and support high-quality science and humane animal use. A Program that includes these elements and establishes a balance among them has the best chance of efficiently using resources while attaining the highest standards of animal wellbeing and scientific quality" (NRC 2011). A well-defined and balanced organizational structure with detailed policies and procedures, quality assessments, and transparency is, however, insufficient without the right culture: a culture of compliance, conscience, and respect. This tripartite culture forms the ethical foundation of the Program and facilitates the creation and operation of an effective IACUC.

Establishing a Culture of Compliance, Conscience, and Respect

Every member of the IACUC, the researchers, and the personnel in the facility who provide daily care for the animals should recognize they are providing stewardship for the animals used in activities approved by the committee. Indeed, all personnel involved in the Program in any capacity should strive to work collaboratively and responsibly in the interest of the animals that are primarily used for human health advances, advances in animal health, and other important societal benefits. This is, in effect, "self-regulation," which is far more beneficial to the research community and society at large than increased federal involvement in oversight and compliance enforcement.

The *Guide* addresses the key concept of self-regulation by stating, "Both researchers and institutions have affirmative duties of humane care and use [of animals] that are supported by practical, ethical and scientific principles" (NRC 2011). Successful self-regulation, however, requires establishment of an institutional culture of compliance, conscience, and respect. This kind of culture means that everyone from the chief executive officer (CEO) on down recognizes the importance of humane animal research, testing, and teaching carried out in accordance with the highest ethical standards. Since ethics goes hand in hand with compliance, activities involving animals must also comply with all applicable requirements of the country, region, and local government. To put it simply, "everyone does the right thing because it is the right thing to do," and relationships are built on trust.

A culture based on the concept of "doing what is right" allows self-regulation to flourish, contributes to animal well-being, minimizes noncompliance, and ultimately reduces costly regulatory burden. Indeed, effective self-regulation helps minimize the ever-present possibility that more stringent animal welfare laws and regulations will be promulgated. The question, of course, that must be addressed is this: How does an institution establish a culture of compliance, conscience, and respect? The answer can be found both at the top and at the bottom of the personnel pyramid. The CEO, with proactive buy-in from the senior administration and other key employees, needs to formulate an unequivocal mission statement that incorporates the concept that the use of animals is a privilege granted by society to the institution, and the institution, in turn, grants this privilege to its researchers after review and approval by the IACUC.

The mission statement should clearly articulate and reinforce the institution's commitment to ensure that the humane care and use of animals meets all regulatory requirements, as well as the universal standards reflected in the *Guide* (NRC 2011). In other words, the ethical use of animals should be "job 1," reflecting the values of the institution. The mission statement should be directly disseminated to all employees, and also be posted in laboratories and animal care facilities where personnel can receive daily reminders of their obligations. Indeed, a compelling case can be made for requiring all researchers and animal care personnel to sign their understanding and intended compliance with the mission statement, at least initially upon employment and perhaps even yearly. This can be easily accomplished using an online educational tracking system (Blackboard 2016) or other similar systems.

The institutional culture described above must emphasize a value approach where all individuals involved in the Program are valued no matter what their assigned role. All personnel should have an open and collaborative relationship with full and proactive participation with each other in pursuit of the institution's mission. Critical elements include the clarification of expectations, information gathering, continuing education, the free flow of ideas, and respect for each team member's input and their role in ensuring the ethical use of the animals and provision of humane care. There must also be trust, as mentioned previously. Trust in the integrity of the researchers and their staff is essential.

The bottom line that should be conveyed to all personnel, and strongly reinforced by supervisors, is a message that reflects both commitment and accountability, for example, "We want you, we need you, we value you. We expect you to live up to the institution's commitment to conduct activities involving animals that are both scientifically and ethically justified. Humane care of all animals will be provided in accordance with the highest possible standards. We hold you accountable for living in a culture of compliance, conscience, and respect where actions are guided by what is right."

The IACUC

It is common knowledge that the time has long passed when researchers could freely use animals without any prior review and approval of a protocol by the IACUC or being subject to any ongoing oversight of their animal use. Indeed, one can reasonably argue that an effective Program is highly dependent on a knowledgeable, dedicated, proactive, and adequately resourced committee that acts as a prominent and empowered agent of the institution, working on behalf of both the animals and the researchers. The members of this important agent of the institution should understand their responsibilities, as well as appreciate the ethical foundation upon which the IACUC operates. Indeed, from an ethical standpoint it is not just a matter of regulatory oversight of the Program by the committee. It is also a shared responsibility and partnership with researchers and other involved personnel for the humane care and use of animals during the pursuit of scientific advancement and other societal benefits.

The responsibilities of the IACUC extend far beyond the review and approval of protocols in a partnership with researchers. For example, the IACUC should regularly evaluate the entire Program. This includes a review of the training provided to researchers and animal care personnel, which should fit the needs of the institution. The IACUC should assess the institution's disaster plan, which should be tailored to the geographical location of the institution and the related risk from events such as flooding or tornadoes. Evaluation of the effectiveness of the occupational health and safety program is a responsibility of the IACUC, as well as inspection of the institution's animal facilities. The IACUC should respond to concerns involving the care and use of the animals at the institution and ensure that changes in the Program

are implemented promptly when they are needed. Finally, the IACUC should evaluate the functionality of the committee itself. Indeed, this should be an ongoing process. An IACUC that is not knowledgeable, engaged, committed, and proactive may not be operating at an optimal level.

The IACUC, which is usually appointed by the CEO or the IO under the delegated authority of the CEO, typically includes a chair; one veterinarian trained or experienced in laboratory animal science, commonly referred to as the AV; one or more scientists; one or more nonscientists; and most importantly, one or more community members who are unaffiliated with the institution. It is not unusual for medium to large institutions to have an IACUC with well over 12 members, which may include one or more clinical veterinarians, in addition to the AV. Considering the broad range of research conducted at many institutions, it is obviously advantageous to have a larger committee that collectively has a greater range of scientific expertise and experience. It may also be useful to have alternate members who can serve when the primary member is unavailable. In addition, expert consultants should be utilized when necessary to help the IACUC complete protocol reviews, provide advice regarding the resolution of problems impacting the program, and assist in identifying ways to enhance the program.

The IACUC should operate in accordance with quorum rules that require the presence of a simple majority of the membership. The utilization of alternate members, when necessary, can help alleviate quorum problems that may arise and require cancellation of a scheduled meeting or termination of a meeting in progress. The IACUC should always be cognizant of the fact that researchers cannot initiate or continue their research without approval by the committee. Therefore, the IACUC has an obligation to remember that the researchers are its customers and take steps to avoid unnecessary delays. Committee activities should be completed in a timely manner and not include bureaucratic impediments. For example, protocol review letters should not suffer from a lack of clarity, contain irrelevant questions, and require modifications that are unjustifiably inconsistent with previous reviews. In addition, researchers should be encouraged to question any requirement they do not understand or think is unreasonable.

Given the threat of various animal rights groups combined with a largely unfounded fear of regulatory inspections, such as those conducted in the United States by the USDA, it is not surprising that one of the greatest contributors to regulatory burden is the IACUC itself. For example, at some institutions, protocol submission forms have unnecessarily increased in both length and complexity, institutional policies and procedures related to animal care and use have proliferated, and inflexible engineering standards have too often become the norm. Too many IACUCs have become overly risk aversive and overzealous in their pursuit of absolute compliance. There has also been a concomitant erosion of trust in the integrity of the researcher, which is very alarming. It would seem the traditional "trust but verify" has, unfortunately, become "verify then trust." Self-regulation simply does not work without reliance on the integrity of the researchers and their staff.

Service on the IACUC should be viewed as a moral responsibility for stewardship of the animals that is shared with the institution's researchers. Since many protocols involve some degree of animal pain and discomfort, and almost all protocols result in euthanasia of the animal subjects, committee members and the researchers should balance the science with the ethics. Scientific need should not prevail if animal welfare will be compromised beyond an acceptable limit. Therefore, the goal of the IACUC in full partnership with the researcher is to ensure there is an acceptable harm–benefit relationship where the potential scientific or societal benefit of the activity outweighs, or at least balances, the harm to which animals will be subjected. A valid assessment of the harm–benefit relationship depends on the researcher submitting a carefully written protocol and the members of the IACUC engaging in a thoughtful review and follow-up discussion with the researcher as necessary. Finally, it is important for each committee member to be cognizant of their role as society's gatekeeper in order to ensure the use of animals is fully justified. Considering the fact that service on the IACUC is a labor-intensive endeavor that has both societal and institutional ramifications, each committee member should be acknowledged and valued by the institution.

The Institutional Official

The IO, as defined by the *Guide*, is "the individual who, as a representative of senior administration, bears ultimate responsibility for the Program and is responsible for resource planning and ensuring

alignment of Program goals with the institution's mission" (NRC 2011). In the United States, the PHS Policy similarly defines the IO as "an individual who signs, and has the authority to sign the institution's assurance, making a commitment on behalf of the institution that requirements of this Policy will be met" (Office of Laboratory Animal Welfare 2015), while the Animal Welfare Regulations describe the IO as "the individual at a research facility who is authorized to legally commit on behalf of the research facility that the requirements of 9 CFR parts 1, 2, and 3 will be met" (APHIS 2013). At most institutions, the IO is the person to whom the IACUC reports and is also responsible for appointing its members.

Regardless of which definition of an IO is applicable for an institution, it is clear that this individual should be a senior administrator or manager, such as a vice president for research, a vice chancellor, a vice provost, or even a CEO. The IO does not have to be an experienced researcher or know all the requirements that govern the care and use of animals. Indeed, most IOs logically rely on the IACUC chair, the IACUC administrator, the AV, and of course, the committee itself. However, the IO must understand and fully support the Program, including the autonomy of the IACUC. This requires an involved IO who meets regularly with the chair, the administrator, and the AV but does not engage in micromanagement. The IO should also periodically meet with the IACUC but refrain from regularly attending meetings in order to ensure committee discussions are not inhibited.

When situations arise where the IACUC and a researcher are in an unresolved disagreement, it is incumbent upon the IO to act as an objective arbitrator in order to help resolve the problem. This can be challenging since the committee must function as an independent agent of the institution and not be subjected to inappropriate pressure from the IO, other senior administrators, or researchers. It is certainly reasonable for the IO to meet with upset or dissatisfied researchers and ask the IACUC for further justification of any given decision when there are legitimate questions or concerns. However, it is not acceptable for the IO to pressure the committee in any way to change a decision. On the other hand, it is possible that an IACUC could become unfettered to Program goals or regulatory requirements. This, in turn, could compromise achievement of the institution's mission. If this situation were to occur, it is incumbent upon the IO to take all necessary steps to resolve the problem up to and including replacement of committee members.

The IACUC Chair

The IACUC chair is responsible for ensuring that the committee, which operates under the chair's direction, fulfills all its responsibilities mandated by federal and other requirements. A successful committee is one that operates under a chair who is a strong leader of process, as well as a respected and skilled leader of people. This can be particularly difficult in an institutional environment where the researchers and other personnel are bright, creative, and independent. In general, the chair should be a person who is well respected within the organization and occupies an upper-level position within the institution, for example, a tenured full professor or senior manager. However, there are community members, such as veterinarians, retired scientists, and individuals from a variety of other professions, who successfully serve as IACUC chairs. The commonly expressed rationale for appointing a chair who has no affiliation with the institution is the absence of any real or perceived conflict of interest.

The IACUC chair should, obviously, be knowledgeable about all applicable regulations and other requirements that govern the care and use of animals. It is also advantageous for the chair to have a successful animal research or testing background. Activities involving animals often require complex protocol design and highly technical procedures. In addition, there is species variability, occupational health and safety hazards, and myriad other factors important to the committee's review. However, a background in animal research, husbandry, or other animal-related activities is certainly not an absolute prerequisite for achieving success as a chair. Some IACUCs have attorneys or other compliance professionals serving as the chair who may themselves lack scientific experience but know how to effectively use the expertise of the committee members.

Regardless of whether the IACUC chair has a scientific background or is affiliated with the institution, the chair must be able to run a thorough and efficient convened meeting of the committee. This is, undoubtedly, the most difficult task that a chair faces, and therefore it deserves particular attention. The chair must

ensure that all relevant scientific and animal welfare issues are identified and discussed, and a satisfactory resolution is achieved. During committee deliberations, it is not uncommon for very contentious issues to arise that impact the science, animal welfare, or both. Indeed, it is not uncommon for heated debate to take place where committee members express strong polarized opinions. In these situations, it is imperative that the chair be able to bring the committee to a resolution that considers the opinions of all members, addresses the scientific needs of the researchers, and ensures the humane use of animals.

It is important for the chair to avoid dominating the committee or allowing other members to dominate the discussion during the meeting or at other committee functions. When an IACUC is controlled by a vocal minority, this will likely stifle participation by other committee members. This, in turn, can create a sense of disenfranchisement, which is obviously counterproductive. The chair should therefore encourage all committee members to fully engage in the process. When a viewpoint expressed by a member is irrelevant or even wrong, a skilled chair can guide the discussion so that no one feels intimidated or insulted. Diplomacy is the key to appropriately handling personality differences or lack of knowledge factors that can impact the effectiveness of the committee.

Whether an IACUC is large or small, not all committee members may feel equal. For example, the scientific members may include both well-known and highly funded researchers and junior researchers who are still striving to achieve a successful career in science. This can create a situation of scientific inequality where junior members of the IACUC may be reluctant to express views that oppose those of senior members. This perception of inequality in status may be particularly prevalent in the minds of the nonscientist member and the nonaffiliated (community) member. Members who do not have a scientific background may struggle with the complexity of protocols and other issues that are integral parts of a Program. Some of their questions could be inappropriately characterized as naïve by other committee members. However, from a voting standpoint all IACUC members are equal. Each member has the power of their vote. It is incumbent upon the chair to ensure that the aforementioned perception of inequality does not compromise anyone's participation in the voting process. No member of the IACUC should feel devalued or experience a sense of not belonging. Every member should feel free to independently cast their vote in favor of or against a motion on the table and abstain as necessary without pressure or undue influence. It should also be remembered that the IACUC is acting as society's gatekeeper. Therefore, one can argue that the nonscientist members and the nonaffiliated members are, in many ways, more important gatekeepers than the scientific members.

Finally, the IACUC chair should develop an amicable relationship with the researchers and avoid being characterized as a bureaucrat whose only role is to enforce compliance. The chair is not a policeman, and certainly the IACUC is not a police force or a punitive body. The goal of the chair and the committee should be to help the researcher both understand and apply applicable requirements in order to maintain compliance and ensure that activities involving animals are conducted in accordance with the highest ethical standards. This, in turn, will help the animals, facilitate worthwhile animal usage, and reduce the risks to the institution for failing to maintain compliance. This is not an easy goal to achieve where researchers are under intense pressure to obtain funding and publish their results in peer-reviewed journals. Failure to maintain sufficient scientific productivity may result in a researcher being unable to achieve that next promotion or even facing the possible loss of his or her position. Thus, the IACUC should work with the scientists to facilitate and improve the quality of science at the institution.

The IACUC Administrator

Medium and large-sized institutions normally provide the IACUC chair with the assistance of an administrator and other support staff. The IACUC administrator should possess an up-to-date working knowledge of all applicable regulations and institutional requirements. He or she should have the ability to maintain a clear and consistent framework while working hand in hand with the chair, the committee, and the researchers. The most important characteristics for an IACUC administrator to possess are analytical thinking skills, organizational ability, written and verbal communication proficiency, and personality traits that allow him or her to work diplomatically with strong-willed, and sometimes difficult, researchers and committee members.

The administrator should be viewed as a professional. Ideally, he or she should obtain certification such as that offered by the Public Responsibility in Medicine and Research (PRIM&R 2016). Certification validates the individual's mastery of the knowledge necessary to serve as an effective administrator, which may be valuable to the Program. It is important to stress the fact that a certified administrator is a professional who may know the regulations in greater detail than the chair or some other members of the committee. Therefore, the chair, the IACUC, and the researchers should recognize the administrator as a valued committee resource.

To best achieve a balance between the regulatory requirements and the concerns and needs of the IACUC and the researchers, we believe the administrator should remain neutral and not serve as a voting member of the committee. To this end, he or she must possess the ability to remove himself or herself from expressing strong opinions, listen to the concerns and needs of all parties (including the researcher who may not be present), help the chair apply the regulations, and suggest solutions that best meet the concerns of the committee and the needs of the researcher while ensuring regulatory compliance. Achieving this balance may well be the most important aspect of the administrator's role.

The Attending Veterinarian

The PHS Policy, USDA regulations, and the *Guide* clearly indicate that the AV is responsible for the health and well-being of all laboratory animals used in research, testing, and teaching at the institution (Agriculture 2011; APHIS 2013; Office of Laboratory Animal Welfare 2015). Fulfillment of this responsibility requires the institution to have a program of veterinary care that meets the American College of Laboratory Animal Medicine (ACLAM) Guidelines for Adequate Veterinary Care or equivalent standards (American College of Laboratory Animal Medicine 2016). The AV is, accordingly, an integral member of the IACUC who provides the necessary expertise in laboratory animal medicine and husbandry. Indeed, depending on the size of the institution, the AV may be the only member who has such expertise. In addition to having the necessary training and experience, the AV should also have a mind-set that focuses on the needs of the science combined with animal welfare, and certainly should keep abreast of rapid advances in the development and use of animal models.

It is critical for the institution to ensure that the AV has the authority and the resources to carry out the above-mentioned responsibility. The AV's judgment regarding adequate veterinary care should never be influenced by institutional interests that are contrary to the provision of such care. It is also important for researchers to recognize that the standards of veterinary care for laboratory animals continue to evolve, and it is therefore essential for the AV to work closely with them in the design and conduct of their research, testing, and teaching activities. It is equally important for members of the IACUC to rely on the expertise of the AV during the review and approval of protocols and in other committee functions, such as program and animal facility review.

The AV, as a laboratory animal veterinarian, cannot always function within the Program in the way a typical clinical veterinarian in private practice would. This, in turn, requires the AV to assume a very challenging role. On the one hand, animals enrolled as subjects in activities approved by the IACUC may experience unanticipated pain and discomfort associated with injuries or diseases that are unrelated to the activities. In this situation, the AV holds the sole authority to treat the animals, and therefore the animal must be either cared for in accordance with current veterinary standards or removed from the study if no longer eligible to participate in the protocol. Neither action requires prior approval by the committee. This authority needs to be communicated to all researchers as part of their orientation to using animals at the institution.

On the other hand, some protocols are designed to test the toxicity of a new agent; produce a disorder, such as heart failure; induce an injury, such as a brain concussion; or cause another health anomaly. In these circumstances, the protocol for scientific reasons may prohibit treatment of pain and discomfort. In such cases, the AV is no longer the sole authority or decision maker regarding pain-related issues. It is, nevertheless, the responsibility of the AV to carefully consider the scientific necessity to withhold pain-relieving agents, evaluate the potential effect on the animals, and advise the IACUC accordingly. Since the AV is only one member of the committee with one vote, ultimately the committee decides on the

approvability of the protocol, regardless of whether the AV disagrees with the committee or casts a negative vote. It is therefore important for the AV to recognize that his or her role on the IACUC is different than his or her role within the Program in general. At times, these roles may create an ethical dichotomy that the AV must understand and handle appropriately.

Regardless of the nature of the protocol in question, it is imperative that the AV and all other members of the IACUC ensure that any pain and discomfort the animals may experience is minimized to the greatest extent possible, consistent with legitimate, literature-supported scientific constraints. To that end, it is particularly important for the AV and the committee to be satisfied that the protocol specifies valid experimental and humane endpoints. The experimental endpoint is reached when the study objectives have been achieved. The humane endpoint is the point at which pain will be relieved, usually by euthanasia. In consideration of the principle of refinement, in many protocols the experimental endpoint should approximate the humane endpoint as much as possible (Wallace 2000). The IACUC should refrain from approving any protocol that does not specify an early humane endpoint compatible with the scientific objectives. It is important for the researcher to consult with the AV during the planning stages to design a study that best addresses any animal welfare concerns prior to review by the committee.

Finally, it is important that the IACUC not be run by the AV, despite the fact that the AV is undoubtedly one of the more important members of the committee and, at times, the most critical member. As mentioned previously, the goal of the IACUC is to ensure that there is an acceptable harm–benefit relationship that justifies the use of animals. A valid assessment of this relationship clearly requires the expertise of the AV, who can help the committee perform the harm–benefit assessment, which can be quite challenging.

Conclusion

Institutions where animal activities involving research, testing, and teaching are conducted have an obligation to develop and maintain a Program where self-regulation without undue regulatory burden works for the optimal benefit of the institution, its researchers, and the animals. This requires a culture where trusted researchers and their staff operate on the basis of doing what is right and there is not a bureaucratically imposed and punitive emphasis on absolute compliance. Such a culture allows self-regulation to flourish, minimizes noncompliance, and ultimately, decreases the cost of the use of animals for societal purposes. The IACUC, which has primary oversight responsibilities of the Program, together with the IO and the AV, should work collaboratively within this culture to ensure regulatory compliance and the humane care and use of animals that meets the highest possible scientific and ethical standards. That is the essence of serving as society's gatekeeper. We can and should do no less.

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4

Bioethics and Animal Use in Programs of Research, Teaching, and Testing

Richard C. Simmonds

CONTENTS

Introduction

The use of nonhuman animals (hereinafter "animals") for the benefit of humans and other animals is a contentious subject throughout many of the world's countries. Cultural morals and traditions, the status of animals in various religions, individual and cultural ethical values, and the diversity of concern for specific species (including the perceptions about the "warm and fuzzies" [e.g., dogs and cats] versus the "creepy-crawlies" [e.g., mice, rats, and reptiles]) all contribute significantly to the complexity of addressing moral (rightness or wrongness) and ethical (what ought to be) issues involved when considering the use of animals in biomedical research, teaching, and testing activities (hereinafter "biomedical activities"). Further, it is most certainly difficult, if not impossible, to define what the moral status of sentient animals (species that can feel pain and suffer), creatures that are not persons yet not mere things, should be that would be universally accepted. These factors also contribute to the complexity of the regulatory climate in the numerous countries in which there is some sort of oversight of animal use in biomedical activities (see Attachment I for examples of U.S. laws, regulations, and guidelines and the list of worldwide regulations [excluding the United States] compiled by AAALAC International) (AAALAC International 2015).

Readers of this chapter will not find a definitive answer to the question "Is it ethical or moral to use animals in biomedical activities?" There are no black or white answers, only many shades of gray. The intent of this chapter is for readers to gain a basic understanding of the philosophical, ethical, and moral basis for the various possible responses to this question. Those wishing to examine the issues involved in the use of animals in biomedical activities will find a plethora of germane literature available. Furthermore, in the interest of full disclosure, I am not a philosopher or ethicist by training (nor will you be after reading this chapter); rather, I am a veterinarian who has had an incredible variety of management positions in the specialty of laboratory animal medicine for more than 50 years and has had a personal interest in fostering the moral, ethical, and legal use of animals in biomedical activities. My personal position regarding the use of animals in biomedical activities may best be described as welfarist or utilitarian.

Implementation of ethical programs for the care and use of animals in biomedical activities requires buy-in from all members of an institution, from the highest-ranking administrators to the animal care and research staffs. The achievement of an ethical, legally compliant, and high-quality animal care and use program is in the self-interest of the institution, as well as those individuals who care for and use the animals. High-quality animal care and use will maximize the quality of the research results, which, in turn, will maximize the prestige of the institution, reputation of the animal users, and likely job satisfaction for the animal care and use staffs.

A tangential usefulness of the material presented herein is that institutional officials and managers of animal care and use programs who understand the origins and foundations for public perceptions regarding the use of animals in biomedical activities will likely be better able to organize their programs to minimize the possibilities for criticism and maximize their ability to respond in a positive manner to any such criticisms.

Finally, all individuals involved in biomedical activities should, at least, believe in their own minds that what they are doing meets their own sense of what is right, moral, and ethical, and it is hoped that the material presented in this chapter may be of help in their ability to make this determination.

Relevant Historical Philosophical Approaches Regarding Animal Use

Philosophical Concepts

The foundation for the philosophy of animal rights may be said to have been laid down by the Greek philosopher and mathematician Pythagoras of Samos circa mid-fifth century BC. Quotes attributed to him include

- "Animals share with us the privilege of having a soul. Alas, what wickedness to swallow flesh into our own flesh, to fatten our greedy bodies by cramming in other bodies, to have one living creature fed by the death of another?"

- "As long as man continues to be the ruthless destroyer of lower living beings he will never know health or peace."
- "For as long as men massacre animals, they will kill each other" (Pythagoras of Samos 2015).

A somewhat contrasting view regarding animals having souls was expressed by the thirteenth-century Saint Thomas Aquinas, as he was reported to believe that animals did not have souls and thus were not worthy of moral concern, but that cruelty to animals was unacceptable because cruel behavior toward animals would progress to cruelty to other humans (Aquinas 1956).

From Pythagoras's time until about the time of the Industrial Revolution (ca. late eighteenth century through the mid-nineteenth century), public interest in animal welfare, let alone animal rights, was largely nonexistent, as the average person throughout the world was more interested in personal survival. Two examples of the emerging interest in animal welfare were

1. The establishment of the first regulations pertaining to the welfare of farm animals in America found in the Massachusetts Body of Liberties issued in 1641, which contained the following regarding animal care:
   a. "Article 92. No man shall exercise any Tirranny or Crueltie towards any bruite Creature which are usuallie kept for man's use."
   b. "Article 93. If any man shall have occasion to leade or drive Cattel from place to place that is far of, so that they be weary, or hungry, or fall sick, or lambe, It shall be lawful to rest or refresh them, for competant time, in any open place that is not Corne, meadow, or inclosed for some peculiar use" (Massachusetts Body of Liberties 1641).
2. During the mid-nineteenth century, the emerging animal rights and welfare movement in England caught the attention of Queen Victoria and led to her recognizing the efforts of the Society for the Prevention of Cruelty to Animals (SPCA) (organized in 1824) to foster animal welfare and bestowing upon them the authority to add "Royal" to their name, indicating her support for their efforts (RSPCA) (Royal Society for the Prevention of Cruelty to Animals 2015).

Returning to the subject of whether animals have souls, the seventeenth-century French philosopher and mathematician Rene Descartes postulated that animals did not have souls; therefore, animals were not subjects of moral concern. In simplistic terms, Cartesian philosophy would allow humans to do whatever they wish with and to animals, without concern for any possibility of the animals suffering therefrom. Without souls, Descartes believed that animals could be viewed as being nothing more than equivalent to machines, and any vocalizations that an observer could possibly interpret as the animals being in pain should be of no more moral concern than a squeaky wheel on a wagon (Rene Descartes 2015). While the Cartesian philosophy might have been the philosophy of choice by biomedical scientists conducting surgical research with animals before 1846, when the first successful use of ether as an anesthetic was demonstrated (Robinson and Toledo 2012), it is unlikely that contemporary biomedical scientists would consider themselves as accepting of this philosophy.

Another ethical position, utilitarianism, was emphasized by eighteenth- and nineteenth-century English philosopher Jeremy Bentham, who published the following:

> The day may come when the rest of the animal creation may acquire those rights which never could have been withholden from them by the hand of tyranny. The French have already discovered that the blackness of the skin is no reason why a human being should be abandoned without redress to the caprice of a tormentor. It may one day come to be recognized that the number of legs, the villosity of the skin, or the termination of the os sacrum are reasons equally insufficient for abandoning a sensitive being to the same fate. What else is it that should trace the insuperable line? Is it the faculty of reason, or perhaps the faculty of discourse? But a full-grown horse or dog is beyond comparison a more rational, as well as a more conversable animal, than an infant of a day or week or even a month, old. But suppose they were otherwise, what would it avail? *The question is not, Can they reason? nor Can they talk? but, Can they suffer?* (emphasis added)

This quote is given in its entirety to provide context. The last three phrases in the paragraph are frequently quoted by animal rights advocates and are generally considered to be the modern foundation for the philosophy of animal rights, as it effectively introduces suffering or, more accurately, sentience, that is, having the capacity to feel pain and suffer, into the moral and ethical equation. Simply, sentient animals should have the right not to suffer (Bentham 2007).

Even though Bentham's quote would seem to imply that he anticipated the contemporary animal rights movement, and certainly opposed gratuitous mistreatment of animals, he did not oppose the use of animals by humans, including the use of animals in biomedical activities. In a letter to the editor of the *Morning Chronicle* (March 4, 1825), he stated, "I never have seen, nor ever can see, any objection to the putting of dogs and other inferior animals to pain, in the way of medical experiment, when that experiment has a determinate object, beneficial to mankind, accompanied with a fair prospect of the accomplishment of it. But I have a decided and insuperable objection to the putting of them to pain without any such view." This stresses the foundation of the utilitarian view that weighs benefits and costs and focuses on the overall good an activity provides. Also, even though Bentham's quote in the preceding paragraph is often quoted by vegetarianism advocates, there does not seem to be any reference to him being a vegetarian himself.

Philosopher Peter Singer, another utilitarian often quoted by animal rights activists, defines *speciesism* as "a prejudice or attitude of bias in favor of the interests of members of one's own species against those of members of other species" (Singer 1975). In "A Philosophical Self-Portrait," he elaborates that speciesism is an "essential philosophical view … [that] is simple but revolutionary. Species is, in itself, as irrelevant to moral status as race or sex. Hence all beings with interests are entitled to equal consideration: that is, we should not give their interests any less consideration than we give to the similar interests of members of our own species. Taken seriously, this conclusion requires radical changes in almost every interaction we have with animals, including our diet, our economy, and our relations with the natural environment." He goes on to indicate that his "ethical position is a form of preference-utilitarianism" (Singer 1997).

Since the philosophy of *utilitarianism* and the "ethical position of preference-utilitarianism" have been introduced at this point, it is worthwhile to provide an abbreviated explanation of these terms here. Utilitarianism is a form of philosophical thought that the "consideration of right conduct should be the usefulness of its consequences; specifically: a theory that the aim of action should be the largest possible balance of pleasure over pain or the greatest happiness of the greatest number" or "the belief that a morally good action is one that helps the greatest number of people" (Merriam-Webster Online Dictionary 2015). *Preference utilitarianism* may be defined as the equal consideration of the preferences of all individuals (both humans and animals) involved (my condensation of various definitions found). A more detailed discussion of the philosophy of utilitarianism is included in a separate section below.

Representing the animal rights view, philosopher Bernard Rollin makes the case that there are no "morally relevant" reasons for excluding animals as "objects of moral concern"; thus, by extension, they are deserving of "rights." In his book titled *Animal Rights and Human Morality*, he states, "From a strictly philosophical point of view, I think that we must draw a startling conclusion: If a certain sort of research on human beings is considered to be immoral, a *prima facie* case exists for saying that such research is immoral when conducted on animals." It seems to me that if one were to accept this point of view, all research on animals would be immoral, and thus unethical, since the research subjects could not give informed consent (although, possibly, a court appointed "guardian" for the animal subjects could give consent and owners of animals could give consent for their animals to participate in clinical therapeutic trials). Further in the same paragraph, he states that this "criterion would effectively curtail the vast majority of research" in basic biological and applied basic biomedical research, the development of drugs and therapeutic chemicals and biologics, the testing of consumer goods, the use of animals in education (demonstration, dissection, surgery practice, high school science projects, etc.), and the extraction of products from animals (e.g., serum, musk, and blood). He does appear to accept the premise that animals can be used in biomedical activities under the same conditions that permit the use of human subjects; for example, the specific animals used will potentially benefit from the specific study (Rollin 1981). In a more recent report, Professor Rollin seems to make the case that there are no moral grounds to support the use of sentient animals in most, if not all, biomedical activities (Rollin 2012).

Philosopher David DeGrazia argues in his book titled *Taking Animals Seriously: Mental Life and Moral Status* that "equal consideration for animals is more reasonable than its denial, given the failure of opponents of equal consideration to meet their burden of proof … those who doubt that animals should be extended equal consideration should note that a commitment to giving animals serious consideration would be enough to support most of the foregoing conclusions" (referring to the cases made in the previous content of the book). Dr. DeGrazia sums up his position by providing the reader with 15 ethical conclusions regarding our treatment of animals, which include (the verbiage in parentheses is my suggested examples) "Don't cause unnecessary harm" (e.g., meat eating is unnecessary for individuals who have viable alternative food options), "Make every reasonable effort not to provide financial support for institutions that cause or support unnecessary harm" (e.g., don't support circuses or movies that include animal acts), "Don't kill sentient animals unnecessarily" (e.g., for food or for most research), and "There is a presumption against disabling sentient animals (that is, damaging their ability to function in ways that significantly interfere with their ability to live a good life) and, if they are non-dangerous, the presumption is virtually absolute" (e.g., research involving any animal impairment would be unacceptable) (DeGrazia 1996).

From a more moral–legal perspective, attorney and professor of law Gary L. Francione makes the case that only by incrementally destroying the legal concept of animals as property can true animal rights ever be achieved. Late in his book titled *Rain without Thunder: The Ideology of the Animal Rights Movement*, he states, "In a sense, we are really only talking about one right—the right not to be treated as property…. As long as animals are regarded as property, we cannot really talk about their rights. That property cannot have rights follows from what it is to be property…. We can be responsible for property, but not to property" (Francione 1996). The content of this 1996 book explains in detail what was meant by the statements in the "Point/Counterpoint" article cowritten by Professor Francione and Dr. Regan, discussed below.

As this chapter is being written, there are at least two current efforts attempting to reclassify animals from merely "property" to "sentient beings," one in New Zealand (Library of Congress 2015) and another in the National Assembly in Quebec City, Canada (Anonymous 2015c), as well as continuing efforts in the United States to obtain "personhood" status for chimpanzees (Slate Website 2015). Interestingly, in a blog post copyrighted in 2006, Professor Francione made the case that the campaign to gain personhood for chimpanzees is "problematic because [it] suggest[s] that a certain species of nonhuman is 'special' based on similarity to humans. That does not challenge the speciesist hierarchy—it reinforces it—in at least two ways" (Francione 2006). This position is completely consistent with his contention in his book.

Melding together the ethical and legal points, Dr. Regan and Professor Francione published an article in which they state, "Many animal advocates hold that there really is no difference between animal welfare and animal rights. Others claim that while there is a difference, advancing animal welfare is a necessary prerequisite to advancing animal rights. Given either assumption, many conscientious activists conclude that we must support welfarist means in our march toward animal rights ends. … We believe these views are mistaken. *Not only are the philosophies of animal rights and animal welfare separated by irreconcilable differences*, and not only are the practical reforms grounded in animal welfare morally at odds with those sanctioned by the philosophy of animal rights, but *also the enactment of animal welfare measures actually impedes the achievement of animal rights*. … The goal of the animal rights movement is nothing less than the total liberation of nonhuman animals from human tyranny" (Regan and Francione 1992, emphasis added). By the use of the phrase "irreconcilable differences," it would seem to me these authors are clearly saying that there is no philosophical way to justify the use of animals in any way that benefits humans and, presumably, other animals. It also seems that they are saying that the enactment of animal welfare laws will impede the ultimate goal of no animal use, presumably because if the general public is convinced that animal "welfare" is achieved, they will not support the more radical implementation of animal rights as envisioned by strident animal rights advocates.

Philosopher Tom Regan also makes the case that animals are "moral patients" deserving of rights. It appears that he bases his argument on an expansion of Jeremy Bentham's "Can they suffer?" test. Moral "agents" have the capacity to speak for themselves, for example, a fully mentally competent adult human.

Moral patients are members of a moral community that cannot speak for themselves and must have someone speak for them, for example, an adult human in a coma or a newborn infant. Regan advances the proposition that sentient animals are deserving of moral "concern" and, by virtue of this fact alone, are deserving of being considered moral patients, leading to the necessity for someone to speak for them and, presumably, protect them from use in biomedical activities (Regan 1983).

Providing a slight contrast to the modern animal rights viewpoint, philosopher Michael Allen Fox states, "The conclusion [that] … so far as it pertains to animals … [their lack of the] various degrees the possession of capacities on which moral autonomy or agency depends, animals fail to meet the conditions specified for full membership in the moral community and likewise fail to qualify for having rights" (Fox 1986). Interestingly, approximately a year after his book was published, Fox published a retraction and indicated that he had changed his mind and no longer supported the case that he made in the book (Fox 1987). Regardless of Fox's recanting his arguments for supporting the use of animals in biomedical activities, what he presented in the book in support of the quote cited above would seem to be valid and would support the necessary and ethical use of animals in biomedical activities, at least in activities with a high benefit-to-risk ranking.

In making the case for animals having moral rights, Professor Jerry Tannenbaum has postulated a number of "myths of the animal rights movement" that are germane to our discussion (Tannenbaum 1995):

- Myth 1: "One must choose between animal rights and animal welfare." He discusses the reasons that aspects of concern for animal welfare might support the conclusion that animals have moral rights to certain levels of care and to limitations on how they may be used or treated; thus, there is nothing to support the position that animals do not have rights. He goes on to make the case that animals have *moral* rights that devolve from the fact that they are sentient and have interests. Since the intended audience for his book, titled *Veterinary Ethics: Animal Welfare, Client Relations, Competition and Collegiality*, is veterinarians, Professor Tannenbaum goes on to make the case that veterinarians (and by extension, those of us involved in biomedical studies with animals?) should accept his premise that animals have moral rights so that they are not marginalized in the public arena of debate over animal rights. That said, one could make the case that these terms are not synonymous; that is, animal welfare is ensuring responsible care and use of animals however they are being used (in biomedical activities, as pets or service animals, in agriculture, in zoos and aquatic parks, etc.), while animal rights, as defined by the strident animal rights movement, would require "nothing less than the total liberation of nonhuman animals from human tyranny" (Regan and Francione 1992).
- Myth 2: "Animals do not yet have legal rights." He makes the case that the various statutes that exist to protect animals from cruel treatment can be considered sufficient to conclude that animals should be considered as having legal rights. In this regard, he also states, "If one believes, as many people surely do, that animals should have some legal rights, one is not thereby committed to the demand of the animal rights movement that animals should be given legal standing to sue their owners, their veterinarians, or other people for money or other kinds of relief. The concept of legal rights for animals, like the concept of moral rights for animals, does not entail the platform of the animal rights movement." While Professor Tannenbaum makes a compelling case here, another possible case could be made that animal welfare statutes do not convey to animals any rights; rather, they simply codify human obligations to animals similarly to many of the statutes that govern the protection of endangered species of flora (certainly such protected plants would not be considered as having rights).

Presenting yet another viewpoint on the use of animals in biomedical activities, Sir William Paton, an eminent British pharmacologist, makes the case that the use of animals in biomedical activities to advance knowledge in medicine [both human and veterinary], biology, and the basic sciences is the *most* ethical use of animals of all the ways humans use animals (emphasis added). His reasoning is that any knowledge gained from such studies would live on in perpetuity, while, the benefits, whatever there are of using animals for other purposes, are time limited (Paton 1984).

Utilitarianism

As noted previously, utilitarianism is a form of philosophical thought that "the determining consideration of right conduct should be the usefulness of its consequences; *specifically*: a theory that the aim of any action should be the largest possible balance of pleasure over pain or the greatest happiness of the greatest number" or "the belief that a morally good action is one that helps the greatest number of people [or animals?]" (Merriam-Webster Online Dictionary 2015).

While it appears that animal rights has emerged as a recognized system of philosophical thought regarding the status of animals, utilitarianism is most likely a philosophy that would be a better fit for most people's views. In the "Summary and Conclusion" of the 1986 Office of Technology assessment report about the use of animals in biomedical activities, it is stated, "Because it extends the scope of moral concern to animals without committing itself to a vulnerable theory of animal rights, Utilitarianism has become the theory of choice among those who would press for more constraints on humans' treatment of animals" (U.S. Congress 1986).

This report from a government committee composed of representatives from many stakeholder perspectives is one of the few attempts to present an unbiased assessment of the pros and cons, or need and value, of the use of animals in biomedical activities—thus the conclusion that the most appropriate philosophical approach to such use is utilitarianism, simplistically, the greatest good for the most individuals. That said, even this approach is fraught with problems since it is unclear who or what should be considered within the term *individuals*, and animals cannot speak for themselves and cannot articulate an "informed decision" to participate as a subject in biomedical activities. Besides, when considering the "utility" of any specific proposed biomedical activity, further questions are evoked, including, what criteria will be used to balance the "good" versus "bad" of the activity? Unfortunately, there are no universally accepted guidelines for how to calculate the utility of any particular use of animals (see also the "Risk (Harm) versus Benefit Assessment" section that follows later).

Another source, philosopher Carl Cohen, says that "utilitarianism appeals to many people—it is practical and concrete and seems to make sense in daily life. Utilitarianism does not say using animals for research is wrong; what it does say is that to decide on the moral rightness of an action you need to look at whether that research might promote an aggregate good for a greater number of people than not doing the research. Some would include animals in this equation since animals do benefit from research. For the Abolitionist, animal research would be wrong since it is morally wrong to use an animal merely as a means, even … to a good end" (Cohen 1986).

Morally Relevant Difference between Humans and Animals

One can make the claim that in order for a living entity to claim rights, it must be a member of a moral community (North Carolina State University 2015), that is, a community in which individual members can make moral decisions and recognize right from wrong. Also, with rights come obligations that members of the community must be willing to accept, that is, obligations to recognize the rights of others. It is unlikely that animals can either recognize obligations to other animals or knowingly accept them. If animals had rights, they would have them even if the human species did not exist, and any prey animal would be able to exercise its right not to be eaten by a predator (an obviously absurd situation). However, to the best of our knowledge, only humans possess the intellectual capacity to make moral decisions and accept reciprocal obligations; therefore, the logical conclusion is that only humans have rights. An objection to this point of view is that there are individual humans who are not able or competent to make moral decisions (e.g., infants, persons in a coma, and persons with dementia); however, an argument can be made that such persons either have the potential to make claims for their rights (e.g., the infant who grows up to be a mentally competent adult) or previously had such capabilities but no longer do (e.g., the person in an irreversible coma). Thus, all persons should be considered members of the moral community.

That said, and even if this conclusion is correct, the fact that only humans have rights does not give us the unhindered right to do whatever we want to, or with, animals. Since all humans are members of a moral community, mostly capable of recognizing right from wrong and accepting the obligations that come with

rights, and it is generally recognized that it is wrong to mistreat animals, we are thus obligated to treat animals humanely. However, this obligation is to us, to our own humanity, and not to the animals per se, although one could say that this obligation also imposes on humans a moral duty to not mistreat animals.

While animals may not have rights, nations and states can and do confer on them legal protections and impose legal restrictions on how they may be used and treated, for example, animal abuse and control laws and international wildlife protection treaties. These legal protections may severely restrict how we may use animals and what we can do to animals. Furthermore, enforcement of these protections may even result in severe penalties for violating the laws. The laws do not convey rights to animals; rather, they simply codify our moral obligations to animals as defined by our various societies and cultures. While there are a number of highly respected philosophers who have made the case that animals have moral rights based on their sentience, one can still contend that in order to have rights, individuals need to be members of a moral community, and no animals currently share this status with humans.

Our body of laws pertaining to animal protection form the foundation for animal welfare within our society. Most importantly in this regard is the generally high degree of public concern for animal welfare that is found throughout most contemporary societies and cultures, including the vast majority of individuals working in various biomedical activities. We should keep in mind that animal welfare as a concept is not synonymous with the philosophy of animal rights, especially as this latter term is defined by the most radical animal rightists. An animal welfarist believes in responsible pet ownership, responsible animal agriculture, humane animal care, and so forth. A true animal rightist demands no human use of animals, including but not limited to pet ownership and agriculture, and no animal care (since animals should not be property requiring care). In the utopian world of the true animal rightist, no animal will be subjugated to human welfare, need, or desire.

One argument made by proponents of rights for animals is that there are no morally relevant differences between a mature animal (see discussion on Regan above), with its full mental faculties, and a severely mentally deficient human, for example, a brain-dead person. However, a case can be made that there is, in fact, at least one significant, morally relevant difference between humans and animals, and that is morality itself. So far as we know and can determine at present, the human species is the only species that attempts to interact with its environment (e.g., protect the rain forest) and other species in some moral way (e.g., save endangered species). Obviously, there may be some variability from culture to culture with regard to the definition of what actions are and are not moral. That said, we are the only species that has ever worried about the fate of other species. It would seem to me that this characteristic of humans in general should certainly be considered a morally relevant difference, thus supporting the conclusion that only humans have rights.

Guidelines and Principles

The 3Rs

Replacement, reduction, and refinement (the 3Rs), proposed by Russell and Burch in their 1959 book titled *The Principles of Humane Experimental Technique*, have become foundational planks for many laws, regulations, guidelines, and local policies governing oversight of biomedical activities involving the use of animals throughout the world, and should continue to be such into the future. While the widespread implementation of these principles most certainly has resulted in more humane animal use, and in some reduction in the numbers of animals used (especially "higher" vertebrate mammals), it is unlikely that the total numbers of individual animals have decreased significantly when all species are counted. The growing importance of zebrafish and genetically modified rodents in biomedical activities may actually lead to an increase in the absolute number of animals being used in biomedical activities in the future.

- *Replacement*: In the original 1959 book, this term was meant to mean actual replacement of animals with "insentient material" (i.e., absolute replacement). Over time, the meaning has evolved to include the substitution of an animal with another animal species "lower" on the phylogenic scale (i.e., relative replacement).

- *Reduction*: Originally defined to mean "reduction in the numbers of animals used to obtain information of a given amount and precision." Some of the ways to implement the reduction of animals are to ensure that proposed activities are well designed and statistically valid, that one is using the best animal model available, that the animals are in the best health possible (including free of confounding microorganisms), and that the animals receive the best care possible to minimize induced variables that can negatively affect the animals, resulting in the need for more animals to obtain statistically valid study results. Interestingly, this may actually require the use of more animals in a given activity if it were needed to ensure statistical validity of the activity, thus negating the need for repetitive studies, which would ultimately reduce the numbers needed to obtain valid results.
- *Refinement*: Originally defined to mean "any decrease in the incidence or severity of inhumane procedures applied to those animals which still need to be used." Today, this R includes using procedures that will minimize pain, discomfort, and distress. One concept for implementing refinement is especially promising: whenever possible, make the animals willing members of the research team. For example, nonhuman primates can be taught to present an arm for a blood draw in return for receiving a desired food treat.

  Another example of refinement is to select or train dogs through positive reinforcement to voluntarily run on a treadmill if required in a project studying cardiovascular function. Unfortunately, this approach is generally reserved for use in long-term studies, as it requires time and enhanced human interaction. Positive human interaction can also improve animal welfare but will likely increase human attachment to the animals. This should be encouraged, as it will benefit the animal; however, for many studies the animals must be euthanatized at the end. In respect for human caretakers, procedures should be in place to minimize the emotional impact on the people who have become attached to the animals, perhaps by having other individuals not so attached conduct the euthanasia and collection procedures. Other, short-term examples of refinement include the use of multimodal analgesia for procedures that historically use no or only one analgesic, or use of nonpharmaceutical therapies (e.g., environmental enrichment, heating pad, and soft bedding) if painful procedures are being performed and analgesics must be withheld for scientific purposes.

  Tannenbaum and Bennett (2015a) have recently published in the *Journal of the American Association for Laboratory Animal Science* an excellent and exhaustive discussion about the 3Rs, including their original meaning and how the meanings and intent have evolved since first proposed. In addition, a letter to the editor, authored by Carbone (2015), along with a rebuttal by Tannenbaum and Bennett (2015b), further illuminates some of the contemporary aspects of the 3Rs. These three publications are well worth reading for a more thorough understanding of the importance of the 3Rs with regard to contemporary efforts to establish ethical programs of animal care and use in biomedical activities.

In Europe, "Directive 2010/63/EU revising Directive 86/609/EEC on the protection of animals used for scientific purposes … is firmly based on the principle of the Three Rs, to replace, reduce and refine the use of animals used for scientific purposes" (European Directive 2010/63/EU).

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

Although intended to be applicable to biomedical activities accomplished with funds provided by the U.S. government, these principles would likely be just as applicable to all biomedical activities involving animals conducted anywhere in the world.

> The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall

be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.) and other applicable Federal laws, guidelines, and policies.
II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be considered.

Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.
VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.
IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

NASA Sundowner Principles

In October 1996, the National Aeronautics and Space Administration (NASA) convened a meeting of a group of diverse individuals to "implement bioethics policies for animal experimentation" sponsored by or involving NASA. The group consisted of a public policy expert, three bioethicists, and representatives from the animal welfare community, AAALAC International, NASA, and other federal agencies involved in animal research. This diverse group concluded that (Rowan 2000)

Among the basic moral principles generally accepted in our culture, three are particularly relevant to the ethics of research using animals: respect for life, societal benefit, and non-maleficence.

- Respect for Life—Killing entails moral costs:

  Living creatures deserve respect. This principle requires that animals used in research should be of an appropriate species and health status and should involve the minimum number required to obtain valid scientific results [reduction]. It also recognizes that the use of different species may raise different ethical concerns. Selection of appropriate species should consider cognitive capacity and other morally relevant factors. Additionally, methods such as mathematical models,

computer simulation, and *in vitro* systems should be considered and used whenever possible [replacement].

- Societal Benefit—Advancing knowledge and health is a strong justification for research: The advancement of biological knowledge and improvements in the protection of the health and well-being of both humans and other animals provide strong justification for biomedical and behavioral research. This principle entails that where animals are used, the assessment of the overall ethical value of such use should include consideration of the full range of potential societal goods, the population affected, and the burdens that are expected to be borne by the subjects of the research.
- Non-Maleficence—Minimization of distress, pain, and suffering is a moral imperative: Vertebrate animals are sentient. This principle entails that the minimization of distress, pain, and suffering is a moral imperative [refinement]. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in humans may cause pain and distress in other sentient animals.

Because of the diversity of this group, representing a broad range of philosophical thought and beliefs, these three principles resulting from the group's deliberations should be considered foundational components of any institution's program for the ethical use of animals in biomedical activities.

Religion

Most of the religions of the world include tenants that encourage concern for animals and their welfare, and some even revere certain species of animals and give them special status within their culture. A few religions so revere all animal life that they will go to great extremes to live lives without harming even the most humble of creatures, such as insects (e.g., Jainism [Anonymous 2015a]). The Reverend Professor Andrew Linzey has also made a case that animals have rights from a theistic perspective, that is, animal "rights [can be] based on the inherent worth of creatures possessing the property of being elected by God in love" (Cahill 2016). Therefore, on a global basis there may be situations where a proposed biomedical activity using animals may be morally acceptable within some segment of a local culture, but the range of animals acceptable for use might be limited by consideration for regional or local religious concerns; for example, dogs are generally considered to be "dirty" in Islam but can be kept as pets with some reservations (Banderker 2015). Persons involved in biomedical activities should be aware of any such concerns and design proposed activities and staffing plans accordingly.

Contemporary Issues

Biomedical Activities Are Not Monolithic

As illustrated in Figure 4.1, the term *biomedical activities* (or more generally referred to as "biomedical research") encompasses a very broad range of activities involving the use of animal subjects, and this diversity presents another very large layer of complexity to ethical issues involved therein.

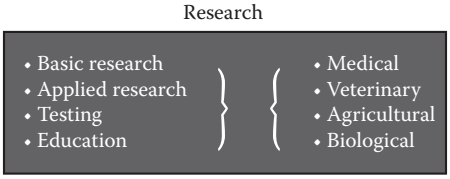

FIGURE 4.1 Illustration of the interrelationships between the types of biomedical activities on the left and the different biomedical disciplines involving the use of animal subjects on the right; that is, all four types of biomedical activities are found in each of the four disciplines.

Often, the public discourse regarding the use of animals in biomedical activities focuses on the benefits that "might" be derived only for humans. However, a significant proportion of such activities are undertaken with the direct or tangential intent of benefitting animals (e.g., development of a vaccine for an emerging disease, such as parvovirus in dogs). Also, in many cases the goal of an activity involving animal subjects is simply the advancement of knowledge without definitive knowledge of its benefit for either humans or animals, that is, basic research activities.

If it is decided that it is "unethical" to use animals in biomedical activities intended to benefit humans, the ethical principle of *justice*, which would include equal consideration of the interests of all (sentient?) animal subjects, would dictate that it is also unethical to use animals in biomedical activities intended to benefit other animals (e.g., endangered species captive propagation research or research to develop a vaccine for a newly discovered disease of dogs or horses), that is, "what's good for the goose is good for the gander." In contrast, one might even be able to make the case that the principle of *beneficence*, that is, the obligation to do good and avoid harm, would dictate that efforts to save an endangered species should be performed, even if it meant that some animals of the same species or another similar species might die during this effort. Another example of this conundrum is the use of some members of an animal species, deliberately infected with a newly identified pathogen resulting in overt disease in the recipients, to develop a vaccine for the newly discovered fatal disease in order prevent the disease in future populations of the species (e.g., Potomac horse fever in horses).

As an example of how this conundrum might apply to, and impact on, public opinion on a global scale, consider the widely accepted concern for endangered species. There are 181 parties currently signed on to the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES 2015), and in the United States, there is strong public and political support for the Endangered Species Act (1973). If there were laws prohibiting the use of sentient animals in biomedical activities, then the critical research needed to protect endangered species, including field studies and captive breeding for reintroduction efforts, would have to cease since such activities would likely involve using animal subjects.

A recent report noted the possibility that research for a vaccine against the Ebola virus using chimpanzees will result in a vaccine that likely can be used to protect the remaining and endangered wild chimpanzees from this fatal disease (Choi 2014). If this were to be the result of current vaccine development efforts, it would be another example of a discovery involving the use of animals that turns out to be critically important to animals. As an aside, Dr. Francis Collins, director of the National Institutes of Health (NIH), announced on November 19, 2015, that the NIH will permanently stop using chimpanzees for biomedical testing and is retiring its remaining chimpanzee population, thus potentially decreasing the probability of development of a successful vaccine (St. Fleur 2015).

Basic research often can seem like we are looking for keys to locks unknown. Because of this level of general ambiguity, basic research is often poorly understood by the general public; thus, what may be perceived as "unnecessary" or "trivial" may lead to public outcry about the cruelty of any use of animals in such pursuits. Senator William Proxmire (Democrat, Wisconsin, 1957–1981) would periodically issue "golden fleece awards." These awards were targeted at federally funded scientific research that he considered wasteful. However, the creation of this award reflected the fundamental misunderstanding of how science works, and how such research can turn out to be extremely important regardless of whether it makes sense to nonscientists. Indeed, such research can have a major impact on society. The nature of scientific research is that its impact is hard to predict (Anonymous 2015b).

However, without the foundation of basic research, followed by applied research, biological and medical advances would be impossible. When speaking to public or lay audiences and describing this point, I have frequently been asked, "How much basic research ultimately turns out not to have been of any particular significance?" My response, "Probably a significant percentage!" often surprises the questioner. I then go on to say, "However, the problem is that no one can, a priori, tell which basic research endeavors will fall into this status." Two examples that illustrate this point involve discoveries in the then emerging discipline of genetics in the 1930s and 1940s:

- During the 1930s and 1940s, there were two investigators conducting basic genetic research. One was Dr. George Snell, who was studying the genetics of mice at the Jackson Laboratory in Bar Harbor, Maine. The other was Dr. Barbara McClintock, who was studying the genes

in corn at Cornell University's College of Agriculture and the Department of Botany at the University of Missouri–Columbia. It is highly unlikely that either Dr. Snell or Dr. McClintock, in the 1930s and 1940s, could have predicted that their basic research would lead to genetic discoveries that proved to be critically important in what is now known as "medical genetics" and would lead to their receipt of Nobel Prizes in Physiology or Medicine in 1980 (shared with two others) and 1983, respectively. Yet, their discoveries proved to be significant foundational blocks in the development of today's medical genetics.

- Another example unrelated to direct human interests that seems to be enlightening for laypersons is the captive breeding programs that have successfully allowed for the reintroduction of the endangered whooping cranes, California condors, and black-footed ferrets into their historic habitat ranges. All these species were on the brink of extinction when the captive programs began. Without captive breeding research efforts involving similar species (sand hill cranes, Andean condors, and nonthreatened ferret species, respectively), these three recovery efforts likely would not have succeeded.

Finally, it is critical to be realistic regarding the speed with which research goes from the bench-top to the bedside. This fact is poorly understood by the general public, which, in turn, can lead to opposition to some basic research studies involving animals when the ultimate value of the activities may not be known for decades. Finding disease cures can take up to a century—from some initial basic science discovery, a single brick in an allegorical huge pyramid, to the final "useful" product at the pyramid's apex is very hard for lay individuals to comprehend. The authors of one analysis, titled "From Scientific Discovery to Cures: Bright Stars within a Galaxy," state, "new treatments depend upon a broad base of scientific knowledge plus special contributions from a few exceptional scientists." Working backwards through the published medical literature, the analysis team looked at the step-by-step advances that were necessary to lead to the development of two drugs. According to this analysis, more than 7000 researchers from 5700 different institutions, working in succession over 100 years, were needed to develop a cancer drug. In support of this concept, the development of a cystic fibrosis drug was also daunting: 2900 scientists with ties to 2500 different institutions, laboring for 60 years. The bottom line, according to study coauthor Alexander Pico, is that "it takes contributions from a surprisingly large and complex network of individual scientists working in many locales to reach a cure" (Williams et al. 2015). Misunderstanding of this aspect of discovery can lead laypersons to oppose, what seems to them, to be excessive or frivolous use of animals in biomedical activities.

Changing the Legal Status of Animals

Recently, some animal rights groups have mounted campaigns to change references to animal "owners" in laws, statutes, and regulations to read animal "guardians." At least three U.S. cities have adopted amendments to their animal welfare statutes to replace the term *animal owner* with the term *animal guardian*: Boulder, Colorado; West Hollywood, California; and Berkeley, California. While the sponsors of this movement allege that their motive is simply to raise the public's awareness of their responsibilities to their animals, it is likely that their real agenda is to give legal "standing" to animals as things other than property (since the word *guardian* has very specific legal meaning and is defined as "a person lawfully invested with the power, and charged with the duty, of taking care of the person" (Garner 2009). It would not be much of a stretch to have this definition revised to substitute the word *animal* for the word *person*.

Such a change could theoretically lead to someone seeking legal guardianship of an animal that is not theirs based on a perception that the existing guardian (e.g., an animal in a research institution) is unfit. Should such a court case be filed, and even if the original guardian prevails in court, the potential legal fees could be significant. Further, if an animal needed expensive veterinary care that the guardian (in this example a private individual) could not afford, he or she might be liable for charges of animal endangerment for not providing the care and could be brought into court by someone suing on the animal's behalf.

While it is highly unlikely that these efforts to change the legal status of animals will lead to such draconian results, it is highly likely that there will be a good deal of turmoil created by this seemingly insignificant change in verbiage among the general public, animal owners, legislators, and most significantly, lawyers and veterinarians.

One development over the last several years that might indicate that these concerns about the possibility of legal turmoil over this issue, as well as other animal-related issues, such as personhood for chimpanzees, are valid is the burgeoning number of law schools that offer or have offered credit for animal law courses or seminars (at least 119 schools) (NABR 2015a) and that have received millions of dollars to support such courses (NABR 2015b).

Perhaps if the efforts to use a term other than *owner* for persons who "own" animals were to advocate for use of the term *caretaker*, or some similar term not fraught with potential legal implications, the goal of recognizing that animals are not just things may advance more rapidly. In regard to concerns that "unfit" owners, that is, those that abuse or treat animals cruelly, ought to be sanctioned, it is worthwhile to remember the many laws, regulations, and international treaties that exist to protect animals include serious sanctions for both individuals and institutions for violations thereof.

Other Contemporary Issues

When attempting to justify the value of the use of animals in biomedical activities, it may be necessary to include consideration of a subset of contemporary cultural and ethical issues:

- Is it morally acceptable to use animals for *any* human purpose? Could the use of any captive or domestic animal for any purpose whatsoever be equivalent to forced human slavery? It is unlikely that this represents the majority ethical viewpoint for most cultures. However, it is possible to say that some individuals might take this ethical position. If one should conclude that the answer to this question is no, further discussion about the value or necessity of using animal subjects in biomedical activities would be purely academic.
- There are different cultural perceptions regarding the moral acceptance of animal use, which can encompass the way the animal is used, the purpose of the use, or even the species being used. It is likely that most cultures and societies accept the use of some species of animals as pets. There are species of animals that are revered in one culture that may be eaten in another (e.g., cows and dogs). There are species that have a significant place in the cultural heritage of various native peoples, and may still be hunted even though they are nationally recognized as endangered (e.g., whales and eagles). These varied perceptions further complicate efforts to resolve the moral and ethical aspects of animal use in biomedical activities.
- What is the "necessity" of any particular use of animals? As will be discussed in more detail in the "Risk (Harm) versus Benefit Assessment" section that follows, what is necessary with regard to biomedical activities is a prominent consideration in numerous laws, regulations, policies, and guidelines that pertain to animal use in biomedical activities. Is it necessary to use an animal for a specific research proposal, and is it necessary to use a specific species? Is it necessary to genetically modify an animal model to do the research, even if it means that the animal may develop a disease that might be painful? Unfortunately, there is no universally accepted definition of what *necessary* means when used in this context. For example, in a study designed to develop a new treatment for some major emerging human disease, would it be necessary that the potential treatment be such as to save a minimum of 1000 human lives, or would the saving of 10 lives be an acceptable "cost" in terms of animals used? Even the eminent medical missionary who fostered a "reverence for [all] life" philosophy, Albert Schweitzer, has been quoted as saying that "it is *necessary* for the advancement of medical understanding" (emphasis added) when asked about his views on the use of laboratory animals for biomedical research (Pittman 1990).
- Problematic words. Many of the terms that we use in discussing the ethical use of animals lack precise or universally accepted definitions. With regard to the use of the term *obscenity*, there

is an old adage; it can be hard to define, but "we know it when we see it." Well, this colloquial expression can apply equally well to the terms *well-being*, *distress*, and *suffering*; we cannot exactly define them, but we know them when we see them.

General well-being: To assess an animal's general well-being, one may use physiological criteria, behavioral criteria, or functional criteria, or a combination of all three, in an effort to arrive at an approximation of well-being.

- Physiological criteria: Animals must be able to maintain internal homeostasis in order to survive. Most physiological parameters can be measured, many by non- or minimally invasive procedures (e.g., body temperature or blood cortisol levels). "Normal" ranges for the parameters can be established, and animals with values within those parameters may be said to have an appropriate level of physiological well-being.
- Functional criteria: *Functional* means can the animal function normally within the circumstances of its life; for example, can it obtain and utilize adequate nutrients to maintain itself, can it engage in adequate reproductive behavior to propagate its species at a relatively normal rate, and/or can it engage in sufficient grooming behavior to prevent injury to itself?
- Behavioral criteria: Many persons involved in trying to assess animal well-being advocate that behavioral criteria are more reliable than are either physiological or functional criteria. They base their position on the proposition that psychological and subclinical physiological stress or distress will manifest in abnormal behavior. The problem with this approach is that there is no uniform agreement on what is the normal behavioral baseline against which to judge whether a particular behavior is abnormal. For example, should we use the normal behavior of tigers living in the wild as the baseline for assessing the behavior of a captive-bred tiger living in a zoo when the cat has never known what life in the wild is like and appears to be physiologically and functionally doing well even though it repeatedly paces in its enclosure (mimicking a tiger's travels over its range?) without injury?

Psychological well-being: The U.S. Federal Animal Welfare Act implementation regulations (Part 3, "Standards," Subpart D, §3.81) require that institutions provide "environment enhancement to promote [the] *psychological* well-being" of nonhuman primates (Federal Animal Welfare Act and Animal Welfare Regulations 2013, emphasis added). While one may be able to assess the general well-being of an animal by using the three criteria above, assessing its psychological well-being may not be so simple. "To assess an animal's 'psychological' state ('well-being' or otherwise), requires [lingual] communication of feelings"; thus, "when evaluating an animal's well-being, the most parsimonious [simplistic] approach is to use behavioral indices. To say that 'abnormal' behaviors indicate abnormal 'psychology' is to make a great leap and say that you are able to get inside the mind of animals" (Rasmussen 2000). Therefore, we can truly assess psychological well-being only in conscious, lingual humans. Even with a nonverbal human patient, psychological well-being cannot be assessed. For example, persons in comas do not receive antidepressant drugs since it cannot be determined that they are depressed. There can be no psychological intervention with a person in a coma since their psychological state cannot be determined.

In truth, there is probably no universally accepted way to assess the psychological well-being of any nonhuman animal, even though it is required in the U.S. regulations for nonhuman primates. To meet this requirement, behavioral criteria appear to be acceptable to ensure compliance with the law.

Distress: Distress may be defined as physical or mental anguish or suffering; however, as has been stated many times, much of the difficulty in achieving a broadly accepted approach to categorizing, and then addressing, pain and distress is due to the absence of a concise definition. From a behavioral perspective, this inability to arrive at a *Webster's Dictionary* type of definition is due in part to the fact that (1) pain and distress are not discrete states, but are a continuum of experience; (2) signs differ between species, and most animals hide signs of pain because such a sign of weakness may provoke an attack from predators or subordinate

members of the group; (3) there is a lack of specific behavioral indicators of pain and distress; (4) in the course of identifying distress, interobserver variability can be large; and (5) there is a tendency to anthropomorphize, which is encouraged by U.S. government principle IV. That principle states that "unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals" (Institute for Laboratory Animal Research 2011). Note that this principle seems to associate distress with pain, which is commonly, but not universally, the case. Distress may be caused by factors other than pain, for example, noise, crowded enclosures, pheromones from other species, and environmental temperatures. As with psychological well-being discussed above, distress is often assessed by the animal's behavior. Physiological and functional criteria can also be used, with behavior, to identify distress.

Suffering: One could define suffering as an unpleasant emotional state associated with pain or distress. However, this definition would not seem to provide practical guidance when attempting to determine whether an animal is suffering when obvious gross indications are absent. Trying to define suffering in a manner that would be acceptable to all, which covers all the possible situations that may be associated with animal use in biomedical activities, is very difficult and, possibly, impossible. The previous discussion regarding well-being would seem to be applicable here, as if well-being is adequately addressed in an institution's animal care and use program, animal suffering would be minimized or eliminated to the maximum extent possible.

Alternatives: The term *alternatives* is most frequently interpreted as meaning the replacement of animals in biomedical activities with nonanimal technology. Tissue cultures (both human and animal), computer modeling and simulation, *in vitro* techniques, and retrospective statistical analyses are only a few examples of techniques that can replace the use of animals in some cases. Several organizations have been established to promote and develop nonanimal alternatives (e.g., the U.S. Department of Agriculture Animal Welfare Information Center [2015], the Interagency Coordinating Committee on the Validation of Alternative Methods [2015], the Center for Alternatives to Animal Testing [2015], FRAME [2015], and the National Centre for the Replacement, Refinement & Reduction of Animals in Research [2015]).

Is there an acceptable alternative methodology that does not require the use of animals? There are a few circumstances where a nonanimal alternative can replace the use of an animal. For example, for some compounds the Corrositex test method for dermal corrosivity can be used as a stand-alone assay for evaluating corrosivity and replace the use of animals (Corrositex 2015). It is likely that as more is learned about cellular biology and function, as well as molecular biology, the development of more nonanimal methodologies will be validated and replace animals used in some research activities. However, the "horns of our dilemma" are that the primary reason animals are used in biomedical research activities is the exquisite complexity of intact living organisms. It is highly unlikely that alternative methodologies will replace most animal use any time soon. However, what is certainly safe to say is that validated, nonanimal methodologies will be welcomed by most individuals responsible for biomedical activities currently involving the use of live animal subjects, if for no other reasons than a simple aversion to the use of sentient animals for biomedical activities and, from a purely pragmatic calculation, the alternative may be less expensive and faster than using animals. Few researchers would prefer the complexity and burden of animal experimentation if there were accurate alternatives.

As is true of general science advancements today, potential alternative technologies are emerging rapidly. For example, recent reports have been published describing the development of a "brain" in a dish (cell culture) that may replace animals in studies of brain cell function in some cases (Erickson 2015). At the 2015 annual meeting of the American Association for Laboratory Animal Science, the keynote speaker, Dr. Uwe Marx, presented an exciting summary of current efforts to develop human "multiorgan chips" or micro test cells. Other presentations elaborated on some of the organ test systems in existence that can simulate one

or two organs that can be used in toxicological testing in lieu of live animals. While these systems are largely in the validation stage, Dr. Marx believes that within 20 years, there will be validated systems that will consist of up to 10 different "organoids" on a single chip that will actually be capable of interacting with each other, thus providing a cell culture–based alternative to a living animal for screening tests of candidate pharmaceutical agents or toxicological studies.

Another relatively new nonanimal alternative to live animals has been developed for teaching veterinary students rectal palpation of cattle and horses using haptic (sense of touch) virtual reality simulators. Using these simulators, veterinary students gain the ability to conduct such exams before they conduct them on live animals, significantly reducing the need for live animals in the students' early efforts to learn how to accomplish these diagnostic examinations (Farminguk Web Page 2015). Along with high-fidelity mechanical manikins, these simulators are reducing the use of live animals in many medical and veterinary school training programs.

As an aside, most individuals proposing to use animal subjects in biomedical activities are usually well informed about the latest *validated* alternative (to animals) technology that would be appropriate for use in the proposed activities and invariably will have already incorporated them into their activities. After all, as already noted, it is in their own self-interest to use the best, and least expensive, technology to obtain the highest-quality data. Besides, most scientists and research technicians will likely be emotionally delighted to use a nonanimal alternative, rather than live animals, so long as the alternative methodology provides equivalent results.

- Where to draw the line?

  If society were to decide that at least sentient animals have moral or legal rights, where along the taxonomic scale should the line be drawn? Today, most laws and regulations governing how we treat animals apply only to vertebrate animals and, in some cases, only certain vertebrate species. The theory for selecting these taxonomic criteria is that only vertebrates have the anatomical and physiological capacity to be considered sentient and thus experience pain. However, it has been well demonstrated that at least some invertebrate species, for example, octopuses, have a level of intelligence that would infer sentience (Borell 2015). Even earthworms produce endorphins, which are hormones that are known to function to reduce pain in humans (DeGrazia 1996), perhaps indicating that earthworms can feel pain and thus might be sentient. It might be concluded that trying to define a firm line dividing animals into those that are deserving of rights and those that are not, based on sentience, would be extremely difficult, if not impossible. Thus, the best ethical approach would be to provide the best, least aversive care for all animals used in biomedical activities.

Public Perceptions about the Use of Animals in Biomedical Activities

As documented in the two references cited, a majority of the public support the use of animals in biomedical activities provided the animals are "humanely" cared for and used and the activity is "necessary" (Cox and Montrose 2016; NABR 2016).

- Many in the general public seem to believe that many animals used in biomedical activities "suffer," at least to some extent. If one were to ask a friend or acquaintance who has nothing to do with biomedical activities if it is okay to use animals in biomedical activities, it is likely that the response would be something like, "Well, it's a shame that they have to suffer, but it's okay if [followed with some qualifying statement]." Control, or preferably elimination of pain and/or distress, seems to be a major concern of many individuals. Thus, control or elimination of pain and/or distress should be a major commitment of all animal care and use programs, and provisions for minimizing pain and/or distress should be well documented in proposals for animal use and in actual application during the accomplishment of animal use activities. When talking

to lay audiences about the pain issue, one may use the following example regarding toothache pain to illustrate how pain can be addressed in biomedical activities:

> Ask those present to recall the last time they had a toothache and follow with the question, "When you first became aware of the pain, did you immediately make an appointment with a dentist or, more likely, did you think to yourself, 'Oh, it will go away'?" Then note that most likely the answer for most in the audience would be the latter; that is, they waited until the pain became intolerable to consult a dentist. Then point out that the first inclination of pain would represent the "perception threshold," and the intolerable point would be the "tolerance threshold," and studies involving some level of minimum pain likely could be considered acceptably humane if the level was only at or near the perceptual threshold and well under the tolerance threshold. This approach seems to be received well by most members of audiences. In addition, a discussion of the availability and use of modern analgesics to control pain in animals used in biomedical activities also seems to be well received by lay audiences.

- Also, it seems that many in the public believe that the use of animals in biomedical activities is, at best, poorly regulated—in spite of the fact that in the United States alone, there are approximately 42 laws and regulations that can govern how animals are cared for and used in biomedical activities, depending on the nature of the studies and the source of funding (see Attachment I for some selected examples). The number and variety of regulations that govern animal use in biomedical activities worldwide is truly impressive (AAALAC International 2015). Unregulated, hardly!

Media Portrayal of Animal Use in Biomedical Activities

The cover art of the December 26, 1988 *Newsweek* magazine issue depicted an illustration of a black and white striped cat sitting in a completely bare, wire cage just slightly larger than the animal. The expression on the cat's face staring at the observer could be anthropomorphically interpreted as "apprehensive." The cover presents multiple subliminal messages that could sway a layperson's perception about biomedical activities involving the use of animals. To begin with, the animal shown is a "warm and fuzzy" cat, not a "creepy crawly" rat or mouse. In addition, the photo implies that the cat lives in a sterile cage that is obviously way too small for it and lacks food, water, a litter box, or a resting shelf. Then, finally, what might be the most powerful subliminal message is in the title and, most importantly, the subtitle, i.e., "The Battle over Animal Rights: A Question of **Suffering** and Science" [emphasis added]—that is, animal suffering is the norm in research using animals (with the "truth" of this statement being "proven" by the obvious "cruelty" of how the cat is being housed)!

Much of the media material about the use of animals in biomedical activities over the last five or so decades appears to be biased toward the animal rights point of view, frequently equating *animal rights* and *animal welfare* as synonyms. These apparent biases are frequently a result of the reporters or commentators not being well versed about the material they are presenting. Another significant reason for this misreporting is the research community's apparent reluctance to present the facts about our biomedical activities. For example, an institution gets a multi-million-dollar, multiyear grant for a project involving the use of animal subjects, but the announcement of the grant emphasizes the dollar amount and alludes to the importance of the project in terms of human health or scientific discovery, but rarely mentions the animals to be used. Announcements of some new, allegedly significant discovery usually laud the institutional support and the scientist making the discovery but almost never includes any acknowledgment of the critical role the use of animals played in making the discovery. One can make the case that emphasizing the use of animals in our biomedical activities carries the risk that those opposed to such animal use may target institutions that are forthcoming. However, by having highly ethical caring and legally compliant animal care and use programs that can withstand public scrutiny, along with being proactive and forthcoming with our public stakeholders, including the media, we should be able to ultimately persuade the general public of the validity of our activities.

Value of Biomedical Activities Involving Animals

If you Google "advances in medicine and science attributed to animal research," you will find more than 7.5 million results. These include numerous lists of advances in biomedical disciplines, as well as numerous sites refuting the "facts" of such claims, using emotional arguments and examples of some misdeeds by some scientists, to denigrate those using animals in biomedical activities.

As is the case with most human activities, there have been examples of inappropriate animal care or use in some biomedical activities at some institutions. However, if there are a few examples of children being mistreated in childcare centers, all childcare centers are not closed; rather, the guilty parties are punished and the management of their specific centers corrected or the centers closed. Thus, because there have been some (likely a very small percentage of individuals or institutions involved in conducting biomedical activities) instances of inappropriate or illegal violations of contemporary standards for the care, use, or welfare of animals in biomedical activities, caution should be exercised not to paint the entire biomedical community with the same paintbrush. In addition, those institutions and individuals that are found to be violating standards, policies, and laws are frequently subject to severe penalties if discovered.

Former U.S. Surgeon General C. Everett Koop, MD, has been quoted as stating, "Virtually every major medical advance for both humans and animals has been achieved through biomedical research using animal models to study and find a cure for a disease and through animal testing to prove the safety and efficacy of a new treatment" (Anonymous 2001). Not only is Dr. Koop's statement true, but also it is likely that the majority of medical advancements and achievements that we take for granted today have been the result of activities using animal subjects.

Some Specific Examples of the Value of Animal-Based Medical Research

In the 1960s, thalidomide (generic name rofecoxib, trade name Vioxx), a drug used in sleeping pills and sedatives, was discovered to help alleviate morning sickness in pregnant women and was widely used in Europe and other countries. However, due to one Food and Drug Administration (FDA) inspector who believed that there were insufficient animal data to support its use in pregnant women, and in spite of much pressure to approve the drug for use in the United States, thalidomide was not approved for sale in the United States for use by pregnant women. Within several years of thalidomide being first prescribed for pregnant women, it became obvious that the drug was causing limb malformations in newborn infants and its sale was halted worldwide. The FDA inspector who held up approval of the drug in the United States was Dr. Frances Kelsey, a Canadian working at the FDA. In 1962, Dr. Kelsey was awarded the President's Award for Distinguished Federal Civilian Service by President John F. Kennedy, largely in recognition of her efforts to keep thalidomide out of the U.S. market (Wikipedia Web Page 2015). In June 2015, she was named to the Order of Canada, again largely in recognition of her efforts to keep thalidomide off the market, but also for being "an instrumental figure in shaping and enforcing drug licensing protocols."

Dr. Albert Sabin, recognized as the developer of the oral polio vaccine, in a personal letter to this author, dated September 28, 1991, noted thusly, "My own experience of over 60 years in biomedical research amply demonstrated that without the use of animals and of human beings, it would have been impossible to acquire the important knowledge needed to prevent much suffering and premature death not only among humans but also among animals." Also, in a paper published in the *Journal of the American Medical Association*, Dr. Sabin noted that "during the preceding four years approximately 9,000 monkeys, 150 chimpanzees, and 133 human volunteers have been used thus far in the quantitative studies of the various characteristics of different strains of polioviruses" (Sabin 1956). Even though use of the oral polio vaccine has been discontinued in many of the world's developed countries (due to the reported incidence of 1 in 2.4 million cases of induced polio in recipients of the vaccine and the increased safety of the injectable vaccine), it is still used in many developing countries due to the ease of administration and some cultural resistance to the injectable vaccine.

Dr. Helen Taussig was the codeveloper (with Drs. Alfred Blalock and Vivien Thomas) of the Blalock–Taussig–Thomas shunt for correcting the malposition of cardiac vessels with or without ventricle

perforations in newborn infants (commonly called the blue baby syndrome, which, uncorrected, invariably led to the death of the affected infants). In a personal conversation with this author (ca. mid-1960s), she indicated that the use of dogs was absolutely critical in the development of the shunt, and because of the results of the dog studies, early surgeries on human infants were largely successful. On September 28, 1962, in testimony before the congressional house hearing of the Subcommittee of the Committee on Interstate and Foreign Commerce, Dr. Taussig affirmed that the use of dogs had been critical for the development of the Blalock–Taussig–Thomas shunt and noted that the procedure had "saved thousands of lives throughout the world. It opened up the field of pediatric cardiac surgery" (Taussig 1962).

Dr. Emanuel Grunberg, while not as well known by the public as Drs. Sabin and Taussig, was a member of the team that discovered the antituberculosis drug isoniazid. In the early 1950s, Dr. Grunberg was working at Roche Pharmaceuticals, where there was a major program to find an antibiotic that would be effective against *Mycobacterium tuberculosis*, the causative agent of human tuberculosis. Prior to the discovery of isoniazid, the only antibiotic that was available to treat tuberculous was streptomycin, but it was more bacteriostatic than bactericidal and treatment could take years and long-term use of the drug could lead to some serious potential side effects, such as vertigo and allergic reactions. Over dinner at his son's house one evening (ca. mid-1980s), Dr. Grunberg told this author that testing of isoniazid in mice was a critical factor in discovery of the drug, as *in vitro* testing with it indicated only marginal effectiveness against *M. tuberculosis*. However, when tested in mice it proved to be highly effective against the bacterium, an effect ultimately determined to be a result of a metabolic product produced by the animals that was the active agent. Isoniazid is still considered to be a first-line medication in the prevention and treatment of tuberculosis.

Is History Prologue?

In a 2011 Hastings Center Report, Dr. Larry Carbone wrote, "History is informative, but not conclusive. To say that dogs were vital to the discovery of the role of the pancreas in diabetes in the 1920s is not to conclude that other approaches could not have worked then, or that the dog studies would be necessary in the twenty-first century" (Carbone 2011). Dr. Carbone's implied caution about using the criticality of some past use of animals as justification for continued use of animals can be problematic when viewed through the lens of contemporary technological knowledge.

However, conscientious application of the 3Rs should maximize the probability that future use of animals in biomedical activities will prove to have been valid in the context of our knowledge today. Contemporary knowledge may still require an animal model for studies of diabetes, but it may be a genetically altered mouse hosting human pancreas cells rather than dogs. More importantly, critical well-designed research, based on well-documented rationale and that can best be completed using animals today, should not be delayed on the hope that a better alternative might be discovered sometime in the future.

Impact of Emerging Technologies

All too often scientific advances occur at a rate greatly outpacing the ability of philosophers, ethicists, politicians, and the general public to address issues that arise therefrom. The cloning of animals, the creation of chimeric animals that host human cells, the genetic manipulation of germ cell DNA to permanently eliminate a genetic disease in future offspring, and so forth, have raised serious ethical issues in the past, are doing so today, and most certainly will continue to do so in the future as yet undiscovered biomedical technologies advance. As a single example, recall the ethical uproar that arose about the use of human embryonic stem cells when early studies required obtaining cells from human embryos or umbilical cord blood. Now, at least in some cases, technology allows us to regress one's own fat stem cells to their pluripotential state and use them to treat some medical conditions, largely negating most of the previous concerns about human stem cell research.

It is impossible to predict here what kinds of new biological or biomedical technologies will emerge in the future. With regard to the use of animals in biomedical activities, review committees need to

be informed about any potential adverse effects that a new technology may have on the welfare of any animals involved in a proposed activity. For example, if the proposed activity involves creating a novel genetically modified strain of mouse, the responsible applicant should be required to provide (1) the best possible prediction regarding adverse impacts on the animals' welfare, (2) the criteria for determining whether any adverse impacts on the animals' welfare occur, (3) a description of how any adverse impacts on the animals' welfare will be addressed when or if they occur, and (4) the criteria that will be used to determine when to terminate the use of an affected animal due to welfare concerns (humane endpoint). The same four aspects of any new technology involving animal subjects should also be addressed in active proposals.

Can Animal Use Be Prohibited?

Could we do away with the use of animals in biomedical activities? Of course we *can*, but at what cost? Abolishment of the use of animals (just vertebrates or all sentient animals) in biomedical activities would most certainly impede advances in human and veterinary medicine, impede foundational basic research, and probably significantly slow advances in knowledge that would alleviate future human and animal suffering. What it would not do is significantly minimize human exploitation or use of animals since the single thing that could be done as a society to mitigate animal use would be to mandate by law vegetarianism or vegan lifestyles, which would immediately "save" billions of future animals that would be produced for consumption.

Application of Ethical Concerns of Oversight Bodies Such as Institutional Animal Care and Use Committees and Ethics Review Committees

In the various countries with regulations regarding the use of animals in biomedical activities, there are instances where committees charged with reviewing the use of animals are specifically expected to consider the ethical aspects and implications of the proposed activities during their deliberations. That said, and considering that references to "ethics" or "biomedical ethics" are frequently absent from regulatory or policy documents, it is proposed here that all such committees, as well as institutional managers and officials, have at least an implied responsibility to consider the ethical aspects of any proposed use of animals, whether or not required by law, regulations, or guidelines. In cases where there may be serious ethical concerns about a particular activity, strong justifications for approving the animal use should be well documented by the individual or unit requesting such use.

For instance, members of an Institutional Animal Care and Use Committee (IACUC), as constituted by the U.S Federal Animal Welfare Act (Federal Animal Welfare Act and Animal Welfare Regulations 2013) and/or the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (U.S. Department of Health and Human Services 2015) (and their respective regulations and policies), should consider the "scientific merit" of a proposed activity. The argument against consideration of merit by these review committees is usually presented something like this: "Since funding agencies base their awards largely on the merit of proposals, and have their own review procedures to specifically evaluate the merit of applications, local review committees should not review proposals for merit." However, if an IACUC member believes that there truly is *no* merit to a proposed animal use activity, only a disapproval vote would make ethical sense. Thus, each IACUC member must be convinced that there is at least some minimal level of merit to vote for approval. Obviously, the acceptable level would be an individual decision. While "merit" has not been discussed heretofore as a component of an "ethical" review, it would seem that approval of an activity that is believed to be truly without merit would be unethical.

In addition, if the members of a review committee determine that there is sufficient merit to consider a request for animal use, they should then determine whether the proposal for the activity has, at a minimum and to the greatest extent possible, (1) addressed the 3Rs, (2) documented that the proposed animal model is the best possible one for use, (3) shown that all care and use procedures have been well addressed so that the welfare of the animals is ensured to the greatest extent possible, and (4) demonstrated that

there are adequate resources available to care for the animals. Only then should a vote for approval be received.

While not always available, effort should be made to identify a person trained in bioethics to be a member of all review committees.

Risk (Harm) versus Benefit Assessment

Generally, cost–benefit assessments are made in regard to the financial costs of a project versus the potential income to be expected or, in the case of some projects, such as a new interstate highway, the potential for fewer vehicular accidents and/or the more efficient movement of traffic, all with reasonably well-established criteria and methodologies for accomplishing the necessary data analyses.

Even risk–benefit assessments with regard to new or potential medical treatments in human medicine can be accomplished using reasonably well-defined criteria; however, integral to these assessments is input and informed consent from the mentally competent patient, human research subject, or competent human guardian for the patient or research subject (Pinkertom et al. 2002). In all these cases, the potential for benefit (to the patient or subject) must outweigh the potential risks or harm.

In regard to the use of sentient animals in biomedical activities, such assessments suffer from four very significant problems: (1) the animals cannot participate in the discussions, nor can they give informed consent; (2) in at least some cases, the animals will be subjected to situations that, even with conscientious application of the 3Rs, will result in at least some discomfort, distress, or [hopefully] minimal pain; (3) in many if not most cases, the animals will be euthanatized at the end of the activity for purposes of collection of organs, tissues, or other biological samples; and (4) consideration must be given to who will approve the animal use. The decision to use animals in biomedical activities may depend on the principal investigator, animal review committee members (including the public members), institutional administrators (such as in-house grants supervisors), representatives of regulatory or funding agencies, or ethicists. Thus, these problems make it imperative that review procedures are structured to be as objective and transparent as possible.

In a recent issue of *Lab Animal*, Drs. Kinter and Johnson (2015) provided an excellent discussion on the use of the terms *risk–benefit* or *harm–benefit* with regard to assessing proposals for the use of animals in biomedical activities. They make an excellent case for maintaining the term *risk–benefit* as found in the American *Guide for the Care and Use of Laboratory Animals* (Institute for Laboratory Animal Research 2011) versus the term *harm–benefit* as found in Article 38 of European Directive 2010/63/EU. The authors conclude by recommending "that scientists, IACUCs, and groups that accredit animal research programs maintain the language and concept of 'risk-benefit analyses' for assessing the risk that research animals might experience pain, distress, or injury. 'Risk-benefit analysis' transparently and unambiguously describes and addresses the necessary considerations of animal research, and its terminology agrees with the specific language in the *Guide for the Care and Use of Laboratory Animals*" (Institute for Laboratory Animal Research 2011). That is, risk (of pain, physical harm, etc.) can be more reasonably predicted and quantified than can the harm, although, some harm may occur even if the risks are low (e.g., euthanasia for collection of tissue samples).

In a 2010 article published in the *Archives of Biological Science*, a case is made for the use of the term *cost–benefit* rather than *risk–benefit*, in that "the term 'cost' defines the expected harm, pain and distress that is likely to be experienced by the animals." However, as noted above, the authors failed to provide objective criteria for quantifying the relative costs (to the animals) versus the benefits to be derived from the studies (Kostomitsopoulos and Durasevic 2010).

Role of Animal Care and Use Administrators, Directors, and Managers in Fostering Ethical and Compliant Programs

As noted in the introduction to this chapter, institutional officials and managers of animal care and use programs who understand the origins and foundations for the variety of public perceptions regarding the use of animals in biomedical activities will likely be better able to organize their programs to minimize

the possibilities for criticism and maximize their ability to respond in a positive manner to any such criticisms. Even though this knowledge of history and the various ethical concepts and philosophies about animal use in biomedical activities will enable managers to establish operational policies and procedures of a truly ethical program, there will never be a program totally acceptable to all the public stakeholders.

Animal care and use program managers should insist on the necessity of quality animal care and use programs and be vocal advocates for the animals *and* the users. These are not contradictory roles. Strongly advocating for quality animal care and at the same time assisting the animal users in designing legally compliant and ethically appropriate proposed activities are complementary and will maximize the probability of quality science.

A major role for managers is to ensure that all members of the animal care and use staff are fully aware of the reasons animals are used in biomedical activities and of the efforts in place to ensure that they are used in the most ethical and humane manner possible. Hopefully, successful managers will help all staff personnel understand that their institution's programs for animal care and use are ethical, necessary, and of high moral quality and will ensure that those beliefs are based on factual knowledge about the institution's programs.

In some institutions, directors and managers of animal care and use programs may be asked to participate with public affairs officers in responding to inquires about animal use since they may be the staff members who are most familiar with the institution's animal use program. In such cases, the institution would be remiss if it did not provide professional media training to the director or manager.

Application of Ethical Concerns by Other Institutional Individuals

While it should be obvious, it is in the best interest of both all institutions and all individuals within an institution to conduct all animal care and use activities in an ethical manner, and it is intrinsically important to do so. Because of the controversies involved in the use of animals in biomedical activities, it is especially important that all personnel, at all levels, be supportive of efforts to foster implementation of ethical and legally compliant animal care and use programs.

The emphasis on an institution's commitment to having an ethical and legally compliant animal care and use program should start with the chief executive officer issuing an unambiguous statement indicating that the institution believes that the appropriate use of animal subjects in biomedical activities is necessary, and that there is a firm commitment to conduct such activities in the most ethical and compliant manner possible. This statement and the commitment it documents should be prominently displayed throughout the institution and included in all in-house training materials. As part of this commitment, there should be well-documented support for quality programs of animal care and use, and this should be prominently advertised through the use of posted policies encouraging the reporting of any concerns about animal care and use, with assurances that persons reporting concerns will not be penalized for coming forward, and listing the institutional officials to whom concerns should be reported.

To maximize the quality of an institution's animal care and use program, and minimize to the extent possible any unethical or noncompliant situation, all ancillary support personnel must be included in the institution's training program so that they are knowledgeable about the requirements for the use of animals in biomedical activities that apply to their respective areas of responsibilities.

Other individuals who may be overlooked as needing information regarding an institution's commitment to, and implementation of, a quality animal care and use program are the members of other institutional review committees that have oversight responsibilities for certain biomedical activities, such as biosafety, occupational health, radiological safety, and laboratory safety, all activities that may involve the use of animal subjects.

Value of External Review of Animal Care and Use Programs

As good as an animal care and use program may be, it never hurts to have a review by a disinterested individual or organization that is not regulatory in nature. Today, the "gold standard" for such external review is accreditation by AAALAC International. While AAALAC International accreditation is not

inexpensive or easy to obtain and keep, it is well worth it. The post–site visit report that the institution receives is of tremendous value in determining the quality of the institution's animal care and use program and will highlight any deficiencies discovered. One of the best aspects of this external review is that it is conducted by highly qualified individuals, who are thoroughly knowledgeable about animal use in biomedical activities, and the results of the review are completely confidential. These external review panels can sometimes identify "problems" that could lead to, or be interpreted as, impacting the ethical status of an institution's animal care and use program, which can then be addressed and corrected if necessary.

Conclusion

As noted in the introduction, there are no black and white answers regarding the bioethics of animal use in programs of research, teaching, and testing, and it depends on a person's experience, knowledge, understanding of the issues, and personal philosophy. Philosophically, none of the various philosophies presented earlier in the chapter, including animal rights, are necessarily wrong, nor are any of them universally accepted. Thus, we may perceive that we are wallowing in a philosophical quagmire. However, a conscientious effort and commitment on our part to establish and maintain animal care and use programs of the highest quality, including the fullest implementation possible of the 3Rs and responsible use of animals, will enable us to be comfortable that we are providing the most ethical and morally acceptable program possible.

Hopefully, the material presented herein will be helpful to new and experienced administrators and managers of animal care and use programs involved in biomedical activities in developing their personal understanding of the complexity of the ethical and moral issues involved in our profession, and in instilling that understanding in those they work with and for at their institutions.

ATTACHMENT I

Selected Examples of the Laws and Regulations That May Apply to Biomedical Activities Conducted in the United States and Canada

- *Federal Animal Welfare Act and Regulations* (http://www.aphis.usda.gov/).
- *Public Health Service Policy* (http://grants.nih.gov/grants/olaw/olaw.htm) and the associated *Guide for the Care and Use of Laboratory Animals* (the *Guide*), published by the National Research Council, and most recently revised in 2011 (https://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-use-of-laboratory-animals.pdf).
- *Good Laboratory Practice Act.* This act and its implementing regulations are enforced by the federal FDA, and the provisions of the act may impact how the care and use of animals is documented when animals are used in biomedical activities resulting in data submitted in support of applications for approval of a new pharmaceutical agent or medical device (http://www.21cfrpart11.com/files/library/pred_rules/mcdowall_glp_annotate.pdf).
- *Good Manufacturing Act.* As with the Good Laboratory Practice Act, this act and its implementing regulations are enforced by the federal FDA and the provisions of the act may impact how the care and use of animals is documented when animals are used in activities involving the manufacturing of pharmaceutical products (e.g., to test efficacy) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm).
- *Lacey Act.* Under the Lacey Act, it is unlawful to import, export, sell, acquire, or purchase fish, wildlife, or plants that are taken, possessed, transported, or sold (1) in violation of U.S. or Indian law or (2) in interstate or foreign commerce involving any fish, wildlife, or plants taken possessed, or sold in violation of state or foreign law. The law covers all fish and wildlife and their parts or products, plants protected by the CITES, and those protected by

state law. Commercial guiding and outfitting are considered to be a sale under the provisions of the act (http://www.fws.gov/international/laws-treaties-agreements/us-conservation-laws/lacey-act.html).

- *Convention on International Trade in Endangered Species of Wild Fauna and Flora* (https://www.cites.org/). Depending on the species of animals being sought for biomedical activities, CITES provisions may preclude using them and/or may require special permits and waivers to obtain them.

Other Import and Export of Animals

- *Animal and Plant Health Inspection Service (APHIS)* (https://www.aphis.usda.gov/wps/portal/aphis/ourfocus/importexport)
- *Centers for Disease Control and Prevention (CDC)* (http://www.cdc.gov/importation/bringing-an-animal-into-the-united-states/)
- *U.S. Fish and Wildlife Service* (http://www.ncbi.nlm.nih.gov/books/NBK19632/).
- Interstate transport—APHIS

State and Local Regulations

Institutions using animals in research, teaching, or testing may be subject to additional state and local laws. State and local legislatures should be consulted for more details. For example, in the state of Nevada, the Nevada Department of Wildlife requires permits for trapping wild native animals for research and for having and maintaining certain prohibited species, such as African clawed frogs.

Guidelines

Many professional societies publish "best-practice" guidelines for use of animals in biomedical activities. While such guidelines may not be legally binding, they may affect public perceptions about an institution's animal care and use program, as well as a program's ability to obtain AAALAC International accreditation. Some examples of such guidelines are

- *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (*Ag Guide*). The *Ag Guide* is published by the Federation of Animal Science Societies (FASS) and was most recently updated in 2010 (http://aaalac.org/about/Ag_Guide_3rd_ed.pdf).
- *Guidelines of the American Society of Mammalogists for the Use of Wild Mammals in Research* (http://www.mammalsociety.org/uploads/Sikes%20et%20al%202011.pdf).
- The Ornithological Council's *Guidelines to the Use of Wild Birds in Research* (http://www.nmnh.si.edu/BIRDNET/guide/).
- The American Society of Ichthyologists and Herpetologists' *Guidelines for the Use of Fishes in Research (2013)* (http://www.asih.org/sites/default/files/documents/publications/asf-guidelines-use-of-fishes-in-research-2013.pdf) and *Guidelines for Use of Live Amphibians and Reptiles in Field and Laboratory Research* (http://www.asih.org/sites/default/files/documents/resources/guidelinesherpsresearch2004.pdf).

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5

Behavioral Management Programs to Promote Laboratory Animal Welfare

Mollie A. Bloomsmith, Jaine E. Perlman, Eric Hutchinson, and Mark Sharpless

CONTENTS

Introduction to Behavioral Management

Animal care in research, teaching, and testing facilities has undergone a remarkable transformation in the past two decades, and there is a heightened emphasis on the psychological status of animals living in these institutions. Today, providing for the psychological well-being of research animals is an integral part of animal care programs and is key to promoting a "culture of caring" within our facilities. This change occurred as the scientific community realized that animals have many behavioral needs, which, if not met, can adversely affect their behavior, physical health, and research utility. Programs to address the well-being of laboratory animals by providing them with more complex and interesting environments are now common across all taxa, including primates, dogs, cats, pigs, sheep, rodents, rabbits, birds, and fish.

The term *behavioral management* refers to a comprehensive approach to improving the welfare of captive animals by employing social housing, environmental enrichment, animal training, facility design, and the assessment of behavior and behavioral problems. Behavioral management builds from a foundation of understanding the behavior of the target species (or of closely related species) in natural conditions, with the aim of improving animal care and enhancing animal welfare. An important premise of behavioral management is that the individual components of enrichment, animal training,