Animal Research in a Global Environment: Meeting the Challenges: Proceedings of the November 2008 International Workshop

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Institute for Laboratory Animal Research

ANIMAL RESEARCH IN A GLOBAL ENVIRONMENT

MEETING THE CHALLENGES

Proceedings of the November 2008
International Workshop

Institute for Laboratory Animal Research

Division on Earth and Life Studies

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Preface

THE GLOBALIZATION OF ANIMAL RESEARCH: SCIENCE AND ETHICS AS A FOUNDATION FOR STANDARDS

Impacts of Globalization

International economist Jagdish Bhagwati has called globalization the "most powerful force for social good in the world today" (Bhagwati 2004, ix). Yet, in the wake of highly publicized news stories about counterfeit pharmaceuticals, the 2007 pet food recall, and tainted heparin supplies, other voices loudly criticize the loss of jobs in America and of quality assurance for products associated with international outsourcing.

In addition, pressures on both the health care industry—which relies heavily on animal models for biomedical research and preclinical trials—and science in general continue to build. A variety of sources provide data showing that demands for new and better medications and for research on health and quality of life will grow, in large part due to the expanding global population.

- In 2006 the United Nations noted that in just 12 years the world population was expected to climb from 6.7 billion to 7.6 billion (UN 2006b).
- The American Veterinary Medical Association has described the health risks to this increasing population: "The convergence of people, animals, and our environment has created a new dynamic in which the health of each group is inextricably interconnected. The challenges associated with this dynamic are demanding, profound, and unprecedented" (AVMA 2008, 3).
- The *World Health Report* states that "the global health economy is growing faster than gross domestic product (GDP)…. In absolute terms, adjusted for inflation, this represents a 35% growth in the world's expenditure on health over a five-year period" (WHO 2008, xii).
- And three of the UN Millennium Development Goals (www.un.org/millenniumgoals) specifically address health: child health (Goal 4), maternal health (Goal 5), and the prevention and treatment of HIV/AIDS, malaria, and other diseases (Goal 6).

Animal research will play an essential role in efforts to meet these increasing demands for global health care. Yet the animal research community faces the challenge of overcoming negative impressions that industry and academia engage in international collaborations in order to conduct work in parts of the world where animal welfare standards are less stringent. Thus the importance of ensuring the international harmonization of the principles and standards of animal care and use cannot be overstated. A number of national and international groups are actively working toward this goal.

The Role of the Institute for Laboratory Animal Research

The Institute for Laboratory Animal Research (ILAR), a program unit of the US National Research Council, is committed to promoting both the welfare of animals used in research and the quality of the resulting science. To that end, it convenes those involved in such research and related activities—investigators, attending veterinarians and animal care technicians, policymakers and oversight committee members, and educators, from academia, industry, professional societies, and government—to participate in workshops that address both broad and particular challenges in the increasing globalization of animal research.

In 2003 ILAR hosted an international workshop to examine the Development of Science-Based Guidelines for Laboratory Animal Care (NRC 2004). Participants discussed the available knowledge that could positively influence a framework of standards of laboratory animal care and identified gaps in critical information. A common thread in the discussions was the subject of harmonization of animal care standards, specifically its merits and challenges. While scientific evidence was certainly identified as critical to decisions regarding animal care, participants also recognized cultural context as an intrinsic factor in such decisions. Many speakers and participants observed that, despite much progress in the establishment of standards for the objective evaluation of animal care and housing practices, a great deal of work remained to be done.

In 2007 ILAR convened an international meeting of laboratory animal medicine specialists to review the regulatory and guidance documents of several countries; the group analyzed descriptions in these documents of the role of the veterinarian in this type of work and also determined whether training in areas specific to laboratory animal species is required or recommended. This review (Zurlo et al. 2009) revealed both commonalities (e.g., in the provision of clinical care) and significant differences (e.g., in the designation of who at the institution has decision-making authority regarding euthanasia).

In 2008, to follow up on the 2003 event, ILAR convened a workshop to define more precisely the types of information still needed and to identify the data necessary to enable prioritization of research and funding support for related initiatives. This workshop, on Animal Research in a Global Environment: Meeting the Challenges, brought together 200 participants from 17 countries with a diversity of perspectives. The speakers and participants noted that the

landscape of animal-based research had changed in some significant ways since the 2003 workshop. Globalization of biomedical research was well under way. Outsourcing of research, sometimes to countries with widely divergent regulatory systems of oversight, had become an important element of the biomedical research enterprise, and academic collaborations across country borders were commonplace. Yet air transportation of animals was becoming more restricted. And there was increasing public concern about the quality of products and services from certain regions of the world. Calls for improvement in laboratory animal welfare and data quality became more prominent and the need for globally accepted approaches to the responsible and ethical conduct of animal research more pressing.

Organization and Content of the Workshop

Fully cognizant of the demands and cautions related to the globalization of animal research, ILAR appointed a Workshop Steering Committee, composed of US and foreign individuals from academia, industry, and the nonprofit sector, to design the program for the 2008 workshop such that session speakers might identify and promote better understanding of important challenges in the conduct of animal research across country boundaries. These challenges appear in the sourcing of animals; the quality of veterinary care; appropriately qualified and competent staff; the provision of a suitable environment (including nutritious food and potable water) for animals, both during transport and at the institution; ethical review of the proposed work and ongoing oversight of the animal program; suitable facilities and equipment in which to conduct the work; appropriate policies and procedures; and protection of the personnel involved in the animal program.

General topics that framed the first day of discussions were challenges and opportunities for harmonization, with representatives from seven organizations providing a variety of international perspectives; operational challenges of working across differing global standards, with representatives from the pharmaceutical industry, contract research organizations (CROs), and academia describing their experiences; and the training and educational challenges of working across different global standards, with colleagues from various regions of the world illustrating how training programs can overcome those challenges.

On the second day speakers examined in more detail specific issues that require attention. They discussed the varying standards and state of veterinary care for research animals around the world as well as potential steps toward harmonizing veterinary education in laboratory animal medicine and standards for laboratory animal care. Presenters also described international principles and approaches to pain, distress, euthanasia, and humane endpoints.

The third day opened with a session concerning efforts to coordinate international rodent resources, for example by facilitating transportation, enhancing databases, and addressing repository issues. The afternoon presentations

were devoted to nonhuman primate resources, reviewing the scope of the need for primates in research, the concept of an International Primate Plan to investigate and report on supply and demand, the need for harmonized care standards, and transportation concerns.

Impacts of the Workshop

The impact of this 2008 workshop has extended beyond the oral presentations conveyed in these proceedings. It has been a vital bridge for diverse colleagues and organizations around the world to advance initiatives designed to fill gaps in standards, professional qualifications, and coordination of animal use.

The World Organization for Animal Health (the OIE), with the involvement of speakers from the 2008 ILAR workshop, has published standards on the use of animals in research as part of its Terrestrial Animal Code, which includes a specific chapter regarding the care and use of research animals. Thanks to the OIE's status as a reference organization for the World Trade Organization (WTO), the Code serves as a standards template for the 178 member countries and territories of the OIE and thus applies to numerous economies and cultures.

In addition, ILAR, the OIE, and the International Association of Colleges of Laboratory Animal Medicine (IACLAM) convened focus groups to assess the laboratory animal veterinary community's perspective on harmonizing global veterinary qualifications and training in laboratory animal medicine. These groups met in 2010 at three pivotal laboratory animal science meetings held in Europe, the United States, and Asia: the June meeting of the Federation of Laboratory Animal Science Associations (FELASA) in Helsinki; the September meeting of the Association for Laboratory Animal Science (AALAS) in Atlanta; and the November meeting of the Asian Federation of Laboratory Animal Science (AFLAS) Associations in Taipei. More than 100 individuals representing 27 countries participated in the three meetings, the results of which will be published in the online *ILAR Journal*.

Finally, development of an International Primate Plan (IPP) continues to gain momentum. In 2009 ILAR hosted an international meeting in Irvine, California, to determine the outline and approach to the plan. The participants represented key stakeholders such as researchers, veterinarians, and suppliers. Focused meetings were held in association with the 2010 AFLAS congress, and the IPP has been discussed with the National Institutes of Health (NIH), EUPRIM-NET (the European Primate Network), and the Interagency Research Advisory Committee (IRAC) of the US federal government. Substantial progress has been made toward the launch of the plan.

The papers in these proceedings describe important topics facing the biomedical research enterprise. Time has not stood still since the workshop and there has been progress in some areas, yet much work remains to be done—

requiring additional attention and resources—to address many of the issues described in the following papers.

A Note about the Transcripts

The transcripts in these proceedings are those approved by the speakers; presentations shown on the agenda but without a corresponding transcript are those for which the speaker did not provide permission for publication. The transcripts have been only lightly edited, largely for clarity, the addition of sources, and, when appropriate and possible, updating to incorporate the outcome of reports issued or events held since 2008. The report and speakers' slides are posted on the ILAR website.

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Kathryn A. Bayne
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References

AVMA [American Veterinary Medical Association]. 2008. One Health: A New Professional Initiative. Available online (www.avma.org/onehealth/onehealth_final.pdf), accessed on April 14, 2011.

Bhagwati J. 2004. In Defense of Globalization. New York: Oxford University Press.

NRC [National Research Council]. 2004. Development of Science-Based Guidelines for Laboratory Animal Care: Proceedings of the November 2003 International Workshop. Washington: National Academies Press.

OIE [World Organization for Animal Health]. 2010. Use of Animals in Research: Terrestrial Animal Health Code. Available online (www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.7.8.htm), accessed on April 14, 2011.

UN [United Nations]. 2006a. The Millennium Development Goals Report 2006. Available online (http://mdgs.un.org/unsd/mdg/Resources/Static/Products/Progress2006/MDGReport2006.pdf), accessed on April 14, 2011.

UN. 2006b. World Population Prospects: The 2006 Revision. Available online (www.un.org/esa/population/publications/wpp2006/WPP2006_Highlights_rev.pdf), accessed on April 14, 2011.

WHO [World Health Organization]. 2008. The World Health Report 2008: Primary Health Care Now More Than Ever. Available online (www.who.int/whr/2008/whr08_en.pdf), accessed on April 14, 2011.

Zurlo J, Bayne K, MacArthur Clark J. 2009. Adequate veterinary care for animals in research: A comparison of guidelines from around the world. ILAR J 50:85-88.

CONTENTS

ANIMAL RESEARCH IN A GLOBAL ENVIRONMENT

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Proceedings of the November 2008
International Workshop

Plenary Lecture

Science and Technology and US Foreign Policy

Norman Neureiter

It's a tremendous thrill to be at this podium. It was 4½ years ago almost to the day that Secretary of State Colin Powell stood here and talked for an hour and brought this packed auditorium to its collective feet in a standing ovation. He talked about the role of science and technology and its importance in the conduct of US foreign policy. It's really that theme that I want to expand and build on today.

Before I begin, let me just say that I'm reminded of the importance of what you all are doing every morning on my way to work. My office is near Metro Center. As one comes out of the subway, there are two big illuminated advertisements. One of them really stands out. The first time I saw it, I actually stopped and went back to read it. What it says is: "Even if it would find a cure for AIDS, I still would be against the use of laboratory animals in testing." And there is a picture of a colony of rats compared with a sick child in a hospital. Those are two really catchy images.

So let me tell you, you are doing some very important work in a very, very important field. As you know, in the United Kingdom, this issue has resulted in violent demonstrations against animal testing; the British are very concerned about it. And some of that activism is beginning to occur in the United States.

On one of my trips to the UK while I was at the State Department, I was invited to appear before a committee of the House of Lords on the subject of animal testing, which at the time I knew very little about. They took this issue very seriously and wanted to talk about our experience in the US. They were deeply worried that stopping animal testing would greatly interfere with medical research in the UK.

So I'm delighted to see so many international visitors here today, so many foreign guests. Your presence demonstrates that this is a global issue and something that we should all be working on together.

But let me go ahead to my favorite subject: science and foreign policy. In 1998 Secretary of State Madeleine Albright called on the National Academy of

Sciences to do a study on the relationship between science and technology and foreign policy. The result of that 18-month study, which was privately funded by a wonderful man from New York named William Golden, was this little green book, as I call it. For years, while I was at the State Department, people kept saying, "This is like Norman's bible—he carries it around like an itinerant preacher." But if you are interested in the subject of the relationship of science and technology to foreign policy, this is probably one of the best pieces ever written, despite its rather cumbersome title—*The Pervasive Role of Science, Technology, and Health in Foreign Policy: Imperatives for the Department of State*. The key point is that sixteen of the stated goals of US foreign policy—and at least in the Clinton administration those goals were actually written down—involve significant considerations of science, technology, and health. There are many examples in the book, and it goes through and develops them very effectively.

After receiving the report, Secretary Albright set up a study team to examine its recommendations. Eventually, she decided to proceed with specific actions to strengthen the capacity of the State Department to deal with the technical dimensions of foreign policy issues. The report had concluded that the Department was at the time not adequately equipped do so. A key decision was to appoint a science and technology advisor to the secretary of state to drive this process. I was lucky enough to get that job. I always recommend to aspiring young people to be the first one to have a new job, because there is no one to compare you with. If you are first, you set the bar for your successor.

It was a fascinating time. I loved the job. It was a 3-year appointment. I would have happily stayed on, but that was the agreement. I met with someone later from State and I told him what we had done and that I thought we had been successful and mentioned some accomplishments. He said, "No, Norman. The success was that you had a successor," because that experiment could so easily have been a one-off experience in the State Department. Not only did I have a successor, but my successor now has a successor.

Interestingly, I visited the AAAS website last night while I was making a few notes for this talk, and came across an item about Nina Fedoroff, who is the present science and technology advisor—she is actually quite a famous scientist, who recently got the National Medal of Science for her work in plant genomics. There was a summary of a big speech that she had given just two days ago on the role of science and technology in foreign policy, and particularly science diplomacy, to which I will come back later.

Jack Gibbons, a former Science Advisor to President Clinton, once called the State Department the most technophobic culture he had ever experienced. What he was saying is that conveying the importance of these issues to a foreign policy culture and to a Foreign Service culture is not so simple. And my office consisted of only three people. So, one thing I decided early on was that we had to get more scientific smarts into the building—more people with scientific backgrounds.

It turned out that AAAS had a fellowship program for PhD scientists who could be placed in federal agencies for one or two years. At the time I started, there were only five of them in the State Department, even though the program had started a few years before. With some splendid help from State's personnel people, we were able during my tenure to greatly increase the number. In addition, three scientific societies supplied additional fellows. And my immediate successor in the job succeeded in creating the Jefferson Fellows Program, which added each year five to ten tenured professors on leave from their universities. That means that at this time there are 40-45 PhD science-diplomat fellows from multiple scientific disciplines distributed among some 12 different bureaus of the State Department. I believe it is really making a difference. I like to say this program has gone far to raise the overall scientific literacy at State and made people much more aware of the great importance of science and technology in all of our international relationships.

However, we do not now have scientific attachés in embassies overseas as we did 30 or 40 years ago when there were such positions in about 20 embassies. Over time, as the State Department budget decreased, financial and other pressures caused those scientific positions in embassies abroad to disappear. There still are science officers, but for the most part they are Foreign Service officers. They are good people, but they are not scientists, which is a great plus when engaging with the local scientific community. Even if one is a physicist, he or she can talk to a biologist or a chemist, because all have the same kind of experience and confidence in evidence-based science. There is among scientists a kind of common language, which greatly facilitates access to the science community of other countries.

Let me give you an example from my own career. In the late 1960s, in the middle of the Cold War, I was assigned as a scientific attaché to the US embassy in Poland, with responsibility for Czechoslovakia and Hungary as well. The Vietnam War was at its peak. Official relations between the US and Poland were absolutely dreadful. But I had wonderful access to the people in the Polish Academy of Sciences. We had some extra funds at the time that we could use for funding cooperation, which I found is a very effective mechanism for engaging with other countries.

Let me illustrate this with some examples from today. At AAAS we have recently created a Center for Science Diplomacy. The point of the Center is to build relationships in science and technology to use as an active instrument of a constructive foreign policy. You have heard a lot about America's "hard" power in action—not all of it favorable in recent years. This is America's "soft" power in action and something in which I believe very strongly. Science cooperation is an instrument that can be very effective in building constructive relationships with other countries.

This means, however, that science is being supported not based purely on peer review but as an instrument of foreign policy. The big problem is finding funds for this kind of activity. The normal peer review mechanisms based purely on merit are not sufficient. We have to find a mechanism in the US through

which we can fund these international scientific activities for the benefits that come from building relationships with other countries, and not just for the scientific results.

The first science program ever created for political reasons in the United States was in 1961. A professor from Harvard, Edwin Reischauer, wrote an article in *Foreign Affairs* magazine called "The Broken Dialogue." He felt that the university community in Japan was being seduced by the message of the Communist Party and that there was an antagonism to the US and to the US military. He wanted to fix what he called the "broken dialogue" between the intellectual communities of the US and Japan.

President Kennedy appointed him as his ambassador to Japan. Shortly after that, at a White House dinner in honor of visiting Prime Minister Ikeda of Japan, President Kennedy raised his glass in a toast and created a program of cooperation that had three committees: an economic committee at cabinet level; a cultural committee, with some university people; and a joint committee on scientific cooperation—the first time that science cooperation was used by the US to improve relations with another country.

This occurred about the time I decided that I wasn't the greatest researcher in the world. I was working at a refinery in Baytown, Texas (which, by the way, is now the largest refinery in the United States; although it had to shut down as the hurricane blew through a couple of weeks ago). I found a job with the National Science Foundation, where I felt I could combine my strong interest in international issues with the science. I went to NSF just as this program was getting under way, and I became the first permanent director of that US-Japan program. That was my "baptism" into the business of international science. I have never quite recovered from it. I am still hooked.

It was curious, though, that we even had criticism of that program from the president's science advisor, Jerry Wiesner, former president of MIT and a very distinguished scientist in his own right. He said, "Look, you're doing science for political reasons. Maybe it's bad science." My response was "No, it is our responsibility as managers of those programs to make sure that the science is good." But if all of those international programs had to compete with the 15 or 20 percent of R01 proposals that get funded at NIH, or even the 20 percent of proposals that get funded at NSF today, they probably would not succeed, because those funding decisions are made purely on scientific merit *and the benefit to US science*.

However, while the joint program was producing quality science of interest to both countries, we had to be certain that it also had the potential to build relationships that could grow and expand and eventually find their own funding. However, this was not always so easy, given the scientific state of Japan in 1961 compared to the US, which had emerged fully intact from the war. In addition, the scientists in the two countries were not familiar with each other and there were significant language and cultural issues.

We were successful in working through all of those challenges, and remarkably, this Japan program still exists today at the National Science Founda-

tion, although of course it has changed. There is no more dedicated money for it. Scientists in each country find their own funding, but the program really has continued for all these years.

Another activity along these lines is the Pugwash Conferences. These were not started by governments but by the scientists themselves (largely physicists). It was people like Andrei Sakharov, Richard Garwin, Frank Long, Leo Szilárd, Harrison Brown—people who had been involved in the nuclear program and who were concerned about the US and the Soviet Union building enormous nuclear arsenals. Some say the US built 75,000 nuclear weapons during the war, the Russians 50,000. The biggest Russian weapon was 100 megatons—100 million tons of TNT equivalent in the biggest bomb. When they got ready to set it off, they were afraid it might throw the earth off its axis, so they actually dialed it back to 50 megatons. There is an incredible picture of the mushroom cloud from that explosion.

So these physicists instituted the Pugwash Conferences, which were funded by a man who was excoriated in this country, Cyrus Eaton, named "the red billionaire" because he was friends with Khrushchev. He funded these conferences in the little town of Pugwash, Nova Scotia, where he had an estate. The scientists began a dialogue. Of course, there was a natural empathy between physicists who had developed bombs on both sides. They built up an atmosphere of trust with each other. Eventually, in my view, which may differ from the views of others, this atmosphere of trust percolated up to the governments.

I was asked to be the interpreter for one of the visits of a Pugwash delegate, who was like myself an organic chemist, on a visit to the United States. It was fascinating. We went around to many universities, where he gave his lecture in Russian and I translated it into English. After the lecture was over, we went into a back room and met with some of the university professors to talk about limiting and stopping atmospheric testing of nuclear weapons.

These conferences eventually led to signing of the Limited Test Ban Treaty in the Kennedy administration, and this effort eventually grew into more comprehensives treaties for arms control. I personally think these types of dialogues between the scientific communities of the two countries contributed in a major way to avoiding mutual annihilation. (Remember, the strategy at the time was mutual and assured destruction for both sides.)

President Nixon and Henry Kissinger were supportive of the use of science as an instrument of foreign policy. When US presidents traveled around the world, they would typically give a gift, such as money or an aid program. As some of you may remember at the beginning of the 1970s when the oil prices were very high and there was a financial problem in the government, the government began to deliver science cooperation as a gift. The idea was to promote cooperation between the US and other countries.

A big year for this activity was 1972, when President Nixon had the big breakthrough with China. That, of course, resulted in a major geopolitical repositioning of the countries around the world, i.e., between the US and China as well as in their triangular relationship with Russia. This was a breakthrough be-

cause there had essentially been no contact between the US and China since 1949 when Mao took over in China. While some countries had diplomatic relations with China, the US had nothing other than some rare, formal discussions at the US embassy in Warsaw, Poland.

As President Nixon's trip to China was being prepared in complete secrecy in the White House, Mr. Kissinger came to my boss Ed David, the president's science advisor at the White House Office of Science and Technology (OST), where I was the assistant for international affairs. Kissinger indicated that the US would like to present to the Chinese something more than geopolitical repositioning. He wanted to show them that there could also be some concrete, tangible benefit from a new relationship with the US. He wanted us to put together some proposals for science cooperation that would demonstrate to the Chinese what could result if in fact the two countries could come to an agreement. But, of course, he also said this should all be done in complete secrecy.

In a few sleepless days and nights, we worked with people at the Academy as well as in our own organization and put together approximately 40 proposals that were taken to China and were part of the discussions at the diplomatic level. Agreement was reached in the form of the famous Shanghai Communiqué, which resulted in a great change in the foreign policy of the United States.

Until 1979, there was a slow beginning of science cooperation with China managed by the US National Academy of Sciences. However just before formal diplomatic relations were established in 1979 under President Carter, his science advisor Frank Press had taken representatives from some 19 federal technical agencies along with some university people and come back with agreements for cooperation in a wide range of disciplines. Over the next 25 years the resulting programs have collectively grown into the largest bilateral cooperative scientific relationship of the United States with another country. A significant part of it was the fact that between 50,000 and 60,000 Chinese students, graduate students, and researchers came to the US every year and worked in our laboratories. Two-thirds of them studied some aspect of science and technology or science and engineering. At the beginning, about 90 percent of those people stayed in the US—they became college professors, they went into our companies, some of them even started companies themselves. Now, however, a much larger percentage of these scientists, some of whom have been in the US for many years, are returning to China. As we are feeling the squeeze on funding for basic scientific research in this country, the Chinese are experiencing an enormous expansion.

Many people say that was all a mistake; however, I disagree very strongly. I truly believe in it and think it is important—I think we must engage with the world by establishing an atmosphere of transparency. We need to know what's going on in other countries. We need to work with them. In fact, I believe it is useful to think of it in terms of brain circulation rather than brain drain, resulting in a mutual benefit.

So I believe that this program was worthwhile and that it should continue. In my present job at AAAS, I'm concerned with science as applied to security issues.

I will be going to Beijing to meet with people who designed their nuclear weapons and who are still willing to talk to us about their nuclear strategy. One hopes that they tell us the truth. I think the only way we can really make sure that we don't have some collision with China is to have as much transparency as possible. And if you are in Washington very long, you will find that there are people who think that China is the eventual enemy and that we have to be prepared now. But I disagree and think we must invest time, energy, and commitment in maintaining transparency and maintaining relationships to ensure that a major calamity does not occur.

In 1972, Nixon also went to Moscow and had a summit meeting with Brezhnev right after the China visit. That was fascinating, too. It was at the height of the Vietnam War when we had just mined the harbors at Haiphong and the war had just been escalated. It was quite a suspenseful week and the administration did not know whether the Russians would cancel the summit. Fortunately, they didn't.

At that summit meeting, seven scientific agreements were signed, one of which I had worked on in the government for a year. That agreement created the first joint committee on science and technology cooperation with the Russians. There was significant opposition to that agreement, but the opposition to the space cooperation agreement, which was signed at the same time in Moscow, was even greater. The space cooperation agreement called for the famous docking experiment, in which our spaceship and theirs actually docked. Many felt that we were going to give them the secrets of our complex docking processes, with difficult maneuvering and complicated software, among other issues. In spite of these concerns, the experiment took place, and today we actually depend on the Russian Soyuz and the Russian space capsule to get our astronauts up and down to the International Space Station because we have lost a couple of shuttles on the way.

So it is remarkable how these things turn out. However, it was very contentious at the time and it remains contentious. Because of the recent Russian actions in Georgia, there is great hesitancy about continuing to buy these Soyuz modules from the Russians. Yet we will have no launch capability to the Space Station after 2010, when we discontinue the shuttle. This is a huge concern that is currently before the Congress. It is not clear whether they will deal with it before this session ends.

There are some other historical examples, which I won't go through. However, my point is that these issues can be extremely important.

So what are we going to do in our new center for science diplomacy at AAAS? We are going to actively try to solve this funding problem, which I mentioned before. The money cannot be given to a science agency because there it must be expended based purely on peer review. This is a huge problem for NSF; the NIH has a better international profile because disease is everywhere, and if they receive a competitive proposal from India, for example, they can fund it. However, this particular type of NIH grant is not for the purpose of co-

operation, it is purely for doing research on a specific problem. If there is cooperation, that is just a collateral benefit.

Money could be given to the State Department. However, the funding process among committees on the Hill is such that it is very difficult to find one that will give research money to the Department of State. It happened once, when the Berlin Wall came down and the Soviet Union collapsed. In that situation, there was money for recovery in the Eastern European countries and for employing former weapons scientists in the former Soviet Union. The Eastern European programs and the money are gone. Some of the so-called cooperative threat reduction programs that were meant to keep weapons scientists from going elsewhere (i.e., selling themselves and their knowledge to bad countries) and keep them working on peaceful issues in Russia and in other former Soviet Union countries still go on today. But money for those programs is slowly going away, and we need to find other sources for our science diplomacy.

We are now working with some people on Capitol Hill who support this idea. People like Nina Fedoroff are making speeches about this subject. One possibility is that money could go through USAID. There was an attempt back in the Carter administration to do a similar thing. It passed through three of the four legislative hoops in the Congress, but in the end it failed. We consider this our big challenge and are committed to working on it.

What countries are of particular interest to us? Consider North Korea. Actually, after five or six years, the [George W.] Bush administration changed US policy toward North Korea, which had emerged from the Clinton administration on a very constructive and positive trajectory. Under the Bush administration, this completely stopped and we switched to a regime-change program. Nothing happened for six years and the North Koreans built a bomb. Now we've started diplomacy again.

We have been trying to do some science cooperation with North Korea. We have made two proposals to them but they were both turned down. They maintain that they don't want us to visit and talk to their scientists. They only want to know how much money the US has for the program and what equipment we will give them. This premise is not a great basis for cooperation, but that has been their position so far.

Iran has been different. President Ahmadinejad is at the UN today. We must listen and hear what he says. This Academy started a relationship with Iran eight years ago run by a fellow named Glenn Schweitzer, a remarkable person in his own right. Glenn has maintained those contacts and I have been involved with them for the past four years.

This has been a remarkable process. Some of the text that I am paraphrasing today comes from a seminar in November 2007 in Tehran, the title of which was "Science: A Gateway to Understanding." It was proposed by an Iranian professor. The former president, Khatami, a reformist, participated in the meeting, along with a very important mullah. In a follow-up dinner, the vice president for research appointed by Ahmadinejad proposed that we do a joint seminar on the subject of "the misuse of science." That seminar is scheduled to take

place in February 2010 in France. In planning the seminar we asked which subjects are off-limits and were told that no subjects are off-limits, even weapons. We shall see what happens.

It is well understood that this seminar will not be a substitute for negotiations on the nuclear issues. In that area there has to date been no progress. However, our aim is to maintain relationships with a very intelligent and very Western-oriented, but diminishing, science community in that country. They are influential people, and we believe that through those contacts, we may have some mediating impact on the relationships between the US and Iran. We shall see what comes from it.

Then there is the whole area of the Muslim world, which I will not expand on at the moment. However, I really think that such science diplomacy programs can be enormously powerful "soft power" instruments of a constructive foreign policy. I am dedicated to trying to get some significant funds into these kinds of activities before I give it all up and retire for the third and last time.

Introductory Lecture

Building Momentum: Lessons Learned from the 2003 ILAR International Conference

Hilton Klein

As a past chair of the ILAR International Committee, I thank you for the opportunity to speak on today's topic, about building momentum and taking the opportunity to highlight lessons learned since the 2003 ILAR International Workshop on Science-Based Guidelines.

As responsible investigators using animals in research, you all realize the importance of the *Guide for the Care and Use of Laboratory Animals* and what it has done for us in the biomedical research community. It has been a significant document of very high impact since it came out in 1996. I doubt that the people on the committee foresaw that this would be a truly international document, but it has emerged as a global document that is used in many countries. It has been translated into at least 12 languages now and serves as the standard for biomedical research where animals are used in laboratories. So its longevity and its global utility have been very impressive.

I want to try to emphasize how dynamic and flexible a document it has been. If you look at the period from 1996 through 2008, you will see that the *Guide* has been very diverse in its applications. It has been used not only in many countries but also in many different types of research programs. It has been able to cover the complexities of biomedical research laboratories and the use of numerous animal species. It has served its purposes very, very well and been a very significant, dynamic, and diverse document.

It would be useful to review why we had the first workshop and provide a historical perspective. As the previous speaker mentioned, the need for more science behind our standards has been in progression over time, evolving to the point where we are today. In 2000 and 2001 when I was on the ILAR Council, there were preliminary discussions about whether or not there was a need for revising or changing the *Guide* in some fashion and whether doing anything was wise. The drafts of the European standards for animal care from the Council of Europe (COE) expert groups were newly released. A major concern was how

much influence the Council of Europe guidelines, Appendix A of ETS 123, would have on the global research community and how that document would drive the need for revisions to the *Guide*. The ILAR International Committee concluded that this was an important juncture where new COE guidelines and the need to revise the *Guide* now presented an opportunity where we should examine some of these issues.

At the same time, many pharmaceutical companies, some academics, and certainly government agencies were performing research in international laboratories and doing animal research on a global scale. I want to emphasize in a positive way that when we were doing studies in different laboratories in different countries with varying standards, the interpretation and the integrity of those studies came into question. Science appeared to offer the unifying solution.

So these two issues—the European activities and what potentially was occurring in the United States and certainly in the global community—were drivers for examining the need to harmonize some of the standards and guidelines. There was some uncertainty about how to do this. The Council felt that it would be rational to convene a meeting and confer on what seemed to be a common lineage among all parties: science-based standards, which joined animal care and use with the research community. In other words, we were talking about science-based guidelines and a conference to bring together and harmonize directions among the different parties.

We prepared a conference agenda that would explore and benchmark best practices not only on the regulatory side but also on the scientific side, covering the issues that drove a common understanding and some common guidelines for animal care and use. The conference was convened with a group of people from at least 13 different countries; they were scientific experts, veterinary medical experts, and people from the political administrations. The proceedings of the meeting, *The Development of Science-Based Guidelines for Laboratory Animal Care and Use*, was the final product published in 2003; it presents many of the scientific and regulatory issues discussed during the conference.

The goal of the workshop was to look specifically at the conditions of laboratory animal care and the science behind it, and more importantly to look at the gaps in our understanding based on what appears in the scientific literature and encourage future research to close those gaps, so that we would have a good science-based understanding of what we were doing for the animals while also trying to help the research community conduct its research in a thoughtful and meaningful way. I will address some of the outcomes of the conference.

After several days of discussion we were able to come to some concrete conclusions. One was that more scientific studies were needed to foster a better understanding of the best conditions for animals in the laboratory and to make sure that the research was conducted in the best possible manner. There were major gaps in our knowledge and the science behind animal care. We also came to a clear understanding—especially with representation from 13 different countries—that this was not only an American problem but an international problem.

There was variation in the interpretation, but this was a clear-cut conclusion. [It was also clear] that these gaps covered all species and all laboratories.

Another realization that emerged from the meeting was that harmonization and working together were the best ways to share information, resources, and knowledge in order to elevate and unify and achieve cohesion for animal care and use programs on a global basis. It was also evident that harmonization needed to be better defined, because there was a great deal of discussion on what harmonization was and what it meant, and more importantly how to accomplish it. Moreover, based on many of the sidebar discussions, it was obvious that a lot more discussion and benchmarking were needed to define the problem. We had over 120 people at the conference and about 150 different opinions on how to do it. It was clear that we needed to address this with all the interested parties.

The next step, to maintain momentum, was to have a focus group and seek the opinions of an international group in a more global setting. [This group met] in Berlin in 2005, as a satellite meeting to the 5th World Congress on Alternatives and Animals in the Life Sciences. Our first task was to look at the 2003 recommendations and outcomes and ensure that they were still valid, to seek suggestions for future research initiatives, [to consider] where we might do such research, and to identify potential funding sources to try to close gaps in our scientific knowledge. Last, the group aimed to set priorities for the research topics to be studied.

One of the outcomes of the Berlin workshop was that we had more harmony and certainly agreement that more scientific studies were needed and that we needed to make sure they addressed key species (I will return to that in a moment). For example, the topics included cage size and determining how important that is and what, if any, scientific evidence existed that could be used as a driver for determining optimal cage sizes. Environmental enrichment was also identified as a very significant issue requiring more study. Particulars of housing conditions in the laboratory emerged as key points of study—e.g., lighting, temperature, humidity, number of air changes, sanitation, and the like. These were the topics identified as very important by the participants in the Berlin conference.

The priority topics were pain, enrichment, housing, and experimental procedures. There also was recognition that training people to do the work, the design and construction of facilities, and facilities operations were critical topics. The group also posed the question of how to condition and acclimate the animals to get them "research-ready." These topics all became the top priorities for the next series of workshops and discussions for the future.

In 2006 the ILAR International Committee concluded that there should be another focus group to initiate discussion of the housing of animals in research laboratories and to look at scientific evidence in support of housing requirements. A decision was made to focus only on the major species that constituted about 90% of the animals used in the laboratories and to examine this information on an international basis. Thus the decision was to focus on monkeys, dogs, and rodents. At this meeting, held in conjunction with the AALAS meeting in

Salt Lake City, there was representation from different countries, including emerging-market countries like China and India. Many professional organizations were also represented on an international basis.

For nonhuman primates, the first point was that cage sizes vary and are important to consider from the perspective of what is needed for the well-being of the monkeys as well as for optimizing scientific outcomes. Almost everyone in that focus group supported group housing. They also recognized the need for environmental enrichment of these animals in a research setting and outlined evidence to support this need. However, while everyone agreed on the importance of environmental enrichment, it was difficult for the group to reach consensus on exactly how that was defined. Even so, they all recognized that it had or could have a significant impact on experiments and could create scientific variability if it wasn't done correctly.

With regard to dogs, the group concluded that cage size guidelines varied greatly and needed focus. Most supported group housing. Environmental enrichment was thoroughly discussed, but there was not consensus about exactly how to do it. There was no clear-cut consensus on the value of exercise for dogs, but there was in-depth discussion and very vigorous and healthy debate.

The same could be said for the discussions of rodents. It was clear that rodent housing varied greatly. Most favored group housing. It was felt that there was a need for more conclusive data and more scientific evidence, especially for the selection of the best bedding types, and whether or not there were benefits or risks associated with wire flooring. As with dogs and monkeys, the group recognized that experimental variations could arise from the wrong type of enrichment.

Other presentations from the international side involved the following individuals: Gilles Demers reviewed harmonization from the ICLAS perspective, David Anderson presented updates of Council of Europe initiatives and revisions, Margaret Rose presented Australian initiatives and how this system worked, and Judy MacArthur Clark gave perspectives on the impact of the Council of Europe and the EU regulations on the international community.

Since then, in 2006 and 2007, the private sector has been working on globalization issues, evaluating the need for science-based guidelines for animal care and use. CHA (Cambridge Health Associates), a commercial organization in Boston, MA, funded fact-finding trips and the preparation of two detailed reports examining future trends in animal research in China and in India. These reports are available from CHA (www.chacorporate.com). Of the two, I believe the second, a very objective and fact-driven report, was an important milestone; it predicted very accurately more studies and research spending in those countries. The data from the emerging-market countries must be as robust and have the same fidelity as what we now enjoy in order to make important decisions on medicines and vaccines from the private sector. In other words, their drug-discovery and drug-development data must have the same level of integrity and be well documented and proven through audit and regulatory agencies, especially since the private sector is highly regulated.

Movement of research activities to emerging-market countries places a clear emphasis on needs in the following areas:

- more training and expertise;
- high-quality animal facilities (the need for a well-controlled animal environment became very important as a result of the findings in this report); and
- consistent, high-quality animal diets, animal quality, colony health, and fundamentals such as high-quality water for use in animal studies.

Some laboratories were described in the report as superb, but there were also laboratories that required improvement in the above areas. It was also clear from the report findings that there is a growing number of laboratories that could meet GLP and AAALAC standards for conducting animal studies. That is cause for optimism.

Among other findings were [a projected] expansion in the number of laboratories doing animal research in these countries. Trend data indicate this is accurate. In several cases pharmaceutical companies are now building animal facilities to conduct research in the countries reviewed in this report.

Also underscored was the fact that several academic institutions either had or were developing cooperative agreements to conduct research in countries such as China, Indonesia, and India.

Thus this is a very rapidly changing landscape and a trend for the future. The question is, How fast will the move be realized?

Turning to other views in the context of global animal research and future trends: The NCRR Strategic Plan emphasizes these issues and the need for increased capacity in basic research, translational animal research, and clinical research. There will be an emphasis on minority institutions. The need for increased capacity is clearly stated in the NIH NCRR report (available at www.ncrr.nih.gov).

It emphasizes also that there is a need for improving comparative medicine expertise as part of this infrastructure. It supports the development of more resources to safeguard animal health and welfare, emphasizing the need for better training of people and staff in these institutions, as well as supporting and sustaining the nonhuman primate centers. All are consistent themes globally.

The report did make another important point: "This plan transcends geographic boundaries and research disciplines." That was very significant in the context of this conference. It demonstrates that the private and the public sectors are well aligned in strategy.

The other point of the strategic plan was emphasis on the use of informatics and the sharing of information. This appears to be a wonderful opportunity for more training enabled by information and technology transfer.

A final critical point is that this strategic plan emphasizes a need to maximize partnerships and to get the most out of research investments by creating partnerships between the public and private sectors. Since so much of the private

sector is now looking toward internationalizing its animal research, I am hopeful that this partnering will either directly or indirectly benefit from NIH and NCRR spending.

We have described the historical perspectives and the drivers for science-based guidelines, the trends, and momentum gained so far. But I hope that, as we go through the conference today, it becomes even clearer that ILAR and the National Academies are uniquely positioned to help enable the development of a global infrastructure for animal-based research that is of the highest scientific quality and in which we use science-based guidelines. Science is the common language and currency that transcends country borders. Using high-quality science we can work more cooperatively and achieve better global standards of care.

We must ensure that ILAR is viewed as a facilitator, in cooperation, certainly, with other international organizations, such as AAALAC, IACLAM, ICLAS, FELASA, ACLAM, and ECLAM. In fact ILAR is well aligned and harmonized with these and other international organizations. Through such partnering based on science-based guidelines, we can amplify our research budgets and be more effective in the way we spend those monies to get more out of the data from studies using animals.

In summary, among the many lessons learned since we started the dialogue on science-based guidelines—on how to share the best regulatory practices and create the best guidelines and oversee the animal facility and the scientific research—is that the biomedical research community can work together very well and that we all seek the common goal of improving animal care and use and welfare in the scientific laboratory. That may have been obvious to a few, but I think it is becoming increasingly obvious to many.

The other lessons: There still remains considerable debate on how to accomplish this. We have close agreement on what we want to accomplish, because of conferences like this one; however, we must illuminate how to more effectively use the existing scientific literature and identify scientific research we should develop and fund for the future to help guide improvements in animal welfare and fill the scientific gaps in our knowledge.

Clearly, there is a need to conduct more research on specific areas of animal care and use. There is also some urgency and important critical timing in the issues to be discussed. We are challenged to look forward to a more unified and cohesive harmonized set of animal care and use guidelines globally as a matter of routine. We are not there yet.

[But] the opportunities, I think, are now clearer. We are a global economy. As countries like China, Indonesia, India, Korea, and Singapore further develop their biomedical research systems to meet medical needs—at about a 10–15% annual growth rate—the increase in biomedical research will also drive the increase in the use of animals in research. We must provide optimal care. Pharmaceutical companies, academia, and the government are increasing the use of animal resource systems in these countries. The infrastructure across all coun-

tries should be brought to higher standards as illustrated by the CHA report from 2007.

Infrastructure needs, which are essential and in need of better scientific drivers and information behind them, as we know from the *Guide*, are: sanitation systems, animal health and quality, animal facilities, feed, bedding, water, and, most importantly, training of both technical and scientific/veterinary medical personnel for optimal animal care and use.

I urge you over the next several days of the meeting to give thought to solutions to these questions and problems. The NCRR Strategic Plan has established a framework for partnering between the public and private sectors to share resources and information globally. Their plan gets at the *how* part of the question we raised. There is the question of *where and what* we should do to improve our scientific knowledge of laboratory animal science and animal welfare, and science and medical research, using what we have in the current literature and doing critical literature reviews and applying them to setting scientifically based standards, and seeking ways to fund new research to benefit the animals in the way we conduct science.

In closing, I thank the ILAR International Committee for creating this initiative for science-based animal care standards, and Dr. Joanne Zurlo and her staff for making this possible. I also thank the [Workshop Steering] Committee for asking me to speak today.

Challenges and Opportunities for Harmonization

PERSPECTIVES FROM INTERNATIONAL ORGANIZATIONS

International Council for Laboratory Animal Science (ICLAS)

Cecilia Carbone

ICLAS is an international nongovernmental and nonprofit scientific organization that exists mainly to provide good principles to achieve good science and to promote high standards in the care of animals used in research, testing, diagnosis, and education. According to its mission, ICLAS strives to serve as a premier source of laboratory animal science guidelines and standards and as a laboratory animal welfare information center.

ICLAS has a strategic plan according to which it promotes worldwide harmonization in the care and use of laboratory animals. ICLAS recognized five or six years ago that the harmonization of existing guidelines for the use of animals in research, testing, teaching, and education is an emerging issue in the context of the regularization of research. Since ICLAS can act as an international umbrella organization, it has worked in these matters since 2004, when it began organizing meetings on harmonization of guidelines. We are going to have the next meeting in conjunction with the American Association for Laboratory Animal Science (AALAS) meeting in November.

The main goal that ICLAS hopes to achieve with this program is the implementation of a dialogue on harmonization of a number of published guidelines on emerging issues, with consensus and recognition of these documents at the international level. ICLAS hopes that the largest impact of this project will occur in developing countries or regions that do not currently have laws or self-regulation and surveillance for the use of animals in research.

It is hoped that this project will (1) ensure the implementation of good animal practices in all parts of the world and stimulate collaboration in animal-based research—for instance, in data sharing and information exchange among investigators; (2) facilitate collaboration among scientists in implementing the 3Rs (reduction, replacement, and refinement in the use of animals); and (3) help

facilitate the movement of scientists around the world—for instance, to participate in meetings or collaborate in multidisciplinary and international working groups.

I want to clarify that for ICLAS, harmonization of guidelines does not mean standardization. This is an important point of this program. ICLAS supports harmonization of animal care and use policies, guidelines, and other forms of regulations on a worldwide basis as a reflection of the globalization of research. It does not mean standardization. ICLAS considers that each country should be able to maintain an animal welfare oversight system that reflects its own culture, tradition, religion, laws, and regulations. One of the big challenges that will face this program is whether the various countries and regions will incorporate this kind of document into their regulations while maintaining respect for their own laws, culture, and religion.

Let me conclude this presentation by saying that the objective in which the ICLAS harmonization program would like to succeed is the international harmonization of existing guidelines for the use of animals in research, teaching, and testing. This will be essential in the globalization of research all over the world. In addition, communication and partnership among national, regional, and international organizations will ensure the global harmonization of the use of animals.

It must be understood that national guidelines will always supersede international guidelines. However, it is also important that each country recognize and implement international core principles for the care and use of laboratory animals.

World Organization for Animal Health (OIE)

David Bayvel

My objective in the short time available is to raise the profile of the OIE, for those people not too familiar with the organization, and to give some indication of the role that the OIE might play in this public policy area in the years ahead.

OIE, Office International des Epizooties, has rebranded itself as the World Organization for Animal Health, the animal or veterinary equivalent of the World Health Organization. It is headed in Paris by Director General Dr. Bernard Vallat. A number of you might be aware that he was the recipient of the inaugural Penn Vet Award in 2007 as the veterinarian who had made the most significant contribution globally to veterinary science.

Here is some background to the OIE: It was established in 1924 to deal with international issues relating to epidemic disease—rinderpest, bovine pleuropneumonia, and others. In the 80-plus years since, it has established itself as an intergovernmental organization playing a vital international harmonization role and with a commitment to science-based standards.

In 1995, with the establishment of the World Trade Organization (WTO), the profile of the OIE increased dramatically. It is the body that the WTO looks to for any disputes relating to SPS (sanitary or phytosanitary) agreements.

In addition to a central bureau in Paris, with approximately 40 members of staff, which is truly international in its makeup, the organization has a regional infrastructure, with something like 20 offices distributed throughout the OIE's five regions around the world.

Moving a little bit closer to the relationship in the laboratory animal science area, for the last two or three years the OIE has been working closely with the International Council for Laboratory Animal Science (ICLAS) and the International Association of Colleges of Laboratory Animal Medicine (IACLAM) in terms of a potential role that it could play globally in relation to laboratory animal science and welfare.

There has been quite a bit of discussion: Where could the OIE add value? What unique role could the OIE play, rather than just duplicating the myriad of current activity?

There is an organization called VICH—whose full title is International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products—that was established 10 years ago with a specific mission to harmonize the regulatory requirements for veterinary biologicals and veterinary pharmaceuticals around the world. VICH was formed under the auspices of the OIE with a mandate to harmonize standards. That obviously relates to the current regulatory requirements in most countries for animal tests, many of which go back 60 or 70 years and, in some cases, have questionable scientific relevance. But conservative regulators are somewhat reluctant to move from tests that they know to, perhaps, scientifically validated tests that haven't yet become mainstream. So it seemed that the OIE could play a significant role in this area, as it is 172 members strong and represents governments, thus OIE delegates have a clear mandate to implement any OIE agreements.

For those of you who are familiar with this area, there is a comparable organization, the International Council on Harmonization (ICH), which takes care of biologicals and pharmaceuticals in the human area—obviously, a lot of animal testing is equally involved in that area.

I would like to highlight three further points to give you some flavor of OIE interests, emphasis, and potential future involvement.

The OIE works by having a permanent Animal Welfare Working Group, which I have chaired since 2002. It establishes ad hoc groups to address specific issues. The ad hoc Group on Laboratory Animal Welfare met for the first time in Paris last December; a number of people in this room are members of that group. Again, it is truly international in its membership. It has commenced drafting some material that eventually will be approved and issued and promulgated as OIE guidelines.

Since the OIE is a veterinary body, there will be a strong veterinary emphasis in terms of veterinary training, reflecting some of the input received from groups like ICLAS and IACLAM. Laboratory animal transport is an area where again the OIE could probably add value. As I have mentioned already, facilitating a more rapid acceptance of scientifically validated nonanimal tests, where that is possible, will probably be an area of future unique emphasis of the OIE.

Adequate Veterinary Care and the International Association of Colleges of Laboratory Animal Medicine (IACLAM)

Judy MacArthur Clark

I am going to present the challenge of providing adequate veterinary care to laboratory animals from the perspective of the International Association of Colleges of Laboratory Animal Medicine (IACLAM).

IACLAM was established in 2005 and comprises the four key global colleges of laboratory animal medicine: the American college (ACLAM), which is the oldest; the Japanese (JCLAM) and the European (ECLAM) colleges, both of which were established within the last 12 years; and the Korean College of Laboratory Animal Medicine (KCLAM), which is our newest member college.

Full membership in IACLAM is restricted to established colleges with bylaws and a constitution, an elected council, approved training programs, credentialing processes for candidates, and a number of other elements that make up a competent and fully fledged college. We also are considering a class of membership, probably called associate membership, for emerging colleges. This latter point touches on some of our concerns for the future in terms of training and provision of competent veterinarians in this field.

It is worth remembering that laboratory animal medicine has been an international field for many years. IACLAM has essentially formalized relationships that have existed for a long time in one way or another.

IACLAM's charter is to provide a common platform at a global level for communication by, for, and with representation of diplomates. Thus it is primarily a communication and representative role. That is manifested in the way in which we promote the welfare and responsible use of laboratory animals through the certification of veterinary specialists in the colleges—that's diplomacy of colleges—education of veterinarians, dissemination of information relevant to the field, and serving as research partners. Those are the four elements of IACLAM's purpose, its charter and mission.

Having given you an introduction to IACLAM, I would like to focus on the major challenge for veterinarians in our field. In the time available, it is important we really get an understanding of that challenge.

The first point is that we believe veterinarians are key to effective control of laboratory animal well-being. That is not to say that it is entirely managed by veterinarians, but the competence of veterinarians in this whole scenario of ensuring laboratory animal well-being is essential. Elements of that control include disease control, refinement of procedures, training of staff, creating a culture of care—all important responsibilities of laboratory animal veterinarians, who have a very significant role to play.

But the effectiveness of that role depends on both the competence and the status of the veterinarians who are operating in the field. Competence derives not only from specialist training but also from the quality of basic veterinary training. Status derives from demonstrating such competence as well as the respect in which the profession is held. I refer here to the respect for veterinary professionalism, and therefore the respect that would be accorded to the views of a competent veterinarian in a research organization.

Underlying all of this, and one of the key issues for veterinarians and scientists, is understanding that promoting good welfare is an important part of delivering good science. Therefore good welfare leads to good science. We have all been through the debates about the interrelationship between science and welfare. Should we apply good standards of welfare for their own sake? Of course, there is an ethical impetus for that. But the argument that most effectively carries weight with our research colleagues is that good welfare improves the quality of their science.

But let's return to the subject of veterinary competence and the status of veterinarians, both of which vary significantly across the world. This is a major challenge for veterinarians, we believe. It has a direct impact on the effectiveness of any regulatory system that involves veterinary input. It is something that urgently needs to be addressed.

We support the development of global standards for adequate veterinary care, harmonization of welfare standards, and so on. But without veterinary training—at both a basic and a specialist level—to meet those standards, benefits will not be realized. Therein lie both a threat and an opportunity. We know that in some countries the veterinary qualification follows a two-year technical training, as opposed to a much longer-term, more complete professional education in other countries. Until we can start to raise the standards of that basic veterinary education and then grasp those well-educated veterinarians and add the specific specialist training that can develop their competency as laboratory animal veterinarians, there will continue to be challenges.

The threat, therefore, is continuation of the status quo. The opportunity is to have an impact on that, which requires a twofold approach.

First, we have to improve basic veterinary training globally. It has to become a professional education rather than a technical training, right across the world in order for this impact to be effective.

Second, we need to develop new colleges for specialist veterinary training in laboratory animal medicine. This is not to say that all veterinarians working in laboratory animal medicine will need to be diplomates of colleges. But colleges will raise standards globally and they will encourage the improvement in competence of all veterinarians in this field—for example, in Asia, where there are already discussions for further colleges of laboratory animal medicine, or in South America, where, again, discussions for colleges are under way. We also need to see ECLAM, the European college, having a greater impact in Eastern Europe. Thus we will embrace essentially all of the countries where we currently see emerging science taking place.

So that's the challenge that IACLAM currently sees and that this conference, I hope, will be able to help us to take forward.

Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International

Kathryn Bayne

The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, like every organization, has challenges and opportunities facing it. One that we are acutely aware of is the necessity to ensure both consistency and flexibility—which one might think are diametrically opposed concepts—in the AAALAC International assessments and in the application of our standards globally. It is a delicate balancing act. The AAALAC Council on Accreditation and ad hoc consultants who conduct site visits must ensure that the institutions they assess adhere to a high-quality standard of animal care and use that is applied consistently worldwide. Because we use the NRC *Guide for the Care and Use of Laboratory Animals* (the *Guide*) in our assessments[1] we strive to ensure that it is applied in a meaningful manner by the institution, with the understanding that each institution is unique, and thus professional judgment is necessary in the application of performance standards per *Guide* recommendations. Other challenges we face are differences in culture, regulatory framework, and available resources where we travel.

I want to take a moment to reflect on two surveys that AAALAC[2] has conducted of its accredited institutions, what we call "accredited units." The first customer satisfaction survey was conducted in 1998 and was the first survey of the accredited units that AAALAC had conducted in its history. There were 600 responses, a 71.5% response rate. Two key areas were identified in those responses: the need for flexibility in applying the standards to unique or cutting-edge programs, and the need for consistency in the way the standards are applied

[1]In February 2011 AAALAC announced that in the fall of 2011 it would begin using, in addition to the NRC *Guide*, the following two documents in its evaluations: the Guide for the Care and Use of Agricultural Animals in Research and Teaching (*Ag Guide*), FASS 2010; and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Council of Europe (ETS 123); accessed March 8, 2011.

[2]AAALAC refers to AAALAC International.

from site to site—in other words, from institution to institution, no matter what country—and for individual programs from site visit to site visit (AAALAC conducts site visits every three years). In that 1998 survey, concern was expressed that there may be relaxation of the standards and the goal to harmonize the many and varied regulatory standards across countries. Written comments expressed this concern, but it was in the context that respondents saw value and benefits in an international accrediting body.

Eight years later, in 2006, AAALAC conducted a follow-on survey to see how our many initiatives developed and implemented in response to the 1998 survey were going and how our internationally accredited institutions felt about those initiatives. There was more than a 75% response rate of our accredited institutions. About two-thirds of the respondents agreed or strongly agreed that AAALAC is flexible in applying its standards to meet the specific context of the institution and that it consistently applies relevant standards from site visit to site visit. About half agreed that AAALAC consistently applies relevant standards from institution to institution, the concern expressed being more how AAALAC conducts assessments across borders of countries rather than within a single country.

Of note, however, is that approximately a third of the respondents think that AAALAC is not flexible enough, perhaps a third think that AAALAC is not consistent enough, and perhaps 50% of respondents have both of these concerns. This feedback creates an opportunity for AAALAC, specifically in the area of applying performance standards. With at least half of the new applications for accreditation coming from the international community, AAALAC has the opportunity to do great things to advance both science and animal welfare through the use of performance standards.

Performance standards are the path to harmonizing laboratory animal care and use, through the support and visionary directives of our board of trustees, to reflect both science- and medicine-based organizations; our ad hoc consultants, who are over 200 in number and represent about 13 countries; and the 49 members of our Council on Accreditation from 10 different countries. So, AAALAC has a tremendous amount of input from different perspectives as we strive to harmonize our approach for accreditation on a truly global basis.

International Air Transport Association (IATA)

Carl Kole

Much like the first speaker today, I don't have a lot of connection with this part of your industry, other than getting your animals from point A to B. The International Air Transport Association is the trade group for over 200 airlines.

I would like to address some issues confronting the animal research community—for example, high fuel costs, over which we have absolutely no control except through hedging; Transportation Act access; and a few other issues. It's interesting to note that we are talking about globalization and how things shrink. The aviation business has had a lot to do with that. However, we are seeing less and less animal transport. There are a couple of reasons for that.

When one looks at the data for the top 15 airlines from 2007, based on revenue (passenger kilometers), it is clear that cargo plays a very small role in the transportation system. The traveling passenger to some extent subsidizes the cargo business for the airlines. Recognizing that the part of the cargo that reflects transportation of laboratory animals probably is .0001 percent it is clear that this does not represent high revenue for the airline business, and it is terribly intensive in terms of handling if it is done right. Consequently, the airlines are not in the business of shipping a lot of animals. This is further compounded by the fact that when we mishandle animals, we have a regulatory system that fines us. So therefore it becomes a situation of spending $5 to make $1.

The greatest fear is that eventually there will be no opportunity, at least internationally, to transport animals for biomedical research. These are a few of the limitations that shippers are faced with today: shippers' expectations and carriers' limitations are not always conveyed or understood by each party; aircraft systems, ground facilities, weather, traffic, equipment, and staffing affect the carrier's ability to provide an adequate shipping environment; strict adherence to a narrow temperature range is not possible without adequate active or passive packaging systems; and, with increasing fuel costs, shipping animals is not a major revenue stream.

So what is needed in the future? Given the current situation, the research community should start talking with the carriers about standard operating plans to ensure the proper handling of animal cargo and ultimately to create an ongo-

ing dialogue with the aviation industry that currently does not exist. Most of those who have been involved in that part of the business have retired and there is no one to take their places.

While this is not good news, it is a realistic view of what is happening in the transportation industry today.

Institute for Laboratory Animal Research (ILAR)

Joanne Zurlo

The Institute for Laboratory Animal Research and the National Academies have a role to play in international harmonization. The National Academies are nongovernmental organizations consisting of the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council. The first three organizations are composed of members elected for their scientific and technological expertise and renown, and the National Research Council is the part of the Academies that produces expert reports on topics that the government requests. Dr. Neureiter talked about some Academy studies that have influenced international policy. The purposes of the Academies are to advance science and technology and to advise the government and the nation on policy for science and on applications of science to policy.

ILAR, a component of the National Research Council, was established in 1952 to develop and disseminate information and guidelines for the care and use of laboratory animals. Our mission is to:

- evaluate and disseminate information on issues related to the scientific, technological, and ethical use of animals; and
- promote high-quality science through the humane care and use of animals and the implementation of alternatives.

The 3Rs—reduction, refinement, and replacement—are the principles that guide our work. ILAR meets its mission through the development of expert reports, through the *ILAR Journal*, through our Web-based resources, and other means of communication. The key issue in the mission statement is that we provide advice to the international biomedical research community.

The *Guide for the Care and Use of Laboratory Animals* (the *Guide*) is our seminal publication, used as a standard of compliance with US Public Health Service policy and for AAALAC accreditation. The *Guide* has been translated into 12 languages as an international resource and thus gives ILAR an international profile.

As was mentioned earlier, ILAR planned the workshop in 2003 to look at the state of the science and to identify data gaps and look at the question of harmonization. ILAR was in a unique position to hold that meeting because of our position in the National Academies. This was the first meeting of its kind and it initiated many of the harmonization efforts that you have heard about.

Some of these issues have already been mentioned by other speakers—for example, the fact that we have to consider globalization, the fact that we have to generate more reliable and reproducible data among laboratories around the world, and the importance of aiding developing countries in drafting guidelines.

The science that supports guidelines for animal care and use is inadequate. Until there is solid scientific evidence to support guidelines, it will be difficult to harmonize internationally. But in the interim, where there is no reliable scientific evidence, animal care and use should be guided by best practice. However, there should be mechanisms to coordinate and share new scientific information.

ILAR can offer the credibility, objectivity, and scientific reputation of the National Academies. ILAR has convened and will continue to convene meetings that offer a platform where representatives of international constituencies can gather and express their views. It can coordinate efforts to identify areas of research needed to produce the best scientifically based guidelines for laboratory animal care and use.

The European Union

Malachy Hargadon

Good morning, ladies and gentlemen. For 20 years the European Union has had legislation in place governing the protection of animals used for experimental and other scientific purposes. For those of you who are not familiar with the way the European Union works, all legislation is subject to regular review by the European Commission. I would have liked this morning to be able to present to you the Commission's official proposal to update the legislation, but all I can say is that it is imminent. I will instead provide some indication of what can be expected.[1]

As everyone knows, the world has changed since 1986. Advances in techniques and knowledge have left the EU legislation outdated because it is somewhat removed from best practice. There has been some difficulty in implementation in the EU member states, as some have pursued significantly more stringent standards than others, and this has led to fragmentation of our internal market in the industry, has compromised harmonization across the European Union, and has also undermined compliance and respect for the law.

At the same time, European public opinion—and not just from so-called animal rights activists—has moved strongly in support of ever-increasing standards of welfare for animals used for scientific purposes. In a sense, what the EU is now trying to do is to play catch-up with the 3Rs principles, which you will all know far better than I. Emblematic of this was the decision by the heads of state and government of the European Union to adopt a protocol to the EU Treaty—an action that might, I dare say, be comparable to modifying the Constitution of the United States, so it is not an insignificant event—requiring that the EU and all its member states pay full regard to the welfare requirements of animals, particularly in relation to EU policy on the internal market and on research.

In line, therefore, with the 3Rs principles, our starting point is an ultimate goal of replacing the use of animals for scientific purposes. I trust that this goal

[1]The EU Action Plan on Animal Welfare 2006–2010 is available on the Internet (http://europa.eu).

will not come as a shock. It is a reasonable goal for an advanced and civilized society. If we can achieve our scientific objectives by means other than animal research and experiment, then that is a good thing.

But we are not there yet. The European Commission fully recognizes this and accepts the conclusions of reports that state that a complete phaseout of animal experimentation is not yet achievable. But that is not a reason to ignore the replacement, reduction, and refinement of animal use.

We intend to present a proposal that offers significant improvement in animal welfare, such as more generous and binding minimum standards in housing and care requirements. We are considering extending the coverage of the legislation to some invertebrates as well as embryonic forms of vertebrates and animals killed for tissue and organ use in experiments. We also intend to restrict as far as possible the use of nonhuman primates and animals caught in the wild.

At the same time, our intention is to strike a balance with the genuine needs of the research community and industry and to ensure a level playing field for all concerned. It is hoped that the legislation will reduce unnecessary and, of course, unpopular bureaucratic burden and boost innovation and development in alternative methods.

Such support for innovation will be a boost for competitiveness, and we expect that one of the consequences will be better-quality science. We hope to reduce the burden, for example, by allowing group authorization of regulatory testing projects to reduce time and administration, and by setting a deadline of 30 days, as a general rule, for competent authorities to provide authorization decisions. The current worst-case scenario in the European Union can lead to delays of up to a year in response to requests.

As an example of flexible implementation in the way we move ahead, let me offer the following. While ethical evaluation and authorization would be compulsory, member states would be free to decide the most appropriate competent authority to carry out this task. That accommodates the existing structures in member states—some of which are more centralized (e.g., France), some of which are more decentralized (e.g., Germany)—to do that.

[These are] brief indications, given the time allowed, of what you and I can expect to see in the proposal, which I would expect to be adopted by the Commission. After that, the European Parliament and the Council of Ministers will examine the proposal. I would guess formal entry into effect will be in about 2010.[2]

For my closing comments, let me emphasize that the EU is pursuing harmonization in this area. We have supported efforts in the Council of Europe (which is not to be confused with the European Union) to encourage greater

[2]In September 2010 the EU adopted Directive 2010/63/EU to update the 1986 Directive 86/609/EEC on the protection of animals used for scientific purposes. The aim of the new Directive is to strengthen legislation and improve the welfare of animals still needed for research as well as to firmly anchor in EU legislation the principle of the Three Rs—to reduce, refine, and replace the use of animals in research.

harmonization among a record number of countries. The Commission's proposal itself is a demonstration of harmonization among 27 member states, but with the crucial element of legal requirement rather than simply an exhortation to be better.

The Commission seeks to advance further harmonization—of course, based on the standards that we support—in the wider international community, and especially through the OIE.

Let me conclude by saying that there should be no real surprises in the forthcoming proposal. Similar animal welfare measures are already in place in a number of countries, including the United States and Canada and Australia, whether in legislation or as established operating practices required by funding bodies. Other countries are also increasingly responding to public opinion in pursuit of animal welfare. The Commission's proposal, therefore, will substantially be about, as I said earlier, adopting best practice, but giving it the force of law.

GLOBAL ISSUES: WORKING ACROSS DIFFERENT STANDARDS

Operational Challenges—Pharmaceutical Industry

Margaret Landi

My presentation is about possible solutions to different operational challenges that might exist in pharmaceutical industries, especially those that tend to work around the globe. I will cover four major topics: the challenges, the criticisms, the charge, the consensus.

The best way to start this topic is to make sure we are all working from the same dictionary, using the same definitions. As an example, the word "standard" is often used interchangeably with words like "principle" or "goal" or "objective." A standard is something formally established as one moves forward in discussions on whatever aspect we are talking about; in this case we are talking about animal care and welfare in the pharmaceutical industry.

Sometimes we use the word "principles." A principle is really a code of conduct. According to what principles are we going to perform studies in animals in multinational pharmaceutical companies?

The last word we often hear is "guidance." Whether it's the *Guide for the Care and Use of Laboratory Animals*, guidance, as you might suspect, deals with influencing, trying to influence a certain way, trying to achieve a particular outcome.

I will give you a perspective from my responsibility at GlaxoSmithKline (GSK), which spreads between the US and the UK and continental Europe. I also have fairly strong ties with our new R&D center in China, which, in turn, has ties with a site in Singapore where we are doing some animal research. We run the gamut from transgenic mice and transgenic rats to large nonhuman primates, macaque species.

What are the challenges when we address global guidance, how will we move forward? As you have probably heard or surmised already:

- There is a lack of consensus on what *best practice* is across various cultures.
- The regulations differ across countries.
- The regulations change.
- There are differences in cultural thinking.

For the last point, I would like to describe the main influences that drive differences in European versus American culture when it comes to animal research. In Europe, as opposed to the US, many things are uniform, because things are the equivalent of federally driven, whether it's a speed limit that goes across the country, whether it's VAT or sales tax across the country. In the US, every state is different. [For example,] the sales tax will be different—we all know the states that don't have sales tax, and if you live near them you tend to visit them so you can get a break of 6 to 7 percent on whatever you are buying. There is a lot of diversity in the US as far as the way we expect things to happen. I'm originally from New Jersey; I travel back there a lot for family. I can use a cell phone in the state of Pennsylvania, and the minute I cross the New Jersey state border I put it away because I'm not allowed to use it unless I have a hands-free model. This is an example of differences.

Our way of living sometimes translates into the way we think about things. Generally speaking, in Europe, many things are consensus-driven—people say "let's have a discussion." Right now, there is the European Directive, driving similar practices in all EU countries. The US, for better or for worse, tends to work on threshold: We tolerate a lot, whether it's national debt or handguns—whatever it happens to be—until a certain threshold is met, and then things happen. The good news is, when a threshold is met, something usually happens quickly. The bad news is that it generally takes a while to hit a threshold. The reverse would be in consensus: sometimes it takes a while to get to that outcome, but people are talking about a topic and thinking about it.

To me, the important question is, Do the variations that exist really result in a big difference in the way we care for animals in different parts of the world? Is it possible to align principles, independent of differing standards, which are the more prescriptive way of looking at animals in research?

Some of the differences, compared to academia:

- Industry usually has a very large internal capacity, there are many things we can do internally. [For example,] we generally have the option to buy equipment if we feel it's needed and we can defend the budget for doing so.
- Industry tends to be a regulated environment. Even the earlier work has probably many more regulations than are normally seen in academia.
- Industry has many different requirements because it spans different countries and includes different types of studies, from efficacy models in transgenic animals to highly regulated GLP studies in macaques.
- Of course, timelines are extremely important.

What then is the criticism? I distilled it down to the concept that "what we think weighs more than what they think." When we have conversations, when we have dialogues, we have already sort of made that internal critique. We need to move away from that preconceived notion before we can start to have the conversation. Otherwise, it will be hard to have consensus or even a conversation.

Again, using GSK as an example, we work across two main cultures, the US culture and the UK (we also have sites in continental Europe, but that is a more modest operation). We have opened some discussions to see if we could come to consensus on guiding principles for the use of animals in research. We did this because we felt it would provide a safe structure for having conversations and would allow the diversity of thought and opinion to come through and have a substantive type of conversation, and try to get some alignment.

Our desired outcome is to achieve alignment and articulate a set of foundation principles with regard to the animals, for us within the institution and also for work done for our institution by CROs, academic institutions, or other places. We started with dogs and monkeys, some of the more highly emotive species. We also defined what the undesired outcome would be. If we couldn't come to some sort of understanding, that wouldn't mean that differences in practices or standards always equate to a difference in care. We wanted to avoid a perception of a dual standard—i.e., a practice done in one place means greater care, not doing it in another place means lesser care. Unfortunately, this is often the initial perception when working in different environments.

Going back to the definitions, consensus, of course, means a general agreement and some sort of alignment or solidarity along a certain belief or sentiment. When we achieve a consensus, I think we can start to move the scales—each side will continue to maintain its own thoughts, but we will get a little more alignment and a little more agreement to ask "What is our objective?" Our objective is the care and welfare of the animals; it's not to say that one side's opinion is more important than the other. So let's keep that in mind as we have the conversations.

But the question always asked is, "Is it truly achievable?" Even in societies where there are many consensus-driven processes it is sometimes difficult to achieve consensus. So my charge has been, How do we handle this?

At GSK, we have certain principles by which we work. We adhere to the 3Rs and we meet all applicable rules and regulations regarding animals in research. We have also established seven core principles of animal care and welfare. These principles are used no matter where we are in the world—whether we do research in China, North Carolina, or Croatia. [This consistency] allows us to look at cultural differences in ways of working and accept that issues identified as important to all groups might be emphasized differently in each place. So the objective was to find some commonality.

Core Principles of Animal Care and Welfare

- Access to species-appropriate food and water
- Access to species-specific housing, including species-appropriate temperature and humidity levels
- Access to humane care and a program of veterinary care
- Ability to demonstrate species-specific behavior
- Adherence to principles of replacement, reduction, and refinement in the design of *in vivo* studies
- Commitment to minimizing pain and distress during *in vivo* studies
- Study design reviewed by institutional ethical review panel

There are those in some parts of my organization who say these core principles are not strict enough and should be stricter. Others say we are stating the obvious, so why even bother?

We bother because these core principles have allowed a dialogue across countries, sites, and cultures. As an example, we require an ethical review process at each institution where animal work is done on behalf of GSK. There are many parts of the world where an ethical review process is not the norm. We are asking for that to be in place. The 3Rs are part of the discussion before animal research happens. Some principles are self-evident such as food and water and there needs to be some common sense applied to implementing them.

Now that we have put together these principles we are audited to make sure we are complying with them by internal auditors who have little knowledge about animal research. They will ask us to prove how we meet the principles. So now we are working through the next level.

Most pharmaceutical companies, like GSK, have something about animals in research on their websites. For pharmaceutical companies there are basically two options. One is to apply engineering standards, and apply the most stringent standards of all the countries no matter where we work. In the case of GSK, the UK has the most stringent standards. So if we are doing work in Croatia, Philadelphia, or China, we will use [the UK] standards. This approach allows some comfort because it is very easy to measure and understand. However, it does not necessarily affect animal welfare proportionately as some would think.

The other option is to use performance standards, such as the standards upon which our core principles are based, and to use international standards such as AAALAC. For GSK, working in multiple countries, it was necessary to have international standards. Why do we use [an international standard]? Here are some of the reasons. It is a global approach and in spite of the numerous regulations, this system works. Obviously, it's voluntary and confidential. It involves looking at practice, not just engineering standards in the program.

These standards require the use of professional judgment, which may make some people uneasy because of the uncertainty of the education, knowledge, or credibility of the person making the judgment. Professional judgment is the issue that usually causes the most difficulty in that one professional differs from another professional. It is said by nonveterinarians that if there are five veterinarians in a room, there will be 10 opinions. It is very difficult sometimes to get consensus and know what the right professional judgment is.

But from our standpoint, the animals benefit if we avoid template thinking. Temple Grandin, whom many of you may know, has written a number of books on animals. She is an autistic woman who has been very successful in the animal behavior/animal psychology field. She often discusses her visits to slaughter plants, where she conducts plant evaluations. She knows that when government inspectors come in they have a 100-step checklist. Temple goes in with five or 10 different things she examines from the animals' perspective. From those few items, she can rapidly tell the state of the slaughterhouse. I believe this is one of the best examples of why professional judgment is important.

So there is a lot of oversight: Our wonderful core principles have now become a way to audit us, in addition to the USDA and GLPs. But that is acceptable in that there is constant challenge and a dialogue to help improve and refine the system.

It is also important to recognize that we and other pharmaceutical companies conduct work outside our institutions. CROs are fairly straightforward, but academic alliances and collaborations with biotech and other companies are not. So we have instituted a process by which we look at those aspects.

Many wonder if that's the best use of resources that might be better spent in hiring more veterinarians or vet techs. However, as stated earlier, it is a balance. We can perform research because society as a whole has stated that research is important. So there is something the companies owe the public in return.

While the standards to which the company holds us may be surprising, it is also understandable that they want to build trust with stakeholders. They feel they must answer certain questions and I and my team have to provide that information.

What are my conclusions?

- Always to remember that we are all in this together. Personally, I feel that the weakest link in all our conversations is the [conversation] we don't have. It is much more important to talk and disagree than not speaking and believing that "never the twain shall meet."
- Standards, particularly engineering standards, should be based on science and show a clear benefit.
- Principles keep both the science and the animal in mind and should allow diversity and professional judgment.

Overcoming Challenges—
Contract Research Organizations (CROs):
Setting Up a CRO in a Foreign Country

Bryan Ogden

Thank you for the opportunity to travel back to the US. I have been in Singapore for four years having left an academic environment at the Oregon National Primate Research Center to help with a startup contract research organization (CRO).[1] I am going to use some of my experiences to illustrate some of the challenges, operationally, that we face as a CRO in working across different standards.

Foreign CROs face the challenge of establishing credibility. Western companies have scrutinized the different CROs that are being established in Asia. There have definitely been some bad outcomes, some disappointing facilities and programs. Sometimes that record is used to make presumptive judgments about new CROs.

I hope that most people know that Singapore is not in China, although if one were to ask where Singapore is there would be many different answers. Singapore is located at the tip of the Malaysian Peninsula. The island where we have our breeding colony in Indonesia is a one-hour ferry ride across the South China Sea. This presentation will focus on the Singapore story.

CROs face the challenge of being competitive. The pharmaceutical companies demand a certain standard and expect CROs to do things similarly to the way they are done in the pharmaceutical industry, which can be a challenge from one country to the next. If the CRO does not meet those standards, it will not get the business, and yet it has to be profitable. The general perception is that a young company in particular needs to be faster, better, cheaper.

[1]CROs provide support to the pharmaceutical and biotechnology industries in the form of outsourced research services (for both drugs and medical devices) such as clinical trial development, management, and postapproval services. This presentation focuses on the challenges of outsourcing to CROs in other countries.

The question becomes, Should the CRO vie to be better than everybody else or just acceptable, to meet the minimum standards? And what would those standards be? Should the CRO appeal to a niche market or do a broad service offering?

Most CROs realize that they will be expected to provide humane animal care and use. Certainly our CRO does not want to attract business from countries with tighter regulations with the intent of doing something more invasive or less humane in our country or in our facility. Certainly the pharmaceutical companies and biotech companies would not want to be perceived as outsourcing to Asia, for instance, so that they can bypass humane care and use standards.

There are also opportunities for preferred provider and partnership arrangements, collaborations. For instance, we have agreements with certain pharmaceutical companies to do some of their discovery work and perhaps some of the toxicology work. These kinds of arrangements occur in different countries in Asia and most likely in Europe and the US. Such studies are important to CROs for their survival and give them a core base of income. These partnerships sometimes also provide an opportunity to work together on novel model development.

However, there are challenges with different standards across different countries and cultures. The problem may not always be due to differences in, or lack of, animal welfare regulation. There may be different government agencies that affect permits related to a CRO's activities without specific laboratory animal welfare regulations. I will give an example.

The other issue is how the regulations are enforced. Do the regulators really understand the best standard of animal care, or at least best practice?

Within a CRO, especially in a country where there is a diverse population, there are different cultural attitudes. For instance, some males will not take direction from a female superior or are less likely to—a technician who was raised in a household with a Filipina maid might not readily accept correction from a Philippine veterinarian. A CRO must deal with these and other interpersonal and cultural challenges.

There is also the issue of the status of the animals in different cultures. What is acceptable use of an animal? In some cultures animals that are considered pets in western culture are actually food.

There are ethical considerations and compliance issues as well. Does the country have a culture of compliance, or even a culture of integrity or ethical principles of integrity? In some countries Westerners are walking wallets—it is common for people in those countries to charge Westerners several times what they would charge someone else for similar services or products. It is considered a real coup for them to cheat people.

A particular concern with CROs is cultural attitude toward saving face versus disclosure. Mistakes on studies are inevitable. If the culture is focused on saving face, there may be a tendency to hide the mistakes, which could affect the data and the interpretation of the data. This could ultimately cause far-reaching

negative effects during clinical trials. It is therefore essential to understand the ethical principles about disclosure as opposed to saving face.

Work ethic across different cultures and countries is another challenge. In some countries the work pattern is for one person to do the work and several supervisors to stand around and watch. This is based on a concept of how many hours of actual work in an 8-hour workday the employer is entitled to.

Another issue concerns the socioeconomic and human living conditions of the workers when compared to animal living standards. It is difficult to persuade a worker to implement sanitation practices for primates when the worker lives in a hut with a dirt floor, blue tarp walls, and a rusty corrugated metal roof.

Pride in workmanship affects the quality of the facilities, and ultimately the quality of the care of the animals.

My company can be used as a relevant case study in operational challenges working across different standards. It started as a spin-off of Monash University in Australia, then moved to Singapore as a preclinical CRO in 2003. Between 2004 and 2005, facilities were designed, financing was obtained, facilities were constructed and then licensed to do research; in 2006, the programs were accredited by AAALAC and began to adhere to FDA GLP compliance. The facility was accredited by the OECD for GLP accreditation in 2008.

In addition to the Singapore CRO facility, the company has a breeding facility for primates in Indonesia. The Indonesian standards for animal care, or lack thereof, will be discussed in a moment.

In 2000, the government of Singapore began an initiative to develop biomedical sciences as a major hub of the economy, with the ultimate goal of becoming the biomedical hub of Asia. They appointed an advisory committee and built some "Field-of-Dreams-style" facilities. That committee was called the National Advisory Committee for Laboratory Animal Research (NACLAR). NACLAR looked at standards across different countries, including the UK, Australia, New Zealand, Canada, and the US, and decided to adopt standards similar to those in the US that would enforce a self-regulation type of oversight of animal care and use programs. They published their guide in October 2004. The Parliament passed an amendment to the Animal and Birds Act covering animals in research, effective November 2004. The Agri-Food and Veterinary Authority (AVA) was assigned a role similar to that of the USDA, overseeing the licensing and inspection of animal research facilities.

Of the challenges mentioned earlier, some result from working across different countries, but others are specific to Singapore. To meet those challenges in part, Maccine hired me, a US-trained, ACLAM board-certified veterinarian, since my career was based on the US standards Singapore was adopting. This helped provide credibility for the company to potential clients. The company also received some backing and support from Quintiles, a UK-based CRO, including some key staff. They recruited people from other countries, too, because there was not a base of study directors or technical staff with experience in laboratory animal care in Singapore.

Maccine has held the Indonesian facility to the NACLAR and AVA standards. In fact, the IACUC in Singapore oversees the animal care and use program at the Indonesian facility, including twice-yearly inspections of the facility. AAALAC accreditation was very critical. We even invited the Singapore AVA to be at the AAALAC site visit in Indonesia, even though AVA had no regulatory authority there.

Training has been a key issue. Through the Singapore Association of Laboratory Animal Science, which we established in 2004, we have offered training for IACUC members, similar to what is done in the US with IACUC 101.

The NACLAR guidelines are different in some minor ways from US regulations. While they are very similar overall, NACLAR does not reflect the difference between the USDA Animal Welfare Act and Public Health Service policy with regard to the definition of an animal: NACLAR guidelines cover all vertebrate animals and the AVA uses the NACLAR guidelines to measure compliance. Another difference is that the IACUC may not do a designated review. Also, to have a quorum of the IACUC, one of the people in attendance must be the nonaffiliated or the nonscientific member.

Animal facilities are inspected by the IACUC and AVA only once a year, although the IACUC program review occurs twice a year. To facilitate the process, we have started doing our IACUC inspections at the same time as the program review, twice yearly. This is similar to what is done in the US and what our clients expect. AVA inspection is scheduled, as opposed to being unannounced as it is in the US. In fact, the AVA has begun to require something similar to an AAALAC program description prior to its inspection. It seems that the AVA is striving to hold facilities to a standard even beyond the regulations and guidelines. It is both good and challenging to have inspectors come to the facility who have both an intimate knowledge of the program and the regulatory power to enforce the regulations.

NACLAR and the regulations under the Animal and Birds Act both require training. IACUC members must receive formal training. Also, anyone who does research must attend a course on the responsible care and use of laboratory animals.

The contrast between Singapore and Indonesia demonstrates an interesting continuum in the amount of regulation. Singapore is one of the most regulated countries with the highest standards in Asia, and Indonesia (and perhaps Malaysia) are at the other end of the continuum. Malaysia is now working on setting up some national animal welfare standards for laboratory animals.

As mentioned earlier, while Maccine has a facility in Indonesia where there are no laboratory animal welfare standards and therefore no government inspections, the company applies the same standards as in Singapore. Even though both countries are CITES members, one can get a CITES permit in three days in Singapore, while it can take weeks or months to get one in Indonesia. The timeline for CITES approval in Indonesia can depend on who you know and in some cases who you pay. In addition, both countries require import and ex-

port permits. Again, the turnaround is very fast in Singapore and very long in Indonesia.

Singapore is very diligent and efficient in both permitting and bureaucratic integrity. Indonesia still has not been able to eliminate influence peddling and under-the-table payments in order to get permits. Without payments, the waiting period can be extremely long.

There was a challenge in Singapore with regard to GLP certification. When the company was started, Singapore was not an OECD member so there was no GLP monitoring authority. In 2006, the Singapore government assigned SPRING as the GLP monitoring authority and it began auditing for GLP compliance in 2008. Singapore became a provisional member of OECD in 2007.

I would like to address a few other CRO challenges:

- financing and cash flow, especially with a startup company;
- design and construction;
- SOP establishment—starting from scratch, then training and achieving compliance; and
- good quality control and validation and quality assessment.

Those are all challenges that are met to one degree or another in different countries, in different CRO facilities.

Credibility is an issue especially if the country is viewed similarly to its neighbors. For example, some people may be under the misconception that Singapore is in China and, if they have heard horror stories about melamine in baby formula or colleagues have revealed their bad experiences in China, they may think that Singapore has the same negative issues. From my own experience, when we have been audited by pharmaceutical companies and biotech companies, the auditors are greatly relieved when they see our AAALAC accreditation.

An additional challenge is being competitive. Singapore does not have much in the way of rodent breeding and there is no commercial rodent vendor there. Within the next couple of years, the country plans to have its own national breeding center. Now, however, we have to import rodents, which is expensive, making it hard to be cost-competitive, especially in the toxicology area.

Communication is another challenge because there is a 12- to 13-hour time difference with the East Coast of the US, so we must have late-night or early-morning conference calls.

Language is not usually a significant problem because the official language of Singapore is business English, although sometimes the accents are difficult to understand. In other countries, however, there are significant language and cultural barriers.

Sourcing supplies and equipment can become a challenge as well as the function of the regulatory agencies with regard to shipping, bioanalysis, pathology. AAALAC accreditation was an important step to becoming a credible CRO

in order to meet the expectations of clients. For CROs doing toxicology, GLP certification is also necessary.

There have been some frustrations in not being able to work with architects, engineers, and contractors that have experience in building animal research facilities. Cost engineering is a problem everywhere, and unfortunately one of the first areas to be cut in building design is storage space. It is also a challenge to get quality materials and have them installed such that the epoxy floor does not come up, paint does not peel off the wall, or the walls don't crack soon after you move in. In Asia, contractors tend to use unskilled labor. In China the laborers are uneducated ethnic minorities, and in Singapore it is the Bangladeshis, Pakistanis, or people from other undeveloped countries. Even with the best epoxy products, inexperienced workers can make a real mess during installation, which can of course also happen in the US.

Here are some pet peeves of mine working in Asia. Workers cannot get a concrete slope floor to drain evenly—one gets pooling of water and water pouring from the room out into the corridor during hose-down washing. Another pet peeve has to do with improper surface preparation of floors for epoxy. There are often not good moisture membranes. There are problems with improper mixing so that a month later feet still stick to the epoxy floor and wheels leave indents. Of course, installation and maturing are issues here. Another pet peeve is the apparent inability to match paint in Asia, which should be possible with a simple computer program. But this does not seem to happen in Singapore. If you are lucky, when a crack is patched, the workers will put a geometric design over it, like a square or a long rectangle. If you are not lucky, it will just kind of patch the crack in a different color in an irregular pattern, maybe using a different texture, maybe a flat paint as opposed to a gloss.

There does not seem to be enough pride of workmanship in many parts of Asia. Simple jobs like applying grout or caulking that should produce a smooth line result in thumbprints, blobs, or smears and the workers appear to be satisfied. It is a real challenge to find people who are qualified. There are the "sea turtles" coming back to China and other countries after working or studying in the US. Their competence in the CRO and in other environments using animals will depend on what their US experience was. In my experience in academia, foreign workers did not always get it, even after 10 years for some of them. If people like this return to their native country and are perceived as understanding animal welfare standards and ultimately become leaders in their companies, you can expect that things are not going to be harmonized.

It is common to hire workers from outside the area, especially in Singapore, where there are only 4 million people and no farms or anyone with any agricultural background. We often hire from other countries and have a large number of employees, including some veterinarians, from India and the Philippines.

Often it is most expedient, at least initially, to hire Westerners to help train employees and to help set the standard and maintain compliance. It is a problem to retain them, however, and it is necessary to make a plan for succession, so

that the people who are left behind are trained. If a CRO wants to be competitive, it is not profitable to keep hiring people at high salaries from the West. Trained workers tend to move from company to company in search of higher salaries and this may ultimately affect cost competitiveness.

Sourcing challenges, vendors—I won't get into that. I think I'm just about out of time.

With regard to regulation, hopefully countries will follow Singapore's example and review the standards in other countries and develop regulations that will be similar or at least compatible to those in other countries. They will certainly learn from the experiences of other countries as well as how to enforce the regulations. However, there is a concern that without a proper understanding of the science and intent behind the different regulations, there may be a tendency for a growing bureaucracy to make things more difficult. The regulators have a steep learning curve and regulatory creep is a real threat. We have seen an evolution in Singapore in the last four years, when we first started out with simple inspections, and now we are required to fill out a lot of paperwork before an inspection. Our annual reports, similar to what we submit in the US to the USDA, have become much more detailed.

In Singapore, an example of bureaucratic creep and lack of understanding of industry needs for biomedical research is the buprenorphine story. Buprenorphine is an analgesic that is commonly used in laboratory animals, but has been overprescribed by physicians in Singapore, resulting in human abuse. The Ministry of Health abruptly removed it from the market and it was suddenly unavailable in Singapore. Both lab animal and private-practice veterinarians appealed to the Ministry of Health and the AVA, and the AVA stepped in and helped make buprenorphine legal for certain veterinarians and lab animal facilities. The challenge has been to get a vendor who is willing to supply it only for veterinary use. A year later, we still do not have access to buprenorphine. However, every quarter, we are still required to submit a report to the AVA saying that we have not received any and have not used any of that which we have not received. I usually forget to file the report and receive a notice from AVA about a month after the report is due. The last notice says, "If you don't submit your report, we're not going to remind you next time. You will not be able to be listed as someone to get buprenorphine." To me, this is an example of bureaucratic creep and the negative effects of not comprehending the impact of regulatory decisions.

In closing, I would like to say that I support what Margaret Landi said about the concerns surrounding engineering standards versus performance standards. I have seen too much misuse of engineering standards, to get letter-of-the-law but not spirit-of-the-law compliance—in some cases, straining at gnats and swallowing camels, if you will excuse the biblical reference. For instance, you come into a room of rodents in Asia with some very nice, expensive ventilated caging, but the paint is peeling off the walls and there is water dripping from the ventilation ducts and the room is filthy. But there is 100 percent fresh air to the rodents. It's HEPA-filtered.

Credibility will continue to be a problem. It is important to continue to look beneath the surface to determine if what is seen is "show" rather than actual improvement in the quality of animal care and use.

I want to thank my company for allowing me to take part in this; Gary Morrow for his help, based on experience he has had in other CRO inspections; and articles by Stacy Pritt and Jayne Mackta.

I also thank AAALAC International, which has been wonderful in sending speakers to our IACUC training courses, materials for conferences, and people to speak at our conferences. AAALAC has sent somebody to support us every time we have asked and I know that they are willing to do that in other countries. AALAS has also provided valuable training materials and certification exams. They are a tremendous resource.

I thank the planning committee for inviting me to this ILAR conference. I thank my wife, especially, for leaving our five grandchildren—the number of which has now grown to seven—here in the US and spending four years with me in Singapore.

Global Issues: Operational Challenges to Working across Different Standards in Academia[1]

Steven M. Niemi

Introduction

While globalization of many human endeavors has become a truism and digital communication channels force-feed us nonstop connectivity, it is important to remember that personal interactions remain invaluable. This is especially true at gatherings like this one where we address multiple scientific, political, legal, economic, cultural, and emotional perspectives on a subject of great interest to many around the world. The Institute for Laboratory Animal Research and the National Academies are congratulated for hosting this meeting to facilitate such face-to-face exchanges and I am honored to be invited to speak.

My assignment is to provide a perspective on current and anticipated operational difficulties and needs (i.e., "challenges") in the use of animals in academic biomedical research across national boundaries, especially involving Americans. In other words, I was asked to describe how US scientists in academia grapple with the variety of national laws, regulations, standards, practices, customs (or lack thereof for any of these) when laboratory animals are involved in multiple countries, and how things may evolve over the foreseeable future. I will begin with a few definitions and a specific framework for my commentary in this field, continue by examining current drivers for transnational academic collaborations, and finish with predictions and recommendations for the next ten years.

At the most basic level, academia differs from government and industry in their respective missions. Governing is the purpose of government, and increasing the value of owners' equity is the purpose of commercial firms. Academe, by contrast, is focused on knowledge, both its discovery through research and its transmission through teaching. These basic differences are noteworthy in the

[1]The views and opinions expressed herein are solely those of the author and not necessarily of his employer or of organizations with which he is affiliated.

context of this symposium because academic research comes with no vested authority over the citizenry, unlike government, and no expectation of near-term financial returns (if the research happens to be paid for by industry, it is industry rather than academia that is expected to translate any new knowledge into something marketable). Thus, one would think that academia should have an easier experience than the other two entities in transnational use of laboratory animals. We will explore whether that presumption is actually true.

Another important difference between academia and these other two elements of society is that the academic scientist understands that new knowledge will be scrutinized and must be verified by others before a discovery is accepted; governments and commercial firms wish just the opposite. In any event, testing the accuracy of new knowledge can be performed by anyone anywhere in the world if he or she has the requisite knowledge and resources, another detail relevant to this discussion.

For definition purposes, laboratory animal care and use will be treated as one and the same in this presentation. This avoids having to distinguish between national differences for animal husbandry and veterinary support versus differences involving actual animal experimentation. And from the public's perception and certainly from the animal's experience, animal care and animal use represent a continuum.

Only vertebrate laboratory animals will be considered in this presentation. This is despite my suspicion that the majority of animals used in academic biomedical research today are actually invertebrates, including but not limited to insects such as *Drosophila melanogaste*r and nematodes such as *Caenorhabditis elegans*.

An Example: China

I will address only one geographical element in an otherwise lengthy equation, i.e., the growing presence of China in academic biomedical research, with apologies to other countries. This is partly because of China's huge population, rapid rate of modernization, and lack of established regulatory oversight of laboratory animals, and partly because of its legacy of major "firsts" in mathematics, science, and engineering[2] and preeminence as the world's largest economy for many centuries. Between around 1000 CE and the Renaissance, it is estimated that China represented more than 75% of global population, production, and trade.[3] And for the subsequent 400+ years, China still generated 30% of global production (until the rise of the Industrial Revolution in Europe in the

[2]Simon Winchester, *The Man Who Loved China* (New York: HarperCollins, 2008), a biography of Joseph Needham, the Cambridge University scholar who rediscovered and published extensively on centuries of Chinese dominance in these fields until its demise at the hands of neighboring countries and colonial powers in the 1800s.

[3]Klaus W. Wellershoff, as quoted by Lee Kuan Yew, "Asia's Growing Role in Financial Markets," *Forbes Magazine*, February 25, 2008, p. 21.

1830s), a percentage larger than that of the US in the decades immediately after World War II. [After Mao's Cultural Revolution and Great Leap Forward, China's output dropped to only 1% of the world's GDP in 1979. China has since rebounded to 5% and its spending on R&D has grown 19% annually over the past 10 years, a rate more than six times higher than in the US, which is still the world's leader in yearly R&D expenditures.][4]

This impressive heritage gives many Chinese citizens great pride and an expectation that their country will eventually resume its global leadership in the sciences. Hence, domestic support for the pursuit of science and technology leadership will continue to be strong. Besides India, no other country comes close to matching China in this context. But because India has chosen to discourage the use of nonhuman primates in biomedical research,[5] China is a logical focus. By contrast, addressing the differences only between wealthy countries with respect to laboratory animals and academic research is less compelling because those differences are minor in comparison with poorer nations. Furthermore, investment in animal-based biomedical research in China and other developing countries will likely accelerate.

Current Drivers and Barriers

Several years ago in his book *The World Is Flat*, Tom Friedman described how Tian Xu, a Yale professor and Howard Hughes Investigator, outsourced bench work and mouse studies to long-time colleagues at Fudan University in Shanghai while his laboratory analyzed the resultant data back in New Haven.[6] Xu's counterparts in China enjoyed new and expansive laboratories, ample federal funding, and could remain in their country rather than traveling to the US for graduate or postdoctoral training. This arrangement permitted the American side to accomplish just as much research with trusted collaborators but at a fraction of the cost of performing that research in the US. At the same time, graduate students in the partnering laboratory in China got access to cutting-edge research, with frequent exchanges of staff in both directions. [It is important to recognize how serious the Chinese government is about recruiting expatriates that historically have stayed abroad. A related trend is the dramatic increase in Chinese students receiving higher education—from 1.4% of the college-age

[4]Philip Auerswald, "China's quick fall, slow return to glory," *Boston Globe*, August 11, 2008.

[5]A.J. Rao. Use of nonhuman primates in biomedical research in India: Current status and future prospects. In *International Perspectives: The Future of Nonhuman Primate Resources, Proceedings of the Workshop Held April 17-19, 2002*, National Research Council. Washington: National Academies Press.

[6]Thomas L. Friedman, *The World Is Flat: A Brief History of the Twenty-first Century* (New York: Farrar, Straus and Giroux, 2005), pp. 247-248.

population in 1978 to 20% in 2005, resulting in almost half a million new undergraduates, 48,000 master's degree graduates, and 8,000 new PhDs a year.[7]]

Other scientists in advanced countries have recognized the same cost advantages, even without close personal relationships, and these types of extramural collaborations are becoming more popular. Consider that for the first nine months of 2004, 53% of the research papers published in *Science* and *Nature* from Chinese laboratories included American scientists as coauthors.[8] When laboratory animals are involved, the cost differential may be even more striking when one appreciates the much greater investment made in each animal in biomedical research today. For example, genetically engineered mice have proven to be a critical tool in dissecting the influences of various genes in diseases and other biological phenomena. But preparing for the actual experiment of interest involving a specific combination of multiple genotypes usually requires several generations of cross breeding, coupled with genetic analysis of every animal from each generation to make sure that the breeding scheme actually yields the genetic components of interest. The result is not only a mouse with a novel and precise mixture of genes but a mouse that represents an investment of perhaps tens of thousands of dollars before the experiment is ever conducted. Cost realities like these in a tight funding environment are leading many to consider less expensive strategies abroad.

Other drivers for transnational collaborations between developed and developing countries involve access to patient populations or environmental circumstances that are not as prevalent in wealthier nations. China is not unique in this regard, but some of its ethnic minorities with their relatively narrow genetic bases, isolated living conditions, and limited diets may offer science a better means of understanding nature versus nurture in specific diseases that also afflict patients elsewhere. For example, Xinjiang Province in the northwest corner of China is home to thirteen nationalities. Here, Kazaks eat a very salty diet and have a high incidence of hypertension and esophageal cancer with short lifespans when compared to Uighurs, who eat primarily grains and fruit and have long lives with a very low incidence of cardiovascular disease.[9,10] On the other hand, there are diseases relatively widespread in China but rare in most other parts of the world. One example is hydatid disease, a parasitic infection affecting 600,000 Chinese, with an additional 60 million estimated to be at risk. Treat-

[7]Howard W. French, "China Luring Scholars to Make Universities Great," *New York Times*, October 28, 2005.

[8]Ya-Ping Zhang and Shigang He, 2004, editorial, *Science* 306: 1861.

[9]He Bing-Xian and Zhang Jian-Yi, "Dietary habits and longevity along the Silk Road," in Proceedings of the Symposium on New Horizons in Preventing Cardiovascular Diseases, Y. Yamori and T. Strasser, eds. New York: Excerpta Medica, 1988, pp. 89-93.

[10]D. Rahmutula, et al. Angiotensin-converting enzyme gene and longevity in the Xin Jiang Uighur autonomous region of China: An association study. J Gerontol A Biol Sci Med Sci 57:M57-M60, 2002.

ment is only 30% effective, leaving many to face premature death.[11] Many scientists are studying this parasite-host interaction because it may provide insight into parasite immunology in general.

Regardless of the increase in transnational research collaborations between developed and developing countries, there are significant risks involved. These include fraud, plagiarism, loss of intellectual property, and perhaps even criminal acts involving theft or smuggling of protected natural resources. Most of these adverse consequences are very rare in contemporary science among wealthy countries, but lack of similar protections and an only recent respect for the ownership of ideas in less developed countries raise legitimate concerns.

Other postulated incentives to increase academic collaboration between scientists in developed and developing countries are *not* as valid, at least here in the US. These include the avoidance of regulations and activist targeting pertaining to the use of animals in biomedical research. American scientists have become accustomed to established standards of laboratory animal oversight, and their respective institutions have administrative and physical infrastructures for compliance with regulations that have been in effect for many years. In fact, the biggest academic concerns to transnational collaborative research involving lab animals involve just the opposite situation, i.e., the lack of those same quality standards and safeguards that protect the health and welfare of today's expensive animal models in developed countries.

When coupled with an unprecedented level of scrutiny available via the Internet, the negative consequences of mere allegations of lab animal mistreatment involving a scientist in a developed country are greater than any theoretical advantage to be gained by conducting animal research in a less rigorous environment. Therefore, the biggest concerns to be resolved if such collaborations are to grow and succeed involve acceptable (i.e., Western) ethical values for and adequate oversight of animal research in developing countries. Additional concerns pertain to the adequacy of the knowledge base of local veterinarians in poorer nations with respect to lab animal biology and medicine, as well as the vested authority of those veterinarians to intercede on behalf of lab animals when (Western) limits on animal pain and distress have been exceeded. Some may claim that this smacks of cultural imperialism and imposition of one ethical standard at the expense of another that has just as much legitimacy. However, even in China, as a middle class becomes more established, pets are becoming more precious to their owners and this trend could expand to greater sensitivity for other animals.[12] As a result, cultural attitudes toward animals may, indeed, converge as living standards rise and more persons gain access to the web and other global connections.

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[11]"Parasitic time bomb," *Scientific American*, July 2005, p. 22.

[12]Nicholas Zamiska, "Chinese Unleash a New Fondness for Their Dogs," *Wall Street Journal*, August 7, 2006.

Current and Future Safeguards

At least two multinational approaches to address these major concerns are currently in effect. Both are laudable, but each has limitations. The first involves the NIH's Office of Laboratory Animal Welfare (OLAW; http://grants.nih.gov/grants/olaw/olaw.htm). OLAW is charged with obtaining official assurances that institutions accepting NIH research funds comply with contemporary standards for lab animal care and use. US institutions must submit a lengthy document every four years that details every aspect of their animal husbandry, veterinary care, occupational safety, and internal (IACUC) oversight programs, for review by OLAW staff before an assurance is approved. OLAW also expects to receive annual updates from those institutions as well as timely notification of any major adverse events affecting lab animal welfare. Foreign institutions that receive NIH research funds also are required to submit an animal welfare assurance, but that document is less stringent, to wit:

> When the grantee is a domestic institution (i.e., domestic grant with a foreign component), PHS animal welfare requirements are applicable. Accordingly, the grantee remains responsible for animal activity conducted at a foreign site and must provide verification of IACUC approval. That approval certifies that the activity, as conducted at the foreign performance site, is acceptable to the grantee. The grantee IACUC may accept, as its own, the approval of a foreign entity's IACUC; however, the grantee IACUC remains responsible for the review. Additionally, the foreign entity must complete the Statement of Compliance with Standards for Humane Care and Use of Laboratory Animals by Foreign Institutions, available from OLAW. This document certifies that the institution will comply with the applicable laws, regulations, and policies of the jurisdiction in which the research will be conducted, and that the institution will be guided by the International Guiding Principles for Biomedical Research Involving Animals. If the grantee is a foreign institution then IACUC approval is not required. The institution completes the Statement of Compliance referenced above. OLAW encourages foreign institutions to use the standards in the *Guide*, which is available in a number of foreign translations.[13]

Currently, institutions in 79 countries have an animal welfare assurance approved by OLAW.[14] OLAW cannot impose US laws and regulations on foreign entities, and regulatory site visits to those entities to ensure compliance with the *Guide* and other standards are impractical and unaffordable. Thus, the

[13]PHS Policy on Humane Care and Use of Laboratory Animals, "Frequently Asked Questions" (http://grants.nih.gov/grants/olaw/faqs.htm, last revised February 26, 2008).

[14]"Foreign Institutions with a PHS-Approved Animal Welfare Assurance" (http://grants.nih.gov/grants/olaw/assurance/500index.htm).

resulting discrepancy allowed between US and foreign institutional oversight of lab animals can be wide. Lapses that affect scientific data or animal welfare could be subject to disciplinary enforcement in the US but may be deemed tolerable in another country. That would result in only the US collaborator being subject to punishment from either OLAW or the public. In addition, such a double standard leaves a US scientist at a disadvantage for research funding when competing against a foreign applicant or another US institution relying on a foreign collaborator for its animal work, if all other aspects of their respective grant proposals are equal and if the first US institution is not able or willing to attain an acceptable assurance from OLAW.

The second approach in effect today is the voluntary accreditation program conducted by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC; www.aaalac.org), a laudable organization that is well represented at this symposium. Over 750 institutions, including academic research centers, in 29 countries are currently AAALAC accredited. But AAALAC accreditation is entirely voluntary and its deliberations and communications with applicants are confidential. Thus, there may be just as much uncertainty about the relative quality and reliability of AAALAC-accredited institutions as there can be about US versus foreign assurances approved by OLAW. However, the AAALAC approach is more rigorous than OLAW's in that site visits are required every three years to maintain accreditation, regardless of past evaluations or parallel approval by OLAW or any other entity. Those site visits are conducted by an experienced team of lab animal specialists to determine whether the institution remains in compliance with the *Guide* and other applicable standards of care and use as well as pertinent national and other laws and regulations. One can envision AAALAC accreditation becoming an international standard of quality in the absence of national laws and regulations that are equal for all countries.

In the meantime, there remains a need to upgrade global lab animal welfare standards not only to establish a more fair and consistent playing field between scientists in developed and developing countries but also to ensure that lab animals used anywhere are provided protection consistent with evolving values. The often referenced International Guiding Principles for Biomedical Research Involving Animals was issued by the Council for International Organizations of Medical Sciences "as a result of extensive international and interdisciplinary consultations spanning the three-year period 1982-1984."[15] It continues to be used as an acceptable foundation to guide lab animal welfare around the world, but has not been upgraded or otherwise revised for the past 23 years. More recently, the predecessor of this conference[16] and a similar one-day

[15]www.cioms.ch/frame_1985_texts_of_guidelines.htm.

[16]*The Development of Science-based Guidelines for Laboratory Animal Care: Proceedings of the November 2003 International Workshop*, National Research Council.

symposium at the AAAS annual meeting earlier this year[17] compared and contrasted various regulatory and cultural mores involving lab animal welfare among only developed nations. But neither gathering would or could go further to propose more modern goals for universal standards of lab animal welfare that would apply to research performed elsewhere.

In light of these circumstances, combined with the need for more modern practices involving lab animals as more transnational collaborations arise, the following objectives are proposed, listed in no particular order:

- Veterinarians responsible for laboratory animal health are sufficiently educated and trained in the biology, husbandry, handling and restraint, spontaneous diseases, and veterinary medicine of the specific species under their care before they are assigned any such responsibility.
- All laboratory mammals produced or used in research, testing, or education receive environmental enrichment unless enrichment is exempted for (valid) scientific reasons.
- All laboratory mammals produced or used in research, testing, or education receive effective postoperative analgesic therapy unless exempted for (valid) scientific reasons.
- Lethal endpoints are not permitted for laboratory mammals produced or used in research, testing, or education. Animals approved to decline to moribund endpoints are monitored frequently enough to ensure they are euthanized before they die.
- Veterinarians responsible for laboratory animal health have authority without interference or penalty to intervene on behalf of animals experiencing unapproved or otherwise excessive pain or distress.

These objectives will be presented to the American and European Colleges of Laboratory Animal Medicine for submission to the International Association of Colleges of Laboratory Animal Medicine, with a recommendation that they be adopted within five years.

Summary

We are witness to a rapidly changing environment for academic animal research in which comparable expertise and resources are available at lower costs in a more transparent and more knowledgeable global society. It is imperative that lab animal welfare standards be adjusted and universally adopted to ensure that good science and good animal care continue to go hand in hand everywhere lab animals are used.

[17]"Optimal Laboratory Animal Care and Use: The Road to International Guidelines," AAAS Annual Meeting, Boston, February 17, 2008.

Overcoming Challenges—Academia in Europe

Harry van Steeg

My presentation will focus on an overview of the animal studies going on in our institute.[1] Most of these studies are embedded in international collaborations, among others, with NIH support and grant money. Differences in standards in animal testing are encountered especially in these international projects. Here is a brief overview of the studies being conducted and the areas of interest.

There are two primary research fields. First, we are interested in developing alternative test models for carcinogenicity and mutagenicity. In particular, we are interested in the mechanisms of nucleotide excision repair, or in general genome maintenance, and p53, the cell cycle control gene. In addition, we are involved in large survival studies in models that have a defect in genome maintenance genes. In particular, what is the effect of this defect on survival and aging in these models? We encountered some differences in regulations in these studies.

Why are we interested in developing alternative tests for carcinogenicity testing? The gold standard is still the rodent two-year bioassay, which is very tedious and uses many animals—at least 500 rats and mice must be used to test one compound—and a very high dose is used, up to the maximum tolerated dose, which is totally irrelevant to human exposure. These assays also require long exposure times over the lifetime of the animals, which is two years or longer. Based on these dose-regimen protocols, these two-year bioassays often produce many false positive results. Thus, the results are not reliable, and these assays are very expensive.

Therefore, we are interested in developing alternative test models to decrease animal use and use lower, more relevant doses at lower cost. The idea was to make animal models that are more sensitive to carcinogens and in that way use fewer animals.

In our institute in the Netherlands, we developed a DNA repair-deficient mouse model, XPA, and we combined it with a p53-deficient model, which was

[1]The National Institute of Public Health and the Environment in Bilthoven, the Netherlands (www.rivm.nl).

developed here in the US. Based on our preliminary results, this is a very interesting model, and we were invited by the International Life Sciences Institute and the Health and Environmental Science Institute (ILSI/HESI) to become a member of a global initiative to foster alternative testing in carcinogenicity. In this program, there were four different transgenic mouse models—among others, our XPA/p53 model. Twenty-one different carcinogenic and noncarcinogenic compounds were tested. Exposure time was six to nine months instead of two years. For each compound tested, there were only 120 animals, with 30 animals (15 males and 15 females) per dose group for each of three doses.

In this global enterprise there were pharmaceutical industries, contract research organizations, governmental institutes like ours, and regulatory entities, like the US Food and Drug Administration (FDA) and the Committee for Proprietary Medicinal Products (CPMP) in Europe. In total, there were over 70 different partners in a big program.

The outcome of the study is that most of the known human carcinogens tested positive in our transgenic models. Some compounds were false positives, which are compounds that test positive but may not actually be carcinogenic to humans. They tested positive because of the dose regimen used in this rodent assay.

These alternative transgenic models may prove to be very interesting if used as an adjunct to the two-year bioassay, which is what is currently happening. Both the FDA and the CPMP in Europe allow the use of transgenic animals as an alternative to the mouse lifetime bioassay.

The current test for pharmaceuticals still uses 500 rats with a two- to three-year exposure. There is an alternative test with the mouse, which uses only 120 animals and exposure times of only six to nine months. This clearly is a big advantage in terms of the 3Rs concept.

The next part of this presentation will focus on the aging studies in the institute. The basic research question is, Do DNA repair systems, or genome maintenance genes, have an effect on aging in terms of survival and pathology associated with aging? The experimental design included different mouse models having one type of DNA repair defect. Every survival study used 50 males and 50 females. The controls were the C57BL/6 animals. In these aging cohorts, we do complete analysis of all the animals when they are still alive, of course. When they are dead, you cannot do autopsy on them and pathology….

In order to determine what happens during aging, cross-sectional studies were done. Samples were taken from many tissues from each of 15 males and 15 females at several time points. The time points were 13, 26, 52, 78, 91, 104, 117, and 130 weeks and the total number of animals was 200.

These are very expensive experiments that we perform in conjunction with many American groups. In doing them, we discovered that there are different standards in the animal testing. As noted already, in the European Union animal experiments are performed based on engineering standards according to local and EU rules and regulations. Animal welfare is a critical issue and, at least in the Netherlands, we are required to prepare an animal welfare book. In the US

the experiments are based more on performance standards, on scientific facts…; when projects are funded by NIH…the rules are more stringent.

In Europe, there are two different regulations. One, designed by the European Union, is the Council Directive 86/609, which is quite old, from 1986; it is currently being revised. This document was mainly based on economic and political considerations, and not animal welfare; however, in the revision there will be attention paid to animal welfare issues. This law will apply to the 27 member states of the European Union. The other document, the European Convention for the Protection of Vertebrate Animals Used for Experimental Purposes (ETS 123) was passed by the Council of Europe, which comprises 47 member states. The focus of this organization is on social and cultural cohesion. The premise of this document is that humans have a moral obligation to respect all animals. While not all the member countries have ratified this document, our country did. Therefore, in Holland we obey both protocols.

An overview of the animals used in the EU from 2005 shows that most are rats and mice as well as some cold-blooded animals. Very few nonhuman primates are used. Research on nonhuman primates is still allowed in the Netherlands, but it is not very common. In the Netherlands, about 50 percent of animal studies are for fundamental research or education; the other 50 percent are for testing pharmaceuticals, vaccines, or other toxicity tests. In total, there were about 600,000 animals used in 2006. In the EU the total was 12 million in 2005; worldwide, it was 100 million to 150 million animals, which is a large number.

Most countries in the EU have signed on to those two documents. But as has already been discussed, Europe is divided on these issues. Some member states have refined the rules to make them more stringent; among those are the UK, Germany, the Scandinavian countries, and the Netherlands. The Netherlands has its own animal welfare law as well, which was passed in 1977 and has been updated since. According to this Dutch law, I am obligated by my institute to submit all new projects. They must be reviewed by the ethical commission. When the project is granted, all individual experiments need to be reviewed as well. So there is very good oversight. (I must provide documents for the US projects to the NIH. I have an assurance based on time; mine is for four years, which is the duration of the project. We have not had a site visit by NIH.)

So what is in the additional law? Nobody is allowed to do animal experiments unless the institute receives a license from the minister of health. Scientists are obliged to ask permission from the IACUC, otherwise we cannot do an experiment. The members judge whether the use of animals is legal, ethical, [and] justified, the number of animals proposed is appropriate, measures are taken to alleviate pain, and so on. Animal studies are prohibited when there is an alternative with respect to the 3Rs—there are no exceptions. Studies with great apes are prohibited, [but] experiments with other nonhuman primates are still possible.

We have three levels of education on responsibilities for people who are involved in animal studies. We have the Article 9 officer, who is a scientist who took a course in animal studies, including statistics; this course only takes three

weeks. The Article 9 officer designs experiments, which are assessed on their scientific content by an institutional scientific committee. The study design is assessed on ethical merits by the Article 14 officer and is approved by the IACUC.

Then we have the Article 12 officer, who is an animal technician and has had a complete study on animal handling, animal anatomy, autopsy, and so forth. The duration of this study is three to four years. Article 12 concerns all animal handling, including breeding, maintenance, critical surveillance, autopsies, and euthanasia.

Finally, we have the Article 14 officer, who is an animal welfare officer with an academic education in a biological discipline and postdoctoral training in laboratory animal sciences. This person is not, per se, a veterinarian in our country, but is involved in all ethical and animal welfare issues.

We are not allowed to let the animals die when they suffer, particularly in the longevity studies we are doing. We have criteria defined as to when we need to kill the animals. Those criteria are when there is extensive weight loss (10-20% of the total weight within two weeks); when there are changes in behavior, such as lower mobility or hunched back; cyanosis; and tumors or ulcers. The final decision on euthanasia is made by the pathologist after consultation with the Article 14 officer. The Article 12 officer euthanizes the animal.

At the end of the animal's life, we prepare an animal welfare book describing animal discomfort, if any. This report goes to the legislated inspection services for review, and information is used to adapt for future experiments.

What does this mean for aging studies? One of the parameters of these studies, of course, is determination of the lifetime of the animals. This is a crucial parameter. However, when animals suffer—for example, when they develop ulcers or tumors—they need to be euthanized…. The Netherlands does not permit keeping the animals alive under those conditions.

In housing, it is not permitted to keep the animals solitary. However, when the animals get older and older, every now and then there will be only one animal in a cage, but because that is not allowed, buddy animals must be added.

The question, of course, is, Do the animals live for shorter times in our hands? We do have one advantage in killing the animals earlier in that we can obtain more end-of-life pathology, and we can determine their causes of death. However, the survival is worse.

The survival curve of C57BL/6 female mice shows that 50% survival is approximately 110 weeks; the survival curve of the XPD female mice with an accelerating aging phenotype shows a shorter survival compared to the C57BL/6 mice. According to the literature, C57BL/6 females typically live between 110 and 115 weeks and in our lab, the survival was about 110 weeks. Therefore, even with the requirement for humane endpoints, the survival did not differ significantly from that of animals who were allowed to die naturally.

Based on these longevity studies I conclude that under our conditions we can still do reliable studies and that the studies are comparable to those of others. Euthanasia is not a restriction. Therefore, although restrictions concerning

animal welfare are more stringent in our country as compared to the US, I believe that the outcomes of our experiments are equally valid. Given the regulation, there is no restriction on the types of research or toxicology testing we do. We can do the studies we want, provided we go to the ethical commission. And our research is still competitive, given the fact that we get some financial support also from the US.

Given all of these points, I believe that we should take animal welfare into account. It does not compromise the experiment and it is beneficial to the animal.

Finally, I would like to mention our collaborators on the many projects, both nationally and internationally. I acknowledge the collaborators on our cancer studies in the Netherlands, at the University of Amsterdam and Leiden, and those on our aging studies at the Erasmus University in Rotterdam. In the US, we collaborate with the Cancer Center at MIT, M.D. Anderson, and the University of Cincinnati. We are intensifying our collaboration with the National Institute of Environmental Health Services, to develop alternative tests for the National Toxicology Program (NTP) for carcinogenicity testing. We collaborate with the Albert Einstein Institute in New York, Lawrence Berkeley Laboratory, and the University of Texas on aging studies. Our financial support comes both from the EU and from the US with three NIH grants.

TRAINING AND EDUCATION

Charles River: A Model of International Training

Marilyn Brown

I would like to thank ILAR for inviting me to speak today. I would also like to recognize my coauthor, who is in the audience today, Sari Tuominiemi. Unfortunately, I have to leave after my talk; Sari has agreed to sit in for me in the panel this afternoon.

We have heard before about general principles; we have heard about the Interagency Research Animal Committee (IRAC) principles. I think the IRAC principles probably were taken from some of the CIOMS (Council for International Organizations of Medical Sciences) principles, which you have also heard about. One of those principles is: "Because of differing legal systems and cultural backgrounds there are varying approaches to the use of animals for research, testing, or training in different countries. Nonetheless, their use should be always in accord with humane practices. The diverse approaches in different countries to the use of animals for biomedical purposes, and the lack of relevant legislation or of formal self-regulatory mechanisms in some, point to the need for international guiding principles elaborated as a result of international and interdisciplinary consultations."[1] You will notice, in talking about diverse approaches, it does not say that they are deficient approaches. I think it's important for us to realize that there are multiple ways that we can approach something.

The *Guide* certainly recognizes the importance of performance standards. We have been hearing about performance standards again and again today. The above quote emphasizes the need for international guiding principles generated by international interdisciplinary consultations. I consider this meeting to be one such consultation that will get us where we want to be. I think that our goals are really similar, regardless of our approaches—that is, the goal of high-quality research done in the most humane way possible.

[1]CIOMS *International Guiding Principles for Biomedical Research Involving Animals* (1985) (www.cioms.ch/publications/guidelines).

Training and education are really the cornerstone of effective performance standards. Such training is going to be based upon:

- Legislation.
- The needs of the institution: This includes the types of research or testing that is being done as well as the resources of the institution. For instance, if you have access to the Internet, you will have access to different types of training materials and training opportunities that you might not have otherwise.
- The needs of the individuals: What types of procedures are they going to be conducting or performing? What is their previous training and experience? What are the cultural factors and learning styles that are involved?

The ILAR *Guide for the Care and Use of Laboratory Animals* discusses training. Examples of some of the types of training resources that are available include the Canadian Council on Animal Care (CCAC) guidelines, the 1991 ILAR report on developing training programs, and FELASA training guidelines for various levels of individuals.[2] I would like to draw your attention to the ICLAS *International Harmonization of Guidelines on Animal User Education and Training in Laboratory Animal Care and Use*. We heard previously that for the last couple of years ICLAS has been working on harmonization guidelines. This is one that I believe was just recently approved by the ICLAS board and hopefully will be published so it will be available for everyone soon.[3]

The components of a training program should include regulation, the roles and responsibilities for all individuals involved (and this includes the IACUC or ethics committee), ethics and the 3Rs, experimental design and the influence of nonexperimental variables, recognition and minimization of pain and distress, euthanasia, principles of animal care, and study- or species-specific characteristics, procedures, techniques, and practices. Like any good training program, there should be some way of assessing the training, assessing competence, and then, of course, documenting training, because, as we all know, if you don't document it, it didn't happen.

As in developing any training program, you must understand your audience. This includes understanding the structure of the animal care and use program. You need to develop an appreciation for the culture of the audience. This includes the culture's attitudes toward training—there are different approaches to training—and the attitudes toward animals. You also need to understand the current level of knowledge and have a sense for the audience's ability

[2]Available online at www.ccac.org; *Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs* (NRC 1991; available at www.nap.edu); FELASA Recommendations for Education and Training (www.felasa.eu/recommendations)

[3]Published online in June 2010 (www.iclas.org/Document/Ethical%20review%20-%20training%20article%20for%20Laboratory%20Animals%20-%20Official%20DOC%20Juin%202010.pdf).

to use or incorporate that knowledge. You need to keep your approaches flexible, but your goals firm. Your goal is to ensure the humane use of animals and quality research.

What do I mean by structure? We have heard about this a little bit today. For example, in the United States, the role of the veterinarian is pretty clearly spelled out in the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*. In addition to providing veterinary medical care, the veterinarian is charged with oversight of animal husbandry, nutrition, sanitation practices, zoonosis control, and hazard containment.

The role of the veterinarian in other countries may differ, particularly if the level of education and experience is substantially different. Such is often the case in non-Western countries. Western laboratory animal experts touring Chinese facilities recently reported that veterinarians may have only an undergraduate Bachelor of Science degree, with little concept of laboratory animal medicine as we know it. But they also noted an enthusiasm and commitment to learning, which has been referenced earlier today.

Initially, I think, veterinarians in China [and other Eastern countries] would be well served to develop open communication and mentoring programs with their Western colleagues—again, something that was discussed earlier. In addition, newly created distance learning programs offer opportunities for growth.

The role of the IACUC and ethics committee may also vary. The importance of these committees has been recognized as a global standard, and the importance of animal care and use oversight has also been recognized. As such, even if there is no regulatory requirement for such a committee, many companies will require such a committee if they have facilities in these locations. As we heard from Dr. Landi, companies may require such a committee if they are going to do collaborations. In fact, at the First Shanghai Animal Welfare Forum on International Standards, held in March of 2008, several laboratory animal experts who visited China were very impressed with the IACUCs and ethics committees that they observed. However, as with the attending veterinarian, there was some concern about the level of actual authority of the committee.

I think this concern can be addressed through a combination of training, institutional commitment, and policy. I think the fact that the *Guide* discusses the role of the institution in ensuring that people are appropriately qualified or trained if they are going to be using animals adds emphasis to this responsibility and should help ensure the IACUC's role. Although the exact roles and responsibilities of the key personnel of an animal care and use program may vary, it's important that the roles and expectations of all parties are well documented and well understood.

The importance of understanding the culture of your audience cannot be overemphasized. To develop a training program, you must understand the cultural attitudes and approach to training. For example, in China, the Confucian way of learning has been practiced for centuries. This method leads to differences in knowledge acquisition and application, and relies a great deal on read-

ing and memorization and practical application of what was learned. This can be enhanced with visual learning in which there is a repetition of practical examples. The Confucian way of learning is particularly well suited for learning steps of the process, such as learning an SOP. However, to be fully effective for animal care and handling, this must be accomplished by well-mentored, hands-on training.

In many Eastern cultures, the importance of saving face must also be considered when training. As in all cultures, when correction is needed, you may criticize the way a task is done, but you have to do so diplomatically, preferably in an impersonal way, and very carefully. You should avoid criticizing persons, particularly in front of others. The proposal method—"How about doing it this way instead of that way?"—is an alternative way of helping someone understand a different mechanism of performing a task.

The trainer also has to be aware of a cultural reluctance to speak up if a point is not understood or if someone thinks something is wrong. Frequent, open-ended questions can help develop topics and help ensure that they have been understood. Asking individuals to propose solutions to problems or events is another way to help ensure understanding and help individuals practice the concept of being comfortable speaking up.

It helps to determine the existing level of knowledge as well as the ability of the individual to apply that knowledge.

Another important cultural component to consider is the general cultural attitude toward animals. Globally, these attitudes have changed over time. In fact, they continue to change all the time, as humans and our standards of living have changed. In societies where providing humans with adequate sanitation and nutrition is problematic, it is more difficult to make the case for the importance of providing those for animals. However, the drive to modernize should not be underestimated. Many countries actively seek to assure the public and businesses of their understanding of animal welfare, and they do understand the importance of animal welfare to global reputation in the biomedical field.

Technical training is relatively straightforward and can be accomplished by providing detailed written guidelines, which can be read and memorized in the Confucian tradition. Competency can also be relatively easy to assess. Attitudes toward animals are more difficult. It can be useful to include a culture of caring, humane care and use of animals as part of a person's written job responsibility. It helps to raise awareness of the importance of animal welfare and helps people understand that this is actually a duty. You will find that in many of these countries, the fact that it's a duty helps to raise people's awareness and provides some assurance of behavior. Many cultures are very sensitive to the idea of duty. Speaking up about something that is perceived to be wrong is also an example of something that you can say is a duty.

Repetition on the subject of gentle handling, respect, and minimizing the potential of pain and distress and the intrinsic value of animals is also recommended.

When Charles River decided to open a contract facility in China, it was not done to try to avoid any regulations or standards but rather, as we heard earlier, to meet the needs of a burgeoning research community that is responding to the health needs of a rapidly growing country. Maintaining our key corporate value of humane care of all animals produced and used in our facilities was always a key point. Also important was providing quality research and testing for the biomedical research community. To do this, we used a concept of knowledge transfer through participation in activities. This is sometimes referred to as the transfer of tribal knowledge.

To prepare us for this, we used intensive cultural training, to help us be most effective and sensitive to our Chinese colleagues. We had key staff from our new Shanghai facility spend one or more three-month rotations at our site in Montreal. These individuals were embedded in the day-to-day activities and were involved in both hands-on experience and decision making. In addition, key qualified individuals from Montreal have spent or are slated to spend one or more three-month rotations in Shanghai. Some individuals are going to spend two to three years at the site to help oversee the development of our corporate culture for quality and animal welfare.

This knowledge transfer allows us to more easily teach attitudes. It fosters personal connections and trusted relationships that are important in all cultures. It allows for immediate assessment of understanding and can more readily accommodate different learning styles. Although labor-intensive, we believe that this will lead to a stronger program.

We have internal animal welfare modules that cover such topics as euthanasia, reporting concerns, and species-specific training, which focuses on how an animal's biology, physiology, anatomy, and so forth, create specific husbandry and handling needs, and how handling affects animal welfare in that species.

In addition to this internal training, personnel from the Shanghai site have attended regional meetings, such as the First Shanghai Animal Welfare Forum on International Standards and AAALAC's accreditation process, as well as international meetings such as IACUC 101 and 201 in the US and the Charles River Short Course. This September, there is a joint workshop in Shanghai with CCAC and the Shanghai Animal Commissioning Agency. We also have ensured that personnel in key leadership roles, such as the attending veterinarian, the IACUC chair, and the operations manager, have extensive experience with programs such as those recognized by AAALAC.

As with all our animal care and use programs, there is a system of checks and balances in place to ensure adherence to the quality and humane care we expect. In addition to various standard regulatory audits and inspections, the Shanghai facility is in the process of pursuing both CCAC and AAALAC accreditation. Sponsors also make regular and thorough site visits. We also have a program of internal corporate audits, which look at all aspects of the program, including animal welfare. Of course, there is corporate review of all IACUC semiannual reviews from all Charles River sites.

In summary, animal research in different countries and different cultures may be different, but this does not mean deficient. I believe that the challenges of animal research in a global environment can be met using training and education. Meeting the challenges requires sensitivity and institutional com-mitment to doing it right. High-quality research and testing and animal welfare can be achieved at many geographic locations. Doing animal research in a different culture does not mean doing animal research using lesser standards. Flexibility, with a clear eye on humane care and quality research, is required.

The FELASA Training Program

Patri Vergara

The purpose of this conference is to discuss and address challenges in animal research in a global context. Education and training are closely linked to quality of performance. Two important features characterize biomedical research nowadays: the number of countries where research is done is continuously increasing and there is a global exchange of research results and of scientists. This creates two important challenges for education and training: an increasing demand for training, especially from emerging countries, and the need to establish globally accepted systems of accreditation. The Federation of European Laboratory Animal Science Associations (FELASA) has been focusing on (1) defining categories of personnel working with laboratory animals; (2) defining guidelines for the education and training of each category; and (3) developing a FELASA accreditation system, to ensure that courses comply with FELASA guidelines and are of a high standard of quality.

Personnel Categories as Defined by FELASA

FELASA has identified four categories of competence for personnel working with laboratory animals (FELASA 1995), which have been adopted by the Council of Europe and have therefore become a standard in Europe:

Category A, persons taking care of animals;
Category B, persons carrying out animal experiments;
Category C, persons responsible for directing animal experiments; and
Category D, laboratory animal science specialists.

Categories A and D personnel are professionals devoted to laboratory animals, while personnel in Categories B and C are professionals from different specialties who design and conduct experimental procedures with animals. The training for Categories A and D focuses on the development of a professional career, and the training for Categories B and C provides the training necessary

for the correct use of animals in research based on the 3Rs principles of replacement, reduction, and refinement.

FELASA Guidelines

The FELASA modus operandi is the establishment of working groups with experts from the associations that compose FELASA to define the guidelines, taking into account the diversity in Europe, and to promote high standards to promote good science and to fulfill the ethical demands in the use of animals that society and the European legal system require.

From 1995 to 2000, FELASA published guidelines for the education and training of each category of personnel (FELASA 1995, 1999, 2000). These guidelines are easy to find on FELASA's website (www.felasa.eu) and they have also been translated into other languages (e.g., Spanish, www.secal.es).

Category A

The guidelines for FELASA Category A are under revision. However, according to current discussions in the working group, the main characteristics of this training will be three, instead of four, levels of training: A0, for new personnel taking care of the animals, this minimum training will consist of a short course of around 20-30 hours; A1 and A2 are more advanced levels and will require several years of training involving a combination of theoretical, practical, and hands-on training at work. A0 training will be able to be easily adopted by developing countries while A1 and A2 programs will be designed to fulfill the requirements of countries with a more developed animal welfare system.

Category B

This training is for animal technicians and laboratory technicians who conduct experimental procedures with animals. In some countries novel researchers (e.g., PhD students) are also included in this category.

FELASA (2000) guidelines recommend a 40-hour course with 50% of practical training supervised by accredited personnel. The practical content can be tailored to the trainee's specific needs. Additional training will be necessary if the person needs to perform new experimental procedures.

Category C

For this category, FELASA (1995) requires the trainee to have a university degree that includes sufficient knowledge of animal biology. The specific training is acquired by way of a postgraduate course of 80 hours or equivalent. The syllabus must include the following topics:

- biology and husbandry of laboratory animals
- microbiology and disease
- health hazards and safe practices in the animal house
- design and conduct of animal experiments
- anesthesia, analgesia, and experimental procedures
- alternatives to animal use
- ethical aspects and legislation
- analysis of scientific literature

In some countries this training is achieved in two stages: a Category B training course at the initiation period, followed by a complementary module when the researcher is going to be responsible for the design of the experiments (scientist).

A comprehensive 80-hour course is becoming the standard in the majority of European countries. This training is provided when a postgraduate initiates his/her research career (e.g., a PhD).

In addition, Category C training is in high demand by scientists in emerging countries. ICLAS and FELASA and other European bodies have supported this training in several regions of the world: Southern Europe (early 1990s), Eastern Europe (late 1990s), Latin America (late 1990s), and more recently in Africa. In these cases the course has to have a broader perspective and be addressed to both scientists and personnel responsible for animal facilities. Experience has shown that the best results for continuity are obtained when:

- local professionals are incorporated as teachers,
- professionals who could take responsibility for teaching specific topics in future editions of the course are included as students (training the trainers), and
- only partial support is provided so that local agents, the student, and his/her institution are jointly responsible.

Quite frequently, the course is implemented with the financial support of an international body. Around $2,000-$5,000 per course per 20 students is the average financial support necessary to promote this training.

Category D

For this category, FELASA (1999) guidelines propose specialized postgraduate training of two years of full-time study or equivalent part-time (including 6 months for a research project). The background training required is a veterinary or other university degree with similar competence in animal biology and welfare knowledge.

This program is included as a requirement for veterinary specialists who hold the Diploma of the European College of Laboratory Animal Medicine (DipECLAM). ECLAM also requires further training on veterinary care.

To provide and/or obtain Category D training is a real challenge even for the well-established European universities and it becomes almost impossible for professionals working in emerging countries. The most common problems are: (1) it is expensive and the training lasts a long time, (2) it requires contact with high-level facilities and professionals who are often not available in the country, and (3) it is preferable that the trainee stays in his/her job/country while receiving the training. Therefore, improving access to specialized training for professionals who are responsible for the growing number of animal facilities around the world must be a goal both for international bodies (e.g., IACLAM, ICLAS, and FELASA) and for the private companies that employ this type of personnel.

Possible solutions are (1) to create an international fund for training, supported by IACLAM, ICLAS, and others and also by private companies; (2) to arrange the existing programs (mainly in Europe and North America) in a modular way or to facilitate online distance learning; and (3) to develop tutor supervision of hands-on training. All these measures will facilitate access to high-quality training for professionals from emerging countries. The fact that the trainee can apply the acquired knowledge in an immediate way will significantly increase the quality of science globally.

FELASA Accreditation

Accreditation systems have demonstrated that they are an important factor in improving standards. For this reason FELASA established an accreditation system of teaching and training in laboratory animal science. The guidelines to fulfill FELASA accreditation have been published (FELASA 2002) and an Accreditation Board was established in 2003; details and application forms can be found at FELASA's website. This accreditation system is not limited to training based in Europe.

Conclusions

The current globalization of animal research is an excellent opportunity, but we need (1) to establish financial support systems for both training programs and personnel, (2) to promote training in countries with emerging demand, (3) to support the continuing education of professionals worldwide, and (4) to use existing international professional organizations (e.g., FELASA, IACLAM, ICLAS) to provide accreditation and validation of the training.

References

FELASA [Federation of European Laboratory Animal Science Associations]. 1995. FELASA recommendations on the education and training of persons working with laboratory animals: Categories A and C. Report of the FELASA Working Group on Education accepted by the FELASA Board of Management. Lab Anim 29:121-131.

FELASA. 1999. FELASA guidelines for education of specialists in laboratory animal science (Category D). Report of the FELASA Working Group on Education of Specialists (Category D) accepted by the FELASA Board of Management. Lab Anim 33:1-15.

FELASA. 2000. FELASA recommendations for the education and training of persons carrying out animal experiments (Category B). Report of the FELASA Working Group on Education of Persons carrying out Animal Experiments (Category B) accepted by the FELASA Board of Management. Lab Anim 34:229-235.

FELASA. 2002. FELASA recommendations for the accreditation of laboratory animal science education and training. Report of the FELASA Working Group on Accreditation of Laboratory Animal Science Education and Training accepted by the FELASA Board of Management. Lab Anim 36:373-377.

Plenary Lecture

Animal Research in a Global Environment: Meeting the Challenges

John Baldoni

Good morning, everyone. It is a pleasure to be here. I thank the organizers for the invitation.

It is really humbling for me to be here because I am not in your field. I am a chemist by training, have moved through the pharmaceutical industry in various jobs, and now head up a group [at GlaxoSmithKline] called Preclinical Development.

I thought for this talk I would go through a bit of scene setting first, describe what it is to work in a core function such as preclinical development in the pharmaceutical industry. Give you some examples of the challenges to drug development on a global footprint on a generic basis, not only in terms of the care and use of animals but also both in geographic terms and what it takes to develop a drug. Finally, I am going to try to translate that to some of the responses that we have implemented to these challenges relating to animal usage in R&D at GSK.

Background on GlaxoSmithKline

First, I would like to give a little perspective on GlaxoSmithKline. GSK is a multinational company with a goal to improve the quality of human life by enabling people to do more, feel better, and live longer. All pharmaceutical companies have a goal and aspiration such as this. This is the reason to operate. This is the hope of every company that develops medicines: to make people better and to give people hope and to enable them to do more things in their lives.

At GSK we have around 100,000 employees; the number is fluctuating all the time. You read the newspapers. There are changes all over in the pharmaceutical industry, and GSK is not immune to them. We have roughly 15,000 people in research and development on more than 20 sites in 10 countries at this point.

Our R&D organization is a little bit different from many. That is one of the challenges that we have in GSK that others may not have. We have therapeutically aligned centers of excellence for drug discovery (CEDDs) in Europe, in the United States, and in China. So you begin to see the geographic diversity of our R&D organization.

In each CEDD there are multiple discovery units, which focus on specific biochemical pathways or specific biological targets. Sometimes it is a biochemical pathway and trying to intervene in that pathway, and sometimes it is a very specific protein that we are trying to design a molecule to modulate.

There is extensive externalization at GSK via partnerships with biotechnology companies. This has been much publicized in the popular press, regarding GSK strategy and externalization. I am going to get a little bit more into that. It is one of the dynamics that is important for us to consider and perhaps for you to consider when you think about your remit in this organization.

We have a very clearly stated strategic intent: to globalize our research. We have acted on that strategic intent tactically, where we have set up a fully integrated functional R&D organization in Shanghai, China. The intent of that organization is not to develop drugs for China but to develop drugs for the world. The organization was set up in June of last year (2007). By June of this year (2008) we had over 270 employees in that research laboratory in a new building and construction of an additional building.

I am giving a perspective on GSK. Any global major pharmaceutical company now will have a similar story. But we are not typical. There are other pharmaceutical companies looking at how we organize, and going from big R&D units to small R&D units, essentially taking advantage of the wisdom of a crowd of discovery units as opposed to that of a single monolithic discovery unit.

With regard to our R&D units, there is a great deal of complexity related to the core processes that we use in conducting our work and delivering our products. We have an extensive network of research facilities in the UK, three in the US, France, Poland, Croatia, Italy, Spain, Singapore, Shanghai, and Canada. This creates opportunity for us to take advantage of the science occurring in these geographic regions. For example, our interest in Croatia was a very specific platform that we felt would transform our ability to address a specific disease. We bought a company in Croatia and have made them a bit entrepreneurial. They are now exploring opportunities to address a specific disease target.

Not all of these sites are fully integrated from discovery all the way through commercialization. The UK sites are, but the Ireland site is not. Italy is, but Spain isn't.

Trends in the Pharmaceutical Industry

There is a mix in a pharmaceutical organization, a confluence of behaviors and attitudes and regulations and cultures. A modern pharmaceutical R&D organization is always going to be driven by innovation and risk taking. This is

because the regulators around the world have clearly told the pharmaceutical industry, "We want different kinds of medicines. We don't want medicines that are incremental and expensive; we want medicines that are transformational and cheap." This is a big change for the pharmaceutical industry, which in the past has been supported by products called line extensions. If you look at the names of drugs and see XR or CR or something like that after the name, it typically indicates a line extension. These extensions create benefit for the patient, but they don't often affect the therapeutic outcome, sometimes they just provide dosing convenience. Many are now questioning the relevance of line extensions.

Scientific rigor is absolutely paramount—without it we are not going to get those transformational ideas. We now assess the risk of developing a drug from a biochemical pathway target, all the way through to the animal model, all the way through to the manufacturing, all the way through the commercialization and the system to distribute and sell the drug.

Our ability to sell a drug 15 years from now depends absolutely critically on the scientific rigor used to identify a target and its pathway, and picking the right molecule to affect the target. Three simple questions: Is it the right target? Is it the right pathway? Is it the right molecule? The answers to those three questions cascade a series of events that ultimately cost over a billion dollars today.

Declining Productivity

There has been a lot in the literature about the productivity of modern pharmaceutical R&D organizations. There have been fewer new drug approvals in the last few years than in the previous ten. A lot of money is being spent in pharmaceutical R&D, and all that money has generated a huge benefit to society. But the financial consequences of that benefit to companies are dropping off very quickly. Within the next four years, over $200 billion of pharmaceutical sales will be lost to generics, it is a big number. Those generic drugs are going to be much cheaper and they are going to be very effective. The next generation of drugs that pharmaceutical companies are developing has to be better than those and to answer different questions, with a different safety profile and with more efficacy.

R&D has to increase its productivity to give us more meaningful medicines. I want you to think about entrepreneurism here, and entrepreneurial spirit. In almost all R&D organizations now, they are talking about entrepreneurism. Looking at the biotech industry in the United States, on the East Coast and the West Coast, there is a lot of entrepreneurial spirit. There is a lot of success. [Companies there] break through barriers, they do things differently, faster, and cheaper. They leave huge gaps in their programs that have to be filled later, but at the end of the day you know whether you have a meaningful medicine, and you can invest very heavily in that meaningful medicine and fill the gaps later.

Increasing Externalization

The trend is to be geographically diverse: "Go to the science." GSK has made a decision that we are not going to bring the science to us, to our sites, to our geography; we are going to go where the science exists. So we made decisions to go into Croatia, into China, and we continue to do that. We have purchased companies in Boston and we have left them in Boston. We purchased a biopharmaceutical company in Cambridge, England, and we left it in Cambridge. We didn't put it into one of our five sites in England. We are leaving the science where it is developed. That creates more diversity in culture, more diversity in behaviors, and we have to ensure that the core principles in our company encompass those people and bring them into using our core principles. I will talk more about that as it relates to animal use.

At GSK, we are exploring our pipeline in different ways. We have in-house expertise; we are partnering externally extensively; and we are going with virtual drug development companies, people who have ideas. We buy the idea and they develop the drug on the outside. That is virtualization.

Externalization means that there is a company out there that has a molecule or a biochemical target that we don't have. We are paying them to explore that target, and when they give us a reason to believe, we will buy that molecule back from them.

At GSK in the past, I would say 80 percent of our work was done in-house. In the future I would say more than 50 percent of our work is going to be done externally—externalization and virtualization.

Maintaining Quality with Simplified Governance

Empowerment is a word that I want you to think about as it relates to the care and use of animals in R&D, against that geographic background. We are empowering our people that run or work in these units, which define the strategies for success. If their strategy for success is to use an internal chemical development group to synthesize their drug, they can do that. If their strategy for success is to externalize synthetic chemistry to a contract manufacturer in China or India, they can do that.

What they can't do is negate the quality standards or the core principles of our corporation. So there is a diligence that we have as a company to ensure that as we discover and develop drugs we don't go outside the boundaries of our core principles or our quality standards in developing drugs anywhere in the world.

Simplified governance falls under empowerment. We are doing away with a lot of review bodies in GSK but keeping key ones. Those retained ask questions like where is the quality in the product, what is the animal model, how are you ascertaining the efficacy of the drug. I already talked about integrating quality into the drug discovery and development process. It is paramount. It is abso-

lutely critical that we have quality at every level, from the biology to the chemical manufacturing controls to the regulatory to the clinical trials.

The industry as a whole is moving very quickly away from industrialization. Industrialization was a platform approach, a checkbox approach to developing drugs. If a machine can make 50,000 compounds a day, I am going to make 50,000 compounds a day. If I have a machine that can screen those 50,000 compounds against 200 biochemical targets, I am going to take 50,000 compounds and screen them against 200 biochemical targets a day. This process generates data that would fill unbelievable computers.

But it hasn't been successful. Over the last ten years during this industrialized pharmaceutical R&D we have gone through a nadir in productivity of new drugs in the pharmaceutical industry. To varying extents, many pharmaceutical companies are now deindustrializing their processes and going to a judgment-based approach, putting smart people on a narrow focus to address the issues at hand in their biochemical pathway or their biochemical target, and design molecules very selectively.

Against geographic diversity, with all of its political and cultural diversity of behaviors and attributes, you can see there is a storm brewing here in the pharma world.

Preclinical Development at GSK

I am going to shift now and tell you a little about my department—it is one of those core functions that enable a lot of the stuff to happen. Then I am going to talk a bit about some of the challenges that we see and our responses to those challenges.

As I said before R&D in GSK is set up with discovery units. On the front end of those discovery units we have machines that generate reagents, biochemical targets, proteins, and we work with the discovery scientists to come up with cell-based assays, to test their hypotheses. That is called molecular discovery research in GSK.

On the back end we also have some major functions, one of which is preclinical development. Behind that is clinical development and behind that is the office of the chief medical officer, and behind that is regulatory and compliance. There are lots of layers of big engines in a major pharmaceutical company.

The one I am most interested in and the one I am most proud of is preclinical development. In preclinical development we have five major departments: drug metabolism, which investigates the absorption, distribution, metabolism, and excretion of our molecules; pharmaceutical development, which develops the dosage form and the manufacturing processes for those dosage forms; safety assessment, which assesses the hazards and identifies the risks of molecules; chemical development, which actually makes the drug substance and scales it up and transfers it to factory; and laboratory animal sciences, which you

heard about yesterday from Margaret Landi, whose group ensures the care and ethical use of animals in R&D in our company.

Preclinical development spans the whole drug development process, encompassing research, development, and commercialization—from the target, lead candidates (the hundreds of molecules that might be drugs) selection of a candidate for development, and then first time into humans, first proof of concept, safety and efficacy trials, filing for approval, and commercialization. To varying degrees each one of those five departments spans the whole drug development process. In GSK about 4,000 out of 15,000 employees work in this core function called preclinical development.

In preclinical development, we take scientists' ideas and translate them into a chain of events that results in the conversion of the idea to a drug substance in chemical development, to a drug product in pharmaceutical development. We distribute those supplies for clinical trials around the world, which then get into patients' hands in very controlled settings in order to ascertain the safety and efficacy of our drugs in an experimental basis.

We do this using two different processes. One is to understand the risks from a biological perspective, which involves in vitro work, and to understand how our drug behaves in in vitro systems and ultimately in in vivo settings. Preclinical in vivo studies involve conducting animal model efficacy studies with discovery scientists, regulatory-required preclinical studies required to demonstrate the safety of a molecule and, importantly, investigative toxicology studies, which constitute a lot of what we do. The drug development process is fraught with a lot of surprises, and a lot of them are manifestations of toxicity. The relevance of those toxicities in humans has to be investigated prior to human testing, thus a lot of investigative toxicology studies.

The other pathway is to deliver the product from the chemistry and pharmaceutics perspective. We develop the physical product that you hold in your hand, whether it is a tablet, an inhaler, an ointment, or a cream or the like. We transfer that to manufacturing and ultimately it is that product that makes people feel better, live longer, and do more things.

So that is a picture of what we do in preclinical development, at a very high level. It is not that simple. It is a very complex process—both of these pathways are among the most regulated processes in the industry.

Challenges of Globalization

Now I will talk a little about the challenges to R&D. In looking at a picture sent to me by Margaret Landi and Jeff Everitt, I saw this sky and asked why the sky is red? It is either a sunrise, which may be the dawn of a new era for pharmaceuticals, or it might be a sunset, which I hope has no metaphor for pharmaceuticals. Then I thought I would take a realistic approach. This is a firestorm and the sky is red because the world is changing in the pharmaceutical industry. So this is the metaphor I am going to use here. I think when that fire-

storm is out, it is going to be a sunrise, and it is going to be beneficial to everybody, because the whole pharmaceutical industry realizes that it has to change.

I mentioned meaningful medicines. What are they? To us they are medicines that are affordable, accessible, and sustainable, and that have greater safety than current molecules with enhanced efficacy. Affordable and accessible—they go together.

It is great for most of us in this audience from the Western world to have access to the most modern and fantastic medicines that make us feel better, that make our families feel better, make us better, able to do more things and to live longer.

But we are actually a small population in the grand scheme of things. There is a world out there that doesn't have access and doesn't have affordable medicines.

Access and Sustainability

When you go to the drugstore to get your prescription filled, or when it comes in the mail, you get a bottle of 30 or 60 or 90 tablets. When people in a developing country get a prescription filled, they say "I have three cents and I can buy one pill. So I am going to buy that medicine for today and I am hoping I can get another three cents to get that medicine tomorrow and the next day and the next day." That is not accessibility.

That is a big challenge for us in our industry. It is a challenge that we at GSK are taking very, very seriously. At the top, the middle, and the bottom of this organization we are thinking about how we can have our medicines be more accessible and more affordable.

What does sustainable mean? It means that when we get a medicine on the market and people are expecting that medicine to make them or someone in their family feel better, or the person they are taking care of feel better, they have to have confidence that that drug is going to be on the market forever. There aren't going to be hiccups in quality that cause a recall. Our company has been burned by that; most have. We are getting better and better at that. But it comes into this global environment in which we work, and global standards.

So we have a single quality standard. It starts very early in the drug development process. We ensure, as we go through our drug development process, that we build quality into our product so that if and when that product launches, we have some assurance that it is going to be sustainable in the market from a quality perspective.

Transparency and Regulation

There are many stories around the safety of our drugs. As we get more experience with patients in the real world different safety issues arise, and we have

to understand those, we have to react to them, and we have to have programs in place to address them. We strive for greater safety.

The industry is very transparent on this. You can go to websites for every pharmaceutical company and look at every drug that is on the market and look at the safety reports for all those drugs. There is a lot of transparency.

I have already addressed the issue of greater efficacy. There is a patient need, there is a financial need, and there is a payer need for drugs with greater efficacy.

There are some challenges, though, to creating meaningful medicines. There are societal expectations: people expect that with all the money they are spending on drugs, the return on that expenditure is better drugs. There is activism—in the animal world, in the patient world, and in the political world, people asking of pharmaceutical companies: What are you doing? How are you doing it? Why are you doing it that way? How can we get this done?

There is also public perception, positive and negative. When people find out that I work for a pharmaceutical company, the binary nature of the reaction is remarkable. My neighbor comes across the street, "I hear you have got this new diabetes drug, is it going to help me?" "Talk to your doctor," I say. Headlines in the *New York Times*, "Glaxo diabetes drug safety issues." He comes to my door, "What the heck are you doing to me?!" I say "Talk to your doctor."

The examples are real. These are real issues that we have to be concerned about. If we don't do things right, we lose our ability to do what we do, because people will lose confidence in us and in our industry. That is the worst thing that can happen, for them because they will be hesitant to take our drugs which will make them better, and for us because then we don't have a reason to exist.

On the other hand, with all of these challenges to pharmaceutical companies, there are some things we can do. We can respond to the social issues. There are cultural differences. There are also some hard issues—there are legal differences in geographic regions, the regulatory requirements in geographic regions are different. The regulatory stringency is ramping up.

We have a group in R&D called the Good Manufacturing Practice (GMP) Quality Council, which I chair. On a quarterly basis, we look at what is going on in the world and ask what is going on that is different from what we know now? What do we have to do in our quality organization to adapt to that? This isn't a talking session; this is a real conversation session. We are very rigorous on ourselves.

As a consequence of what is changing in the world and the geographic expanse and the lack of harmonization in many instances, we are changing our quality approach to adapt. The way we were doing this wasn't sustainable. It wasn't sustainable for us to have a quality standard in R&D that was slightly different from the quality standard being used in Cork, Ireland, for example, or in Shanghai. So we are reacting to that.

The challenges to the industry are coming from two areas (this isn't a comprehensive list, I am using examples here). There is the social, the cultural part of this, and then there is the hard reality, the legal part.

Responding to the Challenges

Those are all things that are putting pressure on meaningful medicines and tipping that balance, so to speak, between what we have to do to develop our drugs—the innovation, the biochemical pathways and all of that—and what we have to do to ensure that we maintain the capability to keep developing drugs.

If I were to present this as a balance, there are a lot of things that are pushing us into the red zone, the danger zone. There are also some things that we can do to respond. For example, we can be better at understanding the science. If we are better at understanding the science, maybe we can have supportive business processes that enhance our ability to build trust. If we build that trust and engage shareholders, we will be able to address the social and cultural parts by taking an approach that links the science to societal needs, so that people have a reason to believe in what we do in the industry. I want to talk about one of these areas as an example.

Ensuring Good Science and Animal Welfare

First, this is fundamental: Understand the science, justify the experiment. Good animal welfare is absolutely necessary for good science. I don't think I have to tell you that. Some of our studies are conducted over a year, two years, and we have to ensure that the variability of the animal does not contribute to the variability inherent in a testing of a biological hypothesis.

We in GSK are now requiring a justification for the rationale for an animal efficacy model on a target-by-target basis. What do I mean? If there is a diet-induced obese model being used to explore diabetes, and one of the biochemical pathways they are exploring is insulin sensitization, justify that diet-induced obese model. If it is the glucose transporter target, question why are you using the same model? Force people to think through the biochemical pathway and the relevance to the efficacy model that they are proposing. This creates a lot of positive tension in the organization; we are asking people to challenge the past and look to the future. Why is the model for insulin sensitization the same as for a glucose transporter in the kidney? If it doesn't make sense, justify it.

Another area we are addressing is to understand the biological variability that could impact the interpretation of the hypothesis to be tested in that efficacy model. At GSK we have statisticians working with our biologists to understand the variability of the efficacy model and correlate it to the variability required to test the hypothesis, both in animal numbers and in the biological response,

We require a challenge for replacement, reduction, and refinement in our review of each protocol. But there are additional challenges coming, too. The biopharmaceutical area is emerging—it is going to explode in the next ten years. That is going to create new challenges for us. RNA interference entails new challenges for us in the use of animals in R&D. Recently we have been getting a lot of questions around how we are going to assess the safety risks of nanotech-

nology. We in GSK have a nanotechnology program and we are thinking that through right now.

Importantly, we invest in platform technologies that underpin our corporate policy in the use of animals in R&D. What does this mean? We spend money exploring technologies that allow us to adhere to the 3Rs and to our core principles that Margaret Landi talked about yesterday (I'll give an example of that later).

Implementing Supportive Business Processes

The second response to the challenges is: implement supportive business processes. You heard about laboratory animal sciences (LAS) in GSK yesterday. It is a global organization. Before we do any work in any site, in any place in the world, that group assesses that organization against our policy on the care and use of animals in R&D. LAS was instrumental in setting that policy with the highest levels, including the CEO of our company. It leads the policy implementation and adherence to that policy, so there is an audit function to it. It reviews internal operations to the relevant standard. We adhere to the most rigorous standard where we conduct work—country or corporate standard.

We evaluate external work done on behalf of GSK, even if GSK isn't sponsoring the work. We set expectations of adherence to GSK core principles for those partners performing work being done either on our behalf or in conjunction with us. If we have scientists working in an academic laboratory doing animal work, we assess that academic laboratory for adherence to our core principles. LAS drives consensus on best practice around the organization, which creates a lot of constructive dynamics and constructive debate in our organization. It maintains knowledge and activities in various regions. So, therefore, they have to have cultural and legal acumen. This again is a major activity in the diligence group in the LAS organization.

Importantly, we reward and publicize desired actions and behaviors. I will give you a couple of examples. We have a group of people that thought there was a technology that would reduce the volume of blood required to do our toxicokinetic (TK) studies. We gave these people a budget, and they came back and developed a technology using materials off the shelf—they just were very creative in how they put it together—that resulted in our ability to take microliters, as opposed to milliliters, of blood from rodents to do TK studies. So the number of animals was reduced and the amount of intervention stress on the animals was reduced significantly.

That is an example of where we built a platform, and that platform is being rolled out across the organization right now. It is not applicable for every compound but it is applicable for over 90 percent of our compounds.

We also have this policy that we want self-disclosure. If somebody in an animal handling facility or an animal facility has an issue, they are encouraged to talk about it, to self-disclose. We have a session where they talk and

learn from each other by asking what happened, why did it happen, how can we do it better.

Senior leaders in the organization, including myself and the head of drug discovery, visit animal laboratories to ensure that the people that work in our animal facilities understand that this is an important function to the organization. They understand that they can approach us if there are issues in their organization or in the way work is being done in their laboratories.

Audits, "Constructive Conflict," and Stakeholder Engagement

Finally, Margaret's organization does internal, independent, and third-party audits. We take this very seriously. We are audited both by our internal group in preclinical development and by a corporate group, so we go through two audits: a self-audit and a corporate audit. Then of course we are audited by regulators.

We have a public statement on the use of animals in research to build trust; I think Margaret talked about that yesterday. We use GSK core principles, which are independent, as I said before, of location, an outside company's relationship with us, or the study size.

Importantly, we get world-class experts in laboratory animal sciences and we make them influential. We put them in front of people, we put them in front in the debate—there is a lot of constructive debate that goes on, there is a lot of conflict. We are a better organization because of that conflict—I call it constructive conflict. We can't have growth in this area unless we have constructive conflict.

We ask challenging questions. A very senior person at GSK when visiting a discovery laboratory asked how much human tissue was used, and the scientist said, "We use a lot, we are really moving in that direction." This very senior leader in the organization said, "How has that impacted your use of animals in research and development, how much has it diminished it?" It is challenging to have the most senior person in an organization ask a scientist at the bench a question like that, but that is our approach.

We acknowledge success and address deficiencies. There is transparency and interpretation of rules and implementation with judgment on legislated standards. That drives the constructive debate that I talked about earlier, not just in our organization but in settings such as this meeting.

With regard to stakeholder engagement, I already talked about knowledgeable senior leaders in the organization. There is a regular dialogue among the users, the caregivers, and the comparative biologists in our organization to ensure the relevance of the animal model, as I described earlier. We have a culture of continuous improvement. We share knowledge across the organization, across those ten countries and those 20 sites.

I sit on the R&D Executive Committee, and on a regular basis we have a session where we talk about the use of animals in R&D. We keep metrics on the use of animals and we act on those metrics.

Externally, we engage stakeholders in meetings such as this. We endeavor to understand the local regulations and, importantly, the environments in which our people are working, so that we can understand the culture in which they work and the stress they are under and how we can help them, through mutual education and exploration of differing views, and, as I mentioned, we encourage audits by external and internal groups.

Conclusion

In summary, the pharmaceutical environment has changed and will change in the future. Standardization across geographic regions and cultures and jurisdictions is not realistic now, because it is too dynamic. We will rely on core policy, principles, and values.

One of the most important principles is that of peer review. This creates the challenge we want to understand of the scientific hypotheses to be tested in animals and to question how replacement, reduction, and refinement are being considered. The first few times we went through this, it was difficult. Now we have our CEDD heads engaging our people and asking them to justify their experimental models. That is the transformation we are looking for, the kind of drive we are looking for in an organization.

It comes only with deep expertise in comparative biology. These people are going to be with some of the world-class scientists in the therapeutic area discussing a biochemical pathway in an animal model. Our comparative biologists have to go toe to toe with them. They have to be just as world-class in their discipline. And they have to have courage, if I could use that word, because they are put in challenging situations.

Diligence ensures adherence to principles and dissemination of learning. It is not good enough to just audit. We have to audit, we have to talk about it, we have to put it out there, we have to air findings and share corrective actions, and we have to make people understand when things have to change.

Finally and importantly, operations based on publicized core principles and continuous improvement enable geographic flexibility in where work is conducted. The standard creates the corporate way of working. We have assurance that, through our policy and processes, through the science that we emphasize, and through our audit functions, we will meet our standard anywhere in the world. If the standards cannot be met, we don't do work there. That drives good behavior in our organization and in those organizations with whom we work.

Veterinary Care for Laboratory Animals

Standards of Veterinary Care for Laboratory Animals

Kathryn Bayne

In June 2007, in association with the Federation of European Laboratory Animal Science Associations and the International Council on Laboratory Animal Science (FELASA/ICLAS) meeting in Como, Italy, ILAR and the International Association of Colleges of Laboratory Animal Medicine (IACLAM) invited representatives of laboratory animal medicine organizations from around the world to meet and initiate a dialogue about appropriate veterinary care standards for laboratory animals. Participants included individuals knowledgeable in regulations and guidelines pertaining to veterinary care of laboratory animals from organizations such as the American College of Laboratory Animal Medicine (ACLAM), Canadian Association of Laboratory Animal Medicine (CALAM/ACMAL), India's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), European College of Laboratory Animal Medicine (ECLAM), European Society of Laboratory Animal Veterinarians (ESLAV), FELASA, Singapore's National Advisory Committee on Laboratory Animal Research (NACLAR), and the United States Department of Agriculture (USDA).

The sources of the various international standards were reviewed and summarized. These sources include standards established by government agencies, in the form of legislation, regulations, or policy, but also guidance derived from professional organizations primarily composed of laboratory animal veterinarians.

Based on presentations summarizing those guidelines and regulations, three main themes of interest could be distilled from the discussions: (1) the qualifications of the veterinarian, (2) the authority of the veterinarian within the program, and (3) the role of the veterinarian. Both convergence and diversity of approach to these three points were described by the participating representatives, suggesting that harmonization is occurring in some areas of veterinary care while in others there remain differences, some of which could be quite significant.

Qualifications of the Veterinarian

Table 1 depicts the wide variety of degrees that denote training in veterinary medicine. Some are bachelor's degrees in veterinary medicine or veterinary science, others are doctorate degrees. Some reflect two years of undergraduate education, others four or more years of undergraduate and graduate education. Some degrees include coursework in laboratory animals, or even a "track" in research, others do not. This range of training may be augmented by postgraduate education or it may not—depending on the country's available educational opportunities. Some veterinarians working in laboratory animal medicine obtain on-the-job training at institutions outside their country, thereby further enhancing their knowledge and expertise in the field.

TABLE 1 Veterinary Degrees Granted Around the World

Recognized Primary Veterinary Medical Degrees Granted Throughout the World
(Primary Information Source – AVMA Listed Veterinary Colleges of the World)

Abbreviation	Actual Veterinary Degree	Countries Awarding the Degree
BS	Bachelor of Science	Afghanistan, Taiwan
BSc	Bachelor of Science	China
BASc	Bachelor of Agricultural Science	China
BVM	Bachelor of Veterinary Medicine	China, Kenya, Libya, Taiwan, Uganda, United Kingdom, Zambia
BVM&AR	Bachelor of Veterinary Medicine and Animal Resources	Saudi Arabia
BVMS	Bachelor of Veterinary Medicine and Surgery	Australia, Iraq, United Kingdom – except Edinburgh University
BVM&S	Bachelor of Veterinary Medicine and Surgery	United Kingdom – Edinburgh University only
BVSc	Bachelor of Veterinary Science	Australia, China, Egypt, Japan, Myanmar, New Zealand, Sri Lanka, South Africa, Sudan, Syria, United Kingdom, Zimbabwe
BVSc&AH	Bachelor of Veterinary Science and Animal Husbandry	India
CMV	Candidates Medicinae Veterinariae	Norway
D	Dierenarts	Netherlands
DCV	Doctor en Ciencias Veterinarias	Argentina
DEDV	Diplôme d'Etat de Docteur Vétérinaire	France
DH	Doktor Hewan	Indonesia
DK	Diploma of Ktiniatrou	Greece

(continued)

TABLE 1 Continued

Recognized Primary Veterinary Medical Degrees Granted Throughout the World
(Primary Information Source – AVMA Listed Veterinary Colleges of the World)

Abbreviation	Actual Veterinary Degree	Countries Awarding the Degree
DMV	Docteur en Médecine Vétérinaire	Belgium, Tunisia, Zaire
	Dottore in Medicina Veterinaria	Italy
	Doctor en Medicina Veterinaria	Cuba, Dominican Republic, Ecuador, Paraguay, Uruguay
	Doctor Medic Veterina	Romania
Dr. vet. Med.	Diplôme Fédéral de Médecin Vétérinaire	Switzerland
DV	Docteur Vétérinaire	Algeria, Morocco
DVE	Docteur Vétérinaire d'Etat	Senegal
DVM	Doctor of Veterinary Medicine	Bangladesh, Canada, Ethiopia, Hungary, Iran, Malaysia, Nigeria, Pakistan, Philippines, South Korea, Thailand, Tobago, Trinidad, United States, West Indies
	Doktor Veterinarske Medicine	Bosnia and Herzegovina, Croatia, Serbia, Slovenia
IASV	Ingénieur Agricole Spécialité Vétérinaire	Cambodia
LMV	Licenciado em Medicina Veterinaria	Mozambique, Portugal
LV	Licenciado en Veterinaria	Spain
	Legitimerad Veterinaer	Sweden
LVM	Licentiate in Veterinary Medicine	Finland
LW	Lekarz Weterynarii	Poland
MV	Mjek Veteriner	Albania
	Médico Veterinario	Argentina, Bolivia, Brazil, Chile, Peru, Venezuela
MVB	Bachelor of Veterinary Medicine	Ireland
MVD	Médico Veterinario Zootecnista	Dominican Republic
MVDr	Doktor Veterinarstvi	Czech Republic
MVMVZ	Médico Veterinario Zootecnista	Colombia, Guatemala, Mexico
SVM	Specialist Veterinarnoj Medicini	Ukraine
T	Tieraerzt	Austria, Germany
V	Veterinario	Brazil
	Veterinaereksamen	Denmark
VE	Veterinary Engineer	Viet Nam
VetMB	Bachelor of Veterinary Medicine	United Kingdom
VH	Veteriner Hekim	Turkey
VL	Veterinaren Lekar	Bulgaria
VMD	Veterinariae Medicinae Doctoris	United States – University of Pennsylvania only
VV	Veterinarnyi Vrac	former Soviet Union

Source: www.worldvet.org/docs/Global%20Vet%20Schools.pdf (accessed July 27, 2009).

To illustrate this point, the following descriptors of necessary veterinary qualifications are drawn from a sampling of different countries that may serve as a model for developing nations in terms of stipulating the precise qualifications of the veterinarian. The content of the veterinary care program under the direction of these individuals is remarkably consistent:

(1) The proposed revision to the European Directive 86/609/EEC (CEC 2008a) states: "To ensure the ongoing monitoring of animal welfare needs, appropriate veterinary care should be available at all times and a staff member should be made responsible for the care and welfare of animals in each establishment." An approved amendment to Article 20 of the proposed revision further notes that "Member States shall ensure that, for the purposes of the authorization, the persons referred to in paragraph 1 have the appropriate veterinary or scientific education and training and have evidence of the requisite competence" (CEC 2008b).

(2) The proposed revision to the Council Directive builds on the current Directive (EEC 1986), which states: "persons who take care of animals used for experiments, including the duties of a supervisory nature, shall have appropriate education and training…. Adequate arrangements shall be made for the provision of veterinary advice and treatment…. A veterinarian or other competent person should be charged with advisory duties in relation to the well-being of animals." Although this language is not very specific, it is clear that "appropriate" training and education will allow the veterinarian to provide sound guidance and treatment for the care and use of animals.

(3) The United Kingdom's Animals (Scientific Procedures) Act (Home Office 1985) stipulates that "the well-being and state of health of such [laboratory] animals are monitored by a suitably qualified person in order to prevent pain or avoidable suffering, distress or lasting harm." The A(SP)A further requires that "no place shall be specified in a project license or as a breeding site unless it is so designated by a certificate, which in turn requires a veterinary surgeon or other suitably qualified person to provide advice on animal health and welfare."

(4) The section of the USDA regulations (USDA 1991) that addresses membership of the institutional animal care and use committee (IACUC) requires that a Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine serve as a member of the committee. Under the section on veterinary care, the regulations require that the personnel involved in animal care and use be qualified to perform their duties. Similarly, the proposed revision to the European Directive includes a requirement for the designated veterinarian to serve on the ethical review committee as well as membership of "the person responsible for the welfare and care of the animals in the establishment."

(5) Singapore has established excellent standards for the credentials of the veterinarian associated with a laboratory animal program. The NACLAR (2004) Guidelines state that "every licensee shall employ an Attending Veterinarian

(full or part time) with relevant training or experience in laboratory animal science and medicine. The veterinarian must also be licensed by the Agri-Food and Veterinary Authority (AVA)."

(6) The *Guide for the Care and Use of Laboratory Animals* (NRC 1996) was the most specific of the guidelines discussed during the roundtable. The *Guide* makes it quite clear that "A veterinary care program is the responsibility of the Attending Veterinarian who is certified or has training or experience in laboratory animal science and medicine or in the care of the species being used." The reference to certification in the *Guide* may be met by specialty board examination, for example by ACLAM, ECLAM, the Japanese College of Laboratory Animal Medicine (JCLAM), or the Korean College of Laboratory Animal Medicine. It may also be met by the FELASA Category D (Specialists) certificate of competence. The individual certified at this level must be able to do the following (USDA 1991):

a. Manage all animal, human, and physical resources in a laboratory animal facility;
b. Make provisions for the health and welfare of animals;
c. Provide advice, instruction, and assistance to investigators on laboratory animal–related matters and provide practical support of research programs;
d. Ensure compliance with all the laws, regulations, and guidelines relevant to the production, maintenance, and use of laboratory animals and related to management of the animal facility;
e. Be responsible for the development and presentation of internal and external education programs in the humane care and use of laboratory animals, which continue to develop the concept of the Three Rs (Russell and Burch 1959);
f. Contribute to the in-depth development of innovative concepts in the humane care and use of laboratory animals, including carrying out research in laboratory animal science.

Thus, Category D includes veterinarians and other professionals of similar qualification. A third example is the certificate in laboratory animal medicine conferred on Canadian veterinarians.

Authority of the Veterinarian

Although this is one of the most important aspects of the veterinary care program, most countries do not describe in detail (or sometimes even mention) the authority the veterinarian must have to ensure good animal health and welfare in the laboratory animal care and use program. However, when the topic is addressed, there is a great deal of general convergence among the various guidelines. In summary, the consensus is that the veterinarian must have appropriate

authority to execute the duties inherent in ensuring the adequacy of veterinary care and in overseeing other aspects of the program of animal care and use.

Role of the Veterinarian

Multiple roles are attributed to the veterinarian, and the scope of these varies among countries. Many guidelines and regulations do not describe expectations for the veterinarian in any detail. What follows is a compilation of the numerous roles defined for the laboratory animal veterinarian.

Often, the veterinarian is referred to as an advisor. The veterinarian may be expected to give guidance regarding surgical techniques, selection of pharmacologic agents, selection of animal models, periprocedural care, euthanasia, and/or training of other individuals in the program (to name a few key areas). Occasionally, this advisory role is augmented to an oversight role, particularly in the United States, where the veterinarian would have an oversight role through his or her function on the institutional animal care and use committee.

As might be expected, the role of the veterinarian in ensuring the health and well-being of the animals used for research, testing, or teaching is a point of convergence among the various regulatory and guidance documents. The source of the animals and transportation of those animals from that source to the institution, quarantine and stabilization, health monitoring, preventive medicine, disease surveillance, diagnosis, treatment, control of disease, surgery, pain and distress, medical records, euthanasia, and/or other clinical duties are listed as key responsibilities of the veterinarian.

Adjunctive roles of the veterinarian include participating in the training of staff; providing expert guidance to the occupational health and safety program (e.g., about zoonotic diseases, animal allergens, and other conditions); advising on biological and chemical hazard policies of the institution; monitoring and advising on hygiene standards; providing guidance on animal facility design; and providing input into the development of the disaster plan.

The Como meeting highlighted two common systems used internationally for the oversight of animal health and welfare: one relies on a veterinarian and supporting animal care staff, and an equally vibrant system in several parts of the world relies on someone other than a veterinarian who has the requisite expertise (e.g., in the species of animals used, the type of research, laboratory animal science), such as a scientist. In the latter system, the veterinarian often has a secondary role in terms of authority and responsibility. Not unexpectedly, these different systems may be correlated with significant differences in the education and qualifications of the veterinarian, as well as his/her authority and role in the program. Individuals who work in countries where the veterinarian has more primary responsibility for animal health and welfare are likely to receive a more extensive education (through the veterinary curriculum and/or postgraduate training and certification) and are more often considered partners in the research enterprise. In countries where the veterinarian serves in a more

technical role, the lead scientist often has primary responsibility for animal care and use oversight.

Elucidation of international similarities and differences in the qualifications, authority, and role of the veterinarian in animal research programs will facilitate efforts to harmonize standards of animal care and welfare. It is important to understand the cultural and regulatory framework in which veterinarians work around the world, as well as the educational opportunities available to them. We should be familiar with the type of education and postgraduate experience achieved by the veterinarian to better gauge our expectations for the responsibilities and expertise of that individual. Any consideration of harmonizing veterinary care should include an assessment of the veterinary school curriculum, opportunities for postgraduate training (either in-country or outside the country), the country's regulatory requirements, and training material resources (especially online resources in a variety of languages).

References

CEC [Commission of the European Communities]. 2008a. Proposal for a Directive of the European Parliament and of the Council on the Protection of Animals Used for Scientific Purposes. Brussels. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0543:FIN:EN:PDF (accessed July 27, 2009).

CEC. 2008b. Report on the Proposal for a Directive of the European Parliament and of the Council on the Protection of Animals Used for Scientific Purposes. COM (2008)0543 – C6 - 0391/2008 – 2008/0211(COD). Committee on Agriculture and Rural Development. Rapporteur: Neil Parish. www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A6-2009-0240&language=EN (accessed July 27, 2009).

EEC [European Economic Community]. 1986. Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes, Brussels. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31986L0609:EN:HTML (accessed July 28, 2009).

Home Office. 1985. Scientific Procedures on Living Animals (Cmnd. 9521). London: Her Majesty's Stationery Office. www.archive.official-documents.co.uk/document/hoc/321/321-xa.htm (accessed July 28, 2009).

NACLAR [National Advisory Committee for Laboratory Animal Research]. 2004. Guidelines on the Care and Use of Animals for Scientific Purposes. Singapore. www.ava.gov.sg/NR/rdonlyres/C64255C0-3933-4EBC-B869-84621A9BF682/8338/Attach3_AnimalsforScientificPurposes.PDF (accessed July 28, 2009).

NRC [National Research Council]. 1996. Guide for the Care and Use of Laboratory Animals. Washington: National Academy Press. www.nap.edu/readingroom/books/labrats/ (accessed July 28, 2009).

Russell W, Burch R. 1959. The Principles of Humane Experimental Technique (2nd ed, 1992 UFAW). London: Methuen. http://altweb.jhsph.edu/publications/humane_exp/het-toc.htm (accessed July 28, 2009).

USDA [US Department of Agriculture]. 1991. Code of Federal Regulations, Title 9, Part 3, Animal Welfare; Standards; Final Rule. Federal Register 56(32):1-109.

STATE OF LABORATORY ANIMAL MEDICINE AROUND THE WORLD

Europe

Hans Hedrich

The most credible training for veterinarians in the area of laboratory animal medicine is through the European College of Laboratory Animal Medicine (ECLAM). Diplomate status in ECLAM goes beyond FELASA Category D, and I personally refer to it as FELASA Category E. It would be desirable to have European governments accept that requiring laboratory animal veterinarians to become diplomates is the best way to control and govern animal experimentation. In Europe, we have a long-standing history of laboratory animal science associations, whose membership is about 50% veterinarians and the other 50% those trained in biomedicine or biology or other sciences. The laboratory animal science perspective, therefore, is encompassed by FELASA.

To address the laboratory animal medicine side of things, in the UK there is the Royal College of Veterinary Surgeons as well as the British Laboratory Animals Veterinary Association. Both are long-standing and laboratory animal medicine has always been an important issue with them. The primary body in Europe is the European Society of Laboratory Animal Veterinarians (ESLAV), which initiated the European College of Laboratory Animal Medicine (ECLAM). However, this is a relatively new approach.

Of the 27 member states in the European Union, 26 have veterinary schools. Europe in total has 31 countries and 80 veterinary schools, but this number does not reflect the size of the population or the culture of the countries. For example, there are 16 veterinary schools in Italy and 16 in Spain, but only one in the Netherlands. Programs in laboratory animal medicine are relatively rare.

Veterinary training in accordance with FELASA Category D occurs in Italy, Germany, the Netherlands, Spain, and Sweden. The program in laboratory animal science in Milan, Italy, includes two years of training. In Germany, specialists in laboratory animal science have to train for four years. In the Netherlands, laboratory animal specialists undergo government-recognized training in Utrecht and several other places for 18 months. In Spain there is a master's degree program

in laboratory animal science and welfare in Barcelona and Madrid that lasts two years. Sweden also has a two-year master's degree at Uppsala. Thus there is quite a variety in the training of laboratory animal science specialists.

In Europe, veterinarians have a special legal responsibility and professional obligation, especially in treating animals with medications, using anesthesia, or administering analgesics, all of which are not permitted to any other profession. However, from a regulatory perspective, there are differences among countries as to how much veterinary involvement is permitted in animal experimentation aside from the requirements for medications or prescriptions and anesthesia. These differences are apparent going from west to east in Europe, with some of the new countries in the EU being rather undeveloped in the field of laboratory animal medicine.

Programs for FELASA Category D based on veterinary training or in veterinary medicine are in Italy, Belgium, Germany, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom. Again, there is inconsistency in the requirements of the various programs. In Italy, a diploma in laboratory animal science takes three years, while in Belgium it takes only two years. In Germany, the program is provided through the veterinary boards and training in approved institutions and takes three to four years; the four-year program is for laboratory animal science or laboratory animal medicine, while the three-year program is for animal welfare, which is also accepted under Category D. In the Netherlands the program is one and a half years, in Norway three years, Spain two years, Sweden two years, Switzerland four years. The United Kingdom has a two-tiered approach, with a certificate in two years and the diploma provided by the Royal College of Veterinary Surgeons in five years.

ECLAM was established in 2000 and in 2008 received permanent recognition by the European Board of Veterinary Specialization, which is our governing and controlling group, to which we must report directly. The founding of the College was an initiative of ESLAV and covers everything important in laboratory animal medicine.

The leadership of ECLAM identified the issues important to the organization and proposed initiating discussion on including ethics in addition to improving animal welfare in order to make these issues permanently a part of the organization's goals.

ECLAM has established guidelines for examination and qualification of veterinarians for diplomate status. Although the examination is difficult, those who pass are highly qualified to direct a program in laboratory animal medicine.

ECLAM encourages research and promotes the communication and dissemination of knowledge in the field of laboratory animal medicine. The European Board of Veterinary Specialization has required training programs to be four years long, at least two and a half years of which should be under the supervision of a diplomate. There are 23 different veterinary specialty colleges and all are expected to have minimum standards.

The alternate training program takes two more years, but again two and a half years under the supervision of a diplomate. There are currently eight pro-

grams in various European countries. Once again, there is diversity among the programs. However, regardless of the training program, all who pass the exam are able to [attain] diplomate status. Reevaluation occurs every five years based on a 100-point credit system.

ECLAM and ESLAV have been involved with FELASA on defining appropriate veterinary care of laboratory animals. A paper describing the guidelines for veterinary care of laboratory animals was published by the FELASA/ECLAM/ESLAV working group in 2008. The working group agreed that care of laboratory animals may be pursued by various professionals with different backgrounds, but the veterinarian is unquestionably the most appropriate person to provide veterinary care. The concepts presented in the paper have not been accepted as yet throughout the European Community.

The guidelines indicate that the professional judgment of a veterinarian trained in laboratory animal science is essential in the application of the recommendations on animal care and use to the specific institution. Veterinarians have specific legal responsibilities and professional obligations with respect to regulatory bodies.

A key part of the guideline paper is that education provides the basic knowledge and enables a person to work as a veterinarian, although legal and professional obligations vary among the countries. Undergraduate education emphasizes mostly the treatment and care of companion and farm animal species without much [attention] to laboratory animals. Because of this, it is critical that the laboratory animal veterinarian obtain specific education, training, and competence in dealing with these species.

Education in laboratory animal medicine needs to be improved throughout Europe and especially in the Eastern European countries. Generally, it is not the veterinary schools that train specialists in laboratory animal medicine; such training is done at medical schools where the actual research on the animals is conducted.

The European legislation currently does not specify further educational requirements for a veterinarian with legal responsibilities for longitudinal care, even in the most recent draft. The multilateral consultation of parties to the convention has adopted the resolution on education and training of persons working with laboratory animals. This resolution is based on the FELASA recommendations for the education and training of persons involved in animal experiments. These recommendations were suggested to be included in EU Directive 86/609, which currently reads "a veterinarian or other competent person." It should be changed to read "a veterinarian trained and experienced in laboratory animal medicine or, exceptionally, another competent person" should be charged with advisory duties in relation to the well-being of the animals, but that person should also have the appropriate authority. Based on the FELASA recommendations, these would be persons trained under Category D and in rare exceptions Category C.

It is now possible to say that consistent veterinary postgraduate specialty training and certification has been fully established in Europe through the efforts

of the veterinary profession, arising from the advice of the Commission's Advisory Committee on Veterinary Training and overseen by the European Board of Veterinary Specialization. There is a recognized European veterinary specialization in laboratory animal medicine, as well as training, certification, and continuing education organized by ECLAM and ESLAV in addition to other organizations such as Royal College of Veterinary Surgeons and other veterinary boards. The Royal College of Veterinary Surgeons announced that, once ECLAM had achieved permanent recognition, they would drop their own diploma in favor of the ECLAM diploma.

Finally, I want to comment on the information received by FELASA and other organizations about the revision of the EU directive. It seems that the various commission directorates, in particular the directorate of research, have not been able to agree on the draft text of the EU directive. The Commission has therefore decided that it will submit the text as it stands to the "oral procedure." This means that the College of Commissioners will decide whether to release the text as it stands into the codecision process or with only minor amendments, or they may decide it requires more extensive amendment and postpone its adoption.

Another possibility is that the College of Commissioners might decide that the directive requires more extensive amendment and may postpone the adoption of the draft. Apparently also in the Members of Cabinet meeting many objections were raised, especially in relation to the current draft, and thus no consensus could be reached.

The discussion that seemed to be most important concerned the excessive limitations on the use of nonhuman primates in Europe and there was potential bureaucracy originating from unclear definitions in the draft.

This may all change with the upcoming elections to the European Parliament in the spring. Also, quite a number of new commissioners will be appointed next year, so there will be different groups of people in Brussels as well as in Strasbourg.

Latin America

Rafael Hernandez

Latin America is the region south of the border of the United States to Chile near the Antarctic. It includes 21 countries, 21 million square kilometers, and purchasing power of $5 trillion. Although most Latin American people are Western oriented, it really is not considered for some cultures part of the West but rather a unique and different region.

Latin American countries share many things, such as language, Spanish-Portuguese background, culture (to a greater or lesser extent) with Indian roots. Some of those countries also have scientific traditions, such as Mexico, where José de la Luz Gómez, using the Pasteur method, produced rabies vaccine in 1888 and became the first laboratory animal veterinarian in Mexico. Carlos Juan Finlay y Barres from Cuba identified the mosquito as the yellow fever agent and was the first scientist to identify an insect as a biotransmitting agent. Oswaldo Cruz, from Brazil, was probably the most well known veterinarian, and Bernardo A. Houssay from Argentina was the first Latin American to win the Nobel Prize in medicine, in 1947.

However, in spite of this glorious past, the present panorama for research and development is not equal and sustained for all Latin American countries. Latin American countries are divided into blocs of nations with respect to the potential economic impact of the region. Countries like Brazil, Argentina, Chile, Colombia, Mexico, and Costa Rica have enough resources and capacity to support the training of researchers [whereas] other countries do not.

The importance of the number of PhDs earned in a country has already been discussed. There is a very large gap between North America and Latin American countries as well as among the Latin American countries. Brazil has the highest number of students enrolled in tertiary institutions. This is also evident in the investment of the various countries in scientific research; on average Latin American countries allocate less than half a point of their GNP, [only] Brazil allocates more than 1%.

Latin American countries are trying to encourage their populations to pursue university educations. Mexico, Cuba, Colombia, Brazil, and Argentina have a large number of universities, but even so they are still distantly behind the

United States and Western Europe. Similarly, Latin American countries lag the four top countries—the US, England, Germany, and Japan—in the number of highly cited researchers.

The scientific productivity of Latin America represents only 4% of that of the world. However, Mexico, Cuba, Brazil, Argentina, Uruguay, and Chile are striving to do high-quality science, in part by producing and using transgenic animals.

Most of the countries have institutional standards, ethics committees, or institutional animal care and use committees, but only Costa Rica (1994), Mexico (2002), and Brazil (2008) have national laws for the care and use of laboratory animals.

In Latin America there are several associations for laboratory animal science; these exist in Argentina, Brazil, Colombia, Cuba, Mexico, Peru, Uruguay, and Venezuela. There are also associations that bridge more than one country, like the Central American, Caribbean, and Mexican Association for Laboratory Animal Science (ACCMAL), and federations, like the South American Federation for Laboratory Animal Science (FeSSACAL), which includes countries in the southern part of Latin America. It is important to note that these associations include not only veterinarians but also technicians and scientists working in the field; there is no specific association or college for veterinary practitioners.

Appropriate courses in a formal educational program for laboratory animal medicine are found only in Cuba, which awards a master's degree in laboratory animal science. Brazil, Argentina, Chile, and Mexico don't have specific programs for laboratory animal science, but it is possible to get master's or PhD degrees in the field by selecting credits on related subjects at veterinary, pharmacy, or medical schools. This is possible in at least two universities in Mexico, several in Brazil, and at the Universities of La Plata and Buenos Aires in Argentina.

In undergraduate veterinary medicine education in Mexico, it is possible to get a four-hour introduction to laboratory animal science, and students who are interested in pursuing laboratory animal science may take a 48-hour laboratory animal course. Similar programs exist in Argentina at La Plata University and Buenos Aires University. In other Latin American countries it is the pharmacy schools that teach care and pharmacologic use of animals, but not breeding, health, genetics, or environmental control.

The majority of animal facilities in Latin America do not have a full- or part-time appointed veterinarian except in Argentina, Mexico, Cuba, Venezuela, and some parts of Brazil.

Distance education is viewed as a very important endeavor in the future. The veterinary school in Mexico is working to sign an agreement with the University of Guelph in Canada to be able to use a Spanish version of their animal medical certification program to provide education not only in Mexico but in all countries interested in the field. Other programs are available in both Spanish and English—e.g., a bilingual institutional training program for scientists offered by the University of Miami.

A certification program run by ConeVet (National Council for Veterinary Medical Education, the academic branch of the Mexican Veterinary Medical Association) for laboratory animal veterinarians aims at improving the quality of education. There are actually two programs, one for accreditation of veterinary schools and one for certification of practitioners. The certification program is board-specific for each species, and each candidate must pass one of two boards: one based on credentials for those who have a lot of training or experience, and the other on an exam for those newly coming into the field. The credential certification process occurred only in 2006, for the initial certification period. The assessment was based on professional experience (500 possible points), continuing education (500), professional education (400), teaching or academic activities (200), publications (400), and related association/college membership (150). The minimal certification score for this evaluation was 1100 points.

For the laboratory animal medical certification process by exam, there is an agreement between CENEVAL (National Center for Higher Education Evaluation) and ConeVet. CENEVAL is an independent organization for testing, very similar to the Educational Testing System in the United States, and runs the license and certification examinations. The certification is actually given by ConeVet.

The exam is long—two days for four hours each day—and is divided into different sections covering diverse areas of knowledge and professional abilities. It is given twice a year, in April and December during the AMCAL (Mexican Association for Laboratory Animal Science) meeting.

The future holds some interesting opportunities. While Latin America covers a large area, there is a real advantage because the countries share the same language (with the exception of Brazil, but Portuguese may actually be closer to Spanish than British English is to American English). Therefore, if we work together to establish high-quality courses for this kind of education, we may be able to consolidate the examination process, particularly if we share experience with similar certification bodies, not only from Latin America but also from Europe or Asia.

We can also benefit by working together to establish an umbrella organization, a Latin American Association for Laboratory Animal Science. This may also serve to help establish a Latin American College for Laboratory Animal Medicine or a Laboratory Veterinary Association. In these ways, we will have an opportunity to encourage and improve the quality of veterinary education in laboratory animal science in these areas.

North America

James G. Fox

I would like to address a very serious issue in terms of the state of comparative medicine and laboratory animal medicine worldwide, particularly the state of the veterinary medicine profession in North America.

I urge all who have not seen the Foresight Report (J Vet Med Ed 34:1-41; 2007), commissioned by the American Association of Veterinary Medical Colleges (AAVMC), to read and digest it since I believe it is critical for the progress and the future of veterinary medicine in general, and certainly for comparative medicine. The summary of the report states that veterinary medicine is the only profession in the health and medical field whose members are trained in comparative medicine. Veterinarians are critical components of public health and essential health care providers to society locally, nationally, and internationally in light of their concern for animals, their health and well-being, and their interface with people. However, the summary also states that veterinarians must first demonstrate relevance to new societal needs and trends in order to be recognized and remunerated for their knowledge, compassion, integrity, and judgment.

Since 1989, the veterinary profession in the United States has been fairly static in terms of the number of veterinarians graduated, which is a little over 2,000 per year. Based on public demand, veterinary schools are primarily training veterinarians to fulfill roles in small animal practice. So about 44,000 veterinarians practice small animal medicine, while a much smaller number are involved in large animal and equine medicine, with the remainder in public and corporate veterinary medicine.

Thus with respect to the veterinary curriculum, the disciplines of laboratory animal medicine and biomedical research are competing against tremendous odds for young veterinary professionals. Several publications of the National Research Council—*National Needs and Priorities for Veterinarians in Biomedical Research* (2004), *Critical Needs for Research in Veterinary Science* (2005), and an earlier document, *New Horizons in Veterinary Medicine* (1972)—stress the need for the veterinarian to become involved in corporate veterinary medicine, academia, and industry to fulfill societal needs.

In recognition of these reports and the Foresight Report, the National Research Council has appointed a committee to assess the current and future workforce needs in veterinary medicine. The report, which is still in preparation, will be an important report exploring both historical changes in veterinary medicine and the adequacy of the current supply of veterinarians in different occupational categories and employment sectors. The report will also explore factors that will likely affect the future demographics of veterinarians.

It has been well documented that there is a tremendous need for adequately trained laboratory animal medicine veterinarians and veterinarians involved in biomedical research. From 1999 to 2002, the average numbers of job postings per year for these positions were 68.5 in academic institutions, 28.3 in industry, and 7.5 in government. Those numbers are not likely to be different now.

What are we doing as a profession in the United States to fulfill the needs in these three sectors? In looking at the number of diplomates of the American College of Laboratory Animal Medicine (ACLAM), from 1996 to 2002 there was a 3% annual increase in membership; from 2002 to 2008, the total number has increased to 718 diplomates, but over those six years there was only a 7% overall increase, a little over 1% a year.

The numbers clearly indicate that the profession has not met the needs of the academic, industrial, and government sectors. Compounding the problem is the significant number of retirements that will occur over the next 20 years. Although we practice the 3Rs and are looking for in vitro models and other alternative methods with which to conduct biomedical research, there is no doubt that animal use is going to remain a considerable part of the biomedical research engine.

In reviewing the NIH grants portfolio over the last 20 years, the data show that an average of 50% of grants involve the use of laboratory animals. It is very likely that the use of laboratory animals in research institutions continues to grow but at a more modest rate in the last several years because of the constraints of the NIH budget. Given the continued need for animal research, we must meet the challenge of eliciting interest and enthusiasm for comparative medicine in our young veterinary colleagues. While veterinary medicine is thought of as a clinical-based profession we need to provide persuasive arguments and opportunities in public health, regulatory agencies, academic, industry, and biomedical research. In addition, we need to promote and transmit this breadth of opportunity to our young colleagues and to the public in general.

The veterinary profession must exert coordinated efforts to communicate to students beginning in middle and high school, provide research opportunities to undergraduates, and, importantly, provide opportunities to veterinary students to work in research laboratories.

Another approach to meeting the needs is to diversify the career interests of the veterinary student body. This means that we must include in the applicant pool individuals who are interested in diverse careers, including biomedical re-

search and comparative medicine. The admission process for veterinary schools must reflect this need.

One of the recommendations that came out of the 2004 NRC report was that all veterinary schools should offer at least an elective course in laboratory animal medicine and more veterinary schools should require course work in this specialty. Also, the National Examination Board should include questions germane to the subject matter on the national veterinary boards. Comparative medicine specialists should actively seek out and mentor students with an aptitude for and interest in comparative medicine.

ACLAM did a survey in 2006; this project, led by Lesley Colby, is in review and will soon be published. The committee asked the question that we posed in our Academy report: Is a laboratory animal medicine course offered as part of the current curriculum to your students? In a somewhat reassuring response, 65% said yes, but 35% said no. Asked whether the students received lectures in laboratory animal medicine as part of other courses, a higher percentage (87%) said yes because having a few lectures scattered through the course is easier in terms of curriculum development. However, when asked if laboratory animal medicine–related problems were used in case studies, only 29% responded yes.

So it is clear that we are not doing a very good job of exposing veterinarian students to career potential in comparative medicine or biomedical research. Dr. Steve Barthold illustrates this outcome very effectively by comparing career choices with pipes: the largest-volume pipe is the one for clinical practice; the pipes for science and laboratory animal medicine are much smaller.

One obstacle in attracting veterinary students into biomedical research is financial debt. A survey of veterinary students revealed that they averaged over $100,000 of debt at graduation. They must weigh this loan repayment obligation with salary expectations over their career. In addition, choosing a career in biomedical research presents the daunting task of having to successfully secure funding over the duration of their career from NIH and other external sources.

These impediments must be considered when trying to help the students understand that the profession of laboratory animal medicine is a viable alternative to clinical practice in terms of remuneration and biomedical research. This requires mentoring and an environment in the laboratory to set the proper tone for a research experience.

I would like to share a quote with you from one of the students at the conference last year: "A brilliant mentor with a great sense of humor will undoubtedly be more inspiring than a brilliant mentor who won't crack a smile or works 18 hours a day." This quote makes me think of my friend Steve Barthold. One must balance the successes and the satisfaction gained from a career in laboratory animal medicine and must transmit that enthusiasm to younger colleagues and high school students to let them know that research and involvement in corporate practice is a satisfying career.

There has been a very aggressive effort by ACLAM as well as the American Society of Laboratory Animal Practitioners and others to establish, critique,

and approve training programs in the United States. There are currently 41 of these training programs that cover a wide spectrum of opportunities for students, including positions in medical schools, veterinary schools, research institutions, pharmaceutical companies, primate centers, and the military.

An important component to consider is funding. The NIH National Center for Research Resources (NCRR) has historically been the catalyst and the major provider of training in laboratory animal medicine and biomedical research, and it continues to do so. Although its efforts and the successes of these programs over the years are truly appreciated, the amount of dollars put into these programs for biomedical training programs has been flat over the last 20 years, with the exception of the relatively new T-35 program, which continues to grow and provides a summer research fellowships for veterinary students. The number of trainees has grown to 146 per year. These are the students who can be cultivated into postgraduate careers in laboratory animal medicine. We must continue to help our colleagues at the NIH convince the legislators of the importance of this occupation as part of the biomedical research enterprise.

NCRR recently announced its intention to build the research workforce as part of its strategic plan. One of its central recommendations is to increase the number of qualified research veterinarians and ensure that veterinarians are recognized partners on translational research teams. This presents a real opportunity for all of us to embrace this plan and to champion the concept of one medicine, one health. We must capitalize on the opportunity and move forward.

In conclusion, there clearly are challenges that lie ahead for us. We have to convince the deans and professors in the veterinary schools that there is a vital place for a veterinarian in a research setting. Clinician scientists may also be involved, but the goal is to create a higher profile for veterinarians in their professional training so they may reach out beyond the clinical track. We want to encourage new career paths and role models. We must try to effect substantive curriculum change in the veterinary profession and encourage students to apply for these T-35 training programs. In addition, we need to expand our opportunities in the comparative medicine programs, not only in veterinary schools but also in other research institutions, including medical schools.

I leave you with the epilogue of the Foresight Report: "This is…a pivotal point in time for the veterinary profession and for veterinary medical education. A decision to broaden the scope and potential of veterinary medical education is fundamental for the profession to navigate this transition."

And finally, as Paulo Coelho said, "The truth is that all problems seem very simple once they have been resolved. The great victory, which appears so simple today, was the result of a series of small victories that went unnoticed" (from *Warrior of the Light*, 2003).

A PATH FORWARD

Role of the OIE

David Bayvel

This presentation is an overview of the nascent role of the OIE in animal welfare, and will emphasize where that role might relate to the theme of this session and perhaps the overall theme of the conference.

One must bear in mind that the OIE's involvement in animal welfare goes back only six or seven years, so we are looking at relatively recent international involvement. My presentation is made wearing two hats, both as Director of Animal Welfare for the New Zealand Ministry of Agriculture and Forestry and as Chair of the OIE Animal Welfare Working Group.

The OIE consists of 172 countries, making it bigger in terms of membership than the WTO, which has approximately 149 countries. Therefore, by any standards, an intergovernmental organization representing 172 countries has a significant role to play in influencing public policy in governments around the world, and also plays a key role in implementing agreed policy.

The raison d'être of the OIE relates to ensuring transparency related to global animal disease and zoonoses, and also to coordinating the collection, analysis, and dissemination of scientific animal health information. The OIE is very conscious of the need to work closely with scientists in a whole range of disciplines. The organization strives to improve the legal framework and resources of national veterinary services and to provide expertise and encourage international solidarity in the control of animal diseases.

In the WTO mandate, the international standards of the OIE safeguard world trade by publishing health standards for international trade in animals and animal products, to provide a better guarantee of animal production food safety and to promote animal welfare through a science-based approach.

Since its inception the OIE has operated from a relatively small central bureau in Paris, with about 40 staff members. It has a network of reference laboratories and collaborating centers around the world, totaling almost 200. Reference laboratories exist for specific disease entities, such as blue tongue, rabies, or foot and mouth, and the collaborating centers are centers of excellence from which

the OIE can draw expertise to assist [in the] achievement of its mission. Currently, there are 171 reference laboratories and 24 collaborating centers.

Animal welfare is a new area for the OIE. There is potential for collaborating centers to be established in each of the OIE's regions to support its work in animal welfare. A group in Italy that has recognition for veterinary training, epidemiology, and food safety is also playing a role in animal welfare. We in New Zealand sought recognition for the animal welfare science and bioethics center at Massey University headed by Professor David Mellor. There is opportunity for other centers to achieve that recognition and assist the OIE over the next few years and decades.

Two or three years ago, the 172 member countries expressed a desire that the OIE play some role in the laboratory animal welfare area. The initial decision was to establish a dialogue with existing international organizations, particularly ICLAS and IACLAM, and to identify common interests. A formal memorandum of understanding (MOU) has now been signed with ICLAS, which is similar to the OIE's MOUs with other international organizations to allow for information sharing and mutual participation in identifying areas for synergy, with the goal of emphasizing the role of the veterinary profession generally and of veterinary services in particular.

The OIE has a four-year strategic planning cycle and in the period from 2001 to 2005 some building blocks for animal welfare were established, and guiding principles in animal welfare were identified at the first OIE global conference in Paris. The profile of animal welfare was further enhanced in the strategic plan for the period 2006-2010. The OIE has published and promulgated a set of nine guiding principles, with emphasis on the linkage between health and welfare, something that often is not fully appreciated and recognized by the public at large or by politicians.

The OIE has a mandate on animal welfare in the use of animals in scientific studies and education. OIE supports appropriate animal use in the fields that are relevant to animal health and welfare and animal production food safety, including research and development of veterinary medicines, diagnostic tests and vaccines, and education of veterinarians and other professionals. Another program established under OIE auspices is the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). In addition, the OIE can help in the international facilitation of adoption of nonanimal tests where scientifically validated. This will complement work done in Europe by the European Center for the Validation of Alternative Methods (ECVAM) and work done in the US by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

The mission of the OIE Animal Welfare Working Group, which I have chaired since 2002, is to provide international leadership in animal welfare through the development of science-based standards and guidelines, provision of expert advice, and the promotion of relevant education and research. The working group represents the five OIE regions; Professor David Fraser from the University of British Columbia represents the Americas. We consider the available

science, but also highlight the importance of ethics to ensure that we take a holistic approach to our mission. The detailed work on producing standards and guidelines is carried out by expert ad hoc groups established by the OIE Director-General; we have had six ad hoc groups established over the six-year period, and the process works very effectively.

The working group follows the established guiding principles and takes an outcomes rather than an inputs approach. The principles emphasize the importance of the linkage between health and welfare, the Five Freedoms,[1] the Three Rs, and the need for a scientific basis for standards, and recognize that better animal welfare can improve productivity and deliver economic benefits.

In 2005 the OIE developed four sets of standards for the transport and slaughter of livestock. At the time, there was concern about diseases like BSE (bovine spongiform encephalopathy) and avian influenza, slaughter practices, and the ethical acceptability and economic justification for transporting animals large distances for slaughter. The OIE is working to implement these standards by using its regional infrastructure to facilitate the process.

We are now following the same process for laboratory animals by looking at principles and guidelines for animals used in regulatory testing and teaching. We are also liaising with the VICH and making sure that we engage with all the international stakeholders, be they industry groups or welfare NGOs. An ad hoc group was established to develop the guidelines, which is the OIE's modus operandi for such tasks. Several participants in this conference are members of the ad hoc group that met for the first time in December of 2007 and will meet for a second time in December 2008. They will address these topics: animal care and use program and committee; assurance of training and competent provision of veterinary care; physical facility and environmental conditions; husbandry; source of animals; occupational health and safety; and importance of postapproval monitoring and validation. The group also identified veterinary training in laboratory animal medicine, transportation of animals, and regulatory testing as topics to be examined in the future.

A second global conference, to be held in Cairo in October 2008, will be a further manifestation of the relevance of global standards particularly to the developing world.[2]

Information on OIE activities is available on its considerably enhanced website or in the OIE Bulletin or Scientific and Technical Review Series publications.

It is certain that the OIE's involvement will not be transient. In addition, the OIE is heavily wedded to the One Medicine, One Health concept. Over the

[1]These are freedom from thirst, hunger, and malnutrition; freedom from discomfort; freedom from pain, injury, and disease; freedom to express normal behavior; and freedom from fear and distress; available online (www.fawc.org.uk/freedoms.htm).

[2]The 2nd OIE Global Conference on Animal Welfare: Putting the OIE Standards to Work was held October 20-22, 2008; the program and presentations are available online (www.oie.int).

next one to two years there will be a major conference sponsored by the OIE and attended by veterinary deans from around the world to ensure that veterinary education meets the needs of society. There will also be a major review of future needs in veterinary education published in the OIE scientific and technical review series in 2009.

Introduction to AAVMC

Marguerite Pappaioanou

I will give a very brief introduction of the Association of American Veterinary Medical Colleges (AAVMC) and some of the key activities in this area, and then introduce Dr. Chaddock, our Deputy Director, who will make the main presentation.

The Association of American Veterinary Medical Colleges represents and has as members all 28 colleges of veterinary medicine in the United States as well as all five colleges of veterinary medicine in Canada and nine departments of veterinary science in the US. AAVMC membership is open to departments of veterinary sciences and comparative medicine. Members also include institutions that provide significant training in veterinary medicine, three colleges of veterinary medicine from the UK, one from Ireland, three from Australia, and one from New Zealand. AAVMC coordinates the affairs of all these institutions.

The mission of AAVMC is to improve the quality of life for people and animals by advancing veterinary medical education, improving animal health and welfare, strengthening biomedical research, promoting feed safety and food security, and enhancing environmental quality. Animal care and welfare are of major importance to us in all of these avenues in achieving our mission. One of our major programs is advocating with the US Congress to increase resources for colleges of veterinary medicine in order to increase class sizes. We need more veterinarians, as there has been no increase in the number of veterinary graduates (2,500) in 30 years. If the number of veterinarians going into laboratory animal medicine tripled, there would be shortages in food animal medicine, public health, or companion animal medicine. We need to recruit more veterinarians into all of these critical areas.

A second major AAVMC program is the development of a strategic plan, which has not been done before. The board of directors, whose president is Dr. James Fox, has undertaken this effort; he has provided leadership in the avenue of animal care and welfare that is so important to education and research.

In considering the roles of the veterinary colleges, a couple of important questions have come up:

1. How should the use of animals in education and research in colleges of veterinary medicine be addressed?
2. What should our veterinarians in colleges of veterinary medicine or veterinary students be taught in this area?

To address these issues, our board of directors has partnered with the American Veterinary Medical Association, the US Department of Agriculture, and the National Institutes of Health NCRR to hold a scientific meeting on animal care and welfare ethics in November 2009 (the agenda and papers are available at www.avma.org/awsymposium).

Dr. Chaddock is our lead in working with partners to plan and conduct this meeting. He is a veterinarian who joined AAVMC with a whole career's experience in different perspectives, working in various areas of our profession and in leadership.

AAVMC Strategic Plan

Michael Chaddock

I will discuss a very exciting program that the AAVMC in collaboration and partnership with AVMA will have here soon. It is important to emphasize Dr. Fox's leadership not only with AAVMC and ILAR but with the AVMA. In the last year, he chaired the animal care welfare committees of both the AVMA and the AAVMC, so it is his vision and his leadership that brought this together for the event that is going to occur. I also want to mention the Morris Animal Foundation, which will help to support this venture.

The title of the conference is Animal Welfare as an Evolving Discipline, and Educating Veterinarians to be Effective Decision Makers and Advocates.[1] It is an international educational symposium that will be held November 8-11, 2009, at one of our premier member institutions, Michigan State University in East Lansing. The program is being designed with requested input from all of our member institutions. It is important to emphasize that our intended audience will include scholars involved in animal welfare, the laboratory animal community, and veterinary medical students in the international realm. The intention is to satellite broadcast the program.

On the first day, the program will address the role of science in society and will include the definition of animal welfare, key policy statements in this area, and how different stakeholders frame and discuss animal welfare issues. The point is to address animal welfare from a scientific point of view, determine how it is measured, how it is perceived by different people, and ethical approaches to assessments of animal welfare. The role of ethics will include cultural norms, differences in religious expectations, morality, and cost/benefit from the perspective of the role of science in society.

The next topic area will be entities and agreements and will consider the different groups involved in animal welfare decisions about which veterinary medical students must know; these groups include veterinarians, scientists, re-

[1]The resulting meeting summary, *Swimming with the Tide: Animal Welfare in Veterinary Medical Education and Research*, and related documents are available online at www.avma.org/awsymposium.

searchers, industry leaders, retailers, advocates, animal welfare groups, the public, lobbyists, and attorneys who are involved in the animal welfare area. The groups will be brought together to speak and participate in roundtable discussions with the aim of informing students about important issues to consider such as agreements, standards, available voluntary schemes, regulations, legal considerations, and international differences. The speakers will address research, the history of animal welfare and animal care research, and the current state of that research today worldwide. It is important to have international presentations so that the students get a well-rounded view of the issues. After the presentations will be roundtable discussions that will include the students so that we can learn what they are being taught in their schools.

The second day will focus on the topic of meeting societal needs through veterinary education and research and will examine models for veterinary animal welfare education. In advance of the meeting, we intend to survey deans, department heads, faculties, and students about how animal welfare is and isn't considered in DVM degree programs. The survey will query the students about what they learned and whether their expectations were fulfilled during the four-year program.

In addition, we will look at preveterinary education and students' background before attending veterinary school. We need to examine the selection criteria for veterinary students in animal care and welfare from [the point of view of] both US and international expectations. This session will also include a roundtable discussion with student participation.

We also want to center some of these discussions on post-DVM education. Since education is a lifelong process, continuing education is essential. The session will include graduate program specialization and the Foresight Report to delve into how we are meeting societal needs in educating not only our students but also our practicing veterinarians.

The last part of day two will present a model for animal welfare research. We will look at program design, the applied priorities of our research programs, access to results, and the application of the research to teaching veterinary students and how to apply it to meet societal needs. We will also address funding for animal welfare research, both private and public. We would like to develop a clearinghouse of funding information resources so new graduates and veterinarians will know how to access funding.

We will conclude on day three with a session on moving forward, focusing on communications with respect to animal welfare. This session will also look at veterinary culture in relation to animal welfare, particularly some special challenges faced by veterinarians employed by industry or a producer or somebody who owns animals in carrying out animal welfare. For example, how can the veterinarian bridge the gap between what an employer or animal owner wants and societal needs and expectations?

Finally, the conference will address the issue of advocacy—how can we get veterinarians involved in becoming activists, community leaders, possibly running for Congress, to be the senator that Dr. Pappaioanou says we need to

contact? Veterinarians need to step up to the plate rather than letting somebody else do it. So the sessions tackle how to become involved, what to advocate, and how to educate the public.

We believe this will be an excellent symposium and encourage all of you to attend. Drs. Golab and Granstrom at AVMA are the lead people for this program.

Online Training and Distance Learning

Patricia V. Turner

My presentation will continue with the theme of providing adequate veterinary care for animals used in research, teaching, and testing. One potential solution for providing veterinary training in this area is through online training and distance learning.

I will focus on some of the challenges in providing adequate veterinary care for animals used in research, teaching, and testing, particularly the aspect of veterinary training. I will also discuss trends in educational delivery that are occurring at universities and colleges across North America and may be occurring in Europe as well. Finally, I will talk about online learning programs for veterinarians and provide an example,[1] with some potential future applications.

Current challenges in laboratory animal medicine (LAM) occur because there is now an increasingly complex globalized research environment, with companies and institutions having multiple sites around the world, and there is difficulty ensuring adequate veterinary care and harmonization of training across all these sites.

Even in countries where there are well-established training programs, there are shortages of well-trained personnel. Increased public expectations for the accountability of scientists and institutions, and for providing adequate veterinary care and ensuring research animal welfare, have led to an increased need for veterinarians. This has resulted in increased employment opportunities for veterinarians; however, there are not enough adequately trained veterinarians to fill these roles.

In addition, there is difficulty in recruiting enough veterinarians to return for graduate work and specialization in residencies in some of these programs, primarily due to debt load. In North America, veterinary students graduate with huge debt load and they cannot afford to come back for additional education or training, although they might like to. The stipends may or may not be attractive to these new graduates, and we don't have enough stipend positions to bring

[1]The slides that accompanied this presentation are available in the online posting of this report at www.nap.edu.

these veterinarians back. Furthermore, the traditional methods for training specialists in laboratory animal medicine are expensive and not necessarily efficient. I say this as a program leader for our research-intensive ACLAM-recognized doctoral training program at the University of Guelph. I still believe this is the gold standard for LAM training, but it isn't geared for a high volume of trainees because it is based on one-on-one intensive mentoring—the program can produce only one graduate every three years, which is not sufficient. Together, all the institutions that are producing these very intensively trained specialists cannot meet the employment opportunities and needs out there.

Other training options to bring enough veterinarians into the field and ensure that they are adequately trained must be explored. The immediate problem is that there is an urgent need for entry-level training for licensed veterinarians in laboratory animal medicine to fill some of these roles. This population includes licensed clinical veterinarians who may be looking for a career change, some who own clinics, who are working or consulting at a biotechnology company or community college, or who are working full-time in a field but are unable to return for graduate studies or a residency because of location, financial constraints, or because they have no desire to go back to school for another three to five years. A new approach is needed to attract these adult learners and provide them with the basic education they need to fulfill their responsibilities as attending veterinarians in these institutions.

Distance education has been increasing in popularity in recent years. One of its main advantages is that the participants are not required to travel to commit to an institution. They may do it from a distance, hence its name. Also, participants can study when it is convenient, allowing them to work full-time and attend to family needs at home, then study during evenings or weekends, when they have free time. I would argue that a distance education program is very well suited for providing both basic and, perhaps in the future, advanced information to veterinarians in laboratory animal medicine.

Current trends in educational development are toward an increasing number of courses taught in the online classroom. Many full-time students attain degrees with these blended programs, with traditional didactic courses on-site and up to 50% of the program provided in online courses. Students seem to like a combination of both. Even with traditional courses, the online classroom is becoming increasingly used, so students may be given an assignment in class, and then a portion of their grade will be assigned to an online discussion group that is monitored by teaching assistants (TAs) or the professors.

However, the program needs to be very well structured with very clear objectives to be effective in educating students. There is no daily face-to-face meeting with the TA or the professor, so the course goals and progression need to be very well structured, learner-centered, geared to developing problem-solving skills, and still provide the interaction that is normally achieved in the classroom, tutorial, or seminar.

Online course participants need to be motivated since they are working on their own. This format is not suitable for everyone, since it is not easy to work

an eight-hour day and come home and have to study at night. However, with motivation it can be done successfully.

It should be noted, however, that it is not necessarily less work for the instructor to conduct online courses. There is a lot of development work in terms of setting up the program, and then in providing feedback and facilitating instruction during the course period. In addition, this format is very different from traditional teaching forums and involves a different educational philosophy. It does not involve just taking PowerPoint presentations, taping an audio, and putting it on a website. This format focuses on short bursts of intensive learning followed by some type of application to evaluate consolidation of learning.

MIT has an absolutely astounding open courseware project with over 1,800 courses available online. Tufts University also has some excellent open courseware available. The MIT Open Courseware website has PowerPoint presentations from all the courses offered at MIT. However, while the information is freely available, the certificate, diploma, and degree programs are not free. Also, it should not be assumed that, because the information is provided for free to the public at large, people are consolidating and learning it. The skill is in the instructors' abilities to provide the information in an online setting to educate people.

It should also be noted that there are costs involved in online courseware: software costs for those writing online platforms, costs for staff who are doing the administration, and in some cases an honorarium for the course instructor.

I would now like to provide an example of how we have tried to deal with the challenge of providing adequate veterinary care for animals used in research, particularly veterinarians working in laboratory animal medicine.

Canada is a large country with a relatively small population. There are about 220 veterinarians in laboratory animal medicine, working across the country in a variety of sectors, often in very remote locations. We sometimes have a language barrier since there are two official national languages.

Since for many years there was only one formal training program in Canada, at the University of Guelph, with a low graduate output, most of the veterinarians working in laboratory animal medicine have entered the field through experience rather than by formal training in LAM. These veterinarians are very well qualified with solid skills in clinical medicine and surgery typical of small animal practice. Several years ago, it became evident that there were facility compliance issues at some smaller institutions because of a lack of adequate veterinary training. Veterinarians did not always understand their full responsibilities as the attending veterinarian in these facilities. In conjunction with the Canadian Association for Laboratory Animal Medicine (CALAM/ACMAL) and the Canadian Council on Animal Care (CCAC), we determined that it was necessary to provide theoretical and applied training to bring veterinarians up to speed quickly. It was also deemed necessary to have mentoring contacts, because these people were physically isolated in many cases.

This situation led to the development of the LAM certificate program, a university-approved academic program of study consisting of a minimum of 160

hours of effort. That time is what the university has approved, but it may actually take a little longer for participants to work through all the material.

There are four courses in the program. The first is the web-based program that is a self-study course. It provides broad-based theoretical information on major themes in LAM. This is followed by three skills-based courses that are held at regional training sites across the country; I will talk about each of these in a little more detail. The LAM certificate program is partnered with the Office of Open Learning at the University of Guelph to provide the distance education platform and the technical support for running these programs.

The curriculum was developed in part from the Federation of European Laboratory Animal Science Associations (FELASA) guidelines for Category D specialists as well as from recommendations developed by the American College of Laboratory Animal Medicine (ACLAM) for formal training of laboratory animal veterinarians. An advisory committee comprising laboratory animal veterinarians from across Canada edited and produced the course content and assisted with question bank development; other veterinarians were conscripted as needed in the program to develop skills lists or to review materials. A skills list has been developed for the applied courses.

Participants who enroll in this program theoretically could complete it in as short as a month but we provide them with up to two years. Some participants are clinical vets who may own a practice and cannot take off four weeks in one year to complete the program. This program is envisioned as an entry-level tool and is not in competition with postgraduate training programs in this area. It is intended for a completely different population of veterinarians who have no intention of returning to school for further specialization.

The course covers bioethics, regulations, animal care committee function, anesthesia, analgesia, euthanasia, occupational health and safety, biosafety, and animal models. It is set up as a combination of online notes and heavy HTML mining, primarily to enable veterinarians to learn how to find sources of information through relevant websites and electronic resources. The program is multimedia to accommodate different types of learning, so participants receive a hard copy reader containing key papers, references, regulatory guides, short video clips, CDs, and DVDs. Some of these items can be used in their training programs in their own facility. Evaluations are both formative and summative. There are several short written assignments submitted electronically for evaluation by the coordinator, as well as multiple choice quizzes for each online topic. Participants must achieve at least 80% on these to pass, and they only get two chances to take any quiz, so the program of study is rigorous and must be taken quite seriously by the participants. Because we have a large question bank for each quiz, participants won't get the same quiz twice.

There are currently three entry points for enrollment in the program throughout the year: October, February, and May. Once the participants are enrolled and the online course starts, they have nine weeks to complete the material, because we want to give them some structure for completing the course in a timely period.

The applied courses consist of 40-hour one-week applied placements at regional facilities across Canada. The sites were selected based on the experience of the veterinarians, the number of vets per site, the quality and diversity of the programs, the species, and locations, with efforts to have wide geographical distribution and inclusion of French language sites. All training sites are CCAC-assessed. Participants take a skills list with them to use as a training passport and placements are facilitated by a course coordinator. The areas in which they receive training are somewhat tailored to their area of employment; for example, if they work with aquatic species they will focus on aquatic training, without much training in nonhuman primates.

The program is approved and has been recognized by the CCAC, which is important in terms of regulatory recognition, as is the professional recognition given by CALAM/ACMAL. Upon successful completion, participants receive a certificate in LAM and can receive a transcript of their marks.

The accompanying slides represent some screenshots from the program. The Home Page has a number of hot links across the top and gives general information and announcements. The Course Outline page provides an introduction, information about the course development, expectations for learning, and other resources. The Time Line for the course shows various activities occurring each week, and assignments and quizzes that are to be done at each time point. The expectation is that participants will move sequentially through each topic before advancing to the next. In terms of actual topic content, there are brief instructors' comments and other readings students must do to consolidate the knowledge.

The Course Resources page includes a broad range of references from many organizations including the Canadian Association for Laboratory Animal Science, ACLAM, and ILAR. Most importantly, the website contains contact information for the course instructor and there is 24/7 online support for participants provided by the Office of Open Learning.

Ongoing related projects include working together with a number of ACLAM diplomates in the US to develop a similar entry-level US certificate program, which will become available soon. In addition, we have been in discussions with veterinary colleagues in Southeast Asia and Latin America to develop similar online programs to meet some of the veterinary training needs in those regions. The online format affords many opportunities to provide more advanced training in other LAM areas such as imaging, cardiology, and pathology, among others.

An example of an advanced program is that being developed by Dr. Bob Cardiff, a comparative pathologist at University of California at Davis. He is developing online courses in genomic pathology geared to different levels of instruction for technicians, graduate students, pathology trainees, and scientists. This program will provide information on informatics, basic pathology, and recognition of lesions in tissues as well as histologic phenotyping. These will be tuition-based courses and will offer credits for graduate students anywhere in the world.

The advent of slide scanning and related software now provides the option of developing online comparative pathology programs for advanced training. Glass slides can be scanned in at very high magnification with excellent resolution for students viewing from their desktops. The particular software (ImageScope, Aperio) is free, and students can download it as long as they can access a server that has the slides saved onto it. Students can annotate the slides by, for example, circling lesions or putting arrows on different parts, save the changes, and send them back to the instructor as part of their online training. This is an excellent opportunity for coaching and facilitation of learning in comparative pathology.

So in summary, we are at a very early stage in the veterinary medical field and in particular in laboratory animal medicine and science for implementing some of this technology. However, there are a lot of exciting opportunities in the future to use online training as one potential tool to provide for harmonization of veterinary training and ensure at least a minimum level of training of veterinarians for the provision of adequate care of laboratory animals.

INTERNATIONAL APPROACHES AND PRINCIPLES FOR DISTRESS, PAIN, AND EUTHANASIA

Distress

David Morton

Mental distress is arguably the biggest single enduring adverse effect on laboratory animals during their lives, and with the greatest impact on the science. It is not pain but fear and poor housing and poor husbandry systems that inflict most animal suffering during their lifetimes.

Although pain and distress are addressed in guidance and legislation, distress is still overlooked as a source of poor animal welfare and also poor science. In my view, pain has been overemphasized, mainly because it is of greater public concern and a more obvious target for nongovernmental organizations. However, this is now changing with current public concern about the welfare of animals in zoos, breeding of companion animals, and particularly farm animal husbandry and rearing systems.

The debate has moved away from pain to one about the quality of an animal's life and how we can measure that. Even though there may be events that cause temporary pain, it is the suffering over a lifetime that probably matters most. Captive animals, including those kept for research, are held in impoverished conditions compared with the ecological niches into which they have evolved. In other words, we do not really meet their physiological and mental needs in terms of their evolutionary background. But of course we meet their vital needs; we have to.

Many laboratory animals have well-developed senses like smell, sound, sight, touch, and taste to survive in the world, and husbandry systems do not normally fulfill many of these evolutionary needs. Neither has domestication removed them, as, when domesticated animals are released into the wild, they soon adopt the ways of their progenitors. So there is still a need to meet these needs.

Imagine what you would miss if you were kept in a cell in solitary confinement. The same diet day in day out, without any sun, wind, rain and other forms of precipitation, with little sensory changes in sound, textures other than metal bars, bedding, or plastic, concrete, metal floors and walls, no choice of mates, without space to run, being unable to go where you want to go, and so on. This is why I say that keeping animals in captivity is impoverished for them. So keeping animals in such life-sustaining but otherwise inadequate housing conditions for the whole of their lives may cause considerable long-term suffering. That is one reason for my statement that fear, poor housing, and poor husbandry systems inflict most animal suffering during their lifetimes. Even best practice still compromises animal welfare considerably.

Of course there is no easy answer to this conundrum, as we have to confine animals to carry out research on them. But I believe we can do more to improve the quality of their shortened lives.

Furthermore, the evidence for what is acceptable or at least unacceptable for the animals is often not there. Only when animals die prematurely is there concern. In the meantime, how does one decide what to do, what to provide? Who gets the benefit of the doubt when the science can provide no answers—is it the human or the animal?

In science, the traditional surgical and physiological procedures that were once carried out are gradually being replaced by investigations using transgenic and genetically modified animals and this makes the issues of meeting their mental needs even more of an imperative. For instance, in the UK in 2007, genetically modified and mutant animals and their breeding accounted for nearly 50% of all animal experiments. Only 39% underwent "traditional" procedures of such severity that they required an anesthetic, and the number used for human clinical research was less than 1%. However, there will be more animals undergoing surgical interventions for purposes other than clinical research and all animals in laboratories will suffer the chronic distress of poor living conditions.

While pain is a well-defined and relatively well-understood area of animal physiology and pathology, it is treatable, and so it is often not necessary to keep animals in pain or to cause pain to animals unless there is an overriding scientific reason—for example, research on pain. This is yet another reason why poor mental health (i.e., distress) is so important: it is often unavoidable. I'm not saying that pain is unimportant—it is (Matt Leach will address pain in his talk); but distress is a neglected source of animal suffering.

The annual reports on animal suffering show some interesting differences between countries and the way they handle distress. Most do not separate distress but combine it with pain. Others do not separate intensity and duration of either pain or distress in any meaningful way. Most countries record only *predicted* adverse effects, while others estimate the adverse effects that actually occurred (i.e., a retrospective recording). The important point is that all countries recognize the term distress as well as pain. So how do we go about measuring pain and distress?

To understand animal suffering it is important to appreciate that animals cannot just be reduced to their component parts, which is the traditional scientific reductionist approach. Pain and distress are more than the sum of their component parts.

Mental distress (which I see as part of mental health) is reflected in several emotional states and is a more complex experience than pain. It embraces feelings like fear, boredom, frustration, malaise, inappetence, thirst. Animals are conscious beings; they respond to adverse external and internal stimuli as a whole, that is, they show an integrated multimodal response to a negative stimulus. Thus animals in pain have raised corticosteroid levels together with a range of physiological and behavioral changes from normal. They are likely also to experience distress states such as fear when they associate their condition with environmental factors such as a particular room or a particular person and an unpleasant experimental intervention, such as an injection. Memory is an important component in mammalian (and probably in all the other classes of the phylum Chordata) pain and distress.

Several of these adverse mental states can occur in the same animal at the same time. An animal is unlikely to experience just one state at a time, especially pain. However, a reductionist approach in science induces us to concentrate on just one aspect at a time. It is very important that a more holistic approach be taken. For example, an animal with a painful broken leg will be in some form of mental distress as well as pain. When the veterinarian who examined the leg reappears the animal may be fearful that she will cause it to feel pain again.

Mental distress causes a mixture of feelings or emotions that can influence bodily responses that increase the possibility for confounding scientific observations. Several years ago, a disturbance index was used to assess how animals behaved after they had had an injection. That was a rather interesting approach, but it has never been followed up. Animals became hyperactive or hypoactive after they had been subjected to a procedure such as an injection of cold saline, or an injection with a large needle size, or large volume. Differences in their responses were observed, and it might be possible to interpret these differences but the work was never completed.

However, there are other indirect and nonspecific physiological measures of distress including blood hormones such as cortisol, organ responses to hormonal changes, neurochemical binding patterns in the brain and spinal cord, and responses to known pharmacological agents. We are aware of many of these responses that potentially will confound the data being collected such as the impact of catecholamines on heart rate and blood pressure, [or] the effects of cortisol on the immune system. We may also be able to use such known actions to make a diagnosis of an animal's emotional state. For example, if animals change their behavior after they have been given an analgesic, then that is some evidence that they were in pain. Increased heart rate, body temperature, and blood pressure as a result of catecholamine release could be a measure of fear

and anxiety. However, measuring hormonal levels is impractical; observing animals for changes in their behavior is more feasible.

Stress physiologists look at hormone levels and use the term "distress" for animals that are not coping with their environment and in which the whole endocrine system can eventually become unresponsive. I call this syndrome dystress, spelled with a *y* after the Greek *dus*, having a connotation of "badness," as in dyspepsia (bad digestion). It may persist to a point where an animal cannot cope. In Europe, *distress* is interpreted more broadly than a physiological state of not coping and incorporates mental states rather than physiological states. That is when animals experience adverse feelings such as fear, anxiety, boredom, malaise, frustration, and the like.

There is a continuing debate about whether physiological levels (e.g., of hormones) are "harder" and more reliable scientific measures than measures of behavior. Some people think that signs are objective only if you can measure them and can assign a number on some sort of continuum. However, other signs (parametric) based on clinical signs or an animal's behavior cannot easily be measured on a continuum (e.g., lameness, difficulty in breathing, stereotypic behavior) but are just as valid and just as objective, in the sense that we can observe them accurately and reproducibly. It is quite important that both sorts of signs be used depending on the circumstances and the adverse effects we are measuring.

Whether metric or parametric measures are used it is still necessary to *interpret* them in terms of understanding an animal's mental state. It is this interpretation of an increased heart rate or increased blood pressure or a behavior that is the subjective step. The observation of the behavior and the measurement of a hormone level are both objective, but both have to be interpreted into [a gauge of the] intensity of mental distress.

In my opinion, in the measurement of animal well-being, behavior normally trumps physiology [in the] final integrated outcome of how an animal is feeling, it "votes with its feet." We could invoke an analogy with people's experience in hospitals today when they are in pain and do not get the treatment they feel they need. A scenario might occur where the nurse/doctor takes a blood sample and says, "No, you cannot be in pain, your blood hormones aren't high enough." What would you say? You know you are in pain and your behavior will most likely show that you are in pain (you may not want to move, feel nauseous, don't feel like getting out of bed, look grey). All these physiological and behavioral signs are the outward integrated response but how you feel is mostly evidenced by your behavior and that is why I think behavior trumps physiological measurements for those that cannot speak and communicate.

In the ILAR working group on distress there were physiologists from the US who took the view that distress was the result of exposure to long-term stressors (I have referred to this as "dystress" above), and those from Europe who considered that (mental) distress could also result from a short-term exposure to stressors and cause mental states such as fear. Of course, it is very important from an evolutionary standpoint to be able to adapt to external stressors for

survival, sometimes referred to as "eu-stress" (Greek *eu* having a connotation of "good"). I recommend you read the ILAR report on distress; it is an extremely comprehensive document and it describes these tensions.[1]

I tried to find out for this conference something about the use of the word distress and what was happening in guidance and legislation in various countries. I emailed several colleagues in various countries with the following questions:

How does your country define distress and what emotional states would it cover? Would it for example cover the mental health of animals held for experiment as well as being in an experiment? (Animals are kept in their housing for possibly 100% of their time, but they are not on experiment for all that time.) Some countries provided a definition of distress whereas others preferred a descriptive approach to distress. That was very similar to what we decided in the ILAR group.

How does your country help users recognize distress? Some countries provided a list of signs and a guide to their assessment based on changes from normality—the more the observation deviated from normality, the greater the impact on the animal and the greater the distress.

How does your country help users treat distress? The emphasis here was on withdrawal—withdrawal of the animal from the stressful situation or avoiding it in the first place. Nobody really answered the question, although I was interested to see the Australian guidelines have started to follow the European Food Safety Authority (EFSA) model of welfare risk assessment. That is quite complicated, and I can give you some references to it. It is a rather tedious approach that looks at the intensity of an adverse state, its duration, the numbers of animals likely to be affected, and the likelihood that they will be affected if exposed to a stressor (or hazard in RA terms), but it does present some very interesting observations and challenging data sets to create. The [NRC report] had a section on treatment of distress, but I really don't think it is going to be practical, because scientists are not going to want to give drugs that are neurologically active in their experiment.

Does your country have any formal guidelines for users? Canada and Australia had some formal guidelines, although I'm not quite sure how practically useful they are. When I looked through the [1996] US *Guide for the Care and Use of Laboratory Animals*, distress was mentioned only in conjunction with pain (i.e., "pain and distress"); there was no separate guidance on distress. But hopefully the ILAR report on distress will change that.

I received only three or four replies to my e-mail. There was resounding silence from the competent authorities in most countries. However, I received a good response from Australia and New Zealand with some really interesting observations. I would argue that is because they are the ones that have been at the forefront in developing broad-based local animal care and use ethics com-

[1] *Recognition and Alleviation of Distress in Laboratory Animals* (2008). Washington: National Academies Press.

mittees and distress would have been an issue for many lay members. The US was very much ahead in setting up ethics committees in the first place, but the formal composition and skill base of these committees was very narrow and different from those in other countries; for example, they excluded animal protection members and did not mandate those with training in ethics.

I had a detailed response for farm animals from Italy, but unfortunately it was all in Italian. Many of the other countries either gave very general guidelines or simply did not address distress as a separate issue, although they often dealt with pain separately.

In the US, the major emphasis has been on pain but ignores its duration and intensity, and that is common to many other countries. However, that is historical, and maybe the revision of the *Guide* will include more information about intensity and duration of both pain and distress, in the same way that EFSA's risk assessment does.

One of the major differences is that the US, in general, is far less willing to give animals the benefit of the doubt in the absence of scientific evidence. This raises interesting and productive tensions, with a more rigorous requirement for validation of welfare measures in the US than in the EU or elsewhere. Validation of welfare measures is becoming a key issue in other areas of animal use—for example, welfare assurance schemes for farmed animals such as the Welfare Quality project in the EU. This is a massive project—17 million euros have been invested in this activity, which includes 44 institutions and 13 member states, plus four in South America. They are trying to develop key welfare indicators that can reflect the quality of life of farmed animals before they are killed—did they have a good quality of life, did they have a life worth living, if you like? The Farm Animal Welfare Council in the UK is also looking into this.

The issues are the same for research animals. How do we assess their quality of life, which will include validation of the measures and how we determine whether a particular measure reflects pain or distress? We need more research on validation of the measures, their robustness, reliability, and how feasible they are to measure, and can they be scored with good observer reproducibility?

The advantage of measuring deviation from normality—measuring the impact of an experiment or system of husbandry on an animal—is that you don't have to label it with a particular mental emotional state. The only reason one might want to label something as pain or distress is for implementing therapy: if an animal is in pain, it should receive an analgesic. However, distress is far more varied and complex and the cause is very important. Fear (e.g., of humans, rooms), anxiety (a raised awareness in general), frustration and boredom (e.g., because of housing and husbandry), malaise (e.g., because of infection) all have different causes and these have to be identified. Treatment will then be based more on causation as opposed to pain, which is generally easier to predict and diagnose and treat. It is also quite important not to label things too restrictively as various mental states often run together.

Most international guidelines emphasize that one should take steps to avoid any adverse effects for scientific reasons. This can be done through better

training of personnel, better techniques carried out competently, closer observations of animals, and early detection of adverse states and their causes.

In conclusion, mental ill health—i.e., distress—is the most common cause of suffering in laboratory animals. It is multifactorial and difficult to treat. There is little guidance in most countries on its recognition, assessment, avoidance, and alleviation. It can be recognized and assessed by measuring the impact of the procedures in animals, but research is needed to identify key validated and robust measures.

Pain: International Differences Across Guidelines and Approaches

Matt Leach

Introduction

Most of the work reported here is the work of the members of the pain systems group at Newcastle University, UK; in particular, the work of Claire Richardson, Claire Coulter, and Paul Flecknell will be referred to.

Before looking at guidelines and approaches a definition of animal pain is required. The most widely accepted definition of pain and the most appropriate in this case is that of the International Association for the Study of Pain (IASP 1994): "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Guidelines and Codes of Practice

The vast majority of countries that carry out animal-based research have guidelines, almost all of which state that "Pain should be 'minimized and/or alleviated…'" or have statements to a similar effect (e.g., ILAR, NIH, Australia's National Health and Medical Research Council [NHMRC], the UK Home Office, the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [ETS 123], JCS, and CCAC). Pain can be minimized and/or alleviated using the principles of the 3Rs. The use of analgesia is critical. As a consequence of the guidelines that exist we should expect analgesia to be commonplace and extensive guidance on when and how to use analgesics to be in existence. So how widespread is analgesic use?

Analgesic Use in Rodents

A 2005 literature-based survey (Richardson and Flecknell 2005) looked at analgesic use in laboratory rodents undergoing painful procedures. It included papers published in bioscience journals in 1990-1992 (100 papers) and 2000-

2002 (100 papers). The proportion of papers reporting no analgesic use, analgesia via anesthesia, and analgesic use is shown in Figure 1.[1]

The high percentage of rodents that were reported not to receive analgesia is not surprising when we consider analgesic use in veterinary clinical practice in general. The work of Lascelles and colleagues (1999) in cats and Capner and colleagues (1999) in dogs demonstrates this (see Figure 2). The problem of low analgesic use is not a new problem as a similar situation was seen in human medical practice around 20 years ago. The lack of analgesic use in medical and veterinary clinical practice could be due to failure either to appreciate the significance of pain or to recognize signs of pain.

However, is this true for laboratory animals? The literature survey by Richardson and Flecknell (2005) carried a follow-up in which they emailed authors who reported no analgesic use in their papers (67% of papers) and asked whether they had simply not reported analgesia use (underreporting) or had not administered analgesics (underuse). The change in the proportions of papers reporting no analgesic use, analgesic use, and analgesia via anesthesia is shown in Figure 3.

Analgesic Use in Other Species and across Continents

Two literature surveys in 2007 looked at analgesic use after surgery in rodents (Stokes et al. 2009) and in larger species (rabbits, pigs, sheep, dogs, and primates; Coulter et al. 2009). The surveys covered studies that were carried out in a number of countries around the world and published between 2005 and 2006; for rodents these involved 86 papers in 10 journals and for larger species 75 papers in 61 journals. The results of these surveys are shown in Figure 4.

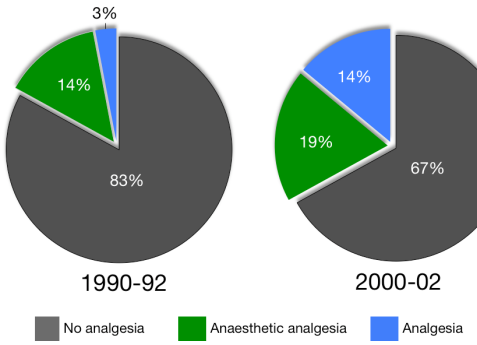

FIGURE 1 Reported analgesic use in rats and mice in bioscience journals in 1990-1992 (100 papers) and 2000-2002 (100 papers). Source: Richardson and Flecknell (2005).

[1]The figures in this article appear in color in the online posting of this report at www.nap.edu.

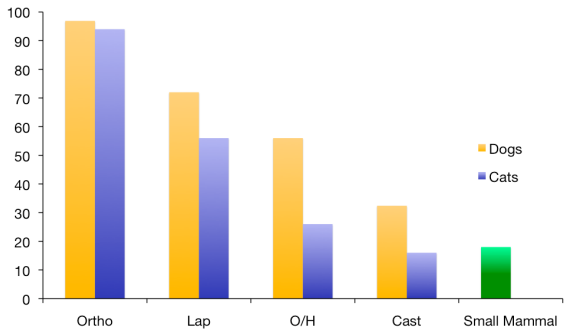

FIGURE 2 Percentage of dogs, cats, and small mammals receiving analgesia after different types of surgery in the United Kingdom. *Source:* Richardson and Flecknell (2005).

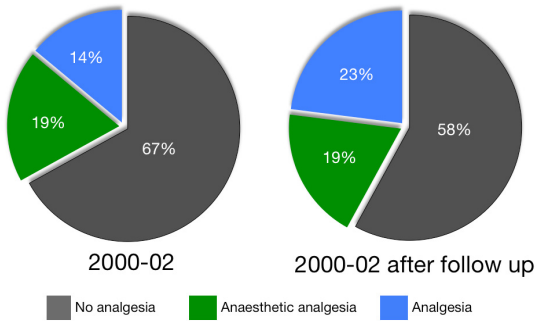

FIGURE 3 Changes in reported analgesic use in rats and mice in 2000-2002 after email follow-up of authors who reported no analgesic use. *Source:* Richardson and Flecknell (2005).

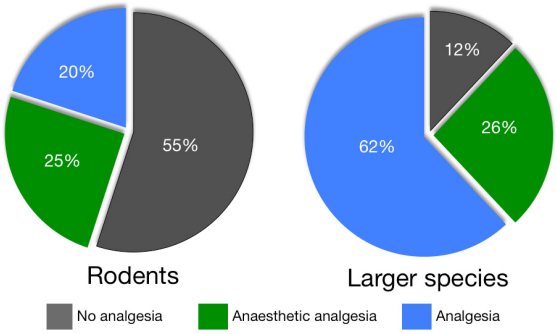

FIGURE 4 Reported analgesic use in 2005-2006 after surgery in rodents (Stokes et al. 2009) and larger species (rabbits, pigs, sheep, dogs, and primates) (Coulter et al. 2009).

These data can also be tentatively used to assess analgesic use by the continent on which the work was completed (see Figure 5). These are the only data of their kind as far as we know, and although they are indicative they should be interpreted with extreme care. The surveys were not designed to differentiate between countries, there was an unequal distribution of papers across countries, cultural differences were not taken into account, and the proportion of animal-based research carried out in each country was not taken into account, [any of which] could bias results.

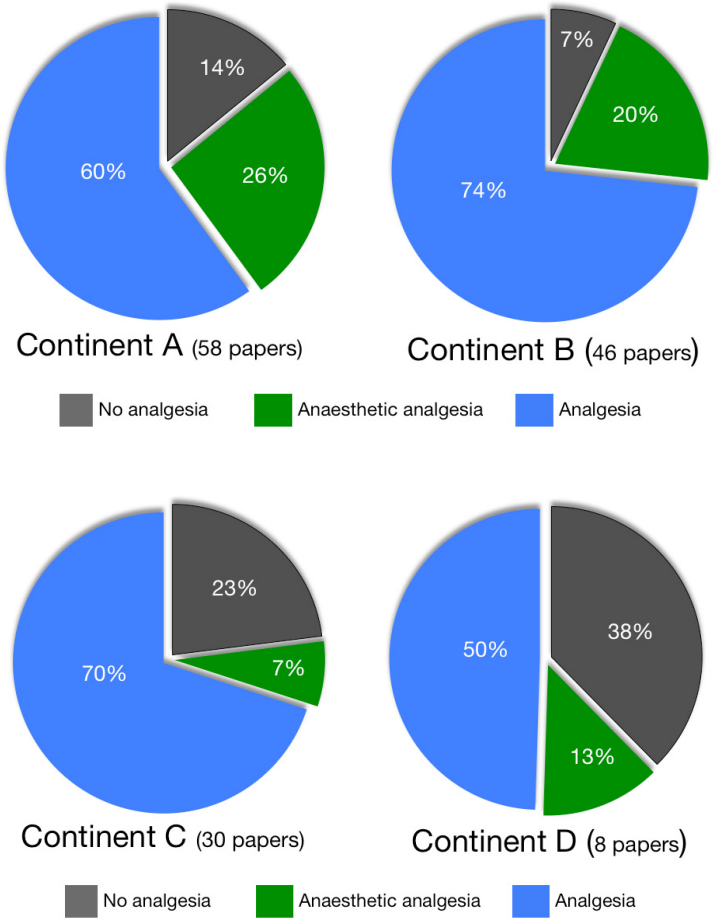

FIGURE 5 Reported analgesic use by continent in 2005-2006 after surgery in rodents and larger species. *Sources:* Coulter et al. (2009); Stokes et al. (2009).

Why Is There Such a Low and Varied Use of Analgesia in Animals?

There are a number of possible reasons for such low and varied use of analgesia in animals despite the prevalence of guidelines:

- Some consider that animals don't feel pain and this is dependent on attitudes to pain in animals, which vary among countries and professions.
- There is no perceived need to give analgesics; however, this is often due to a failure to recognize indicators of pain in animals.
- Concern over interactions between the analgesics we can administer and the experimental protocol being carried out on animals.
- Concern over the extent of potential side effects associated with the analgesics we administer.
- Tradition or historical data showing that a potentially painful procedure has been carried out without analgesics before, used as evidence that it can be again.

In many cases unalleviated pain can cause as much if not more variation in the data as either interactions between the analgesics and experimental protocols or potential side effects associated with analgesics. If there is concern about the effect of analgesic administration on experimental validity then this can be considered with other sources of potential variation in a study (e.g., environmental, surgical) through well-designed and appropriate statistical analysis. In addition, the other effects of unalleviated pain on animal-based research should be appreciated, such as causing the death of animals, which can require the use of additional animals to maintain the study design. Increasing the number of animals used does not fulfill the spirit of the 3Rs.

In Summary

It seems that in many cases the apparent rationales for withholding analgesia do not withstand close scrutiny, which can easily be seen in the peer-reviewed literature, as for a given procedure analgesia will be administered in one case but withheld in another when carried out on different species, or even the same species, both between and within countries. Therefore, despite the prevalence of guidelines there remains considerable variation in the administration of analgesia in animal-based studies.

The final point of this presentation was to ask those who attended this meeting why they think there is such considerable variation in the administration of analgesia in animal-based studies.

References

Capner CA, Lascelles BDX, Waterman-Pearson AE. 1999. Current British veterinary attitudes to perioperative analgesia for dogs. Vet Rec 145:95-99.

Coulter CA, Flecknell PA, Richardson CA. 2009. Reported analgesic administration to rabbits, pigs, sheep, dogs and non-human primates undergoing experimental surgical procedures. Lab Anim 43:232-238.

IASP [International Association for the Study of Pain]. 1994. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd ed. Available online (www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728#Pain).

Lascelles BDX, Capner CA, Waterman-Pearson AE. 1999. Current British veterinary attitudes to perioperative analgesia for cats and small mammals. Vet Rec 145:601-604.

Richardson CA, Flecknell PA. 2005. Anaesthesia and post-operative analgesia following experimental surgery in laboratory rodents: Are we making progress? ATLA 33:119-127.

Stokes EL, Flecknell PA, Richardson CA. 2009. Reported analgesic and anaesthetic administration to rodents undergoing experimental surgical procedures. Lab Anim 43:149-154.

Euthanasia

Gilly Griffin

Introduction

Various organizations around the world have developed guidance on euthanasia. Some have developed guidelines that are specific for animals used for scientific purposes, others have a broader mandate. Some of the organizations are also involved in overseeing animal use in science and therefore have tailored their documents to fit their particular national systems. A comparison of recommendations made in recent guidelines drawn from a variety of jurisdictions is provided. Differences in recommendations can be the result of difference in interpretation of scientific evidence, but may also reflect difference in expert opinion, national systems, and societal values.

Guideline Documents

As national authorities overseeing animals used for scientific purposes have evolved, they have either developed or adopted guidelines as a means of holding animal users accountable to prevailing societal values. Guidelines for the ethical use and care of experimental animals provide the basis for acceptable practices relating to animal-based research, testing, and teaching. Guidelines may address particular procedures, conditions of housing and care, and the behavior of individuals carrying out procedures or caring for animals.

The guidelines themselves are usually implemented at the local institutional level, with local and/or national assurance, depending on the country. In some places, the national authority may be the organization that both develops the guidelines and provides assurance that they are implemented at the institutional level (for example, the Canadian Council on Animal Care, CCAC). In other places, guidelines may be developed by one organization (for example, the American Veterinary Medical Association, AVMA) and implemented by another (for example, the Office for Laboratory Animal Welfare, OLAW). To illustrate this point, OLAW interprets and oversees compliance with the US Pub-

lic Health Service (PHS) Policy on Humane Care and Treatment of Animals, which states that a method of euthanasia used in the United States must be endorsed by the AVMA (OLAW 2002). The organization or authority responsible for overseeing the implementation of the guidelines may itself be operating according to particular legislation or a policy framework that has an impact on the manner in which the guidelines are viewed and implemented as well as on the manner in which they were drafted in the first place.

Development of Guidelines

The development of guidelines involves the translation of scientific evidence into recommendations that can be implemented in practice. Although best attempts are made to ground guidelines in current scientific evidence, there are at least two factors that make straight translation of science into guidelines or policy almost impossible to achieve. First, guideline development happens at a discrete point in time, whereas science is continually evolving. Guidelines therefore need to be sufficiently flexible to accommodate shifts in thinking that may improve the welfare of animals, particularly as guideline documents take a considerable amount of time to produce.

Second, however much one might strive to base guidelines on hard science, in reality that science is subject to expert opinion, the regulatory framework within which the animal-based research is carried out, and current societal values, as most oversight systems are either an arm of government or established to act on behalf of the broader public. These additional factors do not dilute the scientific basis for guidelines; rather, they translate hard science into guidance, and in doing so add value to the guidelines. This ensures that the guidelines can be readily implemented and can be defended both to the scientific community and the public at large.

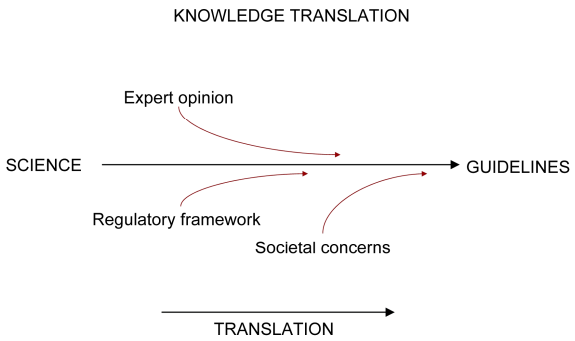

FIGURE 1 International harmonization.

International harmonization of guidelines is becoming increasingly important due to the evolving globalization of science. For this reason, the International Council for Laboratory Animal Science (ICLAS), an international scientific organization dedicated to advancing human and animal health by promoting the ethical care and use of laboratory animals in research worldwide, has been working on harmonization of guideline documents. At the ILAR symposium on science-based guidelines held in 2003, it was recognized that, due to differences in national systems of oversight, guidelines can only ever be *harmonized* and that standardization of guidelines is neither possible nor desirable (Demers 2004a).

Harmonization exercises conducted by ICLAS involve setting up international working groups in various subject areas to establish relevant guiding principles and to formally recognize guidelines that are suitable as international references. This has been achieved for exercises in each of the following areas: euthanasia, humane endpoints, ethical review, and animal user training programs (Demers 2004b; Demers et al. 2006; www.iclas.org/harmonization.htm). The principles are extremely useful as they do not impede a nation's ability to formulate its own guidance appropriate to the oversight system in place. Rather, they provide keystones upon which guidelines can be built. For example, the 10 principles generated by the ICLAS working group on harmonization of euthanasia guidelines (listed below) formed the starting point for the development of the CCAC guidelines on euthanasia of animals used in science (in preparation; since published, 2010). The principles were interpreted to address the particular Canadian situation and formed the basis for guidelines that adopt guidance that is already well established as well as providing additional information and details where new scientific evidence has become available. This approach would be useful for any guideline development exercise.

ICLAS Principles on Euthanasia

The following ten principles on euthanasia prepared by ICLAS provide a means of evaluating euthanasia techniques (Demers et al. 2006):

1. Whenever an animal's life is to be taken, it should be treated with the highest respect.
2. Euthanasia should place emphasis on making the animal's death painless and distress-free. The method likely to cause the least pain and distress to the animals should be used whenever possible.
3. Euthanasia techniques should result in rapid loss of consciousness, followed by cardiac or respiratory arrest and ultimate loss of brain function.
4. Techniques should require minimum restraint of the animal and minimize distress and anxiety experienced by the animal before loss of consciousness.
5. Techniques should be appropriate for the species, age, and health of the animal.

6. Death must be verified before disposal of the animal.

7. Personnel responsible for carrying out the euthanasia techniques should be trained: (i) to carry out euthanasia in the most effective and humane manner; (ii) to recognize signs of pain, fear, and distress in relevant species; and (iii) to recognize and confirm death in the species.

8. Human psychological responses to euthanasia should be taken into account when selecting the method of euthanasia, but should not take precedence over animal welfare considerations.

9. Ethics committees should be responsible for approval of the method of euthanasia (in line with any relevant legislation). This should include euthanasia as part of the experimental protocol as well as euthanasia for animals experiencing unanticipated pain and distress.

10. A veterinarian experienced with the species in question should be consulted when selecting the method of euthanasia, particularly when little species-specific euthanasia research has been done.

Euthanasia Guidelines

The guideline documents analyzed for this paper (listed below) have been developed by nationally recognized organizations. They were determined to be the most frequently used guidelines in this area, although other guidelines on euthanasia are also available.

- *AVMA Guidelines on Euthanasia* (2007, updating the 2000 Report of the AVMA Panel on Euthanasia). This document was prepared at the request of the AVMA Council on Research by the Panel on Euthanasia that convened in 1999 to review and make necessary revisions to the fifth Panel Report, published in 1993. In the 2000 Report, the panel updated information on euthanasia of animals in research and animal care and control facilities; expanded information on ectothermic, aquatic, and fur-bearing animals; added information on horses and wildlife; and deleted methods or agents considered unacceptable. In 2006, the AVMA Executive Board approved a recommendation that AVMA convene a panel of scientists at least once every 10 years to review all the literature that scientifically evaluates methods and potential methods of euthanasia for the purpose of producing AVMA guidelines on euthanasia. During the interim years, requests for inclusion of new or altered euthanasia procedures or agents in the AVMA Guidelines on Euthanasia will be directed to the AVMA Animal Welfare Committee. Revisions are based on a thorough evaluation of the available science and require Executive Board approval. The first interim revision, approved in 2006, added guidance on the use of maceration for chicks, poults, and pipped eggs (AVMA 2007).
- *Recommendations for Euthanasia of Experimental Animals* (Close et al. 1996, 1997). These two documents (Parts 1 and 2) were prepared for the EU Directorate-General of the Environment, Nuclear Safety, and Protection (DGXI)

to be used with Directive 86/609/EEC of 24 November 1986, on the approximation of laws, regulations, and administrative provisions of the member states regarding the protection of animals used for experimental and other scientific purposes (N° L 358, ISSN 0378-6978). They refer especially to Article 2(1), published by the European Commission in October 1995, which defines "humane method of killing" as "the killing of an animal with a minimum of physical and mental suffering, depending on the species." These documents are intended to be used in conjunction with the opinion of the Scientific Panel on Animal Health and Welfare (AHAW) of the European Food Safety Authority (EFSA 2005a).

- *Aspects of the Biology and Welfare of Animals Used for Experimental and Other Scientific Purposes* (EFSA 2005b). This report summarizes the position of the animal welfare panel of the European Food Safety Authority (EFSA), which was asked to consider the scientific evidence for the sentience and capacity of all invertebrate species used for experimental purposes and of fetal and embryonic forms to "experience pain, suffering, distress, or lasting harm." The panel also considered and made recommendations concerning humane methods of killing animals. This report updates recommendations made by Close and colleagues (1996, 1997).
- *Review of Schedule 1 of the Animals (Scientific Procedures) Act 1986: Appropriate Methods of Humane Killing* (APC 2006). The UK Animal Procedures Committee (APC) was asked in June 2001 to review Schedule 1. Recommendations in the report include advice on humane killing of neonatal rodents; use of argon, nitrogen, or other inert gases; use of CO_2; and weight thresholds for cervical dislocation of rodents. The Parliamentary Under Secretary of State for the Home Office responded to the APC's review in August 2007 (Hillier 2007), requesting further consultation on several of the committee's recommendations, while accepting the recommendation to provide advice on humane killing of neonatal rodents. These recommendations have not been implemented to date.
- *Public Statement: Report of the ACLAM Task Force on Rodent Euthanasia* (Artwohl et al. 2006). This report of the American College of Laboratory Animal Medicine is a response to growing concerns and controversy regarding techniques that were commonly used for rodent euthanasia. Three issues were targeted in the report: euthanasia of fetal and neonatal rodents, the use of CO_2 for rodent euthanasia, and the impact of euthanasia techniques on data.
- *Euthanasia of Animals Used for Scientific Purposes* (ANZCCART 2001; under revision). The aim of the publication is to provide investigators and members of Australian and New Zealand animal ethics committees with detailed information on methods of euthanasia relevant for animals used for scientific purposes, including species not generally used elsewhere (e.g., dingos and marsupials).
- *Canadian Council on Animal Care Guidelines on Euthanasia of Animals Used in Science* (CCAC 2010, updating Chapter XII on euthanasia in

CCAC 1993) is based on recommendations made by the International Council for Laboratory Animal Science (ICLAS) Working Group on Harmonization and the two international reference documents on euthanasia recommended by ICLAS: the AVMA *Guidelines on Euthanasia* (AVMA 2007) and the *Recommendations for Euthanasia of Experimental Animals*, Parts 1 and 2 (Close et al. 1996, 1997). This information has been adapted to suit the Canadian research environment.

Differences in Approach

The foregoing descriptions of each guideline document underline the fact that there are differences in the intent for each. The AVMA (2007) *Guidelines on Euthanasia* are primarily to assist veterinarians in exercising professional judgment in the application of euthanasia. The document covers not only animals used for scientific purposes but also those used as companions and for food, animals in the wild, and exotic species. Close and colleagues (1996, 1997) provide guidelines that are specific to animals used for experimental purposes. Euthanasia of these animals would not necessarily be carried out by a veterinarian. The EFSA recommendations are to be used in conjunction with those of Close and colleagues (1996, 1997) and will be legally binding once the new European Directive comes into force. Schedule 1 to the UK Animals (Scientific Procedures) Act 1986 provides a list of methods considered exempt from the requirement for a UK Home Office personal or project license. The CCAC guidelines and the ANZCCART guidelines are specific for animals used for scientific purposes and are targeted to investigators and animal care committees to provide them with the relevant information on which to base their decisions regarding methods of euthanasia.

Irrespective of the framework within which these guideline documents are implemented, there is considerable similarity of intent. In the United States, animals used for scientific purposes essentially fall under the PHS Policy, which requires "avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices" and requires investigators to "consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals" (OLAW 2002b). The Australian Code of Practice for the Care and Use of Animals for Scientific Purposes "assume(s) animals experience pain in a similar manner to humans" (NHMRC 2004). The CCAC policy states that animals must not be subjected to unnecessary pain or distress, and that cost and convenience must not take precedence when deciding on procedures and matters relating to the care of the animals (CCAC 1989). Similarly, European Directive 86/609/EEC requires that "all experiments shall be designed to avoid distress and unnecessary pain and suffering to the experimental animal" (EEC 1986). Last, the UK Animals (Scientific Procedures) Act 1986 regulates

procedures that may have the effect of causing the animal pain, suffering, distress, or lasting harm (the inference being that procedures not covered under the Act [methods of euthanasia listed in Schedule1] should not cause more than momentary pain or distress to the animal) (Home Office 1986).

Comparison of Provisions in the Guidelines

A comparison of euthanasia methods across documents is challenging because of the different approaches in the documents. The AVMA *Guidelines on Euthanasia* (2007) provide a table of methods considered by the panel of veterinarians responsible for drafting the guidelines to be acceptable, as well as tables of methods that they considered conditionally acceptable or unacceptable. Close and colleagues (1996, 1997) and the revised table developed by EFSA provide information based on species groups using a 1-5 rating system. The criteria used to assess the acceptability of euthanasia methods are similar between the AVMA and the EFSA documents, as illustrated in Table 1 below.

TABLE 1 Criteria Used to Evaluate Level of Acceptability of Euthanasia Methods

	Criteria used by EFSA	Criteria used by AVMA
Rapidity	✓	✓
Efficacy	✓	✓
Ease of use	✓	✓
Operator safety	✓	✓
Species suitability	✓	✓
Aesthetic value (acceptability of method by operator)	✓	

Table 2 shows a comparison of methods of euthanasia for rodent species, which are of particular interest because of the large numbers of mice and rats used for research and testing. This table has been prepared using a 5-star ranking, where 1 star indicates that the method is unacceptable under most circumstances; 3 stars indicate that the method is acceptable under some conditions; and 5 stars indicate that the method is acceptable. As the Australian and Canadian guidelines are currently both under revision, they have not been included.

TABLE 2 Comparison of Rodent Euthanasia Methods

Method of euthanasia	European guidelines (Close et al. 1996, 1997) as amended by EFSA (2005b)	AVMA Guidelines (2007, amending the 2000 Report of the AVMA Panel on Euthanasia)
Inhalation anesthetics	*****	*****
Pentobarbitol	*****	*****
T-61	*** (i.v. only)	*** (not available in the US)
Inert gas	***	***
Concussion	*** (rodents under 1 kg)	*
Microwave irradiation	*** (experienced personnel only)	*****
Cervical dislocation	*** (rodents <150 g)	*** (rodents <200 g)
Decapitation	**	***
CO_2	***** (unconscious) * (conscious)	*****
CO	* (danger to operator)	*****
Ether	*	***
Rapid freezing	*	*** (only if anesthetized)
Potassium chloride	*** (only on unconscious rodents)	***** (acceptable if anesthetized)

Carbon Dioxide

The use of carbon dioxide as a euthanizing agent has been increasingly challenged since the AVMA 2000 Panel Report. The principles espoused by all of the various international systems overseeing animal use in science are based on the premise that pain and distress must be minimized. In addition, the ICLAS principles of euthanasia point not only to minimization of pain and distress but also to immediate loss of consciousness as important in euthanasia. A review of the scientific literature provides substantial evidence that animals euthanized with carbon dioxide experience considerable pain and/or distress (depending on the manner in which CO_2 is administered) (Conlee et al. 2005; Leach et al. 2002; Liotti et al. 2001; Niel and Weary 2007; Raj et al. 2004). To try to address these concerns, the following recent publications have made recommendations concerning the euthanasia of rodents by carbon dioxide:

- *Report of the ACLAM Task Force on Rodent Euthanasia* (Artwohl et al. 2006)
- CCAC *Guidelines on Euthanasia of Animals Used in Science* (CCAC 2010)
- *Guidelines to Promote the Well-being of Animals Used for Scientific Purposes: The Assessment and Alleviation of Pain and Distress in Research Animals* (NHMRC 2008)
- *Opinion of the Scientific Panel on Animal Health and Welfare (AHAW) on a request from the Commission related to the aspects of the biology and welfare of animals used for experimental and other scientific purposes* (EFSA 2005a)
- *Review of Schedule 1 of the Animals (Scientific Procedures) Act 1986* (APC 2006).

In light of this concern, an international consensus meeting was held at the University of Newcastle upon Tyne in February 2006. The organizers recognized that there was no definitive guidance on whether and how CO_2 can be administered humanely, and therefore brought together scientists with research experience in CO_2 euthanasia, regulators, and members of the animal care community. The goals of the meeting were to try to reach consensus on the use of CO_2, identify further research needed, meet the immediate need for practical guidance, and consider whether any preferable alternatives were currently available. The meeting concluded that there was no "ideal" way of killing rodents with CO_2. Both methods currently used—prefill (placing the animals in a chamber already charged with carbon dioxide) or gradual fill (placing the animals in a chamber and then gradually filling it with carbon dioxide)—can cause welfare problems. It was decided that it is not yet possible to recommend the use of other gases (such as argon or nitrogen) that cause death by hypoxia, and that more research is needed into the physiological and affective responses to a range of gaseous agents in order to identify good practice and potential alternatives to CO_2 (Hawkins et al. 2006).

In the interim, there are recommendations in guidelines that seek to establish good practice, in line with authors' interpretation of the current scientific evidence. According to AVMA (2007), CO_2 is acceptable for euthanasia in appropriate species; ACLAM (2006) states that the current peer-reviewed literature does not establish consistent requirements for CO_2 euthanasia and/or even provide a clear definition of what constitutes a humane death; and EFSA (2005a) recommends that CO_2 not be used as a sole agent in any euthanasia procedure unless the animal has first been rendered unconscious, and that its use be phased out as soon as possible. Table 3 provides a comparison of recommendations on the use of CO_2 as a method of euthanasia in the guidelines studied.

TABLE 3 Comparison of Recommendations Concerning the Use of Carbon Dioxide as a Euthanasia Agent for Rodents

AVMA (2007, amending the 2000 Report of the AVMA Panel on Euthanasia)	Acceptable method – gradual fill 33% of cage volume per minute
ACLAM (2006)	Acceptable method – gradual fill 20% of chamber volume per minute
CCAC (2010)	Conditionally acceptable – use 2-step method where possible (i.e., inhalant anesthetic followed by CO_2); otherwise use gradual fill >15% and <30% of the chamber volume per minute
Australia	Acceptable method – gradual fill 20% of chamber volume per minute
EFSA (2005a)	Conditionally acceptable – only on unconscious animal
APC (2006) – Schedule 1 Review	Conditionally acceptable – rising concentration (gradual fill)

Conclusion

Organizations responsible for the development of guidelines all work to ground their recommendations in sound scientific evidence. Nonetheless, translation of science into policy necessarily includes a variety of factors, such as the particular regulatory framework in which the guidelines will be implemented and the current opinion of experts in the area, as well as current societal values. It has been stated that there is insufficient scientific evidence to be able to harmonize guidelines worldwide (Kastello 2004, 201), and even if this were overcome, these other factors would present obstacles. However, the harmonization exercises organized by ICLAS, which have resulted in sets of internationally agreed principles, can form the basis for the preparation of guidelines tailored to fit particular national systems for overseeing animal use.

References

APC [Animal Procedures Committee]. 2006. Review of Schedule 1 of the Animals (Scientific Procedures) Act 1986 - appropriate methods of humane killing. London.

AVMA [American Veterinary Medical Association]. 2007. AVMA Guidelines on Euthanasia. Available at www.avma.org/issues/animal_welfare/euthanasia.pdf.

Artwohl J, Brown P, Corning B, Stein S, ACLAM Task Force. 2006. Report of the ACLAM Task Force on rodent euthanasia. JAALAS 45:98-105.

ANZCCART [Australian and New Zealand Council for the Care of Animals in Research and Teaching]. 2001. Euthanasia of Animals Used for Scientific Purposes, 2nd ed. J Reilly, ed. Adelaide, Australia.

CCAC [Canadian Council on Animal Care]. 1989. CCAC policy statement on ethics of animal experimentation. Ottawa.

CCAC. 1993. Euthanasia. In: Guide to the Care and Use of Experimental Animals, vol 1, 2nd ed. Ottawa.

CCAC. 2010. CCAC Guidelines on Euthanasia of Animals Used in Science. Ottawa.

Close B, Banister K, Baumans V, Bernoth EM, Bromage N, Bunyan J, Erhardt W, Flecknell P, Gregory N, Hackbarth H, Morton D, Warwick C. 1996. Re-commendations for euthanasia of experimental animals: Part 1. Lab Anim 30:293-316.

Close B, Banister K, Baumans V, Bernoth EM, Bromage N, Bunyan J, Erhardt W, Flecknell P, Gregory N, Hackbarth H, Morton D, Warwick C. 1997. Recommendations for euthanasia of experimental animals: Part 2. Lab Anim 31:1-31.

Conlee KM, Stephens ML, Rowan AN, King LA. 2005. Carbon dioxide for euthanasia: Concerns regarding pain and distress, with special reference to mice and rats. Lab Anim 39:137-161.

Demers G. 2004a. Current status: Identifying the issues. In: The Development of Science-Based Guidelines for Laboratory Animal Care: Proceedings of the November 2003 International Workshop. Washington: National Academies Press. p 30-35.

Demers G. 2004b. First ICLAS meeting for the harmonization of guidelines on the use of animals in science. In: Proceedings of the Ninth FELASA Symposium (Nantes, France, June), section 2. Federation of European Laboratory Animal Science Associations (FELASA). Available at www.lal.org.uk/pdffiles/FELASA/Section2.pdf.

Demers G, Griffin G, De Vroey G, Haywood JR, Zurlo J, Bédard M. 2006. Harmonization of animal care and use guidance. Science 312:700-701. Available at www.iclas.org/harmonization.htm.

EEC [European Economic Community]. 1986. Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes. Official Journal L 358: 1-28. Available at http://ec.europa.eu/food/animal/welfare/references_en.htm.

EFSA [European Food Safety Authority]. 2005a. Opinion of the Scientific Panel on Animal Health and Welfare (AHAW) on a request from the Commission related to the aspects of the biology and welfare of animals used for experimental and other scientific purposes (EFSA-Q-2004-105). EFSA J 292:1-46. Available at www.efsa.europa.eu/en/science/ahaw/ahaw_opinions/1286.html (accessed October 23, 2008).

EFSA. 2005b. Aspects of the biology and welfare of animals used for experimental and other scientific purposes (EFSA-Q-2004-105). Annex to EFSA J 292:1-136. Available at www.efsa.europa.eu/en/science/ahaw/ahaw_opinions/1286.html.

Hawkins P, Playle L, Golledge H, Leach M, Banzett R, Coenen A, Cooper J, Danneman P, Flecknell P, Kirkden R, Niel L, Raj M. 2006. Newcastle consensus meeting on carbon dioxide euthanasia of laboratory animals. February 27-28, University of Newcastle upon Tyne, UK. Laboratory Animals (www.lal.org.uk/pdffiles/CO2%20Final%20Report.pdf).

Hillier M. 2007. Government response by Meg Hillier, MP, Parliamentary Under Secretary of State for the Home Department. Available at www.apc.gov.uk/reference/2007%2010%2010%20Schedule%201%20Report.pdf.

Home Office. 1986. Animals (Scientific Procedures) Act 1986. London: HMSO. Available at www.archive.official-documents.co.uk/document/hoc/321/321-xa.htm.

Kastello MD. 2004. Point/counterpoint: The cases for and against harmonization. In: The Development of Science-Based Guidelines for Laboratory Animal Care: Proceedings of the November 2003 International Workshop. Washington: National Academies Press.

Leach MC, Bowell VA, Allan TF, Morton DB. 2002. Aversion to gaseous euthanasia agents in rats and mice. Comp Med 52:249-257.

Liotti M, Brannan S, Egan G, Shade R, Madden L, Abplanalp B, Robillard R, Lancaster J, Zamarripa FE, Fox PT, Denton D. 2001. Brain responses associated with consciousness of breathlessness (air hunger). PNAS 98:2035-2040.

NHMRC [National Health and Medical Research Council], Australian Government. 2004. Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, 7th ed. Canberra. Available at www.nhmrc.gov.au/publications/synopses/ea16syn.htm.

NHMRC. 2008. Guidelines to Promote the Wellbeing of Animals Used for Scientific Purposes: The Assessment and Alleviation of Pain and Distress in Research Animals. Canberra.

Niel L, Weary DM. 2007. Rats avoid exposure to carbon dioxide and argon. Appl Anim Behav Sci 107:100-109.

OLAW [Office of Laboratory Animal Welfare]. 2002a. ARENA/OLAW Institutional Animal Care and Use Committee Guidebook, 2nd ed. Section C.2.b. Bethesda, MD: NIH. Available at ftp://ftp.grants.nih.gov/IACUC/GuideBook.pdf.

OLAW. 2002b. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Bethesda, MD: NIH. Available at http://grants1.nih.gov/grants/olaw/.

Raj ABM, Leach MC, Morton DB. 2004. Carbon dioxide for euthanasia of laboratory animals. Comp Med 54:470-471.

INTERNATIONAL APPROACHES AND PRINCIPLES FOR HUMANE ENDPOINTS

Humane Endpoints in Cancer Research

Fraser Darling

The vision of the Institute of Cancer Research is that people may live their lives free from the threat of cancer as a life-threatening disease.

Cancer or malignant neoplasm refers to a class of diseases in which a group of cells display *uncontrolled growth* (in other words division beyond the normal limits), *invasion* (intrusion on and destruction of adjacent tissues), and sometimes *metastasis* (spreading to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumors, which are self-limiting and do not invade or metastasize. Most cancers form a tumor but some, like leukemia, do not. Cancer may affect people at all ages, even fetuses, but the risk for most varieties increases with age; and cancers can affect all animals.

Cancer causes about 13% of all deaths and, according to the American Cancer Society, 7.6 million people died from cancer in the world during 2007. Where effective anticancer treatments do exist they can be very demanding on the patient.

The objective of using live animals in cancer research is to develop rapid diagnosis, better treatments for existing cancers, and an improved prognosis for patients. With this in mind, scientists engaged in experimental cancer research follow four main areas of investigation, some of which use laboratory animals. Cancer research scientists attempt to *discern, detect, identify,* and *develop*.

- To *discern* the biological mechanisms, scientists investigate different sites of origin in the body, why particular cancers are more prevalent in some tissues and not others, and the rate of growth and metastases of cancers.
- The *detection* of potential carcinogens is an important chain in the link to identify agents in the environment such as chemicals, potential carcinogenic materials, exhaust fumes from motor vehicles, and other agents that may be responsible for carcinogenesis.

- *Identification* of individuals at particular risk looks at epidemiological studies and historical data to determine who in the general population may be at greater risk of developing certain types of cancer. This particular area of investigation has taken an important step forward in recent years since the advent of genetic testing. Investigations may involve the examination of particular risk factors, including lifestyle (tobacco use, alcohol consumption, obesity, lack of physical activity) or genetic predisposition.
- *Developing* ways to cure or control clinical disease is usually achieved by improving the prognosis for patients through the use of drugs, chemotherapeutic agents, radiation therapy, and/or surgical intervention.

Laboratory rodents, usually mice and rats, have assisted scientists in the field of cancer research and it is clear that they will continue to do so. They are used as experimental models in cancer research studies only where there is a justified need and only if absolutely necessary. The Institute of Cancer Research does not use animals for research if nonanimal alternatives are available, and endeavors to set humane endpoints for all research involving laboratory animals.

Because we need to use live animals in some research programs, it is essential that these living creatures be afforded the best care at all times. Staff tasked with caring for animals in the laboratory are continually striving to improve and enhance animal husbandry and welfare. An important part of this process is the use of humane endpoints in our animal experiments.

[According to] the OECD, a humane endpoint can be defined as "the earliest indicator in an animal experiment of severe pain, severe distress, suffering, or impending death." Investigators make use of different humane endpoints depending on the tumor model being studied in any particular animal, and try wherever possible to determine accurate, predictive, and reproducible humane endpoints.

Humane endpoints should be a consideration for all experiments involving animals, but are essential in situations that may involve suffering or death (e.g., acute toxicology, infection, cancer, or inflammatory disease). They are just one manifestation in the process of refinement of animal experiments. Humane endpoints are best used with prospective planning for their use, not ad hoc to address specific welfare concerns as they might arise.

There are several considerations in arriving at the objective assessment of pain and suffering and translating this into the appropriate endpoint in a given experiment. An important point is the requirement to continually improve our skills at observing the animals and assigning some objective values to the observations we make (usually these are based on animal behavior and physiology). We also need to know, in any given study, which observations are the most significant indicators of animal pain and suffering, and have scientific acceptance of these measurements; otherwise they become invalid and unworkable. It follows, therefore, that validation and monitoring of other study parameters are required to ensure robust predictability of the endpoint and minimal interference with the scientific objectives.

All personnel contribute to the care and welfare of the animals, and it's important that these individuals be provided with the correct training and knowledge in order to develop their required skills, and for each to progress to a level of competency. It is impossible to recognize signs of pain, suffering, or distress in any animal if you do not, or are unable to, recognize (and have not received training to be able to do so) normal signs of good health in an animal. Training and competency are very important attributes, especially when dealing with humane endpoints. Staff development of skills is an evolving process, and a clear program of training and mentoring enhances animal welfare and staff morale.

Biomedical research encompasses all types of research including research into cancer. All research can be viewed as a giant puzzle. Humane endpoints are an important and essential part of the discovery process. Everyone in the worldwide research community has an individual role to play in creating parts of the puzzle in order to find new treatments, enhanced therapies, and ultimately attempts to cure some of our more difficult and challenging diseases, not just in the field of cancer research but in all areas.

It's important that if we continue to use animals for experimental purposes we do this in the most humane manner at all times. All who are involved in animal research must have a clear sense of responsibility, but more importantly a strong sense of compassion for the animals in their care. By the correct use and validation of appropriate humane endpoints we will help to add important parts to the puzzle.

Humane Endpoints in Infectious Disease

Carol Eisenhauer

The topic of my presentation is humane endpoints in infectious disease. This is a very sensitive and difficult topic, which I deal with almost every day as the IACUC chair at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID). The opinions I am expressing today are my own and not those of my employer, the US Army.

USAMRIID does infectious disease research on some of the most dangerous viruses and bacteria in the world, and we do this under biocontainment conditions, generally ABSL-3 and -4 conditions. USAMRIID is AAALAC accredited and, as IACUC chair I can avow emphatically, does everything under an approved animal protocol.

The study of infectious disease generally involves studies of disease pathogenesis, immune response to infection, and development of therapeutics and vaccines. Because it is ethically and morally wrong to perform clinical efficacy studies with humans, the FDA has developed the animal rule, which allows new drugs and biologic products to be tested in animals as a means to getting approval for human use. Safety testing must still occur in humans, and the animal model is critical to the success of the FDA approval process. It is necessary to understand that the animal study endpoints must be clearly related to the desired benefit in the human; generally these are related to enhancement of survival or prevention of major morbidity.

The animal welfare regulations require that procedures involving animals avoid or minimize discomfort, distress, and pain to the animals. The Public Health Service Policy states that animals undergoing chronic pain or distress should be euthanized as soon as feasible and appropriate, which leads to a discussion of humane endpoints. Death as an endpoint has always been a difficult issue in infectious disease research. Lack of reproducible animal models often leads to the use of death as an endpoint. The argument to support death as an endpoint is that euthanasia and termination of the study before scientific objectives are met compromise study results. On the other hand, the counterpoint is that progression of infectious diseases to death allows unnecessary suffering, which compromises research results.

Simply put, many animal models of infectious diseases are not clearly defined and it is difficult to reliably differentiate animals that will die from those that will recover despite showing severe clinical signs. There have been many instances in which a severely ill animal recovered from its experimentally induced infectious disease. Death of the animal is the final proof that the challenge was lethal and that the vaccine failed to protect. Therefore some investigators are reluctant to euthanize early or to use anything but death as an endpoint. An argument may be made, however, that actual physiological events are missed when death is the only criterion evaluated. The data gathered from monitoring these events can be used to develop early and humane endpoints. Additionally, for a variety of reasons including tissue autolysis, death of the animal diminishes sample collection. Therefore, it is important to consider requirements for the development of early and humane endpoints.

For an early endpoint to be acceptable, it must meet the following criteria: it must be indicative of inevitable progression to death; it must reliably differentiate the animals that will die from those that will recover despite showing severe signs of toxicity; and it must adequately mimic the death endpoint.

The benefits of humane endpoints are many and should be emphasized during the planning meetings with investigators. Specifically, the development of uniform methods to assess endpoint criteria contributes to the validity and the uniformity of the experimental data. Detailed observations of clinical signs may lead to increased discriminatory experimental power. Last but most importantly, use of humane endpoints avoids or terminates unnecessary pain and distress for the research animal.

It is very important to tailor the endpoints to each animal protocol. Different animal species react differently to the same viral or bacterial challenge. For instance, Ebola Zaire is lethal in five to seven days in cynomolgus monkeys, whereas it is lethal in seven to ten days in rhesus macaques. And in Mauritius-origin cynos, monkeypox is 100% fatal while in Chinese-origin cynos there may be only a 43% fatality. This emphasizes the importance of picking the right species and understanding the course of that disease in that species. Outcomes must also be defined; will morbidity suffice or must you go to the moribund condition?

The route of the challenge is very important. The exposure route must be similar to that anticipated in humans per the FDA. This affects the time course and pathogenesis of the disease. It may be important to challenge at two or more doses, because this can help differentiate physiological changes between survivors and nonsurvivors. The viral and bacterial strain to be used should also be considered when developing endpoints. Ebola Zaire is uniformly lethal and has a shorter time course than Ebola Reston, which is also lethal but with a prolonged time course. Finally, it is important to consider human safety when dealing with infectious diseases.

When planning endpoints, one must consider observation frequency. It is critical to set reasonable observation frequencies to ensure human safety, the least stress to the animal, and investigator compliance. The frequency should be

set to minimize stress but allow for euthanasia, sample collection, and avoidance of progression to death. It is necessary to know whether the animal is nocturnal or diurnal and whether disruption of sleep will adversely affect the study. It is also necessary to determine when to increase your observation frequencies so as not to miss critical events.

As mentioned, human safety must always be considered when dealing with infectious diseases. Promoting animal welfare by increased monitoring of animals after exposure can jeopardize human safety. Therefore, investigators and the IACUC should be encouraged to look for other, less intrusive and safer methods of monitoring the animals, such as telemetry and in-room cameras.

Rodent species present their own challenges when developing humane endpoints. Rodents are generally group housed and they are not always individually identified, making their observation difficult. Additionally, clinical signs of illness in rodents can be subtle and nondiscriminatory in nature.

It may be necessary to consider objective versus subjective endpoint criteria. It is important to use a mixture of both, but when using subjective criteria with three different people observing the animals throughout the day, they must be very adequately trained on exactly what these criteria mean—e.g., "What is ruffled fur in a mouse and should it be added to my score sheet?" The IACUC must work with investigators in the development and use of humane endpoints. In many institutions, the IACUCs have developed strong policies stating that death as an endpoint is not acceptable. The IACUC should also require the use of intervention criteria or score sheets that clearly define when the animal is to be euthanized.

As I have already stated, the IACUC should work with the investigator to determine the best schedule of animal monitoring. Personnel that monitor the animals must understand normal species behavior as well as the clinical signs expected during the course of the disease. Observation frequencies should increase as the clinical signs become more severe and these observations need to be documented.

The IACUCs must ensure that there is an available point of contact for euthanasia so that when the time comes the animal will be euthanized promptly. In fact, it may be wise to have an alternate point of contact to ensure that when the score is met and it is time for euthanasia, this happens promptly.

When the clinical course of the infectious disease is not clearly defined for the animal species, the IACUC should consider the use of a pilot study to allow for criteria development. The IACUC should use subject matter experts to assist in developing the criteria and should consider the use of analgesics for each infectious disease, animal study, or protocol.

The IACUC should review the use of observation documentation as part of its postapproval compliance monitoring. Another issue that the IACUC must discuss is whether the humane endpoints should be the moribund or morbid condition. This is a difficult issue and there is no right answer. Each study must be considered separately. Often in assessing the effectiveness of the treatment or vaccine, the moribund state is used, while the morbid state would be used if it is

not necessary to know if the animal will die as a result of the treatment or vaccine failure.

In a score sheet that we use at USAMRIID with filovirus research done in macaques, if the score is equal to or greater than 10, the animal is administered pain alleviation. If it is greater than 20 the animal is considered terminally ill and is euthanized. Exceptions require consultations with the attending vet. The use of score sheets has progressed over the years and with each experiment refinements are made to improve them.

In conjunction with the investigator we have been able to add some objective criteria; e.g., if liver enzymes double, a score of 1 is assigned, and if they triple a score of 3 is given. The hope is to avoid the moribund end state and euthanize when we see liver enzymes increase.

So these are the kinds of things going on at USAMRIID in infectious disease research. Everyone has a score sheet, and every investigator is encouraged to define criteria or do a pilot study within that protocol so that future score sheets may be developed based on these criteria.

In summary, it must be the goal of all infectious disease researchers using animals and of the IACUCs that provide oversight for these animals to develop humane early endpoints. Good science and humane animal care require nothing less.

Humane Endpoints and Genetically Modified Animal Models: Opportunities and Challenges

Margaret Rose

Technologies that enable the targeted manipulation of the genome have created new opportunities to study the role and interplay of specific genes in both the regulation and function of physiological and behavioral processes and the development of pathological conditions. Through the development of new or novel animal models, these techniques enable new insights into the molecular basis of disease processes and provide opportunities to develop targeted therapeutic approaches.

Despite the potential benefits from the use of these technologies, there are ethical issues in relation to their application, some of which relate to the impact on the welfare of the animals involved. The establishment of humane endpoints is a key strategy in achieving the goal of refinement; when the use of animals is scientifically justified but where there is a risk of those animals experiencing pain or distress, applying the process by which humane endpoints are implemented and reviewed underpins an informed and strategic approach to managing such risks.

Genetically modified (GM) animal models present particular challenges when developing criteria to set humane endpoints. I will provide an overview of the animal welfare issues presented in the application of GM technologies and discuss the opportunities and challenges to applying humane endpoints when GM animal models are developed.

Introduction

The development of technologies that permit the targeted manipulation of genetic material—be that by transgenesis or targeted mutagenesis—has created opportunities to explore the organization, regulation, and function of molecular processes in both normal and pathological states in ways previously not possible. Further, the application of these methods has expanded the availability of

animal models that are more accurate analogues of the underlying disease processes and hence can be used to better understand disease processes and to develop new, targeted therapies.

While the potential benefits of the use of these technologies are recognized (Royal Society 2001; NRC 2002; Nuffield Council 2005), there is continuing public disquiet about their use (Einsiedel 2005). A range of issues are being raised, including fundamental ethical questions about the use of genetic modification (GM) technologies and notions of the sanctity of life and the autonomy of the individual as well as concerns about risks to human health and the environment. The welfare of the animals involved also has been a recurring issue and has been addressed in a number of reports and guidelines (for example, Royal Society 2001; Animal Procedures Committee 2001; Dennis 2002; Robinson et al. 2003; Brown and Murray 2006; Wells et al. 2006; NHMRC 2007; CCAC 2008).

The process by which humane endpoints are developed, validated, and reviewed is a key platform in making progress toward the goal of refinement when animals are used for scientific purposes (Morton 2000; Stokes 2000). Humane endpoints are used for two complementary purposes: identifying the onset of a disease process so that early intervention is possible either to initiate treatment or to enable an early, defined endpoint in a study; or, alternatively, to determine the point when an animal's condition has deteriorated such that its involvement in the study should be terminated.

Setting humane endpoints involves identifying potential risks and validating criteria to, first, identify specific physiological or behavioral changes associated with the animal model and, second, assess the impact on the animal in relation to both the predicted effects of the experimental treatment and general criteria to assess the occurrence of pain and distress. Thus criteria are established upon which decisions can be based and outcomes reviewed. This is an iterative process that underpins informed decision making and validates the ongoing refinement of experimental procedures. Although the same processes apply to establish humane endpoints with GM animal models, as highlighted by Dennis (2000) there are particular difficulties in these circumstances brought about primarily by the unpredictability of the effects of GM technologies on phenotypic expression.

In recent years there has been a rapid escalation in the development of new GM models. In the biomedical sciences mice are by far the species most often used, but a range of species can be involved, including zebrafish, pigs, and nonhuman primates. Further, the pace and scope of the development of new GM animal models are likely to continue for the foreseeable future, which presents logistical challenges for the effective management of these animals, especially when this involves significant numbers of animals and many lines with differing phenotypes (Comber and Griffin 2007).

Welfare issues have been identified in relation to both the methods used to produce GM animals and the resulting phenotype.

Production of GM Animals

GM animal models are produced by a number of different methods that result in reduced or enhanced expression or inactivation of a gene. The most common methods used involve (1) transgenesis, where exogenous genetic material from either the same or another species is inserted in a fertilized blastocyst by microinjection, electroporation, or a nonpathogenic viral vector and then implanted in surrogate mothers; (2) targeted mutagenesis, which results in the presence or absence of a specific gene ("knock-in" or "knockout"), which is achieved by inserting modified genetic material in cultured embryonic stem cells that are injected into a blastocyst and implanted in surrogate mothers; or (3) random or chemical mutagenesis, where animals or their gametes are exposed to mutagens that increase the rate of mutations, resulting in the production of novel single gene mutations. Only a small percentage of animals produced will carry the modified genome and significant numbers of animals may be required to produce and maintain each GM line. Consequently, relative to the number of GM animals created, significantly more are produced and culled.

A July 2003 report by a Joint Working Party on Refinement in the United Kingdom reviewed the relative advantages and disadvantages of the production of GM animals by either pronuclear injection or embryonic stem cell techniques and recommended strategies to promote both reduction in the numbers of animals involved and refinement of procedures to minimize impact (Robinson et al. 2003). The report recommended criteria to benchmark the efficacy of procedures so as to ensure production methods to maximize the potential to produce GM animals and management strategies to reduce surplus production. For each step in the process, the report recommends performance benchmarks (indicators when there is a need to review that process) and outlines possible causative factors that should be considered. Thus this report sets out current standards of good practice and provides a process to benchmark animal welfare outcomes in the context of the needs and justification for current methods.

With both these technologies, donor animals undergo various, and sometimes multiple, procedures with the risk of associated pain or distress. Strategies to manage and minimize the impact on the donors of surgical procedures, superovulation of females, and tissue biopsy for genotyping are discussed in this report. The recognition and uptake of opportunities to modify and refine these procedures will continue to play an important role in the future development and use of these methods.

While reports such as this highlight the need to be aware of the impact of these procedures on the animals involved in the production of GM animals, in

the one study to date these procedures were not shown to have a significant effect on the behavioral and physiological development of mouse progeny up to 30 weeks of age (Van der Meer et al. 2001).

GM Animal Models

GM animal models have been applied to the investigation of a range of human diseases such as diabetes, obesity, atherosclerosis, chronic heart failure, hypertension, cancer, autoimmune disease, and musculoskeletal and neurological disorders. However, not all GM animals are bred as disease models. GM animals may exhibit clinical disease but, given that the rationale behind the development of GM technologies is to tease out the role and function of individual genes or gene sequences, in many cases do not do so and that is not the intended outcome.

Wells and colleagues (2006) observed that in only a minority of GM animals are animal welfare problems evident and that, with transgenic animals where most often the purpose is to study the function of a DNA segment, adverse effects are uncommon and that for GM models developed using targeted mutagenesis (knock-in or knockout) where the purpose is to study the function of a single gene, either embryonic death or animals with no evidence of adverse effects are the most common outcomes. However, they noted that both targeted and random mutagenesis can lead to neonatal mortality or animals with compromised health or welfare.

When adverse effects do occur they either are predicted on the basis of the particular genetic modification or, notably, are not of a kind that was predicted to occur or are seen in circumstances where adverse effects were not anticipated. It is the uncertainty and low predictability of such events that present particular challenges when managing GM animal colonies. Such unpredicted adverse effects may arise for a variety of reasons including the overexpression or the absence of the specific gene, interactions with collocated genes, or the influence of the genetic background of donor animals or the background strain that may interact with the targeted modification. Furthermore, adverse effects may not be evident in the first generation and emerge only in subsequent generations (Dennis 2000).

Abnormalities in GM animals may affect the viability of offspring and their long-term survival and welfare and may be linked to the specific gene modification or reflect a peculiarity of the phenotype of the background strain. A diverse range of abnormalities have been reported, including hydrocephalus, cleft palate, malformed limbs, absence of teeth, poor mothering, absence of milk, poor thermoregulatory ability, increased aggression and cannibalism, clotting disorders, enhanced growth of tumors and development of metastases often at atypical sites, diabetes, osteoporosis, degenerative joint disease, respiratory disorders, inflammatory bowel disease, ulcerative colitis, liver and kidney

dysfunction, seizures, and sensory and locomotor abnormalities affecting sight, hearing, smell, balance, and social interactions. The occurrence of one or more of these abnormalities may necessitate the euthanasia of affected individuals but also may indicate the need to review the ongoing production of a particular line. In some of these conditions the impact can be alleviated by the implementation of treatment programs or changes to husbandry practices such as the provision of special diets, the placement of food and water on the bottom of the cage, and increased volume and changing of bedding (Brown and Murray 2006).

A higher than expected incidence of infectious disease has been observed in GM animals (Dennis 2002). As highlighted in the review by Franklin (2006), GM animals respond to infections in a similar way to immunodeficient animals: they develop clinical infections due to common opportunists or to agents that would normally result in asymptomatic infections. GM may affect host specificity of pathogens and infections may result in unusual or new phenotypes not necessarily due to immune defects.

Humane Endpoints

When developing humane endpoints for GM animal models the uncertainty of the incidence, kind, and timing of adverse events presents a significant challenge (Dennis 2000). Furthermore, when animals develop concurrent diseases—for example, 26% of mice developed diabetes in a transgenic model (R6/2) of Huntington's disease (Luesse et al. 2001)—the determination of an appropriate endpoint may be confounded. Unquestionably, the development and implementation of monitoring strategies to assess the impact of a specific genetic modification is essential to effectively manage the welfare of GM animals and to enable the development of effective humane endpoints.

When a new genetic line is created a detailed description of its phenotype must be undertaken. With the rapid increase in the number of new lines being created, especially in mice, reference databases have been established that document the methods used to create and maintain the GM line and its phenotype; details in relation to the onset of changes, disease progression, and suggested endpoints are included in some instances.

Although some concern has been expressed that the monitoring of GM animals could focus on a description of the phenotype with insufficient attention given to animal welfare indicators (Brown and Murray 2006), these processes can and should be complementary and there are important benefits in establishing effective humane endpoints when this occurs. A detailed phenotypic description, including animal welfare measures, will provide both a more accurate picture of the time course and characteristics of a phenotype and identify relevant indicators of negative effects on the animal's welfare. Ideally, the quality of

these data will enable a more accurate determination of the specific settings for a humane endpoint by aligning phenotypic changes with animal welfare indicators and identification of special needs that can alleviate some effects.

Monitoring

Several protocols to monitor the welfare of GM animals have been developed (e.g., Dennis 2002; Wells et al. 2006) with many common elements.

Dennis (2002) emphasized the importance of at least daily monitoring when new lines are created to ensure that signs of illness, physical defects, injury, or abnormal behavior are detected and assessed, noting the importance of documenting what may seem to be unimportant changes—the frequency and specific elements of a monitoring program should detect both predicted and unforeseen changes. Dennis (2002) also stressed the need to include regular monitoring of the health status of GM mouse lines, including serological testing and postmortem examination. These measures also are an important component of developing a phenotypic description of a GM line.

Similarly, Wells and colleagues (2006) proposed a structural assessment of the welfare of new GM lines focusing on the initial phase in the creation and phenotypic assessment, the aim being to create a "welfare profile" so that, once a line is established, monitoring would focus on several welfare indicators specific for that line. However, as noted by other authors, there can be discrepancies in the phenotypic description of a given GM line between different institutions. Consequently, this kind of welfare assessment also should be undertaken when GM lines are newly introduced to an institution.

Wells and colleagues (2006) propose specific welfare assessments to be carried out in neonates and at weaning. In neonates, criteria such as skin color, surface temperature, activity, reflexes, response to touch, and evidence of a milk spot are proposed. At weaning, mice are assessed by appearance, coat condition, posture, gait, activity, clinical signs, and relative size; in addition, preweaning mortalities, evidence of aggression or stereotypies, and body weight are recorded, and more detailed behavioral assessments are recommended if behavioral problems are identified. If no animal welfare problems are identified in neonates or weanlings, animals are monitored during routine husbandry procedures. If animal welfare concerns either are identified in the assessment of neonates or weanlings or subsequently emerge, animals then undergo more detailed assessments to identify special needs and criteria for humane endpoints.

There is a convergence between protocols for monitoring animal welfare and for developing a phenotypic profile. As a minimum, Brown and Murray (2006) suggest that the following measures be included in phenotype screening: clinical chemistries, complete blood count, urinalysis, gross and histopathology of major organs, abnormal gross tissues and target organs, and an assessment of general health, sensory function, motor abilities, and behavioral tests as proposed by Crawley (1999). Proposals such as that developed by Rogers and col-

leagues (1997) and Crawley and Paylor (1997) to develop a comprehensive phenotypic profile have been widely adopted with various modifications and include measures relevant to animal welfare assessment. However, an important addition to these protocols is a comprehensive assessment of behavior that uses a range of laboratory-based tests to assess learning, memory, sensory motor activity, feeding behavior, pain, reproduction, and emotionality. These kinds of data may also assist in evaluating or predicting the impact of the GM on animal welfare.

Finally, when assessing phenotypic changes in GM animals, comparison with their wild-type, littermate controls is important.

Refinement

There are a number of ways to reduce the impact of GM on the welfare of a particular line (NHMRC 2007). The rapid development and refinement of GM technologies that limit temporal or spatial gene expression has resulted in refinements to the way in which the expression of phenotypes can be targeted and benefits the welfare of the GM animal by limiting or negating the expression of negative effects. Two common strategies used in the production and maintenance of GM animals are, when there is an unacceptable level of morbidity, mortality, chronic disease, or abnormal behavior in homozygote animals, to maintain the GM line in heterozygous animals and, when the GM line is no longer needed for current research programs using cryopreservation, to store embryos, sperm, and ovaries.

GM Models in the Neurosciences

There has been a significant increase in the number of GM animal models in the neurosciences used in the study of neurodegenerative diseases such as Alzheimer's, Huntington's, or Parkinson's disease, and psychiatric illness such as schizophrenia, depression, and anxiety, obsessive compulsive disorders, and pain and stress. In some circumstances, for example Huntington's disease, a single gene may be involved, but many of these conditions involve complex gene interactions and the use of transgenic or knockout models provides new opportunities to study the function and interplay of individual genes to elucidate factors that influence the regulation and modulation of neural substrates (see for example the discussion by Mogil and Grisel 1998 in relation to pain studies, and Muller and Keck 2002 in relation to stress). Furthermore, the development of knockout lines has created the possibility of studying the role and function of a single gene in relation to behavior (Nelson and Young 1998; Anagnostopoulos et al. 2001).

An overview of the scope of GM animal models in the neurosciences provides some insight into the opportunities and challenges that GM animals present.

One of the drivers for the development of a battery of behavioral tests to be used in the development of phenotype profiles for new GM lines has been the potential to use these animal models in the neurosciences. Consequently, one of the defining characteristics of these animal models will be changes to one or more behavioral tasks indicative of cognitive, emotional, sensory, or motor function. Changes in an animal's ability to perform such tasks may relate to the experience of pain, stress, anxiety, fear, or depression. In further study of these models, a suite of specific behavioral tasks will be selected relevant to the hypothesis being tested (Crawley 1999).

In many GM lines animals do not show any evidence of clinical disease or abnormal behaviors but demonstrate a change in one or more tasks. For example, in a study designed to look at dysfunction in the serotonergic system, which is implicated in psychiatric conditions such as anxiety and depression, compared to their wild-type controls 5-HT1A knockout mice showed increased anxiety in the elevated-plus maze test and decreased reactivity in the open-field test, whereas 5-HT1B knockouts showed the reverse, but neither line showed any difference in development, feeding behaviors, reproductive performance, or any other evidence of abnormalities (Zhuang et al. 1999). Changes in behavior such as increased aggression, altered maternal care, seizures, and impaired motor coordination and sensory abilities are seen in knockout mice where such changes are linked to the targeted gene (Nelson and Young 1998; Anagnostopoulos et al. 2001). Furthermore, transgenic and knockout mice with these kinds of modifications may develop changes that affect their ability to interact with their physical and social environment. For example, changes to genetic components of the dopaminergic system in mice are associated with changes to their olfactory ability (McGrath et al. 1999), resulting in increased aggression, changes in their social interaction (Rodriguiz et al. 2004), and increased fear response (El-Ghundi et al. 2001).

In these kinds of models, setting criteria for humane endpoints presents particular challenges. This is not an issue when animals display signs of clinical disease or abnormal behaviors, such as seizures, but when the only evidence of behavioral change is in the performance of a behavioral task during a brief exposure to an artificial environment and there is no evidence of change in any other measures, the decision is not so clear. Evidence of altered emotionality or cognitive ability in a behavior test does not indicate that such experiences are part of an animal's day-to-day condition. The animal's negative experiences may be limited to the brief test period and in these circumstances the frequency of testing should be considered in limiting impact. However, the occurrence of these kinds of behavioral changes concurrent with evidence of changes under normal living conditions shifts the weight of evidence and may indicate animal welfare concerns. For example, mice deficient in the extracellular matrix glycoprotein tenascin-R (TN-R) showed increased anxiety when tested in the open-

field and elevated-plus maze tests and decreased locomotor activity, but also showed significant changes in circadian activity in their home cage (Freitag et al. 2003).

There are differing views as to the interpretation of stereotypic behavior in relation to animal welfare and, as shown in a review by Mason and Latham (2004), although in most circumstances where this occurs it is likely to be linked to poor welfare, there are exceptions. There are a number of reports where transgenic or knockout mice display stereotypic behavior with a range of genetic modifications (for example, Ambree et al. 2006; Berger et al. 2006; Chartoff et al. 2001; Hines et al. 2008; Mohn et al. 1999; Rodriguiz et al. 2004). A recent report on the recognition and alleviation of distress prepared by an ILAR committee (NRC 2008) concluded that stereotypies are undesirable and their prevention is likely to improve animal welfare. The weight that is given to the presence of stereotypies in setting humane endpoints may be contentious. The context in which these occur may be relevant, but a special case would need to be made to maintain animals exhibiting stereotypies that cannot be alleviated under home cage conditions.

In the context of neurodegenerative models where there is progressive deterioration of an animal's condition over a prolonged time, there are examples of where the early detection of the onset of the disease identifies early intervention points and provides an opportunity to test therapeutic efficacy. For example, a transgenic model of Huntington's disease measuring behavioral changes in open-field and elevated-plus maze tests detected the onset of a deterioration in motor activity prior to evidence of changes in anxiety levels (Klivenyi et al. 2006), and the development of a transgenic model of Alzheimer's disease showed cognitive and neurophysiological defects before the development of overt neuropathology (Gimenez-Llort et al. 2007). Further, a report by Drage and Heinrichs (2005) shows not only how the husbandry of a seizure-prone E1 mouse can be modified to eliminate the onset of seizures when the mice are held by the tail but also evidence of behavioral and cardiovascular changes that can be used as predictors before the onset of seizures.

There are ongoing challenges in the interpretation of behavioral phenotypic changes in relation to the fidelity to specific gene effects, including the confounding influences of husbandry and housing conditions, which are relevant to the setting of humane endpoints. Changes that result from compensation or developmental effects of the mutation, the influence of the genetic background strain, the influence of maternal behavior on adult phenotype, or pleiotropy can all confound interpretation of a phenotype (Gingrich and Hen 2000); differences in the background strain can result in significant phenotypic differences in pain-related measures (Lariviere et al. 2001); and rearing conditions and neonatal handling can affect behavioral responses to pain and stress in adult mice (Sternberg et al. 2003; Parfitt et al. 2004).

A number of studies have demonstrated the influences of laboratory conditions on phenotypic expression (Crabbe et al. 1999; Wahlsten et al. 2003). Würbel (2001) has argued that more attention should be given to the animal's living

conditions and hypothesized that animals that experience an enriched environment (EE) would be less susceptible to minor environmental changes and therefore provide a more "standardized" response to test conditions. Although Wolfer and colleagues (2004) showed that EE did not result in differences in behavioral tests when applied to two inbred mouse strains and their F1 hybrids, studies in transgenic models of Alzheimer's disease indicate the need to carefully evaluate the influence of EE in specific GM animals (Jankowsky et al. 2003; Richter et al. 2008). Recent studies showing that even subtle changes in EE or cage design are associated with significant changes in tests used for behavioral phenotyping (Tucci et al. 2006; Kallnik et al. 2007; Pietropaolo et al. 2007) highlight the urgent need to further investigate these kind of effects.

Conclusions

The establishment of humane endpoints in GM animal models presents particular challenges due to the unpredictable nature and occurrence of adverse events. However, the scope and depth of monitoring required to accurately describe a phenotype, together with careful monitoring to assess animal welfare, provide a comprehensive framework to establish humane endpoints with a high level of accuracy as well as informing the development of effective strategies to reduce the impact of a specific genetic modification. Studies that can identify and demonstrate ways to modify confounding influences on the phenotypic expression of a specific gene will enable refinement of the setting of humane endpoints that will benefit both scientific and animal welfare outcomes.

References

Ambree O, Touma C, Bortz N, Keyvani K, Paulus W, Palme R, Westaway D, Sachser N. 2006. Activity changes and marked stereotypic behaviour precede AB pathology in TgCRND8 Alzheimer mice. Neurobiol Aging 27:955-964.

Anagnostopoulos AV, Mobraaten LE, Sharp JJ, Davisson MT. 2001. Transgenic and knockout databases: Behavioral profiles of mouse mutants. Physiol Beh 73:675-689.

Animal Procedures Committee. 2001. Rep Biotech. www.apc.uk.

Berger S, Wolfer DP, Selbach O, Alter H, Erdmann G, Reichardt H, Chepkova A, Welzl H, Hass H, Lipp H, Schutz G. 2006. Loss of the limbic mineralocorticoid receptor impairs behavioral plasticity. Proc Nat Acad Sci U S A 103:1995-2000.

Brown MJ, Murray KA. 2006. Phenotyping of genetically engineered mice: Humane, ethical, environmental and husbandry issues. ILAR J 47:118-123.

CCAC [Canadian Council on Animal Care]. 2008. CCAC Guidelines on Genetically Engineered Animals. Ottawa. Draft document.

Chartoff EH, Marck BT, Matsumoto AM, Corsa DM, Palmiter RD. 2001. Induction of stereotypy in dopamine-deficient mice requires striatal D1 activation. Proc Nat Acad Sci U S A 98:10451-10456.

Comber J, Griffin G. 2007. Genetic engineering and other factors that might affect human-animal interactions in the research setting. J Appl Anim Welf 10:267-277.

Crabbe JC, Wahlsten D, Dudek BC. 1999. Genetics of mouse behavior: Interactions with laboratory environment. Science 284:1670-1672.

Crawley JN. 1999. Behavioral phenotyping of transgenic and knockout mice: Experimental design, and evaluation of general health, sensory functions, motor abilities and specific behavioral tests. Brain Res 835:18-26.

Crawley JN, Paylor R. 1997. A proposed test battery and constellations of specific behavioral paradigms to investigate the behavioral phenotypes of transgenic and knockout mice. Horm Beh 31:197-211.

Dennis MB. 2000. Humane endpoints for genetically engineered animal models. ILAR J 41:94-98.

Dennis MB. 2002. Welfare issues of genetically modified animals. ILAR J 43:100-109

Drage MG, Heinrichs SC. 2005. Phenotyping the untouchables: Environmental enhancement of behavioral and physiological activation in seizure-prone E1 mice. Epilepsy Behav 6:35-42.

Einsiedel EF. 2005. Public perceptions of transgenic animals. Rev OIE 24:149-157.

El-Ghundi M, O'Dowd BF, George SR. 2001. Prolonged fear responses in mice lacking dopamine D1 receptor. Brain Res 892:86-93.

Franklin DL. 2006. Microbial considerations in genetically engineered mouse research. ILAR J 47:141-155.

Freitag S, Schachner M, Morellini F. 2003. Behavioral alterations in mice deficient for extracellular matrix glycoprotein tenascin-R. Behav Brain Res 145:189-207.

Gimenez-Llort L, Blazquez G, Canete T, Johansson B, Oddo S, Tobena A, LaFerla FM, Fernandez-Teruel A. 2007. Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: A role for intraneuronal amyloid. Neurosci Biobehav Rev 31:125-147.

Gingrich JA, Hen R. 2000. The broken mouse: The role of development, plasticity and environment in the interpretation of phenotypic changes in knockout mice. Curr Opin Neurobiol 10:146-152.

Hines RH, Wu L, Hines DJ, Steenland H, Mansour S, Dahlhaus R, Singaraja RR, Cao X, Sammler E, Hormuzdi SG, Zhuo M, Husseini A-E. 2008. Synaptic imbalance, stereotypies and impaired social interactions in mice with altered Neuroligin 2 expression. J Neurosci 28:6055-6067.

Jankowsky JL, Xu G, Fromholt D, Gonzales V, Borchelt DR. 2003. Environmental enrichment exacerbates amyloid plaque formation in a transgenic mouse model of Alzheimer disease. J Neuropath Exp Neurol 62:1220-1227.

Kallnik M, Elvert R, Ehrhardt N, Kissling D, Mahabir E, Welzl G, Faus-Kessler T, Angelis M, Wurst W, Schmidt J, Holter S. 2007. Impact of IVC housing on emotionality and fear learning in male C3HeB/FeJ and C57BL/6J mice. Mammal Gen 18:173-186.

Klivenyi P, Bende Z, Hartai Z, Penke Z, Nemeth H, Toldi J, Vecsei L. 2006. Behaviour changes in a transgenic model of Huntington's disease. Behav Brain Res 169:137-141.

Lariviere WR, Chesler EL, Mogil JS. 2001. Transgenic studies of pain and analgesia: Mutation or background genotype? J Pharmacol Exp Therap 297:476-473.

Luesse H-G, Schiefer J, Spruenken A, Puls C, Block F, Kosinski CM. 2001. Evaluation of R6/2 HD transgenic mice for therapeutic studies in Huntington's disease: Behavioral testing and impact of diabetes mellitus. Behav Brain Res 126:185-195.

Mason GJ, Latham N. 2004. Can't stop, won't stop: Is stereotypy a reliable animal welfare indicator? Anim Welf 13:S57-S69.

McGrath MJ, Campbell KM, Burton FH. 1999. The role of cognitive and affective processing in a transgenic mouse model of cortical-limbic neuropotentiated compulsive behavior. Behav Neurosci 113:1249-1256.

Mogil JS, Grisel JE. 1998. Transgenic studies of pain. Pain 77:107-128.

Mohn AR, Gainetdinov RR, Caron MG, Koller BH. 1999. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 98:427-436.

Morton DB. 2000. A systematic approach to establishing humane endpoints. ILAR J 41:80-86.

Muller MB, Keck ME. 2002. Genetically engineered mice for studies of stress-related clinical conditions. J Psychiatr Res 36:53-76.

Nelson RJ, Young KA. 1998. Behavior in mice with targeted disruption of single genes. Neurosci Biobehav Rev 22:453-462.

NHMRC [National Health and Medical Research Council]. 2007. Guidelines for the generation, breeding, care and use of genetically modified and cloned animals for scientific purposes. Canberra: Australian Government.

NRC [National Research Council]. 2002. Animal Biotechnology: Science-based Concerns. Washington: National Academies Press.

NRC. 2008. Recognition and Alleviation of Distress in Laboratory Animals. Washington: National Academies Press.

Nuffield Council. 2005. The Ethics of Research Involving Animals. London: Nuffield Council on Bioethics.

Parfitt DB, Levin JK, Saltstein KP, Klayman AS, Greer LM, Helmreich DL. 2004. Differential early rearing environments can accentuate or attenuate the responses to stress in male C57BL/6 mice. Brain Res 1016:111-118.

Pietropaolo S, Mintz M, Feldon J, Yee BK. 2007. The behavioral sequelae following the prevention of home-cage grid climbing activity in C57BL/6 mice. Behav Neurosci 121:345-355.

Richter H, Ambree O, Lewejohann L, Herring A, Keyvani K, Paulus W, Palme R, Touma C, Schabitz WR, Sachser N. 2008. Wheel-running in a transgenic mouse model of Alzheimer's disease. Behav Brain Res 190:74-84.

Robinson V, Morton DB, Anderson D, Carver JFA, Francis RJ, Hubrecht R, Jenkins E, Mathers KE, Raymond R, Rosewell I, Wallace J, Wells DJ. 2003. Refinement and reduction in production of genetically modified mice. Lab Anim 37(Suppl 1).

Rodriguiz RM, Chu R, Caron MG, Wetsel WC. 2004. Aberrant responses in social interaction of dopamine transporter knockout mice. Behav Brain Res 148:185-198.

Rogers DC, Fisher EMC, Brown SDM, Peters J, Hunter AJ, Martin JE. 1997. Behavioral and functional analysis of mouse phenotype: SHIRPA, a proposed protocol for comprehensive phenotype assessment. Mammal Gen 8:711-713.

Royal Society UK. 2001. The Use of Genetically Modified Animals. http://royalsociety.org/.

Sternberg WF, Ridgway CG. 2003. Effects of gestational stress and neonatal handling on pain, analgesia and stress behavior of adult mice. Physiol Beh 78:375-383.

Stokes WS. 2000. Reducing unrelieved pain and distress in laboratory animals using humane endpoints. ILAR J 41:69-61.

Tucci V, Lad HV, Parker A, Polley S, Brown DM, Nolan PM. 2006. Gene-environment interactions differentially affect mouse strain behavioral parameters. Mammal Gen 17:1113-1120.

Van der Meer M, Baumans V, Olivier B, Kruitwagen CLJJ, Van Dijk JE, Van Zutphen LFM. 2001. Behavioral and physiological effects of biotechnology procedures used for gene targeting in mice. Physiol Behav 73:719-730.

Wahlsten D, Metten P, Phillips TJ, Boehm II SL, Burkhart-Kasch S, Dorow J, Doerksen S, Downing C, Fogarty J, Rodd-Henricks K, Hen R, McKinnon CS, Merrill CM, Nolte C, Schalomon M, Schlumbohm JP, Sibert JR, Wenger CD, Dudek BC, Crabbe JC. 2003. Different data from different labs: Lessons from studies of gene-environment interaction. J Neurobiol 54:283-311.

Wells DJ, Playle LC, Enser WEJ Flecknell PA, Gardiner MA, Holland J, Howard BR, Hubrecht R, Humphreys KR, Jackson IJ, Lane N, Maconochie M, Mason G, Morton DB, Raymond R, Robinson V, Smith JA, Watt N. 2006. Assessing the welfare of genetically altered mice. Lab Anim 40:111-114.

Wolfer DP, Litvin O, Morf S, Nitsch RM, Lipp HP, Würbel H. 2004. Cage enrichment and mouse behavior. Nature 432:821-822.

Würbel H. 2001. Ideal homes? Housing effects on rodent brain and behavior. Trends Neurosci 24:207-211.

Zhuang X, Gross C, Santarelli L, Compan V, Trillat AC, Hen R. 1999. Altered emotional states in knockout mice lacking 5-HT1A or 5-HT1B receptors. Neuropsychopharmacology 21(2 Suppl):52S-60S.

Cross-Cultural Ethical Perceptions and Ways to Resolve Challenges

Bernard Rollin

The concept of animal welfare is inextricably bound up with ethics, with an ethics component. Animal welfare is in essence what we owe an animal and to what extent. This is not very well understood by animal users, particularly by the agricultural community. I was on the Pew Commission where we frequently heard that animal welfare is simply a matter of sound science. It is not. It is a combination of sound science and ethics.

The relevant ethics that figures in the animal welfare equation comes from the societal ethic for animals, and there is in fact a new societal ethic emerging over the past 40 years that will likely dominate not only the West but, insofar as the West is the source of science in the East and elsewhere, the East as well.

In recent years ethnocentrism has become a dirty word and a variety of factors have converged to create a bias against the bias in favor of our own culture. Postmodernism, feminism, atonement for past imperialistic sins, political correctness have all converged in favor of a putative neorelativistic tolerance for multiculturalism that we would have historically dismissed offhandedly.

In fact, we do not accept many principles from other cultures. We don't accept tribal butchery, we don't accept clitoridectomies in young women, we don't accept the Taliban repression of women. But multiculturalism has certainly exacted some costs. Consider for example the extraordinary proliferation of evidentiary baseless alternative medicine, some of which is purportedly borrowed from the traditions of "other cultures" and on which the US public spent no less than $40 billion in 2005. This is not based in evidence and not based in science.

Hence too our current concern: How do we arrive at a conception of animal welfare that does justice to the bewildering array of views of this concept across different cultures? Part of the reason this issue creates perturbation among scientists is their historical disavowal of ethics being integral to science. The mantra is: "Science is value free in general and ethics free in particular."

When I was trained in science in the ’60s I got that mantra. My students are still getting it, although it is not quite as widespread as it was, fortunately, because it really is a detriment to the thriving of science in our society, which already is facing formidable obstacles.

Thus it is widely believed that animal welfare can be explicated without reference to values, simply on the basis of objective biological fact. In reality, the variation across cultures in views of animal welfare can be found historically intraculturally. It is simply magnified by considerations of cultural variability.

Consider the following: In 1981 in response to burgeoning societal concerns about animal welfare, the US agricultural community, represented by the Council for Agricultural Science and Technology (CAST), published *Scientific Aspects of the Welfare of Food Animals*. Reflecting a ubiquitous view among producers, the CAST report spoke of welfare as follows: The principal criteria used thus far as indices of the welfare of animals in production systems have been rate of growth or production, efficiency of feed use, efficiency of reproduction, mortality, and morbidity. In other words, the welfare of an animal is defined and determined by how well it fulfills the human purpose to which it is put, with no reference to how it feels, whether or not it suffers pain, distress, anxiety, boredom, loneliness, frustration, inability to move or be with conspecifics, and so on.

Implicit in this definition are a set of values and a set of moral obligations that are easily extracted: Humans are morally obliged to provide animals only with a set of conditions that allows the animal to fulfill the purpose for which it is kept by humans. In Kant’s terminology, then, animals are in no way ends in themselves, they are strictly means to an end, a human end. Animal welfare is based solely on these human ends. In metaphorical terms, welfare is to animals as sharpness is to a saw, what is needed for both to be functional tools.

At roughly the same historical moment, the early 1980s, other definitions of animal welfare were promulgated. In the writings of Marian Dawkins, Ian Duncan, and myself, one essential feature of welfare was argued to rest in what the animal experienced, its subjective states. The moral position implicit in such views was that animals ought to be at least in some measure in Kantian terms “ends in themselves” because they were conscious, and what they experienced mattered to them. By the way, at that time much of the scientific community was agnostic about the concept of animal consciousness. They overtly denied either the existence or the knowability of animal consciousness; therefore what we did to animals and how we forced them to live didn’t matter.

In my view of welfare, animals have intrinsic value rather than merely instrument value—that is, value merely as tools—because they are capable of valuing in their subjective life what happens to them. There were other definitions of welfare—e.g., the Farm Animal Welfare Council (FAWC) notion of the

Five Freedoms[1] that grew out of the Brambell Commission, and so forth. The point here is that even in British and American culture, one could find numerous very obviously different and incompatible definitions of animal welfare, based in radically differing views of the moral status of animals, separated irreconcilably by disparate ethical values underlying them. Thus, the existence of divergent views of animal welfare, differing across cultures, does not raise any new conceptual problems that were not already present by virtue of the intracultural value-based differences in views of what constitutes animal welfare.

It is in no way surprising that animal welfare should have emerged as a moral issue in the latter part of the 20th century, because of the precipitous changes in the nature of animal use that transpired in the mid-20th century. For the entire history of civilization, the overwhelming use of animals in society was in agriculture—food, fiber, locomotion, and power—and the key to success in agriculture was good husbandry. Husbandry meant putting your animals in the optimal conditions dictated by the animal's biological natures and needs, and augmenting their native ability to survive and thrive by provision of food during famine, water during drought, help in birthing, medical attention, and protection from predation.

This has been called the ancient contract. It was based on the insight that producers did well if and only if animals did well, and vice versa. Thus, husbandry was, in equal measure, a prudential and a moral imperative, sanctioned by what is after all the ultimate motivation for human beings, self-interest. Thus defining animal welfare and animal ethics was a nonissue.

In fact, the only animal ethic that was needed and can be found as early as the Bible arose from the need to cover the case of the small number of psychopaths and sadists who were unmoved by self-interest. In other words, if you were using animals in an agricultural way, which was the primary use of animals, you needed to put them in decent conditions and provide for their needs during famine and drought and so forth and so on in order to be financially successful.

Defining animal ethics and animal welfare became an issue when the nature of agriculture changed from husbandry to industry. The values changed as well. Primacy was now given to the values of efficiency and productivity. Whereas one can characterize husbandry as putting square pegs in square holes, round pegs in round holes, and creating as little friction as possible doing so, the Industrial Revolution provided us with "technological sanders," as it were, that allowed us to force square pegs into round holes, round pegs into triangular holes, while still keeping animals productive—things like air-handling systems, antibiotics, vaccines, etc. If one had tried to develop these systems during the era of animal husbandry, the animals would be dead in weeks of disease spreading like wildfire, but with these sanders we can force square pegs into round holes.

[1]These are freedom from thirst, hunger, and malnutrition; freedom from discomfort; freedom from pain, injury, and disease; freedom to express normal behavior; and freedom from fear and distress; available online (www.fawc.org.uk/freedoms.htm).

What was lost was the isomorphism between the animal well-being and productivity that characterized husbandry, and thus animal welfare and animal ethics became an issue instead of a presupposition of animal use. This was potentiated by the advent at roughly the same time, the 1940s, of large amounts of animal research and testing, again representing significant animal use that violated the symbiosis inherent in husbandry.

The research community typically deflected this issue by being agnostic both about the relevance of ethics to science and about animal consciousness. I was a principal architect of the 1985 federal laboratory animal laws in the United States. In 1982 when I went before Congress to defend them, I was asked to prove that there was a need for such a law. The research community claimed they were already controlling pain in research animals.

So I went out and, with a colleague at the Library of Congress, did a literature search on laboratory animal analgesia. How many papers did I find? I found none on laboratory animal analgesia. When I broadened it to animal analgesia, I found two, one of which said there ought to be papers, and the other said here is what we know: it was a one-pager in the *Journal of the American Veterinary Medical Association* and it was very honest about not knowing anything and how there was a moral imperative to know.

As public cognizance of the radical changes in animal use grew beginning in the 1960s and 1970s, efforts in favor of restoring fairness to animal use began to pervade Western society, beginning in Britain in the 1960s and resulting in the view that animals were entitled to the famous five basic freedoms. The ensuing years saw the emergence in Western society of "the new social ethic for animals."

As anyone attending to cultural history can easily determine, the issue of animal treatment assumed major social prominence beginning about 1970. Whereas 30 years ago in the United States one would have found no federal bills pending in Congress pertaining to animal welfare, the last decade has witnessed up to 50 and 60 per year. On a state level in 2004, there were well over 2,100 bills proposed in state legislatures pertaining to animal welfare; there were over 200 in California alone.

Most Western countries have recently adopted new laws protecting laboratory animals and ensuring control of their pain, often despite opposition from the research community, which preferred a laissez-faire approach. Britain is of course a notable exception, given the act of 1876.

Much of Northern Europe and the European Union have introduced major restrictions on confinement agriculture, probably the most dramatic being the Swedish law of 1988 that abolished confinement agriculture as taken for granted in the US, and created what the *New York Times* very presciently called in 1988 a "bill of rights for farm animals."

Although the US has been slow in developing its concern for agricultural animals, in the last few years it has tended to accelerate, partially due to referenda, legislative initiatives to abolish the most egregious of practices. The Pew

Commission report (PCIFAP.org) also educated a myriad of people who didn't really know about agriculture before.

Well, we can proffer evidence indefinitely, but I think enough has been said and placed in evidence to buttress my claim regarding social concern. So the question that arises is, if there is that much social concern, how is it expressing itself ethically?

Historically, both the laws protecting animals and the social ethic informing them were extremely minimalist, in essence forbidding—and this is language from the legal system, from the cruelty laws as well as from judicial interpretations of those laws—deliberate, willful, sadistic, deviant, extraordinary, unnecessary cruelty not essential, as one judge put it, to ministering to the necessities of man, or completely outrageous neglect.

Those of you involved in animal welfare may well be aware that early efforts to regulate animal research invoked the cruelty laws and tried to present in evidence certain research that was "cruel," and the universal judicial assessment was that research is not the sort of thing that can be cruel. It is not deviant, it is not sadistic, it does not betoken psychopathic behavior, etc. That is why it was essential to develop, as one judge put it, a new ethic for animals, by going not to the judiciary but to the legislature.

The ethic of anticruelty is found in the Bible and in the Middle Ages. St. Thomas Aquinas, while affirming that although animals were not direct objects of moral concern, nonetheless forbade cruelty to them on the grounds that those who would be cruel to animals will inexorably graduate to people. This is an insight that has subsequently been buttressed by decades of social scientific research—our last dozen serial killers all had early histories of animal abuse. Those involved with battered women's shelters know that provisions must be made for the woman's animal or the husband who is a batterer will go back and hurt the animal to get back at the woman. Psychiatrists acknowledge animal abuse…as sentinel behavior for subsequent psychopathology.

Roughly beginning in 1800, anticruelty laws, reflecting the anticruelty ethic, were codified in the legal systems of most Western societies. The key notion explaining why there was a demand for a new ethic can be found in the fact that the old ethic was so restricted in scope. If I draw a pie chart representing all the suffering that animals experience at human hands, how much would you say was the result of deliberate cruelty, a lot or a little? Every audience says a little. One week I spoke to PETA at San Francisco State and the Billings Rodeo Association of Montana, and they both said 1%. Well, if only 1% is covered by the cruelty ethic, then 99% is not. What that means is, as society has begun to concern itself with the other 99%, it has sought a vocabulary, an ethic, of expressing that concern in a manner that doesn't invoke cruelty, which is essentially irrelevant.

Most animal suffering results from putatively reasonable and defensible uses—industrial agriculture, which is meant to provide cheap and plentiful food; scientific research, which advances knowledge, cures disease, and provides medicaments.

In the 1970s when I was hired by a veterinary school to develop the field of veterinary ethics, I realized pretty early that the moral status of animals was a fundamental question in veterinary ethics. That led me to think about what sort of ethics society was likely to develop if indeed it was to continue to be concerned about animals. It dawned on me after about two years that ethics does not come ex nihilo—it doesn't come out of nothing. As Plato said, all ethics builds on preestablished ethics. I surmised that society would look to the ethic we have for people and modify it, change it—mutatis mutandis, as philosophers say—appropriately change it to fit the animal situation.

What aspect of our ethics is in fact being extended? One that is applicable to animal use is the fundamental problem of weighing the interests of the individual human against the general public. Different societies have provided different answers to this problem. Totalitarian societies opt to devote little concern to the individual, favoring instead the state or the Reich or the Volk or whatever their version of the general welfare may be. At the other extreme, anarchical groups such as communes give primacy to the individual and very little concern to the group; hence they tend to enjoy a very transient existence, such as the communes of the 1960s did.

In Western society, however, a balance is struck. Although most of our decisions are made to benefit the general welfare, fences are built around individuals to protect the individual's basic human interests from being sacrificed for the majority. Thus we protect individuals from being silenced even if the majority disapproves of what they say. We protect individuals from having their property seized without compensation, even if such seizure benefits the general welfare. We protect individuals from torture, even if they planted a bomb in an elementary school and refuse to divulge its location.

What are these interests that we protect? We protect the interests of the individual that we consider essential to being human, to human nature, from being submerged for the sake of the common good.

What are these fences around human individuals called? They are rights. I'm not obviously going to be using the animal rights locution in the same way as the animal rights people do. What they really mean is animal liberation. All the legislative flurry of activity, the 2,400 bills proposed and similar acts, is an attempt to provide societal guarantees of proper animal treatment since husbandry no longer ensures it. It is absurd to suggest that these are the same rights that humans have, because animals do not have the same natures that humans have. I thought about not using the locution of rights, but I knew you would realize that the concept was being invoked. However, it is the concept being invoked by the general public.

If you look at surveys (which I don't really tend to trust but they are indicators), close to 90% of the public will affirm that animals have rights. I have lectured to 15,000 Western ranchers in every ranching state. What percentage of them would say animals have rights? In my experience, well over 90% would.

An example of that occurred when the governor called a conference on the effects of animal welfare and animal rights on Colorado agriculture about 18

years ago. The opening speaker was the head of the Colorado Cattlemen's Association. He said, "If I had to raise animals like the chicken people do, I'd get the hell out of the business." I work very closely with these people. I just brokered a deal between the Humane Society of the United States and Colorado agriculture to avoid the costly referendum that took place in California, Proposition 2, banning veal crates and battery cages and gestation crates. It would have cost Colorado agriculture $12 million to fight it and lose two to one, and they didn't have $12 million, so we were able to broker a compromise.

People are seeking to build fences around animals. There were two surveys, one done by Gallup, one by Oklahoma State University, both of which had almost identical results, although you would expect a discrepancy because Oklahoma State is a very strong agricultural school and the poll was not particularly agriculturally oriented. They both found that 80% of the general public wants to see proper treatment of farm animals ensured by legislation.

People in society are seeking to build fences around animals to protect the animals and their interests and their natures, which following Aristotle I have called *telos*. Those of you who studied Aristotle know what he means by *telos*: the biological and behavioral and psychological needs and interests that are constitutive of a given type of animal—e.g., the pigness of the pig, as one of my book reviewers once wrote, or the cowness of the cow. They are trying to protect that from being totally submerged in the quest for human general welfare, and are trying to accomplish it by going to the legislature.

With good husbandry, respect for *telos* occurred automatically. In industrial agriculture where it is no longer automatic, and also in animal testing, people wish to see it legislated.

Very simply, the new ethic recognizes that fish must swim, birds must fly. Clearly, then, the notion that animals ought to have legal protection for fundamental aspects of their natures, a notion actualized in the Swedish agricultural law of 1988 and implicit in the Brambell Commission, is a mainstream phenomenon.

One of the most extraordinary things about writing the laboratory animal laws was the fact that the public did not divide on party lines. Support for controlling pain and suffering in animals, for example, was invariant across Democrats and Republicans.

People were not saying do not use animals in research. What they are saying is, if you use animals in research, control the pain, control the distress. Distress is demarcated from pain in the US laws.

Conceptually speaking in terms of legal theory, animals cannot have rights because they are property. The old slave decisions established that anything that is property cannot have rights. This is a solecism, a legal oxymoron. However, this could not be changed without a Constitutional amendment although a lot of legal scholars are trying to do precisely that.

There was an animal law conference at Harvard Law School two years ago where 350 people filled every space and 300 were turned away. Over 100 law schools have courses in animal law, and a big thrust of most of those law profes-

sors is enfranchising animals and abolishing invasive animal use. But the same functional goal can be accomplished by restricting how animal property is used, which is exactly what the proliferation of laws attempts to do, including the laboratory animal laws. The day they passed I was sitting with Tom Wolfle from NIH and Dale Schwindaman from USDA, and they both shook my hand saying, "Congratulations, you have established certain minimal rights for animals." These men were hardly radicals and essentially what they were saying was that an animal now had the right to have its pain controlled if pain is inflicted in the course of research, unless you were studying pain.

The good news is that we have gone from two published papers on analgesia to more than 11,000, with a correlative increase in its use, however deficient that use may still be.

So with this analysis in mind, we can begin to answer the question of cultural relativity of concepts of animal welfare. If our account is correct, there is not great disparity across at least different Western societies: all believe morally that animals should legally have their natures and interests protected and this should be accomplished by the legal/regulatory system. This is perhaps truer in Europe than in America.

Insofar as this notion seems to pervade Western democratic societies, which dominate the world politically and economically, it appears that this notion will dominate as the key notion of animal welfare, even as Western democratic notions of human rights have dominated discourse regarding human ethics.

People in other countries are beginning to realize that this notion will dominate. For example, two years ago I addressed 300 Southeast Asian agriculture animal producers who were greatly interested in what is happening in the West because they knew that they would have to abide by those standards if they were going to trade with the West. Recent announcements by Chinese government officials explicitly state that pressures of globalization are forcing China to consciously consider animal welfare and animal welfare legislation for the first time in its history.

As more and more US research is being shipped to other countries for economic reasons, we can be morally certain that public opinion will demand that it be accompanied by the new ethic. Judy MacArthur Clark has a project to try to bring Western ethical standards to these countries where the research will be exported.

As we argued earlier, the concept of animal welfare is deeply value-laden, both in what we choose to consider ingredient in an animal's welfare and to what extent we are willing to satisfy those welfare concerns. This in turn first led to producers saying that welfare is what the animal requires to do the job we expect of them. That has been turned around by the new ethic and placed the locus of welfare in the animal, not in our generosity or largesse. That is the source of the notion of rights, that they are entitled rather than simply being a matter of our will.

We have argued that the new ethic is intended to restore the fair contract inherent in husbandry, and it is primarily agricultural. It happened with research first in the US because we are removed from agriculture. My average Columbia PhD friend still thinks farms are Old McDonald's farms. We have argued that the new ethic is intended to restore the fair contract inherent in husbandry and to ensure that animals lead decent lives. We have further argued that the source of our primary obligation to animals is derived from attending to the animals' natures, even as the rights of humans are based in respecting the essentials of human nature. How does this notion transfer to animals?

In the US Constitution and in the foundational documents of other democratic societies, the relevant concept of human nature was derived from people's reaction to being denied certain things, from oppression. Having been denied freedom of religion or belief, people demanded that such belief be protected from governmental intrusion. Similarly, this is true of the seizure of property. Philosophically, the notion of human nature is of course very problematic, with many theories abounding about what human nature is and with some philosophers, notably existentialists and Marxists, affirming that there is no such thing. Interestingly enough, I would argue that whatever position you take on human nature, the notion of animal nature is far less problematic than the notion of human nature.

Animal life is far less plastic than human nature and is far less influenced by culture, and is thus far easier to define. It is more obvious, for example, that lions are predators than that humans are. Determining what animals are evolved for is simpler than answering the same question about humans. So obvious is it that animals have a nature that Aristotle, the greatest philosopher of common sense in antiquity, made it the cornerstone of his biology, and correlatively made biology based in *telos* the root metaphor for explaining everything in the universe. Whereas for Cartesian and post-Cartesian modern biology, biology is best expressed in terms of physics and chemistry, for Aristotle physics and chemistry were to be explained using functional biological categories. Physics was for Aristotle the biology of dead matter, to put it paradoxically. Biological categories, functional categories, are the most appropriate categories for explanation when it comes to living things.

So in *De Anima*, which is his biology, Aristotle lays out a functional template for biology that still serves as the framework for the way biology is taught in high school. Any living thing, says Aristotle, is a constellation of functions constitutive of its nature, and all living things are to be described in terms of how they fulfill these functions—locomotion, reproduction, nutrition, excretion, sensation, and so on. We characterize living things in terms of how they fulfill these functions. These functions, then, I would argue, constitute the *telos* of any type of animal—the pigness of the pig, the dogness of the dog. Aristotle says, tellingly, this nature is knowable simply by intelligent and repeated observation. Respect for the animal's nature was essential for traditional agriculture: the greater the respect, the better the husbandry, the more productive was the ani-

mal. The fact of agricultural success attested to knowledge of animal *telos*. Under extensive conditions, productivity did betoken good welfare.

Modern agricultural use circumvents respect for *telos* and forces square pegs into round holes. Other animal uses ignore *telos*—for example, zoos and maintenance of animals in research settings, where animals are housed in conditions developed largely out of convenience for us but in violation of the needs flowing from their natures, as when nocturnal burrowing creatures are kept in polycarbonate cages under bright illumination or when social animals are kept in isolation in zoos, or the most egregious example I ever experienced in my youth, a giraffe cage in which the giraffe could not stand up. Such a situation would not occur today, which in a weak way attests evidentially to the claim that society is worried about animal *telos*.

Both Tom Wolfle and I in the early 1980s and David Morton today have pointed out that the conditions under which we keep animals are probably more invasive and more harmful to the animal than the number of overt invasive protocols. My understanding is that maybe 10-15% of protocols are seriously invasive in research. But 100% of animals are kept under conditions that are inimical to their basic natures.

I would thus argue that in today's world, animal welfare is being defined in terms of animal *telos*—that is, meeting the needs and interests that matter to the animal by virtue of its biological and psychological nature. According to my analysis, complete satisfaction of the animal's *telos* would constitute what could be legitimately called happiness for the animal. Thus, a happy lion would be a lion kept under extensive conditions with other lions, allowing the full range of lion behavior, including predatory behavior. A miserable lion would be one kept alone in a small cage. The relevant ethical judgment for lions in captivity would be to create a space that functionally approximates the ideal, as the research community has done with primates. Thus, pigs in a straw-based pen system would be happier than a sow in a sow stall, but not as happy as a sow with free access to foraging and shelter from inclement weather. There is a huge body of empirical data from Edinburgh on natural behavior in pigs, particularly sows. In my view, part of the job of what is called animal welfare science is getting as close as possible to happiness for the captive animal.

So there is more to being ethical to the research animals than simply minimizing pain. There are all these other parameters. I find personally talking of animal happiness unproblematic. Indeed, I would argue that animal happiness is far clearer than human happiness, given the curse of human reflective consciousness. A person may have every wish he or she ever wanted fulfilled, yet not be happy for a multitude of reasons. Everyone has friends like this—for example, people possessed of neurotic worry about losing it, neurotic worry about whether they deserve it or not. We have no reason to believe that animals are capable of such nonproductive navel-gazing. There are few human cases of happiness as paradigmatic as the horse let out of the small corral after winter into a large green pasture, after being fenced for months: the kicking up of the heels,

the breaking of wind, the exuberance of the gallop, and the whinny express joy more clearly than any human affirmations. Typically, animals don't lie.

In sum, we have argued that emerging social ethics for animals in democratic societies will largely dictate the form animal welfare takes, and particularly in the research area, since social and economic pressure will help impose it on other societies. This emerging ethic emphasizes the rights animals should have based on their biological and psychological natures or *teloi*. The extent to which such *telos* can be accommodated will vary with circumstance, but the ideal remains clearly demarcated. This idea was necessary to counter the 20th century tendency to see animal welfare as strictly determined by the human purposes to which the animal is put.

Coordination of International Rodent Resources

Mice Traveling the World: Issues in Sharing and Transferring Mice

Lili M. Portilla

This presentation focuses on some legal issues having to do with mice transfers. I am not a lawyer, but I have associated with lawyers throughout my career. My disclaimer is that the views and opinions I am expressing are those of NIH. If there is any legal question, my advice is that you seek legal advice from your institution.

I will first set the stage on how NIH approaches the sharing of animal resources, data, and other things. A lesson learned at NIH is that we do not patent research tools. When this happens, the flow of these tools to researchers is restricted and academic research is hindered. Hence NIH's position, like that of most academic centers in the United States, is that these research tools will not be patented.

However, if industry requests some of these research tools, there is nothing to prohibit us from licensing them, even though they are unpatented, and we can still realize some profit if they are used for commercial purposes. So patenting in and of itself is not the only way of guaranteeing a royalty stream for your institution.

The basic precept at NIH is that we expect our funded researchers, as well as our internal researchers, to make resources developed under our grants available to the research community and as unencumbered as possible. The NIH model organism-sharing policy covers all projects that may produce model organisms with the intent that they will be made available to the research community.

In 2003 NIH produced a new guide notice, that grant applications of $500,000 or more of direct costs in any single year are expected to include a plan on data sharing, meaning that the research institution and the researcher have to demonstrate to the NIH how they are going to make these resources available, be it through a material transfer agreement (MTA) or deposit in a repository. A general consensus is that this position promotes good citizenship in the life sciences community.

As a matter of policy at NIH and many academic institutions, the technology transfer offices ask for documentation of data sharing using an MTA. This agreement specifies how these resources can be used and limits the transfer to a third party, and thus prohibits transfers to other institutions. Also it puts the requester on notice that they have to attribute the donor, the person that gave them the resource, in a publication. Without an MTA it is not clear to NIH whether investigators get proper attribution on transferred materials.

We at the NIH found that the existing agreements did not address the uniqueness of animal models and crossbreeding issues. Therefore, we developed our specific form to transfer animals called the "Material Transfer Agreement to Transfer Organisms." It is a modified NIH standard agreement, but contains special terms. First, it specifically defines the allele. From an intellectual property perspective, this criterion is of most value in these resources so it is necessary to clearly identify the special allele or knockout; for example, the form would define a Brca1 floxed mouse (Brca1 floxed allele expressed in a mouse). The agreement may be used for any animal model. The information in the form also defines what is included in the material—for example, unmodified derivatives and unmodified progeny, zygotes, embryos, and cells, tissues, etc.

There is also language that allows for crossbreeding. This language is primarily for nonacademics, so they know NIH allows it and if you plan to distribute this crossbreed, please let the recipient know that this original allele was obtained by the NIH.

The agreement also contains addenda that address some of the intellectual property issues that come up with mice like Cre-lox and OncoMouse. There is also an animal transfer addendum; the form is available online (www.ott.nih.gov/forms_model_agreements/).

Finally, if you think your mouse incorporates third-party intellectual property, it is best to consult with your technology transfer office to determine how best to deal with this. In most cases, transfers between academics incorporating third-party intellectual property are not a problem. The problem and the sticking point come when these transfers are done for commercial purposes, in which case it is best to get some advice on how to proceed. In addition, check to see if your institution already has a license agreement in place, because this may facilitate the transfer. Sometimes these license agreements define how you can further transfer these mice—for instance, research purposes only and to academic institutions, no transfer to commercial entities. Your tech transfer office or your legal office can help you if there is an existing agreement at your institution.

Following are some questions that are posed frequently about animal transfers:

- *Can I transfer a mouse that I receive from my colleague at institution A to another colleague at institution B?* Most of the time, the answer is no. If you signed an MTA, in most cases it says that you cannot transfer to a third party. In these cases we always go back to the original person that gave us the mouse or

the intellectual property and make sure it is okay to transfer it to another individual. In most cases it is not an issue, but it should not be done if the agreement you signed prohibits it.

- *Can I crossbreed a mouse developed in my lab with one that I received from my colleague in another institution?* Proceed carefully. Usually, we make sure that crossbreeding language was put into the agreements if that was what the investigator intended. But many times people sign agreements containing a statement that you can't crossbreed. My advice is to read what you sign. If you want to modify it, go back to that institution to say that you want to modify the agreement
- *Why is the institution asking me to sign both a material transfer agreement and an animal transfer agreement?* The animal transfer agreement is very different from a material transfer agreement. The MTA specifically deals with intellectual property issues, whereas the animal transfer agreement deals with the care and use of a particular animal and is usually signed off by the vet in the institution. When these two documents are put together, they cause confusion. So in the new agreement that I just discussed, all these terms have been incorporated in order to avoid having multiple signatures and too much paper. They are different and they do serve different purposes.
- *Is it okay for me to deposit mice that I developed in my lab in a public repository?* My answer is a big yes, but make sure that there is not any kind of intellectual property issue that would prohibit you from doing that. It may be necessary to consult with your legal and tech transfer people to make sure that's not going to be an issue. From the perspective of NCRR, depositing an animal is ideal and removes the financial and resource burden from the lab of having to ship mice. We encourage our grantees that develop resources through grants to deposit them in many of the NIH-funded repositories.
- *A colleague requesting my mouse wants me to ship it to their animal contractor. Is this allowable?* The answer is: it depends. For example, a particular institution used a contracting facility, like Charles River, to clean their mice and cage their mice. Once the mice were ready for the experiment to start, they would be shipped to another location. We thought that was fine, because that contractor was acting as an agent for the institution. But the issue comes in if the contractor is collaborating with the institution, in which case they almost become a third party in the transaction. It may become necessary to ask questions or have your tech transfer people ask some questions on how to proceed. Most of the time this is not an issue, as long as this relationship with the contractor is one of an agent with the institution.

Some helpful hints have arisen over the years. One is to keep your tech transfer office or legal office informed of what you are going to be doing with these mice. Tell them ahead of time if you plan on crossbreeding the mice or sharing them with another institution. It is better to address these terms at the beginning of the negotiations as opposed to after an agreement has been exe-

cuted, which is always more difficult and time consuming. So tell us as much as possible upfront. Another issue is defining the timeline for experiments. In our office, if we knew that an investigator had something time sensitive coming up, if they had to time it right with the animal shipping folks, the forms would get bumped up in priority in order to get processed, because the last thing we wanted to hear was that the mice were past their prime for the experiment and the investigators were not able to do anything.

When publishing results, if a paper is coming out describing a new knock-out, it is useful to presign agreements with the mouse model on them so that when the investigator gets requests, s/he only needs to sign the agreement and ship the mouse off. As noted earlier, NIH encourages our investigators and our grantees to deposit their mice in repositories, to save time, effort, and money in their labs.

Another issue deals with shipping and timing. It is not advisable to ship mice in the heat of the summer. It is helpful to work with the shipping staff to make sure that the agreement is done so they do not need to wait for the paper-work to ship mice.

Knockout Mouse Databases: The Knockout Mouse Project and Repository

Franziska Grieder

The mouse has played a key role in many discoveries and advances related to biomedicine and has contributed to improvements in human health. In part, this is because mice offer the following advantages (in addition to their small size and relatively short reproductive cycle): mice are well characterized (e.g., their entire genome has been sequenced), they are genetically similar to humans, and they exist as inbred lines and strains. Further, these strains can carry different mutations that mimic pathologic or disease conditions seen in humans.

In the past, spontaneous genetic mutations in mice have contributed to understanding the biology of human disease in significant ways, but today's focus has shifted to induced, genetically engineered, or modified mouse strains. Specifically, the ascent of new powerful genetic methodologies applied to molecular biology has allowed scientists to delete or insert genes. Attention has shifted from the original inbred strains developed by Castle and Lathrop almost a century ago to technologies that produce tissue- and disease-specific biomedical models. These transgenic technologies have led to the creation of "knockout" animals, using targeted mutagenesis or gene replacement approaches that allow scientists to inactivate single genes by replacing or disrupting them with the introduction of exogenous DNA constructs. Seminal to this revolutionary development were studies conducted by three scientists who received the 2007 Nobel Prize in Medicine or Physiology for their achievements: Drs. Mario Capecchi, Oliver Smithies, and Martin Evans.

Recognizing the power of knockout mouse technology and its general widespread benefit to biomedical scientists, a group of scientists and experts from around the world assembled in 2003 at the Banbury Conference Center at Cold Spring Harbor Laboratory to explore the feasibility of creating a comprehensive, genomewide, and publicly available knockout mouse resource. This effort would generate a library of mutant mouse embryonic stem cells (ESCs) containing knockout or null mutations in every protein-coding gene in the mouse genome. The driving force behind this effort was the recognition that only a small fraction

of the approximately 20,000 to 22,000 mouse genes had already been knocked out and published, and most of these knockout mouse models were neither readily available nor accessible to the wider research community.

The creation of a comprehensive, widely available, and standardized (e.g., mouse strain background, genotype testing, and specific pathogen–free) knockout mouse resource in a timely and cost-effective manner would require a highly coordinated effort among several international partners. Thus the foundation of several knockout mouse projects was born.

Three independent but collaborative efforts have been launched to address the original challenge posed during the Banbury Conference: the Knockout Mouse Project (KOMP) funded by the National Institutes of Health (NIH) in the United States; the North American Conditional Mouse Mutagenesis (NorCOMM) Project funded by Genome Canada and its partners; and the European Conditional Mouse Mutagenesis (EUCOMM) Program funded by the European Union. I will focus on KOMP.

In a collaborative effort among different NIH institutes and centers, a five-year and greater than $50 million mutant mouse resource initiative was started in 2006 that aims to (1) use gene targeting to make a resource of null alleles marked with reporters, (2) support a repository to archive and distribute the products of this resource, (3) develop improved and robust ESCs on the inbred mouse strain C57BL/6, and (4) implement a data coordinating center that allows all scientists easy access to data relevant to this effort.

The KOMP Repository (www.komp.org) activities were awarded to the University of California, Davis (UC Davis) and Children's Hospital Oakland Research Institute (CHORI) in Oakland, CA. They will, in a collaborative effort, be responsible for the preservation, protection, and distribution of about 8,500 knockout mice and related products for use by the research community. Additionally, the repository provides expert advice and assistance for scientists with all questions related to mouse biology and reproduction, cell culture techniques, molecular biology, and insight into the selection of the most appropriate model or approach for their research project.

The specific activities of the KOMP Repository include acquiring vectors, ESCs, and mice from the KOMP production teams. Next, all ESCs received are archived and expanded for quality control testing, including viability-growth-morphology and pathogen assessment. Prior to release for distribution, a percentage of clones undergoes genotype verification and chromosome counting. The repository also performs in vivo testing, which includes microinjection to produce high-percentage chimeras and germline transmission testing. Any generated products as a result of the testing (e.g., germline-transmitted mice, embryos, and sperm) are archived as well.

The repository allows the customer to learn about KOMP and its operations, and also provides access to the KOMP catalogue, to order products and express interest in and nominate genes that will be targeted with higher priority by the production teams. The KOMP website allows researchers to obtain help

(e.g., protocols for genotyping, microinjection) or information on issues related to material transfer agreements.

During KOMP's first two years of operation, numerous joint meetings among the knockout mouse production programs have been held on an international level (i.e., KOMP, NorCOMM, and EUCOMM). Participants work hard to establish collaborations and coordinate activities in order to avoid duplication of efforts. The projects in North America and Europe have agreed to share their gene lists and data in order to help with the coordination. Ideally, resources produced by one project would be available to scientists on a different continent, thereby enabling scientists to simply order all mouse strains locally, thus avoiding the hassle of international transport. The future will tell if this becomes a reality and if sharing of mutant mouse resources can happen across international borders.

NorCOMM, the North American Conditional Mouse Mutagenesis Project

Colin McKerlie

The focus of this presentation is NorCOMM, the North American Conditional Mouse Mutagenesis Project, in particular where it came from and the contribution of my laboratory, which is the archive and distribution program. In 2003, some collaborators and I at Mount Sinai Hospital Samuel Lunenfeld Research Institute were engaged in a genomewide random mutagenesis project using ethylnitrosourea, or ENU, to produce point mutations randomly across the mouse genome. We then applied a very comprehensive set of screens or phenotyping to try to identify the expression of those mutated genes by looking for abnormal phenotypes.

My contribution was from my pathology phenotyping lab, where we were using gross, histo-, and molecular pathology techniques to try to identify novel mutations or the expression of those mutations as pathology phenotypes. We were also using our pathology techniques to characterize phenotypes in unusual or abnormal mice screened out by my colleagues.

As pathologists tend to do, we collected and kept a lot of information and were, by necessity, in large part establishing a repository. It was a necessity because in a dominant screen that we were using for ENU, we were often analyzing, often at necropsy, uniquely mutagenized genomes. If we needed to go back and study a particular mouse because we were interested in that mutation or phenotype, we needed the ability to go back to the freezer, recreate that mouse, and put it through the process. In essence, then, we established a very comprehensive archive, starting with tissue, sperm and ovaries, and, of course, embryos.

Recognizing the increasing demand across Canada among investigators using the mouse as a model system, we took the opportunity to start archiving and distributing their lines, driven by two requirements. One was for ease of distribution, to take some of the burden from these individual investigators and centralize the resource, making distribution more efficient, and provide an ad-

vantage in terms of protection from a disaster as well as some additional opportunities. Thus, we established the Canadian Mouse Mutant Repository (CMMR).

New space was built for this; we have just relocated fairly recently into the Toronto Centre for Phenogenomics (TCP). Space was designed for receiving mice and allowing us to freeze them in various formats in liquid nitrogen or mechanical freezing—somatic tissue, embryos, sperm, ovaries, etc. The facility also allows us to go back into our repository to restore a mouse line. Large and secure capacity is an essential part of our repository and we also have redundant capacity to guard against catastrophic loss. In summary, the TCP, a large mouse-based research-enabling center with very large capacity (36,000 mouse cages), offers a very comprehensive set of services to enable the collective research enterprise to archive and distribute their mice efficiently.

The CMMR was established to focus on requirements of investigators prior to the more recently emerging International Knockout Mouse Consortium (IKMC). The CMMR website showcases all the mutants and our samples. All our lines are catalogued through the international mouse strain resource, hosted by the Jackson Laboratory (JAX). The importance of this repository is not only to make lines available and visible but also to make them accessible, although accessibility does not necessarily always correlate with usability. Our services are also identified, including embryo services, ovary, sperm, or somatic tissue.

The IKMC is an attempt to essentially have a single Web portal for the mouse-using investigator community to find a mouse that may be potentially useful to enable their research and move it forward. A big advance in this field of repositories was the paper by Francis Collins and colleagues on the IKMC published in the journal *Cell* in 2006. A significant part, postproduction, of an embryonic stem cell library comprehensively covering every protein-encoding gene across the mouse genome is a repository network to be able to deliver that resource to the rest of the world. So KOMP, EUCOMM, NorCOMM, and the Texas Institute of Genomic Medicine have been established as an IKMC repository network.

NorCOMM has been funded by Genome Canada to establish a Canadian academic-industry lab network. The CMMR became the repository and distribution center for the NorCOMM resource. The project is working toward 2,000 conditional-ready targeted genes and 10,000 nonconditional trapped genes (genes mutated in embryonic stem [ES] cells using an alternative technology called gene trapping).

A component of the project is to create mouse lines from these ES cells. We are also performing functional analysis of candidate genes identified as important determinants of specific human disease. This is also funded by Genome Canada.

We are using two approaches to mouse mutagenesis or to ES cell mutagenesis. Gene trapping is a random process, inserting a vector randomly across the genome. The vector is tagged and so may be found as would the gene in which it was inserted. Another approach is gene targeting, a more focused approach where the insertion replacement relies on homologous recombination.

The element is targeted to maximize the mutagenic potential in the specific gene that we are interested in.

The project is focusing on 866 genes on a prioritized list. The first 100 gene targets will be used for some quality control and to address some of the germline transmission issues associated with these ES cells, and 50 of these lines from our prioritized list will be those of specific Canadian interest—related to disease areas in which our research community is actively engaged.

NorCOMM has a website (www.norcomm.org) that describes our partners, production labs, repository, and target construction groups. It provides the opportunity for us to engage the Canadian as well as the international research community. Anyone has the opportunity to use our gene submission process.

Our gene prioritization process addresses high-impact Canadian health research community genes; those that are not targeted by EUCOMM or KOMP; those whose gene structure is amenable to our particular allele and our approach. We focus on the 2,000 genes that are available to us and are not being done by another consortium.

The genes available in the pipeline are being posted at the Wellcome Trust Sanger Institute (www.sanger.ac.uk/htgt) by KOMP, EUCOMM, and NorCOMM.

One can see from the pipeline summary how many genes are involved in each group, whether the design has been requested or, more specifically, if the vector construction is actually in progress. ES cells in the pipeline are also included. This is an evolution from the CMMR in that where we were doing tissue, germ cell, and embryo archives, we are now also responsible for the embryonic stem cells for the NorCOMM project.

Our main contribution in the international arena is the trapping technology. Each of the resources or production centers has been or is currently engaged in trapping some component of their unique alleles across the genome. We would like to trap 10,000 genes and currently hold about 90,000 cell lines. The target is to trap about 38,000 genes across the different centers with a significant number of cell lines. These repositories are large-scale infrastructures that will be able to support those production objectives.

For targeting the genome, we are focused on 2,000 genes at NorCOMM. The target for all the repositories is to hold ES cells representing over 18,000 genes, and working together we eliminate redundancies.

We have tried to increase accessibility by creating as many launching points into the NorCOMM resource as possible, through the international gene trap consortium or through all the Web portals. You get to the CMMR (hosted by the TCP website; www.phenogenomics.ca) and essentially move through a very simple process. Rather than a materials transfer agreement (MTA), we have instituted a conditions-of-use agreement for not-for-profit users, which is simply a checkbox stating that the user agrees to our online conditions of use. With for-profits, we still deal with MTAs. Once the user has agreed to the conditions, s/he makes a payment, and we can confirm and ship the clone.

Requests for material are international, with the United States being a significant requester. In 2007 shipments went to 11 countries in Europe, Asia, and Australia in addition to North America.

There are challenges ahead for our repository that are shared by other repositories. For example, when ES cell resources need to be developed into mice, there is likely to be a parallel centralization of the production of these genetically engineered mouse models, or GEMMs.

The basis for the IKMC is to develop all the 22,000 protein-encoding genes in the mouse genome, in BL/6 ES cell lines. Because BL/6 ES cell lines present challenges with germline transmission, success in development, and culture conditions it is quite possible that not every lab or transgenic facility will achieve the same efficiencies with BL/6 ES cells that they have had with the more robust ES cells of the past. So if investigators come to rely on centralized facilities to create these mice, this would create issues in transporting live mice.

Sperm cryopreservation is also an option and there has been great progress in sperm efficiencies after cryopreservation. However, the preference for BL/6 background continues to be challenging because of the problems in sperm thawing and reanimation processes. While the Jackson Laboratory in particular has made great progress with this, the efficiency has increased only from 3% to 40%. This is not efficient enough for the needs of the international community, since even 40% efficiency is achievable only by experts and is likely to be lower in the hands of those more unfamiliar with the techniques.

I think sustainability and accessibility of these international knockout mouse resources (IKMRs) are challenges. For example, NorCOMM is funded in the same four-year lifecycle as the production. When the funding cycle ceases for the production, the repository is left with the resource, making its sustainability an issue. In addition, the resources will need to change as the science changes. The IKMC must also provide a quality, standardized, and secure resource; it must be innovative with its technology, procedures, and offerings; and it must establish partnerships, platforms, and processes based on sharing.

However, along with the challenges there are opportunities. One is comprehensive biobanking that goes beyond embryos and sperm, and moving to serum for blood-based biomarker or proteomic research. In addition, there are a number of techniques and technologies to provide the user with other ways to access these banks. Laser capture microdissection is one in which we can load up tissue sections and then purify and amplify RNA or DNA from specific homogeneous cell sets. For example, if the requester is interested in respiratory epithelium and wants to run some gene expression experiments on that, we can send the cells of interest or the purified RNA from the cells. Whole-tissue slide scanning is another important technology that can be applied to these repositories of ES cells or to mice. We use whole-tissue high-resolution slide scanning in the pathology setting and make the slides available to users around the world. We can interact with investigators while looking at the same slide and discuss the pathology phenotype that we are describing. The same technology can be applied for an investigator accessing the repository, i.e., looking at a model

that's sitting in the archive to ask questions about the pathology to determine, for example, whether a mouse really needs to be transported.

Another development in comprehensive biobanking is the use of induced pluripotent stem (iPS) cells. The international collaboration and distribution of these resources will result in building better models and in reducing attrition, which relates to the number of mice moving around the world. We can induce skin fibroblasts with four genetic factors to become pluripotent stem cells, develop an allelic series of mutations across a gene of interest, and provide the tools to characterize them early, to assist investigators in making the decision about whether they really need this mouse model shipped around the world or not.

Also, for secondary modifications, again the models that we are characterizing, that we are depositing in our repository, have typically come through a phenotyping pipeline. They have information. They have engaged investigators somewhere. But maybe it is not exactly the mutation in their gene of interest that they need. I think the older approach would be to go back, retarget, pick your clones, create a mouse, expand—all the breeding that is required for that—germline transmission. We have the potential with iPS cells to have homozygous cells recovered from the skin fibroblasts, induced to iPS cells, make a secondary modification genetically, re-create a mouse, save all that additional effort, and ultimately save a lot of transport and distribution of mice.

To summarize the progression, we were taking tissue, sperm, ovaries, and embryos, and developing a relatively simple scheme for archive and distribution. Now ES cells have been added and we are working on iPS cells, banking serum and tissue, and creating accessibility tools and layers like laser capture microdissection to provide a molecular resource, or virtual slide consultation to provide a pathology resource and be able to make all these resources as exportable as possible, in appropriate formats.

I need to recognize my collaborators and colleagues: Janet Rossant, Geoff Hicks, who lead the NorCOMM project; and my very hard-working group in the lab at the CMMR. We are hosted at the Toronto Centre for Phenogenomics. Of course, we are working very much and embedded and learning from our international collaborators in the IKMC repository network.

EUCOMM, the European Conditional Mouse Mutagenesis Program

Martin Hrabé de Angelis

My presentation will focus on the European Conditional Mouse Mutagenesis Program or EUCOMM, the European part of this international endeavor to knock out every single gene, and will go a little further to describe our program on mouse phenotyping and on the outcome and distribution.

The challenges for the future are very clear:

- Identification of all the functional elements (that term is used rather than *genes* because the definition of *gene* is very complicated)
- Generation of a mutation for every gene in the mammalian (mouse) genome, which only provides one aspect of the function of a gene, because an allelic series may be needed for full understanding
- Phenotyping of these mice, which is the most important and the most challenging task
- Linkage of the models to human diseases
- Archiving and dissemination

EUCOMM produces vectors, conditionally mutated mouse ES cells, and mutant mice as a public resource, available to everyone. The goal is to have 13,000 mutations in the ES cells, which comprise a mixture of knockout and homologous recombination in ES cells; 320 of them are being made into live mice as test cases, [and] those 320 will eventually go into a phenotyping pipeline, which we set up in Europe. There are also currently available 2,500 genetrap clones and over 600 clones mutated by gene targeting.

The consortium is headed and coordinated by Alan Bradley and Wolfgang Wurst; Wolfgang is at our center and Alan is at the Wellcome Trust Sanger Institute. The consortium is spread around Europe, and each center has different tasks. While it is not expedient to fully describe all the centers here, the information is available at a common website (www.eucomm.org), which is very valuable and convenient. It is possible to order clones from the website by clicking

the database to find the gene of interest and then contacting the person in our center, who will send you the ES cell lines. Information for prioritization of genes may be obtained from eucomm@sanger.ac.uk.

A limiting factor at the moment is annotation of the genome. Making the vectors proceeds automatically; however, if the annotation is not done properly then it is very difficult to design the vectors. Distribution of the cell lines is done through our center and for the mouse lines it is through EMMA, the European Mouse Mutant Archive.

Intellectual property for the gene-trap lines is handled by the tech transfer unit at our facility and at the Wellcome Trust Technology Center for the targeted lines.

An example of how we are using the different areas of mutagenesis, phenotyping, and archiving is with the disease osteogenesis imperfecta, or brittle bone disease, which is a group of genetic disorders. We created a mouse from our mutagenesis screen carrying a point mutation for collagen-1, alpha-1 gene, which is similar to the human situation. We treated these animals with bisphosphonates that target the osteoclast; this is also similar to human treatment. The result is that we were able to partially cure the bone phenotype. However, the lethality stayed absolutely the same, which was quite surprising. At this point, the idea of the mouse clinic came into play.

The German Mouse Clinic offers systemic phenotypic analysis of mouse mutants on the basis of scientific collaboration and primary screening of more than 320 parameters—I call this a hypothesis-generation machine. It consists of a consortium of people who are specialists in their areas—they all have a satellite lab in our mouse clinic—from urology to clinical chemistry, dysmorphology. There are 14 different indication areas. At the end of the day, once we phenotype the mice, everybody comes together again to discuss it and generate hypotheses.

With regard to the osteogenesis imperfecta mouse, we found a lung phenotype and a heart phenotype, based on a metabolic pathway. Clinicians felt that these phenotypes were secondary, because of the affected bones; however, from our work we know they are primary. This is an example of how early systemic phenotyping in the mouse clinic can provide critical information. In this case the story must be rewritten to reflect the fact that it is a systemic disease, affecting not only the bones but also the heart and lungs, which are relevant to the early death of these animals.

A roadmap for a European strategy for research infrastructure was designed over the last five to six years in Europe. One of the projects I am coordinating is the Infrafrontier program. Infrafrontier is in a pilot phase of building up the European infrastructure for phenotyping and archiving. We plan to create more mouse clinics and scale up the activities in EMMA. A second mouse clinic has been created that works closely with industry in which drugs can be tested in a systemic way. Steve Brown then created one at MRC Harwell, UK, and now there are clinics at the Sanger Institute, in Barcelona, and in Monterotondo. There is one in Toronto as well, with Colin McKerlie. However, despite this

growth, the repositories and phenotyping services are not yet adequate to handle the thousands of knockouts available as well as thousands of alleles from other mutagenesis programs. Thus, it is our hope to raise money for the Infrafrontier project, to bring the right people together, be ready in three years to meet this challenge.

FIMRe, the Federation of International Mouse Resources, is one of the examples of archives on a global level. The problem was exchange of material and exchange of mice. We weren't able to agree on a common strategy so we started these bilateral science contracts now between our center, the Medical Research Council (UK), Mammalian Genetics Unit (UK), the National Center for Scientific Research (CNRS) in France, as well as with the Jackson Laboratory and UC Davis in the United States, with RIKEN in Japan, and others.

The Infrafrontier consortium, which also takes part in FIMRe, consists of several countries. With the next amendment of the contract, Canada will join the consortium, as will the Academy of Sciences in the Czech Republic. The consortium consists of scientific labs and funding agencies that develop a plan for future endeavors. The goal is to have a very clear strategic plan by 2011, including a business plan for how to run the resource and a memorandum of understanding between all the different countries. The consortium is open to additional partners.

In summary, I have presented the European strategy for mouse mutagenesis, phenotyping, and archiving. The European knockout project, EUCOMM, focuses on mutagenesis and is only one part of the European roadmap. There are also other technologies, such as RNAi, that play a very strong role. There is also EUMODIC, the European Mouse Disease Clinic, a consortium headed by Steve Brown, where we have a pilot project combining mouse clinics. Another component is EMMA, where we have currently some 1,500 mouse lines, not counting the ES cell lines. In the next three years there will probably be 4,000 to 5,000 lines. Finally, Infrafrontier is one plan to come up with the proper infrastructure and funding for these different areas.

The RIKEN BioResource Center

Yuichi Obata

The RIKEN BioResource Center (BRC) was established in 2001, making it relatively new in the field. It was established to produce an infrastructure for advancement of life sciences. The center focuses on five major activities:

- collection, preservation, quality control, and distribution of bioresources
- key technology development necessary for production, preservation, and distribution of bioresources
- bioresource frontier program, including a mouse clinic
- training and education
- international collaboration

We have focused on five major resources that include not only the mouse but also the experimental plant *Arabidopsis* as well as cell lines and genes from mammals and microbes and the microbes themselves. Finally, we focus on information itself as an important resource now and in the future.

RIKEN BRC serves as a station for dissemination of research products or bioresources produced by Japanese and RIKEN scientists to the international scientific community. All materials come in with material transfer agreements to protect the intellectual property rights of the developer and to ensure their proper use by the recipient.

Coinciding with the RIKEN BioResource Center, the Japanese Ministry of Education, Culture, Sports, and Science and Technology inaugurated the National Bioresource Project in 2002. The aim of this project is to distribute biological resources of the highest quality by 2010. The first term ended in 2006, but it will continue through a second term to 2010. Twenty-eight bioresources were selected for the project: 10 mouse and 9 plant bioresources, and 9 microbes and cell lines and others. RIKEN is responsible for five of these. These projects are run by a government committee and evaluated by an external review committee.

With respect to mouse strains, we now hold over 3,200, a quarter of which are traditional inbred or mutant strains, a quarter are transgenic mice, and a

quarter are knockout. About 20% are ENU (ethylnitrosourea) mutants, developed by RIKEN and the Korea Institute of Toxicology, and 3.5% are wild-derived mouse strains, which are unique to our bioresource center. Because of the genetic diversity of the commonly used laboratory mouse these mice are very useful for dissecting gene functions. They are also very popular with overseas users.

In addition to mouse resources, the RIKEN BRC distributes embryonic stem (ES) cell lines from C57BL/6 and in some of these the germline transmission is confirmed. RIKEN also has ES cells of inbred strains from nuclear transfer, mouse induced pluripotent stem (iPS) cells (as well as human iPS cells, developed by Dr. Yamanaka). In addition, 369 ES gene-trap clones and the *Mus musculus molossinus* (MSM) wild-type-derived mouse BAC (bacterial artificial chromosome) library are distributed from the gene bank at our center.

From 2004 to 2008, nearly 8,000 shipments were made, with 80% for domestic use and about 20% for international use. We distributed to over 20 countries; the most frequent users are the United States overall and Korea in Asia, followed by Germany and Belgium. Minimizing the shipping time for embryos and sperm is very important since they must be kept frozen. International shipping times range from 30 hours (China) to 81 hours (Italy); the longest shipping time to the United States is over 60 hours to Oregon. All mice are transported safely, but the cost of shipping the mice is unacceptable. Since international shipment of mouse strains is expected to increase drastically in the next few years, more economical transportation is needed for the global scientific community.

As a member of the Federation of International Mouse Resources (FIMRe), RIKEN can help to rederive a mouse strain sent from somewhere else in the world. For example, we help Japanese scientists with material from the Mutant Mouse Regional Resource Centers (MMRRC) or Jackson Lab.

For the RIKEN repository, the quality control of mouse strains is most important from deposition to distribution. All mouse strains are tested for microbial infection status and according to their status are housed in positive- or negative-pressure rooms for breeding. All mouse strains received are cleaned up by caesarean section or IVF. After confinement, if they are negative for all microbes, they go to a barrier facility for further production. Mice are tested for eight most hazardous microbes and viruses when they arrive and also bimonthly. Seven additional microbes and three parasites are tested for bimonthly. Three microbes that cause opportunistic infections are also tested bimonthly. Eight other viruses are tested at the request of our users. It has been very difficult to agree on a list of microbes to test since the infectious status is different from country to country and continent to continent. However, if cross-border shipping is going to increase, a list of minimum testing should be agreed upon by international mouse repositories.

Genetic quality control is also important. Our facility does allele-specific PCR and the genetic background is monitored by microsatellite markers. It is

important to have a uniform background, since the background of the mouse strains influences the phenotypes.

Since we have so many mouse strains to be developed, cryopreservation is very important. We now have 2,000 strains frozen as well as a backup facility 700 kilometers from the main campus, since Japan is an earthquake-prone country. Although shipping frozen material in a dry shipper is cheaper than shipping live mice, it is still expensive. We conducted a test with the MRC in the United Kingdom where we froze mouse testes at −80°C and shipped them to RIKEN in dry ice. We then rederived the mice by microinsemination. This process can cut the cost of the shipping but the facilities must be familiar with the technique of microinsemination.

Another function of our facility is providing training courses. The courses we currently offer are

- Experimental Animals: Cryopreservation of Mouse Embryos and Sperm
- Experimental Plants: Culturing Method for Plant Cell Lines
- Genes: Recombinant Adenoviral Vector
- Microbes: Culturing and Preservation Method for Anaerobic Microbes
- Terminal RFLP[1] Method for Analysis of Intestinal Bacteria

These courses are offered to universities, nonprofit institutions, and for-profit institutions. We also have international trainees from other places in Asia.

Finally, I would like to talk about our collaborations with Asian institutions. We have bilateral memoranda of understanding (MOUs) with institutes in China, Korea, and Taiwan. Based on these MOUs, the scientists come into our center and our fellows go to their country to teach the techniques.

Also, three years ago the Asian Mouse Mutagenesis Resources Association (AMMRA) was created to promote the mouse mutagenesis project and facilitate access to mouse strains in Asia. Its goal is the use of mouse models for understanding the genome function and improvement of human health. The first meeting was held in 2006 in Shanghai, the second in 2007 in Nanjing, and the next will be in Korea.

[1]RFLP, restriction fragment length polymorphism.

Repository Issues—Lessons Learned

James Womack

This presentation will be in two parts. First, I will convey information I have learned from workshops similar to this, as well as some reports and recommendations, and evaluate how well we have been able to implement the past recommendations. Second, I will describe a positive lesson learned in my laboratory, which shows the value of repositories specifically. This was not with transgenic or genetically modified animals but a very valuable rat strain that was produced in the old-fashioned way.

The need for genetic repositories has existed for 100 years. When Little, Castle, Wright, and others started making inbred strains at the beginning of the last century, it was obvious that the years of breeding and the amount of money that was put into making an inbred strain of mouse certainly could not be wasted by letting that strain become extinct. Consequently, places like the Jackson Laboratory and later commercial institutions, such as Charles River, Taconic, and others, have served as repositories for these valuable strains.

The need for live animal repositories has now been replaced by cryopreservation technologies developed over the last 50 years. In 1990, the ILAR Committee on Preservation of Laboratory Animals was convened to discuss what could be done with repositories. Basically, the discussion addressed what could be done best with live animal preservation versus cryopreservation? A very nice set of recommendations resulted from the deliberations and appeared in *ILAR News* No. 32.

Although we had begun making transgenic mice, this was well before gene knockout technology was developed. At that time, there was no idea what a germplasm repository might look like today.

With the advent of genetic technologies, the NIH, through the NCRR and Child Health and Human Development, convened another workshop last year. The goal was to reexamine repositories for germplasm in light of what was on the horizon from genetic modification and all of its implications. The recommendations from that workshop were:

1. Encourage the development of high-throughput and scalable technologies for germplasm collection, evaluation, processing, and cryopreservation;
2. Establish multidisciplinary teams to develop new approaches to the collection, cryopreservation, and distribution of germplasm for high-priority translational species;
3. Support research on the biosecurity of cryopreserved animal germplasm, and the detection and elimination of laboratory animal pathogens that might compromise research findings;
4. Support research to address long-standing bottlenecks to cryopreservation of animal germplasm, such as cold shock, chilling injury, protocol optimization, male-to-male variation; and
5. Support novel "high-risk/high-return" preservation technologies that are not dependent on freezing or cryopreservation and break new ground.

In looking at the recommendations one notices that informatics and databases are never mentioned, even in 2007, when it was obvious that the numbers of unique germplasm resources would eventually number in the tens of thousands. We have already achieved these numbers with mice, but there is also a zebrafish mutagenesis project and the technology is beginning to be developed in rats. There will be tens of thousands of unique germplasms and yet not much attention has been given to the development of informatics and databases.

In my view as a user, this is a bottleneck. While the conclusions from the workshop were to make the biological materials readily available to biomedical investigators at low cost, most of us have no idea what is available. As we have learned from others at this conference, the major repositories for genetically modified mice—the targeted mutagenesis, the knockouts—are developing databases. But when you access them, if you know the name of the gene, you can find your knockout if it exists. However, if you are interested in a phenotype, as many of us are, unless these mutants are written up in a scientific publication that we can access through PubMed or some other way, they are essentially lost to the biomedical science community. The goal of most investigators is to learn which genes underlie a specific phenotype, thus they cannot search for a gene.

So as a user, my word of admonition would be that we look seriously at the future needs in informatics and databases to support these tens of thousands of mutant mice, rats, zebrafish, and any other species that will be included.

Two ILAR resources that are simply catalogues should be highlighted here. The first is a catalogue of available databases and search engines that each of the repositories has put out. This is a very useful place to begin searching. Second, ILAR has an animal model search engine, which begins to address some of the phenotypic information. However, the point remains that our ability to make useful laboratory animal resources is outstripping our database development and capacity at this time. Those of us who use resources may very well be located close to a resource that we need and never know it.

The second part of my presentation consists of a quick real-life story—a positive one. It does not involve genetically modified mice but a unique germplasm resource. It is a nice story that is not quite finished.

Rift Valley fever is an infectious disease caused by a bunyavirus. As the name indicates, it was identified in the Rift Valley of Africa and the virus is mosquito borne. In the cycles of flooding that very often occur in central Africa and into the sub-Saharan region, there are extreme epidemics of Rift Valley fever. Tens of thousands of livestock are killed as well as some humans, although the human death rate is usually low. But the livestock industry is devastated.

C.J. Peters, who was at Fort Detrick in Frederick, Maryland, in the 1980s, isolated some of the major strains of Rift Valley fever virus and did some laboratory animal experiments. When he did a strain survey of rats, he found that the Lewis rat strain was resistant to the Rift Valley fever. All other strains that he infected died within several days.

In doing some simple genetics (i.e., typical backcrosses), the resistance segregated as a simple Mendelian trait. Resistance was dominant to the susceptibility in all of the strains. He then made a congenic strain—he backcrossed Lewis onto a Wistar-Furth background, each generation selecting after challenge, over a period of about three years, in which the resistant gene from Lewis had been placed on the Wistar-Furth background.

For a variety of reasons, funding was stopped. The NIH was not particularly interested in a livestock disease in Africa. C.J. put his congenic strain down as a frozen embryo resource with the animal germplasm resource bank at the NIH. It later was moved to the Rat Research and Resource Center at the University of Missouri where it sat for 15 years.

After 9/11/01 many things in this country and around the world changed, including some of our research interests. Suddenly we became concerned about biological terrorism and agricultural bioterrorism. Rift Valley fever was targeted as one of the diseases that we should learn more about because, if introduced accidentally or intentionally into this country, it would have a devastating effect.

Fortunately, C.J. had published a paper—through PubMed we were able to find that he had made this congenic strain of rat resistant to Rift Valley fever—and he is still doing research and was available. It was through personal communication that I learned that he had had the congenic strain frozen.

When I contacted the NIH and they directed me to the University of Missouri, I was told that, yes, the embryos had been there. They had been frozen for 15 years, and they could be brought out.

Genomic resources had changed tremendously in 15 years: now we had a gene map of the rat, DNA-level markers, and microsatellites that enabled us to do things that C.J. and others could not do back in the 1980s.

While the embryos were being rederived, we took a piece of tissue from these congenic strains and very quickly did a genome scan with highly polymorphic microsatellite markers. We tested across the genome with markers that had a high probability of distinguishing Wistar-Furth alleles from the Lewis alleles.

Then we found that some of these were monomorphic as far as Wistar-Furth and Lewis were concerned: they carried the same allele.

When we looked at the congenic strain, even before the embryos had been rederived, we found Lewis markers on chromosomes 9 and 3. So in making the congenic strain, C.J. and his colleagues had incorporated the Lewis genome into the bottom of chromosome 3 and up near the top of chromosome 9. The question, of course, at this point is, Since it behaves as a Mendelian single gene trait, which of these two sites is actually the gene and which may be the hitchhiking material? We did a quick cross and determined that, in fact, it was the bottom of chromosome 3.

To date we have narrowed it down to a little bit more than a megabase. Almost all the genes in this region are transcription factors. We are now in the process of finding which of these is responsible for conveying the total resistance to the virus to the Lewis strain.

In summary, this is a model that was developed as far as the technology would allow in 1990. The investigators had the foresight to cryopreserve something that they no longer had funding to work with but felt was important. The technology and the repository for cryopreservation and maintenance and rederivation were all there and used very efficiently and very effectively.

Meanwhile, a tremendous battery of new genomic tools was developed. So when we rederived this model, we were able to narrow down to a megabase region and will very soon have the gene.

To go back to my original point, we found this model by good fortune. The phenotype was available in the literature and we found it by PubMed. But until we start getting phenotypic data into the databases that accompany many of these great repositories that we are seeing developing around the world we will not be able to use these resources to their full extent.

Transportation and the "Mouse Passport"

William White

In this presentation I will discuss the "mouse passport" and key issues in the transportation of rodents, and propose some recommendations to remedy looming problems. The mouse passport is a product of the UK National Center for Replacement, Refinement, and Reduction of Animals in Research (NC3Rs; www.nc3rs.org.uk). It is not actually a legal document but rather a "detailed packing list, with assembly instructions and an operating manual." The goal is to have a lot of information about the animals in one place. Some of the information in the mouse passport is nomenclature/lineage, background strain, number of backcrosses, whether it is inbred or outbred, type of mutant (knockout, chemical mutant, etc.), genotype, phenotype, immune status, animal husbandry details, breeding information, and special considerations.

It is important to provide enough details about genetically modified animals to establish a new colony. Often not enough information is included in publications describing the model. In my opinion, the current document needs further expansion to ensure that all the necessary information is captured; there needs to be a "fill in the blanks" approach to minimize subjective evaluations.

Moving to the subject of transportation, there are essentially two alternatives: moving live animals or some type of cryopreserved material. Embryos, sperm, and the like may be shipped, but the facilities at the receiving institution must be able to recover the live animal. This is an important consideration as is the health status of the animals in the receiving facilities. This process makes good sense if complex long-distance shipment is required. Rodent germplasm is transported in liquid nitrogen dry shippers, which are approved for air transport. Shipping frozen material minimizes health risk at the receiving institution. However, there are some drawbacks, particularly in terms of time. When germplasm is shipped, there is a time delay until founder animals are generated, typically about five weeks. There are certainly variable recovery rates, which means more material must be shipped and more implants need to be done. Shipping of frozen resources also assumes that the institution can recover and maintain the animals at a desired health status. And if the animal is reconstituted at a repository, live animals may still need to be transported somewhere.

The key to shipping live animals is knowledge about the system and thoughtful planning. Whether the animals go by air or by truck, across a few states or, in Europe, from one country to the next, it is necessary to anticipate what might go wrong. It is critically important to understand the transportation system. Animals are being put into air commerce that moves a lot of other material, and animals tend to be at the bottom of the list in terms of volume and economic value. Therefore, it is up to the shipper to understand how things move from one point to the next and what the options are if shipments are to be successful.

Animals are transported in commerce every day, particularly laboratory animals between institutions. But the total number of all animals shipped represents a tiny fraction of all goods that are moved—well under 1%. By and large, the journeys are successful. That, obviously, depends on your measure of success. If the shipment is delayed a day, but the animals are still in good condition, it may still be considered a failure because it didn't come on time. The overall transportation failure rate (even if the failure was not directly due to transportation), based on statistics from breeders, is about 0.07% out of about 2 million containers. This is almost equally split between air and land transportation (about 0.035% each). Involved in the failure rate is any condition that might be cause for rejection upon receipt—even the wrong sex of animals in the box or only one animal with an abnormality out of a group of animals in the container.

Many factors can affect ground transportation, but the most frequent is temperature control related to the thermodynamics and ventilation in the cargo compartment of the aircraft or vehicle. These parameters are based on how containers are loaded and the type of containers used, coupled with the animal mass in the containers. These factors influence the ambient environment surrounding the container and the effective ambient environment in the container, which affects the animals.

HVAC (heating, ventilation, and air conditioning) systems are not capable of rigid temperature and humidity control for a wide range of ambient conditions. These systems can break down; some companies use redundant HVAC systems in case of that happening. However, if the system breaks down in the middle of Montana, chances are slim for finding a place to repair it. Available ground transportation carriers may be regional or long distance in the United States and in Europe. The problem is there are not many choices because it is not a big business.

Another factor to consider is that commercial carriers may transport other perishable and nonperishable cargo from multiple institutions along with the animals for all or some of the journey. While the use of a dedicated truck is possible, it is expensive ($1.50 to $3.00 a mile a few years ago, charged on a round-trip basis). A shipment of animal containers large enough to fill a tractor-trailer driven across the United States costs about $20,000. Those prices have increased between 15% and 25% due to fuel charges.

Only 40% of the commercial air fleet in the world is capable of carrying animals and not all compartments in an aircraft may have appropriate environ-

mental controls. In a 747, the first two compartments are incapable of carrying animals; only the three compartments in the back can carry them, but this varies with the aircraft. Another problem is that there are mixed loads. For example, if several containers of rodents are shipped in the same compartment with a cargo of flowers that needs a lower temperature, the carrier will try to select a temperature range that is acceptable to all of the temperature-critical cargo. It is not possible to dictate tight temperature ranges or the animals will not fly.

Another issue with air transportation is that there is always a ground component. If arrangements have not been made to retrieve the animals, they might languish in the customs warehouse for quite some time.

With regard to air transport, it is important to remember the following:

- It is the fastest way to transport, even when there is a ground component.
- Live animal shipments account for less than 0.1% of all air cargo, and lab animals are an even smaller fraction of that.
- It may be necessary to enclose as many as 39 separate documents for transport under certain conditions; generally, however, it is less than a third of that. Errors and missing documents can stop or delay the shipment. When the carriers cross borders, if everything isn't there, the shipment will not move.
- There is limited liability in air cargo. If two mice have an estimated value of $10,000, the airline is only liable for $100 if something goes wrong. You need to have other insurance to cover any loss.
- Many factors can affect air transport of animals. Pilots or airlines can refuse to carry animals. Some things, like the mail, human remains, domestic farm animals, etc., can bump lab animal shipments. So even though all the arrangements are made, there is no guarantee that the animals will be transported as scheduled.
- The shipper is ultimately responsible for the microbiological status of the animals transported by air or land. It is the shipper's responsibility to pack the animals in a microbiologically secure container to prevent contamination in shipment.
- Similarly, the shipper is responsible for escaped animals. Animals can chew out of containers, particularly those being reused. Escaped animals have grounded 747s and the shipper must pay the per-hour charge while the plane sits on the ground until the animals can be retrieved and any damage to the plane repaired.
- Anticipate weather delays, temperature embargoes, and canceled flights. If a huge snowstorm is coming to Chicago and the shipment is going to be routed through it, don't start the journey.

Some things are important to keep in mind regarding any animal transportation:

- Once an animal leaves your institution, you have limited control over the environment and handling.
- The only way to minimize the risks in shipping is by journey planning and anticipation of potential problems. It is important to evaluate the risks and act accordingly.
- Animal transportation is highly regulated. It is important not to make any assumptions about what is needed, especially when shipping internationally. These rules change regularly. The International Air Transport Association (IATA) revises the Live Animals Regulations (LAR) yearly, and publishes the Air Cargo Tariff (TACT) book, which is updated every 6 months and contains the tariffs and shipping standards.
- Animals will experience some stress in transit but there are too many variables to precisely control it. Occasionally, animals will become sick or die either during or after transit, which may or may not be the result of errors in transit. Working with the transportation provider and collecting and analyzing the facts, and not making assumptions, can help in developing preventive action to lessen the chances of recurrence.
- When receiving animals, assume that the outside of the container is contaminated and take appropriate steps. The outside of the box should be disinfected.
- Separation of species during transit is not achievable. You are going to be in the same microbiological space. Rodents from multiple sources may be transported in the same van delivering animals to and from the airport.

When shipping genetically modified (GM) animals, some countries require special documentation and approval to enter or move within the country. Occasionally, a phenotype can make the animals less tolerant of transport conditions or the animal might have special requirements. It is important to remember that there will not be precise temperature or other controls en route. However, in most cases, these animals can be shipped as normal animals, as long as there is no overt disease or debilitating phenotype. GM animals are not considered dangerous goods by airlines or other groups. There may be specific regulations in countries as to classifying and handling them, but as far as transit goes they are not considered dangerous goods.

Authoritative references and shipping documents include the TACT book and LAR produced by IATA. IATA's Live Animals and Perishables Board sets the standards for air transportation, which are followed by 260 airlines. Many governments and international bodies use the LAR as the primary transportation standard.

It is essential to comply with the receiving country's requirements, which may be determined by calling the consulate or through an export agent or your consignee. It is best to have the receiving party coordinate documentation and the ground transportation.

To minimize problems:

- do not reuse shipping containers;
- plan for at least 24 hours in delay;
- ship at the beginning of the week and remember to consider holidays—many people do not work on Saturdays and Sundays, and holidays may differ depending on the country;
- develop a detailed journey plan;
- don't transport during temperature or weather extremes;
- arrange for airport pickup by the consignee; and
- use the most current editions of resources such as the LAR.

There are ways to make live animal transport work more safely and efficiently in the future. It is better to ship germplasm if possible, but if it is necessary to ship live animals certain things are needed.

The scientific community needs to engage the air carriers through IATA on issues of air carriage of lab animals. This should be done by building a relationship with a sustainable commitment to a continuing dialogue. It is not enough only to complain when there is a problem. To assist IATA and to cultivate a relationship with the carriers, it is necessary to develop proactive materials to present to the heads of airlines that help reinforce the concept that laboratory animals are important to the biomedical research community and are a legal and essential cargo.

It is important to have a strategy and structure on which to base this interaction, perhaps under the umbrella of a scientific organization or a consortium of organizations. This should be international in scope, which may suggest a role for the OIE. You need the participation of multiple stakeholders, not just a couple in one country.

Training materials for all those involved in the shipping of live animals are advisable. It is our responsibility to provide access to correct practices and help carriers to better understand the needs of the animals they are shipping. To this end, IATA, in conjunction with ACLAM, has produced an interactive DVD aimed at shippers of rats and mice that will be released shortly. IATA also has formal training programs for air carriers. However, collaboration there could be helpful. A similar program for ground transportation carriers is needed.

Another resource that is needed is an electronic master system for preparing required documents for international and national shipment, somewhat akin to a tax preparation program. The user enters certain required information and the system selects all the required documents and fills them out. Such a system would avoid a lot of delays in shipping. However, it needs to be developed in a way that allows it to be continually and rapidly updated. It might start with rodents, but then expand to some of the other common laboratory animals. It would need to be maintained by a stable organization and underwritten by fees and/or grants. The same system could assist in journey planning and provide worksheets to guide shippers through the required steps and considerations before putting the animals into the system. A system like that has actually been

developed in Germany; unfortunately, the author of that computer system suddenly died and it is no longer available, but it should be pursued again.

Another helpful resource would be the implementation of an "e-freight" system for lab animal shipments. This would allow all documents required for a shipment of animals to be paperless and to be sent for preapproval to catch any errors that might halt or delay shipment or importation. It would also address the issue of losses in shipment. This sort of system is being worked out for other types of air cargo. IATA is very supportive, and if the scientific community were to do the same and worked with them in developing it, it would go a long way in reducing errors in shipment.

Another consideration is the development of government-supported, academic-based, and commercial nodes for streamlined movement of animals. This would require a lot of organization and would need a variety of alternatives. Some of this is already available on a commercial basis and by cooperation between repositories. Key issues here are funding and access. In addition, there must be allowances for protection of intellectual property and downstream liability for errors in the process.

Last, there is the cold chain process used for shipment of critical products and ingredients. This monitoring process involves looking at the temperature and other environmental conditions of materials as they move through the transport system. Much of the information about transportation failures, especially with ground transportation, is anecdotal. An effort to proactively track environmental conditions and to work with transporters could be very helpful. This may be done with devices like the TurboTag, which will do 700 interval recordings of temperature and can be disinfected and reused. It is read with an RFID (radio frequency identification) reader and the readings are downloaded into an electronic record. Each TurboTag costs about $20; the reader is about $75. We have started putting them throughout shipments to look at airflows and temperature mapping. They will help us to get a better understanding of where failures are and how we can prevent them.

International Coordination of Nonhuman Primates

Framing the Issues

Joseph Kemnitz

We are entering a very exciting era indeed of discovery in nonhuman primate (NHP) research, which I will illustrate with a few points.

The emphasis on translational research during Elias Zerhouni's tenure as director of NIH has certainly stimulated interest in the pathway connecting basic science to human health, not only in the direction of basic to human but also taking information from human clinical work back to animal models and to the bench. NHP research does not represent a wayside in this highway but rather is often an essential vehicle in the process of transferring information from one end of the spectrum to the other.

A second point worth mentioning is that the genome of several NHP species has now been sequenced, with more to come soon. The -omics associated with this are developing very rapidly. The study of genes, proteins, and biochemical reactions in complex primate organisms is enormously exciting at this time.

Being from the University of Wisconsin in Madison, I am personally very excited about the potential application of embryonic stem cells and induced pluripotent cells to alleviate human disease. [But] before transplant therapies can be applied in humans, a great deal of work must be done in nonhuman primate models.

Much work also needs to be done in the realm of vaccine development for HIV, flu, and other viral diseases. The HIV vaccine summit last spring pointed to the need to step back from clinical trials and redouble efforts using NHP models, which will, of course, increase the demand on our animal resources.

Finally, the development of informatics and information technology systems now can enable better organization, management, and sharing of data and dissemination of new knowledge from these studies. This is contributing to the overall excitement in the field.

This era must be enabled by careful consideration of several issues and overcoming current obstacles. The identification of appropriate species and the supply of these species need careful attention. Identifying sources of animals of specific species, characterizing these animals in terms of genetics and their backgrounds, and ensuring quality control in terms of viral status are all impor-

tant issues for animal health, human occupational safety, and efficient use of these animals in studies.

Forecasting needs must be done in terms of not only species but also the important characteristics: age and sex. To emphasize the age aspect, in studying diseases of aging and processes of aging in rhesus monkeys, we must keep in mind that it takes 25 to 30 years to grow an aged rhesus monkey. That fact is sometimes lost in discussions of supply-and-demand issues. One cannot make short-term shifts in trajectories in managing the supply of nonhuman primates.

Deliberate action pertaining to identifying needs and careful management of primate resources along these lines constitutes refinement, in itself, and will enable achievement of research goals with fewer animals in the long run. It will also lead to financial economy in this endeavor.

Given the globalization of the effort in primate research, and the practicalities of the work, such as transportation of animals and biological materials, it is increasingly important that we consider local, national, and international policies and politics. The next presentations will address many of these points.

SUPPLY AND USE OF NHP AROUND THE WORLD

The United States

William Morton

My presentation will focus on the use and numbers of nonhuman primates (NHP) in research in the United States. To determine these numbers it was necessary to visit a lot of regulatory agencies—including the CDC, USDA, and NCRR/NIH (for chimpanzee data)—and Indonesia. The bottom line is that it is very difficult to quantify this in any meaningful sort of way. It seems that nobody really has the number of nonhuman primates that are used in research. In addition, different organizations and agencies count these numbers in different ways.

In some instances, it was necessary to go to the animal rights groups or to Wikipedia to find out numbers. After averaging all the numbers, the total is approximately 70,000 to 75,000 nonhuman primates each year, and that includes all types of use, whether they are being bred or held or actually used in research.

The CDC has 27 different registered NHP importers in the United States (information provided with the assistance of Bob Mullan and Gail Galland). In the early days of this field, there were over 100 importers of NHP, suggesting that greater regulation has resulted in fewer animals being imported. It is interesting to note that nearly half of these importers are commercial importers, with the rest scattered among zoos and academic institutions.

CDC has requirements for licensing a facility. All NHP are required to stay in a federally registered quarantine for at least 31 days before they can be transferred to another institution. Most institutions quarantine them for a longer period of time.

One of the confounding regulations was the requirement for records on these primates as they moved from the initial importing institution to other institutions. The importing institution has to document whether the animals are being held for scientific, exhibition, research, or educational use and that wherever they send the animals will likewise register in the same category. The intent is to keep these animals out of the pet trade. The CDC inspects facilities, reviews

import plans, monitors arriving shipments, assesses disease control measures, reviews animal health records, and investigates illness reports.

The data on NHP importation from 1994 to 2007 show a continual increase. In 2005 to 2007, the last three years for which data are available, the number rose to over 25,000 or 26,000 primates per year being brought into this country. This suggests a greater use of nonhuman primates in the United States. If the data are broken down further one finds that over 93% of imported NHP are *Macaca fascicularis*, or cynomolgus; 5% are *M. mulatta*, or rhesus, probably from China. The rest are scattered among other species.

If one looks at the data by importer, each importer brought in from one to over 10,000 animals, with the number of shipments per importer ranging from one to 70 a year. A significant statistic is the percentage of dead-on-arrivals: zero to 0.2%, which is very low. This is a huge improvement from many years ago when a 10% to 15% mortality rate was considered good. Reportable illnesses are very low now as well.

Looking at the importation data further, 60% of these animals are coming from China, followed by Vietnam and Mauritius. Over 85% of the animals are coming from three countries.

NIH (through NCRR) supports eight national primate research centers, which collectively contain almost 28,000 nonhuman primates, with the majority being rhesus monkeys. It becomes clear that it is the rhesus monkey that is used in research, not *M. fascicularis* (cynomolgus). Cynomolgus monkeys are used by commercial industries, pharmaceutical industries, or CROs for toxicology, efficacy, safety, and pharmacodynamics.

NCRR is moving toward the development of so-called specific pathogen–free colonies, which consist primarily of rhesus colonies, *M. mulatta*. Those colonies are primarily SPF-4, meaning they are free of SIV, STLB, SRV, and herpes B. There are other colonies called "superclean" that have even more viruses eliminated, such as cytomegalovirus, foamy virus, and perhaps others. At this point, roughly 5,000 rhesus monkeys in SPF-4 colonies are being produced for research by investigators throughout the country. There are plans in the national primate research centers program to create even more SPF colonies in the years to come.

The major types of research conducted at the primate centers are AIDS and other infectious diseases: these account for over 40% of research activity. Neurobiology research is also prevalent, at almost 20% of activity, and various other areas make up the rest.

Many specialized resources emerge from primate center programs. Perhaps one of the more important ones is the NHP tissue program, from which over 42,000 primate tissue samples, organs, genetic samples, cells, fluids, and more are supplied to investigators throughout the nation and internationally.

USDA annual reports provided information about how many primates were in use in registered facilities throughout the United States. There are roughly 46,000 or so NHP listed in these reports, either in column B (used for breeding) or columns C and D (used in research, in situations where there is no

pain, momentary pain, or pain alleviated with analgesia). Interestingly there were no reports of animals in column E (unrelieved pain and/or distress). This is difficult to understand since there are clearly projects going on at various facilities that fall under column E.

In summary, based on these and the previous data, an estimated 70,000 to 75,000 primates are used in research.

Now I will address the use of chimpanzees, and I would like to acknowledge the contribution of Tom Butler for the information I will share with you. The most important thing about chimps is that they share roughly 98.5% of their DNA with humans. Therein lies both the benefit and the curse of the issue of chimps in research, and there are many different thoughts about whether or not they should be used for this purpose.

Using chimps means increased expense due to the need for larger cages, larger facilities, stronger people, and more educated people. Six centers in the United States maintain chimpanzees: the Southwest Foundation for Biomedical Research (San Antonio, TX), Michale Keeling Center for Comparative Medicine (Bastrop, TX), New Iberia Research Center (Louisiana), Yerkes Primate Center (Atlanta, GA), Primate Foundation of Arizona (Mesa), and Alamogordo Primate Facility (New Mexico). All but the last two conduct research on chimpanzees.

The population of chimpanzees is continually declining.[1] From the latter part of 2006 to the first part of 2007, there was a decline of nearly 100 animals or almost 10% of the chimp population. The population has been declining primarily for health-related reasons. Another consideration is that about half of the animals are owned or subsidized in part by the federal government, which traditionally does not make these chimps available for research by private industry.

A key factor is animal age. The desirable age for chimps in many research projects is roughly up to 21 years of age, which is about the time health problems begin developing, particularly cardiovascular problems. As of 2008, only about half of the US chimp population was below the age of 21, further accentuating the declining usable numbers of chimps for research. Given the current rate of decline, the number of chimps for research will be close to zero by the year 2030. While age can exclude chimpanzees from use in research, other factors to consider in choosing animals include behavioral characteristics, health status, experimental history, and current research.

So there are very few chimps available for research in the United States. Yet there are those who insist that the chimpanzee is the only animal that can be used specifically for pharmacodynamics in a way that the human is used, to test monoclonal antibodies. Many of these monoclonal antibodies cannot be tested in other warm-blooded mammals or in other NHP species because they are elimi-

[1]Data in this and the next paragraph are from an unpublished workshop presentation by Thomas Butler, DVM, DACLAM (currently Chair of the Board of Directors of Chimp Haven in Keithville, LA), "The Future of Chimpanzees in Biomedical Research," on October 17, 2007.

nated very rapidly. The chimp is the only animal that processes these monoclonals in a way that they can be tested.

Vaccine development is another huge concern in considering research on chimpanzees. The chimpanzee was integral to development of the hepatitis B vaccine and is used to make improvements in it. In addition, it is the only known animal model for hepatitis C and is being used in attempts to develop a hepatitis C vaccine. However, it should be noted that in the early days of AIDS researchers thought chimps would be extremely valuable, but that was not the case.

In terms of emerging infectious diseases, many scientists feel strongly that the chimpanzee should not be allowed to disappear from the US research scene. Some argue that it would be foolhardy to let the chimp population disappear and then need the animals again for future critical research.

In 1997 the National Research Council published a report that set the stage for the future of chimps with regard to breeding (*Chimpanzees in Research: Strategies for Their Ethical Care, Management, and Use*). The breeding ban for chimps in federally funded facilities continues today. The report also recommended that euthanasia not be allowed for population control. Along with this, there was a suggestion that a national chimpanzee sanctuary facility be created; Chimp Haven, in Shreveport, Louisiana, took in its first animals in 2005 and now houses about 110 chimps in retirement. Although the NRC report recommended that there be 1,000 chimps available to meet current research needs, there would need to be 60 births per year. With the federal ban on breeding, there are only about 15 births per year at privately held facilities. Because the population of chimps is aging, it seems certain that the numbers will continually decline. In addition, most chimps have been used for experiments, so there will be virtually no naïve animals for future studies.

In the last part of my presentation, I would like to highlight Indonesia, a typical exporting country for NHP. Most people in the United States are unaware of Indonesia, yet it is the fourth-most populous country in the world, made up of 13,000-plus islands, and home to numerous species of nonhuman primates, including vast numbers of *Macaca fascicularis*. Much of the following information was obtained from the Indonesian quarantine group, which is responsible for export.

Between 2004 and 2007, there was a rapid increase in the numbers of nonhuman primates exported. Most have been going to China, which is rapidly becoming the giant in terms of NHP use as well as NHP export to the United States and other countries. In China, and to a lesser extent in Indonesia, primate centers and research centers are being built. These countries will no longer want to supply NHP to the US and other countries as they will want to develop research enterprises in their own countries. Many people from those countries have been educated in the United States and Europe and are beginning to feel ready to do research back home.

For example, the Bogor Primate Research Center in Indonesia has the capacity for many major types of research procedures, including those that involve ABSL-3 facilities. Many cutting-edge research projects are ongoing in conjunc-

tion with laboratories in that country. The center has virology labs that are as large and as well equipped as those in the United States. This is happening because the Indonesian government and others have invested money and training and now they are prepared to undertake research projects on their own. These types of activities are occurring in many other countries of origin of NHP. These countries are very capable and they are looking to increase these activities.

I will conclude by explaining why there is an increase in NHP exportation. Breeding colonies are developing everywhere in Indonesia because new laws prohibit the exportation of feral animals. Countries of origin such as Indonesia, China, India, and others will be requesting outsourcing of research from the United States.

In summary, obtaining accurate numbers of NHP used in research is difficult at best, but the trend is increasing, not decreasing. The need for research using chimpanzees remains controversial, but they will continue to be used at least in the short term.

I would like to thank Bob Mullan and Gail Galland from CDC, John Harding from NCRR and NIH, Tom Butler for giving me the chimp data, Joko Pamungkas and others from the Bogor Primate Center and the quarantine division of the Indonesian governments, and Pam Ferguson and Patti Rosendahl from Paris NHP.

China as a Resource for NHP

C.K. Hsu

In this presentation I will highlight how big the Chinese nonhuman primate (NHP) production capability is, the quality of the animals, animal welfare considerations, and how the animals are exported worldwide.

China has been a leading and major supplier country for NHP, not only to the United States but to Europe, Japan, and now to Korea. The numbers of NHP used by various countries in 2002 and estimated for 2007 are 52,000 and 59,000, respectively, by the US[1]; 4,000 and 5,000 by France[2]; 3,000 and 4,000 by the UK[3]; 2,000 and 3,000 by Germany[4]; 2,000 and 3,000 by Canada[5]; and 3,000 and 5,000 by Japan.[6,7] China has also been exporting NHP to the Netherlands and Spain and, particularly in recent years, has been exporting macaques to Canada.

[1]Data extrapolated from USDA Report of Animal Welfare Act in these two years.

[2]The numbers of NHP used in France were extrapolated from Chinese suppliers/breeders and the report from the European Commission to the Council and the European Parliament on Statistics on the Number of Animals Used for Experimental and Other Scientific Purposes (2002). I also referred to the Ethics of Research Involving Animals, Appendix 2: Statistic-Research Involving Animals in the UK, EU, USA, and Japan.

[3]The numbers of NHP used in the UK were extrapolated from Home Office (2004) Statistics of Scientific Procedures on Living Animals Great Britain 2003 and from other sources, including the Ethics of Research Involving Animals, 2005.

[4]The numbers of NHP used in Germany were extrapolated from Chinese export sources and from the European Commission report cited above.

[5]The numbers of NHP used in Canada were extrapolated from Chinese export data and a personal survey of Canadian importers.

[6]The numbers of NHP used in Japan were extrapolated from Chinese exporters' information as well as information provided by Japanese users and from Chinese government records. I also referred to a survey from April 2001-March 2002, performed by the Committee for Laboratory Animal Care and Use (2003).

[7]Author's note: The UK, France, Germany, Canada, and Japan do not have yearly compulsory reports on the use of laboratory animals like the US. I believe that the extrapolated numbers of NHP used in 2007 in these countries are fairly close to the reality.

If one looks at the total number of the macaques imported into the US in 2006-2007, the number was higher in 2006.[8] In 2007, 27,000 macaques were imported, of which cynomolgus constituted 93% and rhesus only about 5%. Based on the data from Asia that Dr. Morton presented, almost 25,000 NHP were imported from Asia, representing 93% of the total NHP imports worldwide to the United States for research use.

Specifically looking at China over the past two years, in 2006 the US imported about 11,000 cynomolgus monkeys and about 1,400 rhesus, and in 2007 about 15,000 cynomolgus and 1,350 rhesus.[9] As a clarification, cynomolgus monkeys are not native to China. They have come into China from various countries in Asia. Of the cynomolgus monkeys imported in the US from Asia in 2007, 68% are from China compared to 13% from Mauritius. Imports from Cambodia, Indonesia, and the Philippines are rising.

In the past two to three years, Chinese breeders have imported a large number of cynomolgus monkeys from Cambodia. The Chinese government exerts tight control and either restricts or approves the process. For example, in order to import 2,000 or so of the animals by charter from Cambodia to China, it is necessary to acquire an import permit, which usually takes about six months. During this process, the government, both local and central, sends representatives to a region or supply farm for inspection. They check on the number and quality of the animals and whether they are wild-caught or purpose-bred animals.

In the past three years, China has increased the number of breeders. All the primate breeding facilities must obtain a license for production of the nonhuman primates through the Bureau of Wildlife Protection and Conservation in the central government. They must also be approved by a similar office in the provincial government. The government does not allow breeders to sell their animals for up to six years from the start of the facility. Many want to know how many NHP facilities there are in China. There are 32 "qualified" facilities in China, meaning that the facilities are monitored for the number of animals and their quality. Of these facilities, in 2008 23 of them were able to sell/export cynomolgus monkeys and 16 of them rhesus. Some of the facilities engage in cynomolgus monkey breeding only, some of them have both cynomolgus and rhesus, and some of them breed only rhesus monkeys.

Among the 32 NHP facilities half of them are large, meaning they have over 10,000 animals. Some of them are medium-sized or small, with 5,000 to 9,000 animals.

[8]The total number of the macaques imported into the US in 2006-2007 was obtained from the CDC presentation at the annual Conference of the Association of Primate Veterinarians.

[9]The numbers of cynomolgus macaques and of rhesus macaques were from CDC reports at APV meetings.

The number of the facilities has been increasing because there is a perceived increasing demand for macaques and particularly for cynomolgus monkeys.

China has a commercial quota system. Toward the end of each year, the Bureau of Wildlife Conservation and Protection as well as the provincial government and an ad hoc committee visit each facility and count the animals in terms of how many young, the ages of the animals, and the total number of breeders. Based on this information, they assign each facility the number of animals allowed to be commercialized (i.e., exported or used domestically in research).

From 2006 to 2008, the quota for cynomolgus production and sale increased. The quota for rhesus increased only slightly and most of the large facilities are not involved in the breeding of rhesus monkeys now.

It should also be noted that most of the breeding facilities for cynomolgus monkeys are in the southern part of China, and facilities for rhesus monkeys are mostly in the central or western part of China.

The number of breeding females in the 32 facilities was obtained from each facility as well as from government data. In 2008 there were about 62,000 breeding cynomolgus monkeys and 8,600 breeding rhesus monkeys.

About 18,000 to 19,000 macaques are exported from China each year and the mortality rate is very low, on the order of 0.06% in 2007. Transportation of NHP has not presented any problems in China. Several airlines—Air China, China Eastern, China Southern, and Hainan Airline—are willing to transport the animals from China worldwide—to the United States, Europe, Japan, and Canada. Since many of the animals come from the south of China, they are shipped from Guangzhou Airport. Animals are also shipped from Shanghai and Beijing. The major receiving airport in the US is Los Angeles, with the second being New York (JFK and Newark). Chicago and Seattle airports also receive animals. Thus, transport of nonhuman primates to worldwide places from China is not a problem.

In looking at the practices related to supply and quality of NHP in China, it usually takes about 2-3 months to obtain the commercial quota as discussed earlier. There is also a quarantine program that is very similar to that in the US for animals to be exported. The quarantine process lasts from 1½ to 2 months, during which the animals must receive three TB tests at two-week intervals and are also tested for various viral, bacterial, and parasitic diseases. China has very good diagnostic methods in terms of simian immunodeficiency virus (SIV) and B virus. However, since the US has the Virus Reference Laboratory (VRL), the viral status of animals imported into the US will be confirmed by the VRL. The animals receive vaccinations for measles and hepatitis A prior to export. Finally, each animal receives a certificate of health by the Provincial Administration of Quality Supervision, Inspection, and Quarantine (AQSIQ). Since 2007, the vast majority—about 90%—of animals are virus free. They also can be vaccinated upon request.

One issue I would like to address is the concern that China is not concerned about animal welfare. In fact, China has five regulations related to welfare of laboratory animals.[10] Violation of certain of these regulations carries a penalty.[11]

[10](1) Statute on Administration of Laboratory Animals (1988), issued by the Ministry of Science and Technology. (2) Project on Laboratory Animals during the Ninth Five Years (1997), issued by the Ministry of Science and Technology. (3) Guideline of Beijing Municipality on the Review of Welfare and Ethics of Laboratory Animals (2005), issued by Beijing Administration Office of Laboratory Animals. (4) Guideline on Humane Treatment of Laboratory Animals (2006), issued by the Ministry of Science and Technology. (5) Regulations on Punishment of Dishonorable Behavior in Science and Technology Projects (2006), issued by the Ministry of Science and Technology.

[11]Furthermore, most CROs conducting animal studies or testing as well as all AAALAC-accredited primate facilities have an IACUC.

New World Primates in Research

Chris Abee

By way of definition, New World monkeys and neotropical primates are the same thing and comprise primates that are indigenous to the Americas. There are four main genera of New World monkeys that are used in research: squirrel monkeys (*Saimiri* spp.), owl monkeys (*Aotus* spp.), marmosets (*Callithrix jacchus*), and tamarins (*Saguinus mystax*).

New World monkeys are used in virtually all the same ways as the Old World monkeys in biomedical research. They are used for discovery research and for preclinical research. It is essential to draw a distinction between the two [types of research], because the vast majority of primates that are imported are used for preclinical studies, safety, and efficacy studies.

Discovery research focuses on discovering something new, something previously unknown, and is typically investigator-driven research funded by the NIH. Preclinical research focuses on verifying what was learned in discovery research under the highly controlled GLP conditions that are required by the FDA or equivalent regulatory bodies in Europe. Both types of research contribute to the translational science that we talk about in the United States—from bench to bedside.

Genomic comparisons are often used as a rationale for why primates are important for certain kinds of research into human disease. New World monkeys and Old World monkeys share approximately 92% and 94%, respectively, of DNA with humans. Chimpanzees, of course, are even closer, sharing over 98%.

Among the squirrel monkeys (genus *Saimiri*), three species or subspecies are used in research, primarily in the United States. *Saimiri sciureus sciureus* is the common squirrel monkey and the one most frequently imported to the United States; *S. boliviensis boliviensis*, the Bolivian squirrel monkey, and *S. boliviensis peruviensis*, the Peruvian squirrel monkey, are also used for research. Three species of owl monkeys are used in research: *Aotus nancymaae*, *A. vociferans*, and *A. azarae*. Marmosets (*Callithrix jacchus*) are used in Europe more than in the United States, but there are several colonies around the country: one at the Wisconsin National Primate Research Center, one at the Southwest National Primate Research Center, and a small colony at the New England Primate

Research Center. Tamarins are used probably the least of the four genera, and *Saguinus mystax* is the most commonly used one in the United States.

Bolivian squirrel monkeys are no longer available through importation due to bans in the country of origin—Bolivia no longer exports squirrel monkeys, so we are not likely to get more of these. Bolivian squirrel monkeys have been very useful in malaria research because they are susceptible to *falciparum* malaria and *Plasmodium vivax*. They have also been used in prion disease work, the transmissible spongiform encephalopathies. Squirrel monkeys are susceptible to every prion disease with which they have been infected, including wasting disease of deer, which is a growing problem in the United States. If one looks at lesions from brains with sporadic and variant Creutzfeldt-Jakob disease (CJD), there is a little difference in the lesion. In sporadic CJD there is a generalized spongiform change. In the variant form of the disease, which is thought to have come from eating contaminated beef from animals that had bovine spongiform encephalopathy, the lesion creates a rosette around accumulations of abnormal prion protein. Squirrel monkeys develop these lesions and they look virtually identical to those seen in humans.

Owl monkeys have been used for malaria research, pathogenesis, and vaccine development work with malaria. In our colony we have seen a high prevalence of cardiomyopathies and the sequelae to chronic hypertension. These animals exhibit aortic aneurisms and hypertrophic cardiomyopathy. In the end stages of the disease they develop chronic heart failure, and instead of the heart pumping it just appears to vibrate—the contractility of the heart is virtually gone. This is, as far as we know, the only spontaneous or naturally occurring chronic severe hypertension model in a primate species.

Marmosets have been used for a number of studies of obesity, metabolic syndrome, aging, and reproductive biology. They are valued in reproductive biology because about 80% of these animals produce dizygotic twins, which share the same placenta, so there is a very high prevalence of chimerism.

Tamarins were very important in the development of hepatitis A vaccine. They are susceptible to GB virus B, which is closely related to hepatitis C virus.

In the United States there are three sources of New World monkeys. One is through importation. Second is through an agreement between the Pan American Health Organization (PAHO) and NIH through the Peruvian Primatology Project to provide small numbers of New World monkeys to NIH and through NIH to others that need them for research; not very many animals are imported that way, but it is a source. Then finally, animals can be obtained from the Center for Neotropical Primate Research and Resources at the University of Texas M.D. Anderson Cancer Center, and specifically at the Michale Keeling Center for Comparative Medicine. The Center for Neotropical Primate Research and Resources is supported through two grants from NCRR, one for squirrel monkeys and one for owl monkeys.

To obtain specific information about importation of these species, I went to the CITES[1] database and looked up importation data over a 5-year period, from 2002 to 2006. Of all the species, squirrel monkeys are the most commonly imported around the world. Between 2002 and 2006 over 4,000 monkeys were exported to North America and almost 3,000 to other regions of the world.

Looking at the number of squirrel monkeys imported into the United States by year from 1997 to 2006, the highest number was in 2002 (>500); in most years it averaged between 200 and 300 a year. These numbers do not take into account animals procured from domestic colonies, and do include research colonies at institutions around the country.

Owl monkeys imported to the United States have come from two countries, Argentina (*Aotus azarae*) and Peru (*A. vociferans* and *A. nancymaae*). Virtually all of these animals have been used for malaria research.

Animals supplied through the Center for Neotropical Primate Research and Resources have been primarily squirrel monkeys. The owl monkey resource, for which funding began in 2004, has begun to grow, but as with all breeding resources of primates, it takes years to develop them.

To determine the types of research done in various species of NHP, I queried the CRISP database.[2] Macaques are by far the most frequently used NHP, with over 650 grants/contracts in 2008 citing their use. About 40 grants this year cite the use of the squirrel monkeys, 15 cite owl monkeys, and 6 cite marmosets. One must be careful in interpreting these numbers because they only reflect NIH extramural research and do not take into account NHP used by the Department of Defense, which used many, as well as the Food and Drug Administration and the Centers for Disease Control and Prevention.

The intramural research program of NIH also uses primates, and they use more macaques than any other genus of primates. However, the NIH Office of Animal Care and Use provided information that imports through PAHO from 2002 to 2006 totaled 230 owl monkeys and 68 squirrel monkeys.

To try to bring it into perspective, New World monkeys are valuable for several key diseases. The owl monkey is an emerging model for cardiovascular disease and chronic hypertension. In the United States in 2008, an anticipated 400,000 people will die from cardiovascular disease. Looking worldwide of course it will be far, far greater.

These animals have been used extensively for malaria research. While not of foremost importance in the United States, malaria remains one of the most devastating diseases worldwide. Mortality in 2008 is expected to be almost 3 million people, and 75% of those who die from malaria are women and children.

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[1]The Convention on International Trade in Endangered Species of Wild Fauna and Flora (www.cites.org).

[2]The NIH Computer Retrieval of Information on Scientific Projects system, since replaced by the RePORT Expenditures and Results (RePORTER) query tool (http://projectreporter.nih.gov/reporter.cfm).

Half of the children in Africa that die before the age of 5 die from complications from malaria.

Finally, these animals are important in studies of hepatitis B and C. Although there is now a vaccine for hepatitis B, these diseases remain a big problem. Tamarins were very important in the development of hepatitis A vaccine, and they may provide answers to some questions about hepatitis C. It is hard to determine numbers for the impact of hepatitis B and C worldwide, but it is probably on the order of 3 million or more people, and people who survive with hepatitis C for 25 years have a very, very high incidence of hepatocellular carcinoma and hepatomas. So it is also a risk factor in cancer.

I want to thank Jim Taylor, Don Bordine, and Alfie Caesar, who helped me with some numbers, as well as Larry Williams and Laura Zapalac in my department.

CHALLENGES IN OUTSOURCING STUDIES

An Academic Perspective

James Macy

A paradigm shift is beginning to occur with regard to academic collaborations across borders. Historically there has been a lot of collaboration between US academic institutions and those in the United Kingdom, Canada, and Europe. There was certainly a comfort zone in these interactions in terms of animal care and use regulations—they are not the same in each area, but clearly they functionally accomplished the same things.

More recently, countries such as China and India have the scientific and the physical infrastructure to perform cutting-edge science. With China as an example, there is technology developed there that is innovative and when attached to an NIH individual or program project application makes it very attractive for funding. So the academic agency has to determine how to best collaborate with this other institution. Unlike a CRO, it is not necessarily a choice of the institution but a choice of the research.

The problem is that our academic institutions do not have much experience with the local animal care and use regulations, especially in countries like China and India. Thus the two central questions that need to be considered are: Is the animal care and use being performed under reasonably appropriate conditions in a humane and ethical way? And are the resulting data of acceptable quality and integrity? There have been some recent updates in regulations regarding human clinical studies, which center on the last point and probably apply to animal studies as well.

In an academic institution, oftentimes most of the funding is predicated on the US Public Health Service (PHS). The following is a scenario outlining the institution's responsibility when there is a PHS award with a foreign component. That foreign component is usually executed through a subaward or subcontract. A foreign component is defined as performing a significant element of the project outside the United States. It is performed either by the grantee or an individual working for the foreign institution, and funds do not necessarily change

hands. For example, an investigator may be listed as key personnel under a grant. Even though the investigator might not be getting paid for it, it still can be a foreign component as long as there is a significant element in the work that is being performed for that project. So a foreign component involves human or animal subjects. It also includes what we would consider field studies, if somebody is going to a foreign site and collecting samples from animals. If the investigator is acting as a consultant, the institutions must grapple with that, because consultants are not included in the NIH foreign component entity.

Looking at the terms or conditions of a subaward or subcontract language related to animals, there are several points to consider. One is that the foreign entity must file a PHS assurance or provide evidence that acceptable standards for the humane care and use of animals will be met. All performance sites have to be operating under an assurance and there has to be verification of an IACUC approval. What does the foreign assurance entail? It is essentially a one-page document with three major components: a statement that the institution must comply with whatever the local regulations are; the institution needs to be guided by the International Guiding Principles for Biomedical Research Involving Animals issued by the Council for International Organizations of Medical Sciences (CIOMS), which are very similar to the US Government Principles; and the institution has to make a reasonable effort to ensure that the people doing the work understand the regulations and their responsibilities.

The foreign assurance is now in the process of revision. In contrast to a domestic assurance, the foreign assurance does not have a statement about the Animal Welfare Act, does not mention the need for accordance with the *Guide for the Care and Use of Laboratory Animals*, does not address lines of authority for administering a program, does not ask for the qualifications of the veterinarian, and does not have reporting requirements. The IACUC review, reporting and understanding the qualifications, falls to the primary recipient, which is the institution receiving the grant.

From an institutional perspective, the initial challenge is knowing that there is a grant with a foreign component. In an IACUC protocol, the investigator may forget to check the box for off-site research or may forget to indicate all the locations where the research will be done. There also may be some confusion as to whether the work being performed off-site has to be listed in the IACUC protocol.

The IACUC protocol is often one way to monitor off-site research, but the key is to ensure that your institution is doing a congruency review, i.e., certifying that what is in the grant matches the IACUC protocol. When doing a congruency review, the person reviewing the grant will see the subcontract including a description of the work and the justification for having it done off-site. The reviewer will determine whether there are procedures in the grant that are not in the IACUC protocol. So this is a very good protection mechanism that needs to occur.

Another important issue to consider is export control, not necessarily with respect to animals but other things that can go back and forth. This is highly

regulated by the US State Department, the Commerce Department, and the Treasury Department. Although most of these regulations do not apply here, and it is a low-risk situation, the consequences are very high if they are not followed. There may be fines up to a million dollars and imprisonment up to ten years. So it is critically important to determine that if there are to be animal-related items or products going back and forth, they are not on the commerce control list or part of any other export regulations.

Once an institution enters into an agreement to perform animal research at a foreign site, there needs to be a risk assessment to determine what the institution needs to do for monitoring and oversight. What kind of oversight is there? Is the institution AAALAC accredited? Are there local regulations? What infrastructure is available? What is the physical plant like? Are the human resources skilled or unskilled? What are the reporting lines of authority? There are also concerns about conflict of interest, e.g., is the person in charge of animal welfare reporting to the investigator doing the work? Also, the species involved may matter—the higher the species the more concern. Other concerns surround whether the procedures are invasive or noninvasive, the appropriateness of the number of animals, and whether the study is large or small. It is important to know whether the institution has a track record of collaborating with other institutions and whether any of their work has been published. If so, what does the materials and methods section say in the paper? This information can give a lot of insight into how the institution conducts its work.

After the risk assessment, a monitoring program needs to be implemented. There is an auditing clause in the subaward or subcontract, which primarily involves following the money to see how it is spent. However, it also gives the primary institution the ability to audit any documents related to regulations. In addition, the auditing clause allows the primary recipient to audit many aspects of the project according to the terms and conditions of the subcontract. The terms of auditing need to be very clear. If the institution wants to perform a specific document review, it needs to specify which documents should be kept and the frequency of the audit review.

Physical monitoring of the facility is the best option. There are multiple ways to do this, but the best is a site visit at least initially. Physical monitoring may also be done by requesting pictures and videos, or by looking through webcams. These methods all have security issues but as it has been said before, a picture is worth a thousand words, and going there is probably worth 10,000 words.

What happens if through the monitoring review noncompliance is observed? Who reports? Recall that the foreign assurance does not require that institution to report; reporting is the responsibility of the primary grant recipient. Who is held accountable for investigation and correction? Since the foreign country is out of OLAW's jurisdiction, the main responsibility is on the primary institution. On the OLAW website there is a document that describes what happens during progressive noncompliance. Certainly one repercussion would be

cessation of the financial support to the foreign institution if noncompliance was not resolved.

The last thing I wish to address is the recent trend with clinical trials. The FDA has put out new standards for the conduct of clinical trials. The new standards mandate that foreign clinical trials must now have an independent ethical committee and must be in compliance with the FDA's good clinical practice. In the past, the standards were similar to what the requirements are for the foreign assurance now, i.e., the work must follow an international guideline. However, the stringency has increased to ensure that the data are reproducible and of appropriate quality to support a New Drug Application.

In an academic collaboration the onus is on the primary recipient to make sure that all of these things are occurring. If issues arise that are numerous and serious enough, it may be that this kind of regulation for animals will follow.

Perspective from China

Alex Zhang

To begin, I would like to say that I am not a specialist in laboratory animals but rather a biologist, with a specialty in stem cells. For the past eight years I have been working in a medical university in Beijing and I am currently involved in an effort to build a primate research facility in China from the ground up. I would like to tell our story of how to build such a facility.

In the past few days, almost all the talks mention China, and yet I am the only person who came from China, and I am not even a specialist in this particular area. At the end of my presentation, I would like to offer suggestions for those who are either planning on or now working with Chinese entities on scientific projects.

In 2003, most of my research [on stem cell therapy] was with mice. Before going to human trials I wanted to move to nonhuman primates. At that time the SARS epidemic rampaged through China and all animal transportation was stopped throughout the country. Consequently I wanted to find out where it might be possible to do NHP studies in China, i.e., where the monkeys were, where the good facilities were.

Most of the monkey breeders are in southern China; almost all the Chinese rhesus colonies or breeders are to the southwest. The area north of Vietnam is where many of the breeders of cynomolgus monkeys are located.

In visiting the area, I found many monkey breeders. For the bigger ones, the basic unit is 10,000, so they have 10,000 or 20,000 or 30,000 monkeys. But there were no good research facilities at all, and certainly not the type of facility we would like to have to do stem cell cultures or brain surgeries. So we decided to build our own.

We chose the city of Nanning for two reasons. One is that it is a small city by Chinese standards, with a million people, but the air is good, there is no traffic, and there are many direct flights to the big cities like Beijing, Shanghai, and Guangzhou. A second reason is that there are many good breeders in that general area, and most of them provide high-quality cynomolgus monkeys. Most of these facilities sell the monkeys abroad.

We talked to local people and rented space from them to set up our own facility. We immediately faced a problem that has already been discussed and that is an overall lack of awareness of animal welfare. Things have improved in the past two or three years, but it is still a problem. Also, there is a lack of expertise in veterinary care and technical skills. This is now recognized as a problem, and some remote education programs or lecture series have become available in China, but unfortunately at that time there were none.

Also, the quality of the animals is variable. Most of the breeders that sell to foreign countries are very good, but others are not, so we must stringently screen those animals.

All this is quite understandable. A quote from a commentary in *Cell* [129(6):1033-1036] published last year says: "There are 135 million Chinese living on less than $1 a day, which the World Bank defines as abject poverty. In comparison, 'monkeys listen to music, have toys to play with and drink purified water' in Wincon's AAALAC-accredited lab.…" Even with the economic boom in the past few years, there are still many people at a very low standard of living. In such places it is difficult to provide care for our monkeys in such a way that they listen to music, have toys to play with, and drink purified water. With regard to purified water, I have a relevant personal experience. When we decided to install water purification systems for our monkeys, our technician came to me and asked if we could install a faucet in the office for the staff: people do not have purified drinking water—they normally boil the tap water for drinking. This small anecdote provides a view into the situation in China.

In developing our program, we decided to adopt a high standard, starting with the *Guide*. While this was a very good decision, in the beginning it was a very tough plan to carry through. Staff, including myself, had no experience with the *Guide*. It is embarrassing to say here that I became aware of AAALAC only in 2004. However, since we decided to go for this particular standard and apply for AAALAC accreditation, it has forced us to do everything properly and acceptably to the international community.

We were very fortunate to develop a collaboration with the University of Wisconsin, National Primate Research Center, and with Joe Kemnitz in particular. The center sends staff to our facility for days and sometimes weeks to help us implement the *Guide* in our facility and laboratories. This activity is continuing, but now people come not just to tell us what to do but also to collaborate with us on scientific experiments.

The third piece of developing our program involved the implementation of continuing education for our staff.

The final aspect of our program development was working with the local government to educate them and the local community. These efforts serve to bring support from the local community and funds from the local government.

It has been amazing how quickly things have progressed. In 2003 I visited Nanning and we were able to convince some local business people and the local government to put in some modest investment to rent a space on the second floor of a building beside a breeder, a big monkey farm. In 2004 we decided to

work toward the standards set by the *Guide*, and in 2005 we had laboratory animal professionals from the University of Wisconsin come in to help us. By the end of 2005 we were able to apply for AAALAC accreditation, and we received it in 2006.

Since then everything has been progressing even faster, like everything in China nowadays. First, we immediately started getting phone calls from various pharmaceutical companies about our company. Second, we suddenly received investment money to build a new facility, which is to be completed by next year. Third, on a personal level, I have become one of the bigger clients of this company but am no longer involved with it. A large portion of my research grant goes into this company to support my study. But I feel happy about the outcome because I am a scientist, not a businessman.

Finally, I would like to offer a few additional suggestions for those planning to work with Chinese entities. The first is that it is important to spend more time going to China, and not just for site visits. It is important to spend time with the people who work there and this will help to solve a lot of problems such as language. Even though the English language capability of Chinese staff is not great, much may be accomplished just by working side by side. Also, it helps to build trust. Once everyone knows each other, it is possible to determine their trustworthiness, which is something that cannot be done by teleconference or videoconference.

Another consideration is that flying human primates is cheaper than flying nonhuman primates, given the restrictions with transportation. Even though travel to China is expensive, it is worth it, especially if one is working with nonhuman primates.

An additional suggestion is that people coming from abroad should work with the Chinese government, which, at the local or federal state level, is very receptive to advice from abroad and is also receptive to collaborations. In the last few years we were able to convince a major science funding agency in China to add requirements for major grants, mandating that facilities doing animal studies must comply with international standards, either by AAALAC accreditation or adherence to the *Guide*.

Finally, we are lobbying the Chinese government to support sequencing of the cynomolgus monkey genome so that we can compare the various subspecies as well as do genomic comparisons of Chinese and Indian rhesus. Working with the government may require additional effort, but it helps to tap into government resources.

Transportation Issues with Nonhuman Primates

Saverio Capuano

I am going to focus on the transportation issues surrounding nonhuman primates (NHP). It is important to remember that almost 27,000 monkeys came into the United States in 2007.[1] Even though there is a financial crunch and there is not as much money for research and fewer carriers are flying animals, there were still 27,000 monkeys that came into this country—and I am still worried about transporting animals.

Not only are there fewer carriers flying animals but there is no air transport within the US. We are converting to ground transport internally, and there are several companies that are very good at it.

It has been said previously at this conference that there are very few deaths during transport of NHP. But every year about 200 deaths occur in quarantine and it should not be considered a successful transport until the animals get out of quarantine. While some of these animals travel huge distances, even thousands of miles, a 1% death rate is still unacceptable. Facilities should be examined to find out why, if the animals are preconditioned and healthy before transportation, 1% of those animals die in quarantine.

There is a veritable cornucopia of laws and governing bodies that must be dealt with in order to move animals domestically or internationally and various agencies to enforce these laws and guidelines. Many times these regulations contradict each other and there may be [a lot of] ambiguity. Sometimes it is very difficult to know what the rules are. In addition, it is necessary to deal with officials at every one of these governing bodies and their interpretation of the laws. My plea to all of the attendees here is to get together and work with the agencies to develop an interagency agreement. The goal of such an agreement would be to bring all the documents together to give us better guidelines.

The difficulty in finding air carriers that will transport NHP has already been discussed. The profit margin for airlines to carry the animals is very low,

[1]Data from G. Gale Galland, Nonhuman primate importation and quarantine, United States: 2007. 35th Annual Workshop of the Association of Primate Veterinarians. October 11-13, 2007; Charlotte, North Carolina.

and it costs them money to train their employees, put them at risk, and deal with the public relations aspect of it. It is likely that in the future there will be even fewer carriers that will transport these animals.

Good transport practices are based on common sense, on experience, and on knowledge of the animals. It is important to know the inspectors, know the rules, know all the officials, and know your shipping company, especially when it is a large or long shipment. Know what is going to happen with those animals every step of the way. Remember that regardless of how the animals are cared for in your facility, once they leave it they are under the control of others. One thing is to anticipate the weather, particularly in the summer, when there is cause for worry because of potentially high temperatures.

Another consideration is space allocation. While the animals are housed in a facility more space may be better, but during transport small is much better. Large spaces mean more chance of animals falling, of rolling, of problems with motion in transport. Food and water of course must be considered. Anorexia and adipsia may occur during transport. It is not prudent to include large volumes of water because it causes changes in temperature and bad sanitation in your transport. With regard to handling, it is extremely important to precondition and acclimate the animals. They should be prepared by becoming acclimated to the transport cages and to the food they will eat during the trip.

It is prudent to instruct the driver or whoever might be moving or handling the animals about how to act with them, what behaviors to look for, and to be careful with them, remembering that the transporter likely has little or no knowledge about the animals.

It is important to provide for a way to monitor the animals throughout the trip and to prepare emergency procedures for a worst-case scenario, such as the truck breaking down or the need to euthanize an animal. It may be necessary to have alternate places for the animals to go if the unexpected happens.

Other issues that should be considered are training, shipping containers, and biosecurity. Initial training and continuing education should be given to transporters. With regard to shipping containers, ideally each container should have an overcarrier, but this may not be feasible. However, it is necessary to ensure that the container will endure a trip of thousands of miles. This is particularly true when it comes to biosecurity. If urine or feces were to penetrate to the outside of the container, workers may be exposed to infectious agents the primate might be carrying. This also raises the issue of having the workers wear personal protective equipment. Ideally, they should, but doing so might raise concerns among the public who see them. The workers should ideally also be aware of biocontainment issues, but without specific training it is unlikely that they would be.

In summary, it is important to consider all of these issues before transporting animals in order to make it safe, especially for the animals.

The Future of the Use of Nonhuman Primates in the UK

Judy MacArthur Clark

This presentation will focus on what we have recently been doing in the UK in terms of reviewing the use of nonhuman primates and whether such use can be justified. It will consider the Weatherall report,[1] including the goal of that review, the methodologies, conclusions, and recommendations in the report, and the responses to the report. I will end with some personal ideas in terms of the way forward. I am taking the place of Professor Roger Lemmon who was unfortunately not able to be here.

A snapshot of primate use in the United Kingdom (from 2007 UK Home Office statistics) shows that use of primates is significantly less than in the United States. We performed about 4,000 procedures on primates in 2007, which constitutes about 0.1% of all procedures. The actual number of primates used was about 3,125, and most of those would have been Old World macaques, with a much smaller number of New World monkeys, primarily common marmosets. The number of animals and the number of procedures differ slightly because some animals are used in more than one procedure and are thus counted more than once.

The statistics indicate that 87% of animals used are in regulatory toxicology and about 13% in basic or applied research, which was the area of greatest interest to the authors of the Weatherall report; thus I will not say much about regulatory toxicology. The ratio of rhesus to cynomolgus macaques in the UK is slightly different from that in the US, where rhesus monkeys are used in most basic and applied research. The data show that the use of Old World monkeys has stayed relatively stable from 1995 to 2007. On the other hand, the number of New World monkeys seems to be on the decline.

The background to the generation of the Weatherall report was a report from the Boyd Group in 2002. The Boyd Group is a very diverse group of indi-

[1] *The Use of Non-Human Primates in Research and Testing* (2002). Jane A. Smith and Kenneth M. Boyd, ed.; the Boyd Group. Leicester: The British Psychological Society.

viduals from a range of backgrounds, including science, government, welfare, and antivivisection organizations. In 2002, they produced a report on the use of nonhuman primates in research and testing.[2]

That information was also then taken into consideration by the Nuffield Council on Bioethics, which was also a very interesting group of which I was privileged to be a member. We produced a report in 2005 on the ethics of research involving animals.[3] I recommend that report to provide a breadth of understanding of the ethics of use of animals in research, which is an excellent starting point.

Arising from the realization in the Nuffield Council report that there were significant views being expressed about the ethics of using primates in research, the Royal Society and others in the UK set up the Weatherall Committee. It reported in December 2006 on the use of nonhuman primates in research. The focus of the report, however, was much more on the scientific justification as opposed to ethics.

The sponsors of the report were the Royal Society, which is somewhat the equivalent of the National Academies, the UK Academy of Medical Sciences, the Wellcome Trust, and the Medical Research Council, the last two being the major funders of basic and applied research involving primates. It was focused on hypothesis-driven research in academia and looked at the use of primates in communicable disease research, neuroscience, and reproductive biology. There was a small amount about fetal development research and aging, as well as a brief consideration of drug discovery and development. The report also considered alternatives, welfare issues, and ethics to an extent, but those were not major components.

The central goal of this study was to examine the scientific case for the use of nonhuman primates for research into the prevention and treatment of disease or for fundamental research that has the long-term potential for achieving the same end. This was a fairly unique approach to looking at the use of primates and justification for their use in research.

The methodology was to set up an "independent" committee. This means that all members of the nine-person committee were nonusers of primates in research, although some of them were academic researchers, including those from overseas, and there was also representation from lay people. There was a public call for evidence to which 62 responses were received. In addition the committee took oral evidence from 35 witnesses. Both breeding and using sites were visited by the committee. The committee sat for some 18 months, and took a fairly rigorous approach to writing the report.

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[2] *The Use of Non-Human Primates in Research* (2006). A working group report chaired by Sir David Weatherall. London: The Royal Society, Academy of Medical Sciences, Medical Research Council, Wellcome Trust.

[3] *The Ethics of Research Involving Animals* (2005). London: Nuffield Council on Bioethics.

This is an appropriate place to state that the UK regulatory control system is very stringent, with a requirement for three licenses for any primate use. There are also local ethical review processes.

Many recommendations emerged in this report. First, it concluded there was a strong scientific case for the carefully regulated use of nonhuman primates when there are no other means to address clearly defined questions of particular biological or medical importance.

The second recommendation reiterates that point in relation to the fields considered in the study—communicable diseases, neuroscience, and reproductive biology—confirming that nonhuman primates were needed at least for the immediate future. There is a sense in this report that there are developments occurring all the time that may or may not affect the justification for the use of primates in the longer term.

The third recommendation is that major specialist organizations should regularly collate information involving their fields, and the information should be disseminated to funding bodies, ethics committees, and regulatory agencies.

Fourth, the major funding organizations should undertake a systematic review of the outcome of all research using nonhuman primates supported over the last decade. That is being done by examining the benefits resulting from funding those areas of research.

The fifth recommendation refers to the development of alternatives, and there is strong support for greater funding to develop alternatives to the use of nonhuman primates both in research and in toxicology. Funders should expand their support for research into refining nonhuman primate research practices particularly in behavioral neurosciences.

A sixth recommendation related to retrospective reporting of severity of procedures. This would entail introducing a system to report severity actually incurred during procedures, either to a local ethical committee or more centrally. Obviously such reporting would take place after the procedures have been performed.

The next recommendation called for improvements in the training of research workers in nonhuman primate research.

The committee also addressed housing issues, specifically minimum cage sizes, avoidance of single housing, and how cage fittings and conditions can be accommodated to the purpose of the experiment, thereby relating the housing to the purpose of the research. They also called for better assessments of the advantages of things like access to outdoors and the general need for visual stimulation for primates.

The next three recommendations relate to regulatory toxicology, particularly in areas where alternatives may be feasible, and pursuing regulators to consider what may be unnecessary tests or duplication of tests.

There was a recommendation toward the end of the report that looked at the creation of UK centers of excellence, which I will address further when I talk about future activities.

The Weatherall report was produced in December 2006, and in June 2007 there was a flurry of activity in response to the report. The funders and government produced a combined response that was generally supportive of the recommendations and gave commitment to take them forward and to work together on the strategy of how to move forward.

Shortly thereafter, the UK National Center for the Three Rs (NC3Rs) published a critique of the report. It was a constructive critique that sought a more rigorous review and analysis of the use of primates in research. It talked about the need for a national strategy, which is something now being explored. It also mentioned that the NC3Rs has set up an annual meeting on the welfare of primates, which has been serving a very useful purpose. It draws a very diverse audience and serves as a very useful forum for comparing best practice across the community that is involved and interested in research using primates.

What is next then? We are embarking in various areas on thematic reviews of the use of primates. One area that needs to be explored is the use of primates in neuroscience. My team of inspectors in the UK looks at how the cost-benefit assessment is applied in those studies and how we can help our licensees to adopt best practice. Looking at retrospective severity is also an interesting exercise, including options for alternatives and how effectively those are being applied.

In addition, there are moves toward development of a national primate strategy, including determining the need for centers of excellence. In the UK there are far fewer centers that use primates than in the United States. Some question whether it is necessary to develop new centers of excellence rather than have existing centers become better networked together. The national primate strategy will also look at things like training and sourcing, which were not addressed in the Weatherall report but are nevertheless very important. Also, it will be important to heed the recommendations from [the] Weatherall [report] about media and public understanding about why primates are used.

But as already stated, the use of primates is a global issue, not solely a UK issue nor a US issue. While we do some small-scale breeding of primates in the UK, many of our primates are sourced from overseas, primarily China, Vietnam, and Mauritius.

It's clear we have to think of primates as a global resource. We are currently competing with other countries for our needs; we should not be in competition but rather exploring the needs of science together. There are significant transport and welfare issues to consider as well. And there are significant opportunities to share best practice, especially between countries, such as the US and UK, with well-established programs of primate research and those that are emerging scientifically in this field.

Those are just some of the issues that come with the fact that the use of primates in research is not only a highly sensitive issue but also something that has global impact.

My conclusion is that this is an ideal opportunity for global collaboration and harmonization, so that we are not competing for use of these animals but truly ensuring that this global resource is being used as effectively as possible. We must achieve this by sharing our ideas and by sharing access to those resources.

Proposed International NHP Plan

Joseph Kemnitz

In lieu of the last item on the agenda for this afternoon in terms of presentations,[1] I will simply mention that the ILAR Council and staff would like to capture the content and the spirit of this afternoon's session and use it to launch an international primate plan to enable the best use of global resources to maximize research progress that requires the use of nonhuman primates while minimizing the numbers used and the negative consequences for the animals.

We have a draft plan that is not completely polished. Our hope is to launch it within the year. We need some additional resources in order to do so. Then we have a time line that would call for completion of a written plan within two years.

Finally, I thank all of you who participated in this conference, especially the speakers, and very especially Joanne Zurlo and the ILAR staff as well as the sponsors of this meeting.

Text of Joseph Kemnitz's Slides on the Proposed International NHP Plan

Background

First primate plan developed in 1978 by the Interagency Primate Steering Committee established by the Director of the National Institutes of Health (NIH).

Recommendations were made to ensure:

- Expansion of domestic production of nonhuman primates (NHP)
- Action to ensure effective use of NHP

[1]This session reached the end of its allotted time and eclipsed Dr. Kemnitz's presentation about the International Primate Plan; the text of the slides he prepared for presentation is included here.

- Stable supply and long-term availability of NHP from countries of origin

The 1978 Plan was quickly outdated (e.g., ban on exportation from India, AIDS crisis). Great pressure was put on Indian-derived rhesus monkey resources.

A workshop on International Perspectives: The Future of Nonhuman Primates Resources was convened by ILAR in 2002.

- Reports on NHP resources and programs in 16 countries
- Updates on issues such as nutrition, genetics, microbiology and transportation

A companion workshop, Rhesus Monkey Demands in Biomedical Research, was convened by NIH's Office of AIDS Research (OAR) and National Center for Research Resources (NCRR).

- Emphasized pressure on Indian rhesus monkey supply
- Encouraged use of alternative species
- Develop a comprehensive plan to preserve and expand resources for biomedical research using NHP models

Rationale for a New Plan

- Increasing need for human disease research and testing
- Disease threats that compromise quality and supply of NHP
- Globalization of research
- Need for conservation
- Need for renewed investment in infrastructure

Overall Scope

To address the current and future needs of NHP supply and use in biomedical research on a global level with consideration of multiple issues

Scope

1. Supply and demand issues based on input from countries and facilities that are major producers and/or users of NHP
   - Projections for NHP demand in the US over the next ten years will be determined in part by examination of US Department of Agriculture data and import/quarantine information from the last 10–15 years and in part by examination of trends and anticipated future trajectories of those trends.

- Assessment of needs for NHP in other countries by enlisting expertise from these countries in the project.

2. Factors affecting the breeding of various species of NHP used in research
   - This will include breeding of NHP both in the US and abroad, and will address issues such as nutrition, age of dams, pregnancy success rates, genetic management.

3. Infectious diseases affecting NHP and the standardization of microbial characterization of individuals and colonies with a focus on quality control and the development and use of reference reagents to minimize variability among laboratories and facilities.
4. Genetic management of animals including either genetic diversity or genetic similarity, depending on the needs of the research with recommendations for standardizing practices.
5. Behavioral management of the animals with recommendations for best practice in maintaining psychological well-being, optimal housing conditions and colony management.
6. Transportation issues specific to NHP, including the control of microenvironment of the animals during shipping, transport of biological samples from NHP, and current international regulatory obstacles to importation and transportation of animals.
7. Training of individuals involved with the care and use of NHP, including research and husbandry staff, and addressing the shortage of veterinarians specializing in NHP medicine.
8. Recommendations for the conservation of NHP resources, including the creation of formal mechanisms to facilitate sharing of samples and animals, detailed databases of genomic information on individual animals and development of small animal models to replace NHP where appropriate.

Some additional issues to be addressed:

- Elaborate on the translational value of research on NHP to human disease
- Identify priority areas of basic research for which NHP resources will be essential

Abbreviations

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
AAAS	American Association for the Advancement of Science
AALAS	American Association for Laboratory Animal Science
AAVMC	Association of American Veterinary Medical Colleges
ABSL	animal biosafety level
ACCMAL	Central American, Caribbean, and Mexican Association for Laboratory Animal Science
ACLAM	American College of Laboratory Animal Medicine
AMCAL	Mexican Association for Laboratory Animal Science
AMMRA	Asian Mouse Mutagenesis Resources Association
APC	UK Animal Procedures Committee
AQSIQ	Provincial Administration of Quality Supervision, Inspection, and Quarantine (China)
ASLAP	American Society of Laboratory Animal Practitioners
AV	attending veterinarian
AVA	Agri-Food and Veterinary Authority
AVMA	American Veterinary Medical Association
BAC	bacterial artificial chromosome
CALAM/ACMAL	Canadian Association for Laboratory Animal Medicine
CAST	Council for Agricultural Science and Technology (US)
CCAC	Canadian Council on Animal Care
CEDD	center of excellence for drug discovery
CENEVAL	National Center for Higher Education Evaluation (Mexico)
CHORI	Children's Hospital Oakland Research Institute (California)
CIOMS	Council for International Organizations of Medical Sciences
CMMR	Canadian Mouse Mutant Repository
CNRS	National Center for Scientific Research (France)
ConeVet	National Council for Veterinary Medical Education (academic branch of the Mexican Veterinary Medical Association)
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals (India)
CPMP	Committee for Proprietary Medicinal Products
CRISP	NIH Computer Retrieval of Information on Scientific Projects system
CRO	contract research organization
ECLAM	European College of Laboratory Animal Medicine
ECVAM	European Center for the Validation of Alternative Methods

EE	enriched environment *or* environmental enrichment
EFSA	European Food Safety Authority
EMMA	European Mouse Mutant Archive
ENU	ethylnitrosourea
ESC	embryonic stem cell
ESLAV	European Society of Laboratory Animal Veterinarians
ETS 123	European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes
EUCOMM	European Conditional Mouse Mutagenesis
EUMODIC	European Mouse Disease Clinic
FDA	US Food and Drug Administration
FELASA	Federation of European Laboratory Animal Science Associations
FeSSACAL	South American Federation for Laboratory Animal Science
FIMRe	Federation of International Mouse Resources
GEMM	genetically engineered mouse model
GLP	good laboratory practice
GM	genetically modified *or* genetic modification
the *Guide*	*Guide for the Care and Use of Laboratory Animals* (NRC report)
HO	Home Office (UK)
HVAC	heating, ventilation, and air conditioning
IACLAM	International Association of Colleges of Laboratory Animal Medicine
IACUC	institutional animal care and use committee
IATA	International Air Transport Association
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICH	International Council on Harmonization
ICLAS	International Council for Laboratory Animal Science
IKMC	International Knockout Mouse Consortium
iPS	induced pluripotent stem [cell]
IRAC	Interagency Research Animal Committee
JAX	Jackson Laboratory
JCLAM	Japanese College of Laboratory Animal Medicine
KOMP	Knockout Mouse Project
LAM	laboratory animal medicine
LAR	Live Animals Regulations
MMRRC	Mutant Mouse Regional Resource Centers
MOU	memorandum of understanding
MSM	*Mus musculus molossinus*
MTA	materials transfer agreement
NACLAR	National Advisory Committee for Laboratory Animal Research (Singapore)
NC3Rs	UK National Center for Replacement, Refinement, and Reduction of Animals in Research
NCRR	National Center for Research Resources (at US NIH)

NGO	nongovernmental organization
NHMRC	National Health and Medical Research Council (Australia)
NHP	nonhuman primate(s)
NIH	US National Institutes of Health
NorCOMM	North American Conditional Mouse Mutagenesis [Project]
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OIE	Office International des Epizooties, now the World Organization for Animal Health (but still goes by OIE)
OLAW	Office of Laboratory Animal Welfare (at US NIH)
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PETA	People for the Ethical Treatment of Animals
PHS	US Public Health Service
RFID	radio frequency identification
SARS	severe acute respiratory syndrome
SIV	simian immunodeficiency virus
TA	teaching assistant
TACT	Air Cargo Tariff [book]
TCP	Toronto Centre for Phenogenomics
USAMRIID	United States Army Medical Research Institute for Infectious Diseases
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
VRL	Virus Reference Laboratory

Appendix A

Animal Research in a Global Environment: Meeting the Challenges

National Academy of Sciences
2100 C Street NW
Washington DC

September 23–25, 2008

Program

Tuesday, September 23

7:30 a.m. Registration/Continental Breakfast
C Street Lobby/Great Hall

Morning Session
Judy MacArthur Clark, *Chair*
Auditorium

8:45 a.m. Welcome
Joanne Zurlo, Director, ILAR

9:00 a.m. Plenary Lecture – Science & Technology and US Foreign Policy
Norman Neureiter, AAAS

9:45 a.m. Building Momentum: Lessons Learned from the 2003 ILAR Workshop
Hilton Klein, 2003 Conference Chair

10:15 a.m. Break
Great Hall

10:30 a.m.	Challenges and Opportunities for Harmonization Cecilia Carbone, ICLAS David Bayvel, OIE Judy MacArthur Clark, IACLAM Kathryn Bayne, AAALAC International Carl Kole, IATA Joanne Zurlo, ILAR Malachy Hargadon, EU
12:00 p.m.	Lunch *Great Hall*

Afternoon Session
Kathryn Bayne, *Chair*
Auditorium

1:00 p.m.	Global Issues – Working Across Different Standards Operational Challenges Margaret Landi, Pharmaceutical Industry Bryan Ogden, Contract Research Organizations Steven Niemi, Academia (US) Harry van Steeg, Academia (EU)
3:00 p.m.	Break *Great Hall*
3:15 p.m.	Global Issues – Working Across Different Standards Training and Education Marilyn Brown, Charles River: A Model of International Training Ann Turner, AALAS Patri Vergara, FELASA Training Program Leslie Retnam, Training in Asia
5:00 p.m.	Welcome Reception *Great Hall*

Wednesday, September 24

7:30 a.m. Registration/Continental Breakfast
C Street Lobby/Great Hall

Morning Session
Coenraad Hendriksen, *Chair*
Auditorium

8:30 a.m. Plenary Lecture – Animal Research in a Global Environment: Meeting the Challenges
John Baldoni, GlaxoSmithKline

9:15 a.m. Veterinary Care for Laboratory Animals

Standards
Kathryn Bayne, AAALAC
Challenges: State of Laboratory Animal Medicine Around the World
Hans Hedrich, Europe
Rafael Hernandez, Latin America
James Fox, North America

10:30 a.m. Break
Great Hall

10:45 a.m. Veterinary Care for Laboratory Animals: A Path Forward

Solutions
David Bayvel, The Role of the OIE
Michael Chaddock, AAVMC Strategic Plan
(Introduction by Marguerite Pappaioanou)
Patricia Turner, Online Training and Distance Learning

12:00 p.m. Lunch
Great Hall

Afternoon Session
Jeffrey Everitt, *Chair*
Auditorium

1:00 p.m.	International Approaches and Principles for Distress, Pain, and Euthanasia David Morton, Distress Matt Leach, Pain Gilly Griffin, Euthanasia
2:15 p.m.	International Approaches and Principles for Humane Endpoints Fraser Darling, Cancer Carol Eisenhauer, Infectious Diseases Margaret Rose, Genetically Modified Animals
3:30 p.m.	Break *Great Hall*
3:45 p.m.	Cross-Cultural Ethical Perceptions and Ways to Resolve Challenges Bernard Rollin
4:30 p.m.	Adjourn

Thursday, September 25

7:30 a.m.	Registration/Continental Breakfast *C Street Lobby/Great Hall*

Morning Session
Stephen Barthold, *Chair*
Auditorium

8:30 a.m.	Coordination of International Rodent Resources Plenary Lecture – Two Mouse Tales Oliver Smithies, Nobel Laureate

9:30 a.m. Mice Travelling the World

Sharing Resources: Licensing Issues
Lili Portilla

Knockout Mouse Databases
Franziska Grieder, KOMP
Colin McKerlie, NorCOMM

10:30 a.m. Break
Great Hall

10:45 a.m. Knockout Mouse Databases *(continued)*
Martin Hrabe DeAngelis, EUCOMM, FIMRe
Yuichi Obata, RIKEN

Repository Issues, Lessons Learned
James Womack

Transportation and Mouse "Passport"
William White

12:00 p.m. Lunch
Great Hall

Afternoon Session
Joseph Kemnitz, *Chair*
Auditorium

1:00 p.m. International Coordination of Nonhuman Primates (NHP)

Framing the Issues
Joseph Kemnitz

Supply and Use of NHP Around the World
William Morton, US
Sam Poulle, Mauritius
C.K. Hsu, China
Chris Abee, New World Primates

2:15 p.m.	Challenges to Outsourcing Studies
	Control of Safety Testing Studies Michael Ballinger
	Academic Collaborations across Borders James Macy
	Perspective from China Alex Zhang
3:00 p.m.	Break
3:15 p.m.	Transportation Issues Saverio Capuano
3:30 p.m.	The Future of NHP Use
	The Future of the Use of Nonhuman Primates in the UK Judy MacArthur Clark
	Need for NHP in Biopharmaceuticals David Ruble
	Alternatives to NHP for Biopharmaceuticals Kathryn Chapman
	Proposed International NHP Plan Joseph Kemnitz
5:00 p.m.	Reception (admission by ticket only) *Rotunda*
6:00 p.m.	Conference Banquet (admission by ticket only) *Great Hall*
	Dinner Speaker
	Cosmopolitanism: Ethics in a World of Strangers Kwame Anthony Appiah

Appendix B

Steering Committee Bios

Coenraad F.M. Hendriksen, DVM, PhD, *Chair,* is Head of the Netherlands Centre for Alternatives to Animal Use, Chair of the Alternatives to Animal Use at the Veterinary Faculty of Utrecht University, and Senior Scientist at the Laboratory for the Quality Control of Biologicals, Central Animal Laboratories (RIVM). His expertise is in animal welfare concerns and lab animal issues in Europe. His research activities are focused on the development and validation of methods to replace, reduce, and/or refine the use of laboratory animals, especially in the field of the production and quality control of immunobiologicals. He is coeditor of several books and congress proceedings. At the time of the workshop he was a member of the Central Committee on Animal Experimentation (CCD) in the Netherlands, chair of the ECVAM Steering Group on Biologicals, and a member of the Institute for Laboratory Animal Research (ILAR) Council (2002–2008). He also served on the steering committee for the 2003 ILAR International Workshop on Science-Based Guidelines for Laboratory Animal Care.

Stephen W. Barthold (IOM), DVM, is Distinguished Professor of Veterinary and Medical Pathology at the University of California, Davis, and Director of the UC Davis Center for Comparative Medicine. His professional specialty is infectious diseases of laboratory rodents and biology of the laboratory mouse, with a primary focus on pathogenesis of Lyme borreliosis for the last 25 years. Dr. Barthold was elected to the Institute of Medicine (IOM) in 2001 and has received a number of career awards. He has served on numerous national scientific advisory and review committees and published over 300 peer-reviewed articles, chapters, and books. Dr. Barthold was a member of the steering committee for the 2003 ILAR workshop and a member (2002–2005) and then Chair (2005–2011) of the ILAR Council.

Kathryn A. Bayne, MS, PhD, DVM, DACLAM, CAAB, is Global Director for the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International). In this role she directs the accreditation program worldwide and travels extensively to advance AAALAC's accreditation program and laboratory animal welfare. Prior to this position she worked at the National Institutes of Health leading a research program on nonhuman primate psychological well-being and environmental enrichment programs for primates, dogs, cats, and swine. She has published over 40 articles on the subject and has also published extensively on accreditation of laboratory animal care and use programs. Dr. Bayne is a charter member and part of the Executive Team of the International Association of Colleges of Laboratory Animal Medicine (IACLAM). She has been a member of the ILAR Council since 2006 and also served on the NRC committees that prepared reports on the *Psychological Well-Being of Nonhuman Primates*, *Occupational Health and Safety in the Care of Nonhuman Primates*, and *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*.

Jeffrey Everitt, DVM, is Director of Comparative Medicine and Investigator Support at GlaxoSmithKline (GSK) Research & Development in Research Triangle Park, North Carolina. Dr. Everitt spent 17 years on the senior scientific staff of the CIIT Centers for Health Research in Research Triangle Park before joining GSK's global Laboratory Animal Sciences department. He is also an adjunct faculty member in the Department of Pathology and Laboratory Medicine at the University of North Carolina School of Medicine in Chapel Hill and at the North Carolina State University College of Veterinary Medicine. He served on the ILAR Council (2004–2010) and on the Board of Directors of the American College of Laboratory Animal Medicine. He is a diplomate of the American College of Veterinary Pathologists and of the American College of Laboratory Animal Medicine, as well as a Fellow of the International Academy of Toxicological Pathology.

James G. Fox (IOM), DVM, is Director of the Division of Comparative Medicine and a professor in the Department of Biological Engineering at the Massachusetts Institute of Technology as well as an Adjunct Professor at Tufts University School of Veterinary Medicine and the University of Pennsylvania School of Veterinary Medicine. He is a Diplomate and past president of the American College of Laboratory Animal Medicine. Professor Fox is the author of over 525 articles, 80 chapters, and 4 patents and has edited and authored 13 texts in the field of in vivo model development and comparative medicine. He has given over 250 invited lectures, consults nationally and internationally with government, academia, and industry, and has served on several journal editorial boards. He has been the principal investigator of an NIH postdoctoral training

grant for veterinarians for the past 23 years and has trained 50 veterinarians for careers in biomedical research. He also has an NIH training grant for veterinary students and has introduced over 100 veterinary students to careers in biomedical research. He is a past member of the NIH/NCRR Scientific Advisory Council and of the ILAR Council (2005–2011).

Joseph W. Kemnitz, PhD, is Director of Translational Technologies and Resources at the Institute of Clinical and Translational Research and professor in the Department of Cellular and Regenerative Biology at the University of Wisconsin, Madison. Until recently he was based at the National Primate Research Center and served as its director from 1996 to 2010. Prior to that he was a member and chair of the IACUC for the Graduate School. His research has focused on nutrition and metabolism in the contexts of reproductive physiology and aging, primarily using rhesus macaques. He was a member of the ILAR Council from 2005 to 2011.

Hilton J. Klein, VMD, MS, is former Senior Director for Comparative Medicine at Merck Research Laboratories. He was also an adjunct assistant professor in the Department of Laboratory Animal Resources at the University of Pennsylvania. His research interests are in laboratory animal science, particularly in the field of laboratory animal infectious disease and surgical production of animal models. He served as a consultant to the Pan American Health Organization as Merck's representative on nonhuman primate conservation. He was a member of the steering committee of the 2003 workshop and of the ILAR Council (1998–2005).

Judy A. MacArthur Clark, CBE, BVMS, DVMS, DLAS, DipECLAM, DACLAM, FSB, FRAgS, is Chief Inspector in the Animals Scientific Procedures Inspectorate of the Home Office in London, United Kingdom. From 2005 to 2007 she was Vice President of Worldwide Comparative Medicine at Pfizer in Groton, Connecticut, and before that (1992–2005) served as Director of Marketing and Sales at BioZone Ltd., which she cofounded. For over 20 years she has consulted on ethical policy development and improving public understanding of science. She is a member and former President of the UK Royal College of Veterinary Surgeons and has chaired or served as a member of many high-level national and international advisory committees on topics such as xenotransplantation, farm animal welfare, research funding priorities, and bioethics. She actively works on research regulation and policy development in the United Kingdom, Europe, and the United States. She is a member of the ILAR Council (2006–2012).

Appendix C

Workshop Speakers[1]

Christian R. Abee, DVM
The University of Texas M.D. Anderson Cancer Center
Houston

Kwame Anthony Appiah, PhD
Princeton University
New Jersey

John Baldoni, PhD
GlaxoSmithKline
Philadelphia, Pennsylvania

Michael B. Ballinger, DVM, MS
Amgen
Thousand Oaks, California

Stephen W. Barthold, DVM, PhD
University of California, Davis

Kathryn A. Bayne, PhD, DVM
Association for Assessment and Accreditation of Laboratory Animal Care International
Waikoloa, Hawaii

David Bayvel, DVM
MAF Biosecurity
Wellington, New Zealand

Marilyn J. Brown, DVM, MS
Charles River Laboratories
Wilmington, Massachusetts

Saverio Capuano, DVM
National Primate Research Center
University of Wisconsin, Madison

Cecilia Carbone, DVM
University of La Plata
Argentina

Michael Chaddock, DVM
American Association of Veterinary Medical Colleges
Washington, DC

Kathryn Chapman, PhD
National Center for Replacement, Refinement, and Reduction of Animals in Research
London, United Kingdom

[1]Affiliations shown are those at the time of the workshop.

Fraser Darling, MA, BSc (Hons), CBiol, MIBiol
Institute of Cancer Research
London, United Kingdom

Martin Hrabé de Angelis, PhD
GSF-National Research Center for Environment and Health
Neuherberg, Germany

Carol Eisenhauer, DVM
US Army Medical Research Institute of Infectious Diseases
Fort Detrick, Maryland

Jeffrey Everitt, DVM
GlaxoSmithKline
Research Triangle Park,
North Carolina

James G. Fox, DVM
Massachusetts Institute of Technology
Cambridge, Massachusetts

Franziska B. Grieder, DVM, PhD
National Institutes of Health National Center for Research Resources
Bethesda, Maryland

Gilly Griffin, PhD
Canadian Council on Animal Care
Ottawa, Ontario

Malachy Hargadon
European Commission
Brussels

Hans J. Hedrich, DMV, Dr.rer.biol.hum.habil
Zentrales Tierlabor und Institut für Versuchstierkunde
Hannover, Germany

Coenraad F.M. Hendriksen, DVM, PhD
Netherlands Vaccine Institute
Bilthoven, The Netherlands

Rafael Hernandez, DVM, MSc
Universidad Nacional Autónoma de Mexico
Mexico City

C.K. Hsu, DVM, PhD, MPH
Shared Enterprises, Inc.
Richlandtown, Pennsylvania

Joseph W. Kemnitz, PhD
University of Wisconsin, Madison

Hilton Klein, VMD
Merck Research Laboratories (retired)
Lansdale, Pennsylvania

Carl Kole
Kole Consulting
Chicago, Illinois

Margaret Landi, VMD
GlaxoSmithKline
King of Prussia, Pennsylvania

Matt Leach, PhD
Newcastle University
United Kingdom

Judy A. MacArthur Clark, DVMS
Animals Scientific Procedures Inspectorate, Home Office
London, United Kingdom

James D. Macy, DVM
Yale University
New Haven, Connecticut

Colin McKerlie, DVM, DVSC, MRCVS
University of Toronto
Canada

David Morton, PhD
University of Birmingham
United Kingdom

William Morton, VMD
Paris NHP
Edmonds, Washington

Norman Neureiter, PhD
American Association for the Advancement of Science
Washington, DC

Steven Niemi, DVM
Massachusetts General Hospital
Charlestown

Yuichi Obata, PhD
RIKEN Tsukuba Institute and BioResource Center
Saitama, Japan

Bryan Ogden, DVM
Maccine Veterinary Services, Ltd.
Singapore

Marguerite Pappaioanou, DVM, MPVM, PhD
Association of American Veterinary Medical Colleges
Washington, DC

Lili Portilla, MPA
National Institutes of Health
Bethesda, Maryland

Naraina "Sam" K. Poulle, DVM, MVSc
Protection of Animals Welfare Society
Mahébourg, Mauritius

Leslie Retnam, BVetSc, MLAS, MRCVS
National University of Singapore

Bernard E. Rollin, PhD
Colorado State University
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University of New South Wales
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Oliver Smithies, DPhil
University of North Carolina
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Ann Turner, PhD
American Association for Laboratory Animal Science
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Patricia V. Turner, DVM, DVSc
University of Guelph
Ontario, Canada

Patri Vergara, PhD
Universitat Autonima de Barcelona
Spain

Harry van Steeg, PhD
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