The Future of Animal Research

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Background and Introduction

The 2nd Brazil-USA Workshop on the Future of Animal Research was convened at the Fundação Oswaldo Cruz (FIOCRUZ[1]) in Rio de Janeiro September 13 and 14, 2001. The objective was to strengthen the ties between Brazilian and US scientists and students by exchanging perspectives about the use and care of laboratory animals in the two countries. Workshop participants explored the future directions of research in this field, fostering creative and visionary thinking and citing opportunities for exchange of scientists and students. The workshop was a sequel to the highly successful 1st Brazil-USA Workshop on this topic, which took place at the same site in 1999. Both workshops featured invited speakers from Brazil and from the United States in a roundtable format that allowed ample time for discussion.

This workshop series provides a forum for exchange of ideas and information between the two countries with the largest laboratory animal research programs in the northern and southern hemispheres of the Americas. The workshop brings together investigators, veterinarians, regulators of animal research, and providers of information and guidelines. This impressive array of professionals from Brazil and the United States brings a wide variety of perspectives to bear on the issues and engenders lively discussions. Topics in the most recent program included Laws, Regulations, and Animal Welfare; Genetics and Cloning; Research with Farm Animals and Conditions for Their Well-Being; Research with Rodents; and Research with Nonhuman Primates.

Two days before the opening ceremony, the tragic events of September 11 shocked the world. Although it became apparent in the hours that followed that some of the US participants would not be able to travel to Brazil in time for the workshop, the organizers decided to proceed. In retrospect, it was a sound decision. A total of 150 registrants participated, and all agreed that the workshop was highly successful in achieving its goals. At that time of international conflict and uncertainty, it was gratifying to participate in a venture aimed at strengthening international cooperation and collaboration and advancing science for the betterment of humanity.

The local host and co-organizer, Dr. Antenor Andrade, opened the workshop with a poignant statement in deference to the tragedy in the United States. Dr. Andrade requested 1 minute of silence before the welcoming addresses.

The welcoming addresses by Dr. Andrade, Dr. Ekaterina Rivera, Dr. Paulo Marchiori Buss, who is the President of FIOCRUZ, and Dr. John VandeBerg emphasized the following common themes: (1) Animal models have become increasingly important in research on the prevention and treatment of diseases not only of humans, but also of pets, farm animals, zoo animals, and research animals. (2) Genetically manipulated animals hold great promise for understanding and treating human diseases, and they bring new challenges in regard to animal well-being. (3) Appropriate care and use of research animals require an emphasis on ethics pertaining to their well-being. (4) International cooperation and collaboration in research and in developing harmonized standards for animal care and use are essential for maximizing the rate of progress in improving the quality of life for human beings and for animals.

Laws, Regulations, and Animal Welfare

The Chair of the first session, Dr. Sylvia Ortez, as well as subsequent speakers, emphasized how much the tragic events in the United States 2 days earlier had raised their consciousness in regard to international issues. Dr. Ortez remarked that what happened in the United States impressed on her that we are all citizens of the world, that our work is aimed at improving the human condition, and that in doing so it is critical to consider carefully the laws, regulations, and even the politics of what we do with our lives and what we do with the lives of animals with which we work.

Dr. Célia Cordoso presented a detailed summary of the history of animal welfare in Brazil and of the laws, regulations, and policies that have been implemented. This summary was exquisitely complemented by Dr. Pekow's presentation regarding the history and status of these topics in the United States. The presentations made clear that both countries have established strong traditions in animal welfare and both have established numerous laws, regulations, and policies to ensure the appropriate care and use of animals. The parallels in establishing and implementing ac-

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cepted practices for animal care and use were striking and most encouraging.

It also was apparent that the complexity of laws, regulations, and policies has in some instances created regulatory burdens that impede scientific progress without affecting animal welfare. The Brazilian government, in an effort to reduce regulatory burden while at the same time enhancing animal welfare, passed a law in 1997 that consolidated all previous laws pertaining to the breeding of animals and their care in teaching and research. In the United States, at the request of the Congress, the National Institutes of Health (NIH[1]) has established a committee that is developing recommendations to reduce regulatory burden without affecting the intended outcomes of existing laws and regulations.

A common theme of this session was that although laws and regulations are important for ensuring appropriate animal care and use, the education of researchers and technical staff in regard to care and use is equally important. In this context, the roles of the American Association of Laboratory Animal Science (AALAS[1]) and the Colégio Brasiliero de Experimentação Animal (COBEA[1]) are increasingly critical. Both have established excellent programs for training and education, and the annual AALAS and biannual COBEA conferences provide a superb mix of sessions and workshops on aspects of laboratory animal science, management, and care, with an emphasis on training and education.

Also discussed in the context of animal welfare was the role of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC[1]) International, an organization that accredits institutional animal care and use programs. Accredited institutions are site-visited every 3 years, and the recommendations provided by the veterinarians and researchers on the site-visit team are invaluable in improving the animal care and use procedures as well as the physical facilities.

Another point that surfaced during this session was that the pressures of the animal rights advocates have had a beneficial impact in bringing together laboratory and veterinarians and scientists from around the world. The mutual objectives of these groups are to work in concert to ensure the integrity of animal care and use programs and to provide better educational opportunities for researchers and caregivers.

Genetics and Cloning

The recent development of novel genetic and reproductive technologies has revolutionized animal research, particularly with rodents. The number of rodents used in research is increasing at a dramatic rate, and many institutions in both countries are building major new facilities to accommodate the burgeoning population. Workshop speakers summarized the technologies involved and discussed the potential for extending them to nonhuman primates. Nonhuman primates so closely resemble humans genetically and physiologically that they can serve as models for complex physiological systems and diseases in many instances in which rodents are less useful. Indeed, nonhuman primates are the link between research with rodent models and the technologies used with human patients. For this reason, only primates and rodents are used in increasing numbers in biomedical research, at least in the United States, although the use of all other mammalian species is decreasing. Although progress is being made in developing the technology to produce transgenic monkeys, none that expresses an inserted gene has yet been created. Dr. Joao Ramalho-Santos presented a very insightful evaluation of progress in this most challenging area.

Another topic in this session was the use of animals and alternatives for tests of mutagenicity. Concerns regarding mutagenicity are principally related to the widespread use of pesticides. The topic is especially pertinent to the Brazil-US dialogue because the United States is the world's largest user of pesticides, and Brazil ranks third. Most mutagenicity tests measure somatic mutations, but the significance of somatic mutations to cancer and other aspects of human health, and to risk of germ line mutations, is not clear. One difference between the laws of the two countries is that Brazilian law is based on prohibition of pesticides that have demonstrated mutagenic effects, whereas US law is based on risk assessment. The speaker, Prof. Alberto José Centeno, suggested that adoption of a risk assessment approach by Brazilian legislators would be very advantageous in simultaneously protecting human health and economic objectives.

Another topic discussed was the advent of transgenic crops that can reduce the use of pesticides but that pose other risks (e.g., the risk of transgenes being transported into wild varieties of domestic crop species and disrupting ecological balances and the risk of causing food allergies in humans). Current Brazilian law prohibits transgenic crops, whereas US law is supportive of them in specific instances in which safety requirements have been satisfied. A consensus of the participants was that new tests for mutagenicity and carcinogenicity are needed, and that laboratory animals as well as alternatives will be important in resolving concerns about the safety of pesticides and of transgenic crops aimed at reducing pesticide use.

Research with Farm Animals and Conditions for Their Well-being

In this session, Dr. Mateus Costa provided a very interesting and often overlooked view of the interactions between farm

[1]Abbreviations used in this report: AAALAC, Association for Assessment and Accreditation of Laboratory Animal Care; AALAS, American Association for Laboratory Animal Science; COBEA, Colégio Brasiliero de Experimentação Animal; FIOCRUZ, Fundação Oswaldo Cruz; NIH, National Institutes of Health; SPF, specific pathogen-free.

animals and humans. The first scientific approach to livestock production was recorded in France in 1843; and in 1893, the concept of farm animals as machines for the mass production of food was articulated. This concept was later severely criticized, leading to the implementation of laws that provide farm animals with basic liberties (e.g., to stand, lie down, turn around, extend their limbs, and care for their bodies). The discussion emphasized that despite legislation to protect farm animals, the mere existence of laws does not ensure welfare for farm animals just as it does not for laboratory animals. Engineering standards that dictate pen size and other mandatory specifications do little to ensure animal well-being. Rather, the consensus was that performance standards are just as important for farm animals as they are for laboratory animals, and that this concept should be emphasized in laws, regulations, and practices.

Dr. Yurij Sobestiansky discussed research with swine, which were selected for discussion in part because the United States is second only to China as the world's largest producer of pork, and Brazil is the eighth largest producer. In addition, swine are used for many purposes in human medicine (e.g., the provision of insulin, thyroid hormone, heparin, hemoglobin, skin for burn treatments, cardiac valves, and other biomaterials). They also are used in a wide variety of biomedical research areas because some aspects of their anatomy and physiology, and some of their pathologies, closely resemble those of human beings. However, perhaps the most exciting aspect of current research with swine is xenotransplantation. Transgenic swine with human genes have been created to reduce the risk of rejection of swine organs transplanted into humans, and gnotobiotic swine are also being developed to prevent the risk of transfer of swine viruses into humans who receive these transplants. State-of-the-art research involves transplantation of swine organs into baboons, to develop safe and effective technologies that can be applied to humans. It is too soon to know whether xenotransplantation will become a clinically important application of swine research, but if the technology becomes widely used, it will improve thousands of human lives.

Research with Rodents

This session reviewed the technologies for producing transgenic and knock-out animals, with a focus on the production of mouse models that promise to accelerate further progress in animal research greatly. Dr. Eliane Sul Abdelhay presented new strategies to prevent and treat human diseases using these unique animals.

The session also included a discussion of mouse research on Chagas' disease, which is a major health problem in Brazil and other Latin American countries. Chagas' disease is of increasing concern to the United States because of migration from Latin America and risks of transmission of the causative organism, *Trypanosoma cruzi,* by blood transfusion and organ transplantation. Different mouse strains exhibit varying degrees of resistance to infection with *T. cruzi* and disease progression, and different strains of *T. cruzi* vary dramatically in their ability to cause disease. The complex interactions between the genetic makeup of a host and the genetic makeup of the pathogen are critical factors in the etiology of many diseases. It is apparent that the mouse model will be important for investigating how these interactions influence immune function and for testing new drugs for treating *T. cruzi* infection. Although the speaker, Dr. Alejandro Luquetti Ostermeyer, stated that at present, there are more questions than answers, the lessons learned from this research may eventually be applicable to understanding and preventing other parasitic diseases in humans and in domestic animals.

Research with Nonhuman Primates

Brazil has a rich primate fauna, whereas the United States, which has no native nonhuman primates, is the world's largest user of primates in biomedical research. Because of their close phylogenetic relation to humans and their highly developed cognitive abilities, nonhuman primates deserve and are accorded special consideration in regard to well-being and to their appropriate use in biomedical research. The growing need for nonhuman primates for biomedical research raises additional concerns pertaining to policies that govern their conservation and their capture for research purposes. The speaker, Dr. Alcides Pissinatti, lamented that little research with nonhuman primates is conducted in Brazil despite its rich resources. The primate species would benefit from increased public and government awareness that nonhuman primates are important to medical research. Regrettably, as long as Brazilian primates remain largely invisible to the public and the legislators, habitat destruction and hunting will continue to thwart conservation objectives.

Another topic in this session was the development in the United States of specific pathogen-free (SPF[1]) rhesus monkey colonies. SPF monkeys are free of herpes B, a life-threatening hazard to humans, and also are free of retroviruses that interfere with AIDS-related research. There is a worldwide shortage of rhesus for biomedical research, and significant efforts are under way in the United States to increase domestic production especially of SPF monkeys. Data presented by Prof. William Stone supported the contention that establishing and maintaining SPF rhesus monkey colonies pose little or no risk to the health and survival of the animals.

The session concluded with a discussion of nonhuman primate models of Chagas' disease. Whereas mice are ideal models for many types of basic investigations, they do not closely mimic humans in some aspects of the immune response and they do not develop human-like symptoms. Primates, as the "step to man," are clearly needed as models for this incurable and lethal disease. The workshop host institution, FIOCRUZ, has conducted research with rhesus monkeys experimentally infected with *T. cruzi* for many years;

and a population of thousands of pedigreed baboons at the Southwest Regional Primate Research Center in San Antonio, Texas, was recently found to have a high incidence (8%) of naturally infected animals. Dr. John VandeBerg suggested that the baboon model is likely to be important in future research on the epidemiology of *T. cruzi* infection, the genetic and immunological bases of resistance to infection and disease progression, and the development and testing of new drugs to prevent or treat Chagas' disease.

Closing Session

The overriding theme of the workshop was that improving the quality of human life will continue to be heavily dependent on the use of animals in research. The degree of progress will in turn depend on appropriate care of laboratory animals and their judicious use to achieve experimental objectives.

There was an overwhelming sense of exuberance at the conclusion of the workshop, even in the face of deep sorrow and concern elicited by the tragic events in the United States a few days earlier. This exuberance reflected the success of the workshop in its goals of fostering international cooperation, and in developing dialogues at many levels involving established researchers and veterinarians, as well as the many students and postdoctoral researchers present. Participants left the workshop with renewed resolve to continue and enhance efforts to help humanity as well as the animals that serve in that endeavor. Participants agreed that new acquaintances and contacts will continue to enable Brazil and the United States to develop closer ties and interactions in fostering the appropriate care and use of animals. Brazil and the United States are playing a critical world leadership role in meeting these objectives and providing a model for international cooperation and collaboration, which surely will strengthen the prospects and rapid scientific advancement for world peace.

Toward that goal, the organizers have agreed to develop plans for hosting the 1st International Congress on the Future of Animal Research. Like the previous Brazil-USA workshops, it will convene on the campus of FIOCRUZ, which is the federal organization in Brazil that is most nearly equivalent to a combination of the NIH, the Centers for Disease Control, and the Food and Drug Administration in the United States. The Congress will be scheduled during 2003. Individuals who want to be included on the mailing list should contact Dr. John VandeBerg (e-mail <jlv@sfbr.org>).

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