A HASTINGS CENTER SPECIAL REPORT

# Animal Research Ethics

## *Evolving Views and Practices*

EDITORS
Susan Gilbert
Gregory E. Kaebnick
Thomas H. Murray

The Hastings Center

## ▶THE PROJECT

Research involving animals has been a cornerstone of medical progress for more than two centuries. For much of that time, it has also met with moral objections because of the suffering it can cause the animals. Though animal welfare laws in the United States and abroad have reduced the number of animals used in biomedical research and ameliorated their pain, ethical concerns remain, and it is not only animal rights groups that have them, but also veterinarians, physicians, policy-makers, ethicists, and biomedical researchers themselves.

There are strong indications that the nature of the arguments about animal research is changing in fundamental and profound ways. New initiatives in the United States are seeking alternatives to animal testing. To better understand the changing landscape, The Hastings Center organized a one-and-a-half day workshop in November 2011 to bring together people with different points of view and areas of expertise—veterinary medicine, medical research, animal welfare advocacy, philosophy, and law—to share their knowledge, exchange ideas and insights, and produce educational resources. The project was funded with a grant from The Esther A. and Joseph Klingenstein Fund and drew on the expertise of the Yale-Hastings Program in Ethics and Health Policy, a partnership between the Yale Interdisciplinary Center for Bioethics and The Hastings Center.

This report contains commentaries on what the participants learned from the workshop. The participants were: Kathleen Conlee (The Humane Society of the United States), Larry Carbone (University of California, San Francisco), Jeffrey Kahn (Johns Hopkins University), Susan Kopp (LaGuardia Community College and Yale Interdisciplinary Center for Bioethics), Stephen R. Latham (Yale Interdisciplinary Center for Bioethics), Joel Marks (University of New Haven and Yale Interdisciplinary Center for Bioethics), D. Eugene Redmond, Jr. (Yale University School of Medicine), Gregory Reinhard (Merck Research Laboratories), and Joanne Zurlo (The Center or Alternatives to Animal Testing, Johns Hopkins University). Additional updated resources on animal research ethics can be found at http://animalresearch.thehastingscenter.org.

# CONTENTS

# Progress in the Animal Research War

Some years ago, Deborah Blum, a Pulitzer Prize–winning science journalist, nailed the divide between scientists who conduct research on animals in the hope of advancing medical knowledge and people who object to that work for being immoral and inhumane. They are "like two different nations, nations locked in a long, bitter, seemingly intractable political standoff," she wrote in her 1994 book, *The Monkey Wars*. The two sides certainly have been like nations locked in a long, bitter standoff. That standoff has seemed intractable. But when Blum talked to people on both sides, she found glimmers of hope—a few individuals willing to listen to one another and find common ground. "When they can be freely heard," she concluded, "then we will have progressed to another place, beyond this time of hostilities."

Today, while we are not yet beyond hostilities, we have progressed to another place. Perspectives on the use of animals for biomedical research are changing in fundamental and profound ways. Scientists still depend on animals for a wide array of research, ranging from learning about disease processes to testing the safety and effectiveness of new drugs and, most recently, to finding ways to grow replacements for damaged body parts. But through new initiatives, researchers are seeking ways to greatly reduce the number of animals used. Particular concern has focused on the ethical justification and scientific necessity of research on chimpanzees and other primates. The longstanding view that one either supports medical progress (thus endorsing the status quo of animal research) or animal welfare (thus settling for fewer lifesaving treatments in exchange for ending or drastically reducing animal-based research) is giving way to more nuanced thinking that upholds the values of both medical progress and animal welfare while promoting the use of alternatives to animal research.

The problem is that nuanced thinking has not had a voice. Many scientists who work on animal research have "complex views" about it, concluded the journal *Nature* after polling readers on the subject a few years ago, but they are reluctant to express their views because of fear of recrimination from animal activists, as well as pressure from colleagues to remain silent on the subject. Susan Kopp, a veterinary professor and codirector of Yale University's animal ethics study group, put it this way in a discussion with some of us from The Hastings Center: There are few "safe forums" where researchers and others involved and interested in animal research can have a civil discussion about ethical issues—where different perspectives can be shared and respected.

In November 2011, The Hastings Center held such a forum at Yale University, with generous support from the Esther A. and Joseph Klingenstein Fund and invaluable guidance from colleagues at the Yale Interdisciplinary Center for Bioethics. We invited people with different areas of expertise and different points of view for a frank discussion about the state of the debate over the use of animals in biomedical experiments—the ethical concerns, the scientific arguments for and against using animals in particular kinds of studies, and the availability of alternative models that might replace whole animals in some research. The goal was to harness their knowledge and capture their exchange of ideas to produce educational resources that would be useful to multiple audiences: biomedical researchers, students in biomedical research and law, members of institutional animal care and use committees, policy-makers, and anyone else who follows animal research issues. This special report is one of those resources; the other is our Web site (http://animalresearch.thehastingscenter.org), a hub of information that includes this report, along with other major reports, significant news, scholarship on animal studies, and links to groups engaged with biomedical research and the development of models to replace animals in that research.

Most of the commentaries were written by participants in the workshop on the topics of their presentations and were enriched by the conversations that occurred afterward. Several of the commentaries were also informed by major news announced a month after the meeting took place: the Institute of Medicine's groundbreaking report that concluded that "most current use of chimpanzees for biomedical research is unnecessary" and recommended that government-funded research on chimpanzees be sharply cut—a recommendation that Francis Collins, director of the National Institutes of Health, promptly accepted. These developments were highly significant because they concerned perhaps the most controversial of all animal experiments—those involving humans' closest relative. The United States is one of only two countries in the world that still permits invasive research on chimpanzees.

Susan Gilbert, "Progress in the Animal Research War," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S2-S3. DOI:10.1002/hast.98



Three of the commentaries concern research involving chimpanzees and other nonhuman primates. In "Raising the Bar," Jeffrey Kahn, the director of the IOM committee that wrote the chimpanzee report, assesses its implications. Despite its limitations, which he cites, Kahn concludes that implementing the report's criteria "will impose the strongest restrictions to date on the use of any animal species for research in the United States, a major change in animal research policy in general." In "The Case for Phasing Out Primate Research," Kathleen Conlee and Andrew Rowan, of The Humane Society, see the new restrictions on chimpanzee research as an opportunity for the United States to lead an international effort to take a hard look at the ethical issues and the scientific necessity for experiments with all nonhuman primates. D. Eugene Redmond, Jr., argues forcefully that some research on nonhuman primates remains essential. In "Using Monkeys to Understand and Cure Parkinson Disease," the focus of his work as a physician and researcher at Yale, Redmond agrees that alternative models are desirable but asserts that—for the time being, at least—there can be no breakthroughs in treating this disease without research on monkeys (he uses a species that is not endangered).

Fortunately, the outlook for alternatives to animal models is brighter in other areas of biomedical research, especially toxicity testing. In "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," Joanne Zurlo, of the Center for Alternatives to Animal Testing at Johns Hopkins Bloomberg School of Public Health, reports on the federal government's commitment to start replacing whole animals with systems based on human cells to assess the toxicity of tens of thousands of environmental and industrial chemicals and drugs. Noting that toxicity tests of pharmaceuticals in rats predict human toxicity only 43 percent of the time, Zurlo thinks that the new systems will be more relevant to humans, work faster, and cost less than animal models. She calls this paradigm shift "the most significant force to date leading to the ultimate elimination of animal use for biomedical research and testing."

Despite the progress toward that goal and the strong support for it, most of the commentators here do not think that it can realistically be achieved any time soon—at least, not if we remain committed to answering important basic questions about ourselves and other animals and developing treatments and cures for conditions that cause suffering. That "if" is central to the commentary by Joel Marks, codirector of Yale's animal ethics study group. He constructs a philosophical argument in which he concludes that the ends—basic and applied biomedical research—do not justify the means—causing animals to suffer and die. For Marks, nothing short of full replacement of animals in research is justifiable. But several of the writers identify concrete ways that everyone with a role in animal research can improve the welfare of laboratory animals. Bernard Rollin discusses how researchers can to do more to provide laboratory animals with the best possible living conditions compatible with their natures. Susan Kopp describes recent efforts to train veterinarians and lab technicians in humane animal care that are helping to provide the conditions that Rollin has in mind. Larry Carbone challenges researchers to justify their selection of particular kinds of animals in proposed experiments by showing that the information they seek is valuable and could not be obtained by other means. Stephen Latham suggests ways U.S. laws that govern animal experimentation can be amended to reduce unnecessary animal suffering. One example is to permit institutional animal care and use committees to explicitly balance harms to animals against the hoped-for scientific gains when evaluating research proposals. To those who fear that giving IACUCs this power could inhibit worthwhile research, Latham notes that institutional review boards are already empowered to engage in such balancing in human subjects research, "and this has not caused research to grind to a halt."

Given that our aim with this project was to produce educational resources, we labored to make the language absolutely clear. That proved easier said than done, since animal research ethics is notable for chameleonlike terminology. The word "alternatives," for example, can mean research models that replace whole animals, "lower" animals that replace "higher" animals, or new ways of doing things in order to inflict less pain and suffering. Therefore, we have included a glossary of terms used in discussions of animal research ethics. And when the writers use ambiguous terms like "alternatives," they clarify what they mean. In addition to being freely heard, the "nations" grappling with ethical and scientific disputes over animal experimentation must also be clearly understood if they are to progress to a place beyond hostilities and toward constructive solutions.

***—Susan Gilbert***

# The Moral Status of Invasive Animal Research

BY BERNARD E. ROLLIN

During the 1970s and 1980s, two veterinarians and I conceptualized, drafted, and ultimately, in 1985, persuaded Congress to pass federal legislation assuring some minimal concern on the part of researchers for the welfare of laboratory animals.[1] As part of that activity, I had occasion to study the scientific community's attitude toward the ethical issues emerging from the use of animals in biomedical research. I searched the scientific literature for an explicit articulation of the moral position underlying such use, but I found nothing save for an occasional gnomic statement such as, "Animal research is not a moral issue; it is a scientific necessity"—as if it could not be both. I came to see the failure of the scientific community to engage that issue as an inevitable consequence of what I have called "scientific ideology," or "the common sense of science," which is to science what ordinary common sense is to daily life.[2]

This ideology rests on two assumptions. One of them is that science is "value free" in general and "ethics free" in particular—that science, which concerns only what is observable or empirically testable, has no place for ethical judgments. The second is that scientists must be agnostic about consciousness (and pain) in animals. This assumption explains how it was possible that a literature search I performed in 1982 with the Library of Congress on "analgesia for laboratory animals" unearthed only two references, one of which merely affirmed that there ought to be papers on the subject. The ubiquity of the "common sense of science" ideology was dramatically illustrated when James B. Wyngaarden—then the director of the National Institutes of Health, arguably the chief biomedical scientist in the United States, and, therefore, science's principal spokesperson—was reported as saying that "ethical issues such as gene sequencing are always controversial, but research should not be hampered by moral considerations."[3]

Scientists, like any other subgroup of society, must operate within the boundaries of the *consensus social ethic* at a given historical moment or else risk loss of autonomy at the hands of restrictive social regulation or legislation. Our laws for research animals passed, despite very vigorous opposition from the research community, because they accorded well with burgeoning societal concern about the welfare of animals used for social benefit. In essence, the research community had failed to meet societal expectations for the proper treatment of research animals. A commitment to such treatment, particularly control of pain, should have been part of researchers' *professional ethics*.

Even today, it is doubtful that animal researchers understand the social expectations regarding animal care and use. Historically, society has not had a robust, institutionalized ethic for how animals should be treated. Before the Animal Welfare Act, the only laws constraining animal use in society were the anticruelty laws forbidding sadistic, deviant, purposeless, deliberate, unnecessary infliction of pain and suffering on animals, or outrageous neglect. These laws, both by statute and by judicial interpretation, did not apply to socially accepted animal uses such as research or agriculture. Because the overwhelming use of animals in society was in agriculture, aimed at providing food, fiber, locomotion, and power, and because the key to agricultural success was having healthy animals, good husbandry and good care were enforced by the most powerful sanction, self-interest; the anticruelty laws were only there for society to manage sadists and psychopaths unmoved by self-interest. But with the emergence of new kinds of "normal" animal use—such as intensive agriculture and animal research, both of which caused animal pain and suffering that did not fall under the anticruelty ethic—society was forced to create a new ethic for animals that went "beyond cruelty." The Animal Welfare Act was a start, but it did not address all of the ethical concerns that society has had about the treatment of animals. As evidence of the need for a new ethic for animals, thousands of bills pertaining to animal welfare have been promulgated across the United States in the last decade.

The new ethic for animals essentially applies much of our social ethic for humans, *mutatis mutandis*, to the treatment of animals and embodies the desired protections in the legal system. There are three layers of ethical concern regarding invasive research on animals:

***1. What entitles humans to use animals in ways that harm, hurt, kill, or distress them in research for human benefit?*** We cannot use humans—even socially disvalued human beings such as prisoners, mentally impaired persons, and unwanted children—for the benefit of the majority or of society as a whole without making sure that they understand the research and participate in it willingly. The researchers responsible for the Tuskegee experiments on untreated syphilis in black men argued that such people were "worth less" than other citizens, and thus, their interests could be sacrificed, without their informed consent, for the good of the majority.[4] But any such position was categorically rejected when the study came to light during the 1970s, prompting detailed federal restrictions on the use of human subjects in research. So what are the arguments for using animals in these ways?

***2. The only plausible argument for using human beings in these ways is the utilitarian one that they generate more benefits than costs.*** Society has categorically rejected that claim. But perhaps, in the case of animals, such an argument is socially acceptable. If so, we are led to another ethical concern about the use of animals in scientific experimentation. If the only justification for it is the benefit it provides—and that this benefit far outweighs the cost to the animals—then it follows that the only allowable animal use in experimentation would be that it provides greater benefit than the cost to the animals. But this is clearly not the current state of affairs. Animals are deployed in painful ways in myriad experiments that do not provide significant benefit. These experiments range from toxicological experiments that only provide some legal protection for corporations from lawsuits regarding product liability, to experiments in pursuit of new weaponry, to psychological experiments designed to inflict learned helplessness on animals as a model for human depression (illegal in the United Kingdom), to seeing how many bites an "intruder" animal into an established animal colony sustains, to numerous other experiments augmenting knowledge that appears to be of no practical value.[5]

***3. Given that practitioners of animal research essentially disregard the previous two ethical concerns, we are left with a third.*** If researchers fail to attend to the question of our right to use animals in invasive ways and ignore the clear-cut moral demand that the benefits from the research outweigh the costs to the animals, at the very least common sense and common decency dictate that animals used in research should be treated as well as possible. But even if, as the research community claims, the vast majority of experiments performed on animals do not cause significant pain, 100 percent of research animals suffer because the environments in which they are kept fail to respect their biological and psychological needs and natures. Social animals are kept in isolation; nocturnal animals are kept in twenty-four-hour-a-day light; housing and husbandry conditions are designed in accordance with human convenience, not animals' needs. Cage design is primarily determined by ease of cleaning, not animal comfort. Appallingly, even the death of the animals in the service of research is not the most painless and comfortable death possible. The vast majority of animals "euthanized" for research purposes do not get a "good death"; asphyxiation or suffocation by inhaled carbon dioxide is by no stretch of the imagination humane, despite its being approved by the American Veterinary Medical Association. AVMA is ostensibly the arbiter of humaneness of euthanasia, but its track record shows greater concern for human convenience than for animal welfare.

The only reference in the law to the many ways that animals used in research can suffer beyond the infliction of physical pain upon them—including fear, anxiety, separation from family and other animals of the same species, unnatural diets and food acquisition, severely truncated possibility of movement, denial of opportunities for play, disturbance of routine—is the statutory requirement that pain *and distress* be controlled. "Distress" is both a catch-all term and a

*Accommodating animal* telos *in a way that eliminates "negative mattering" and providing occasions for "positive mattering"—what we may call "animal happiness"—can go a long way towards making animal research a moral science.*

Bernard E. Rollin, "The Moral Status of Invasive Animal Research," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S4-S6. DOI: 10.1002/hast.99

placeholder for better understanding of the varied and subtle ways that animals used in laboratories can be harmed. Given the ideological resistance researchers have shown to even acknowledging physical pain in research animals, little progress on "distress" has been made by the animal research community.

The overwhelming majority of attention paid to ethical issues in category three has been devoted to control of acute physical pain and development of analgesic regimens. Little progress has been made in relieving chronic pain and in the control of any pain in farm animals used in research, since the Animal Welfare Act excludes agricultural animals. But an adequate account of animal ethics must transcend exclusive concern with pleasure and pain and recognize the full range of possible "matterings" unique to different sorts of animals. To accomplish this, we must look to Aristotle, the greatest common-sense philosopher of the ancient world, and specifically to his concept of *telos*, or animal nature, a root notion of his functional, teleological biology. Whereas modern biology focuses on reductionist, molecular, and mechanistic explanations, Aristotle's biology emphasizes the unique set of traits and powers that make the animal what it is—the "pigness" of the pig, the "dogness" of the dog.

Aristotle recognized that different animals evidenced different ways of fulfilling the fundamental nature of living things, such as nutrition, locomotion, sensation, cognition, and reproduction. How an animal fulfills these functions is what constitutes its nature. Secondary school biology is still studied in the Aristotelian way. There is nothing mystical about *telos*; it is simply what common sense recognizes as "fish gotta swim, birds gotta fly." The only departure that must be made from Aristotle today is to see *teloi* not as fixed and immutable, but as slices or snapshots of a dynamic process of evolution, genetically encoded and environmentally expressed.

An example from coyote behavior strikingly illustrates how *telos* needs can trump even major physical pain. It has been recounted for years that coyotes, caught in a leg-hold trap, will chew their legs off, enduring terrible pain, rather than submit to immobility. (This is also true for other animals, such as raccoons.) This is understandable given the coyote's *telos* as a free-ranging predator (or, on occasion, prey). It is not plausible to suggest that the animal chews its leg off to avoid death, since it is not possible that a nonlinguistic being has a concept of death, though it understands the inability to escape. Clearly, the animal is not chewing the leg in order to escape the pain, as any attempt to chew the leg off will greatly increase the pain.

Novelty of any sort evokes stress in most if not all animal *teloi*. Researchers know that animals can be trained by reward to willingly accept some physically painful experimental procedures. In one instance, a friend of mine was drawing blood from dogs daily for a vaccine study. She would enter the facility, play with each dog, draw the blood, and then give the dog a treat. On one occasion, one of the dogs set up such a howl as she was leaving that she raced back to see if his paw was caught in the cage door. It turned out she had forgotten to draw blood from that dog, and he had missed his play and his treat, which bothered him more than the blood draw. Such examples illustrate three major points:

1. Pain, as a physical phenomenon, does not begin to capture all the ways that what we do to animals matters to them.

2. Other things we do to animals can be worse for them than physical pain. Unfortunately, we have no words for many of the myriad ways we can harm or cause animals to suffer.

3. In general, interfering with or impeding actualization of *telos* creates a negative experiential state for an animal.

In sum, and in spite of the laws, the animal research community has been remiss in failing to address all three levels of ethical concern emerging from animal research. It is unlikely that society will force researchers to address the first level—namely, whether there is any moral justification for using animals in research. Restricting invasive animal use to what is patently beneficial will probably evolve in time, but very slowly, since such an evolution will depend in part on the creation of nonanimal alternatives. But the third level of ethical concern—providing animals with the best possible living conditions compatible with their natures and eliminating negative conditions—is currently practicable. Attention not only to physical needs and control of physical pain, but also to accommodating animal *telos* in a manner that eliminates all forms of "negative mattering" for the animals and provides occasions for "positive mattering"—what we may call "animal happiness"—can go a long way toward making animal research a *moral science*. Inevitably, a research environment that makes the life of an animal used in research a pleasant one can do a great deal to counterbalance the issues that arise from invasive animal use.

1. B.E. Rollin, "The Regulation of Animal Research and the Emergence of Animal Ethics: A Conceptual History," *Theoretical Medicine and Bioethics*, 27 (2006): 285-304.
2. B.E. Rollin, *Science and Ethics* (New York: Cambridge University Press, 2006).
3. P. West, "Director Addresses Health Research," *The State News,* February 27, 1989.
4. This was in fact communicated to me in a private conversation by one of the members of the Tuskegee research team. The Nazis presupposed such a principle in their research on unwilling subjects.
5. B.E. Rollin, *Animal Rights and Human Morality* (New York: Prometheus Books, 1992), 141-46 and 149-51; T. Hartung, "Toxicology for the Twenty-First Century," *Nature* 460 (2009): 208-212.



***Monkey Frieze***, by Franz Marc, oil on canvas, 1911, 75.5 x 135.5 cm.
Photo: Hamburger Kunsthalle, Hamburg, Germany / The Bridgeman Art Library

# Using Monkeys to Understand and Cure Parkinson Disease

BY D. EUGENE REDMOND, JR.

Research with nonhuman primates is essential to medical progress and will still be necessary for the foreseeable future. Almost all research scientists agree that animal research is critical to understanding basic biology, discovering new treatments for human (and animal) diseases, and maximizing the safety of new medicines while minimizing their harm to humans. All but two of the Nobel prizes in medicine awarded over the last one hundred years have depended on animal research,[1] and the list of modern medicines, vaccines, and other treatments, as well as basic science discoveries, is so extensive that it could not be adequately covered in even a huge volume.[2] Increases in average life span in the last century are the result of improved public health measures, and many diseases may be related to lifestyle choices. But animal research has contributed to understanding these factors and to the development of vaccines and lifesaving treatments. The philosophical debate regarding the benefits and moral costs of animal research has also filled many volumes by ethicists and philosophers. The major arguments against the use of animals in medical research have been explicitly refuted by a few brave scientists,[3] as well as implicitly by the vast majority of the working biomedical science community.

My contribution to this discussion is to provide a personal perspective on my decision if, when, and how to use monkeys in research experiments on Parkinson disease. I do not claim to speak for all scientists. Many of them prefer not to speak on this issue because people with strongly held opposing beliefs have been willing to engage in distortion of the facts, violence, and intimidation as a way of advancing their views. Universal and unequivocal support for animal research is reflected in collective statements by all of the major medical and scientific organizations, which state, in summary, that

D. Eugene Redmond, Jr., "Using Monkeys to Understand and Cure Parkinson Disease," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S7-S11. DOI: 10.1002/hast.100

the benefits to humans are worth the cost of some animals, as long as humane animal welfare guidelines are met.

As a physician researcher, I have been working for many years to understand and cure Parkinson disease. I became a physician in order to cure, alleviate, and understand diseases and to "do good" if possible. As prescribed in the Hippocratic Oath, I also want to do "no harm." In the real world of medicine, however, these categories are subject to probability—prescribing the right medicine to treat a disease sometimes leads to a harmful, even fatal, side effect, such as an allergic reaction, and harm is done. Balancing the risks and benefits is necessary to arrive at a reasonable course of action, and sharing the information with patients so that they can help decide what should be done is now the standard of medical practice. Similarly, sharing the risks and benefits of animal research with the general public is important for future patients (a group that will include nearly everyone at some point) to make an informed choice about the medicine of the future. I do research with monkeys to understand a serious, debilitating, and often fatal disease (a probable good) knowing that the use of some monkeys will certainly be harmful to them. But studies in monkeys will increase the probability of a benefit—as well as minimize the extent of harms from those treatments—to patients if and when the treatments are tested.

***What are the criteria for conducting research on monkeys?*** There must be a potential scientific or medical benefit of the research, and useful knowledge from the monkey research should be likely and unobtainable from alternative approaches. Basic research to understand diseases is ultimately as important as research with specific treatment goals. Rodents and other mammals are excellent models of many physiological processes and diseases in humans, but the central nervous system and higher brain functions are sufficiently different that monkey experiments are often essential for progress with neuropsychiatric and brain-related problems. Parkinson disease represents a research problem for which monkey studies can be justified. It is a poorly understood and often fatal disease affecting millions of people worldwide for which there are only palliative treatments. We know that a small population of neurons in the brain that produce the neurotransmitter dopamine dies prematurely, leading to the signs and symptoms of the disease, which include resting tremor, slow movement, rigidity, postural instability, and other motor problems. L-Dopa, a drug that increases dopamine concentrations in critical brain areas, mitigates many of the motor problems, but unfortunately does not always control all the symptoms. The drug also has diminished effects over time and often causes unacceptable side effects, such as hallucinations or incapacitating, abnormal movements.

A number of models are useful to understand the disease and test potential therapies. They include cells in a culture dish, genetically modified fruit flies, and rats with dopamine systems destroyed by a neurotoxin to induce some signs of Parkinson disease. But each of these models has limitations and may not predict results in humans. The brain systems responsible for dopamine function that underlie Parkinson disease differ between rats and humans. The rat model responds consistently to some drugs that have effects against Parkinson disease in patients, but it also responds to other drugs that have no effect.[4] A different compound, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), was tested in rats and was not found to have any deleterious effects, although when tested in patients, it made them worse. It was later discovered that MPTP actually destroys dopamine neurons in humans and monkeys and reproduces nearly every reported effect of Parkinson disease in monkeys.[5] Accidental exposures of humans to MPTP simulate Parkinson disease almost completely, confirming that monkeys exposed to MPTP are a reasonable model for studying the condition in humans.

Possibly better animal models are being developed as a result of new knowledge about several genes associated with Parkinson disease. At the present time, however, the monkey with MPTP-induced Parkinson disease is the best model we have and can predict benefits and side effects of new treatments. The species of monkey we use, *Clorocebus sabaeus*, is not endangered in the West Indies, and its closely related "parent" species, *Chlorocebus aethiops*, is widespread in Africa, with an estimated population in the millions.

Finally, there are considerable data supporting the main hypothesis of my work—that the dopamine neurons destroyed by Parkinson disease (or experimentally by a neurotoxin) could be replaced by neurons derived from fetal brain tissue, stem cells, or gene manipulations that would lead to therapeutic dopamine release and symptom relief.[6] We don't know, however, whether the cells would survive, develop, and connect properly in an adult brain affected by Parkinson disease. It is necessary, therefore, to test potential therapies in an animal model that simulates the conditions of the disease as closely as possible.[7]

***When should the research be done?*** The first steps in research with animals should begin with the simplest animals that are appropriate. There are economic—and, some would say, moral—reasons that experiments should progress with models up the phylogenetic scale where possible. Extensive neural tissue transplantation studies were first done in rodents, showing that cells survived. Monkeys should not be used without knowing the results from studies in simpler biological systems, although, as in the case of MPTP, rodent studies do not always predict what would happen in monkeys or humans.

For cell replacement therapy, using dopamine precursor cells derived from fetal brain tissue, stem cells, or from other adult cell sources such as skin, it is important that the potential treatment be well characterized. We should know what types of cells they are and what they become in culture, what



*I have great empathy and respect for animals, but I also accept the fact that the careful selection and use of animals in experiments to understand biology or to improve medicine is justified, even though this often represents a significant harm to them.*

genes and proteins they express, how neurons are activated electrophysiologically, and what neurotransmitters and other chemicals they release. Then they should be tested in the best Parkinson disease model to see if they survive a new environment, what cells they become, where they go, and if they relieve the signs and symptoms of the disease.

The fact that monkeys are genetically closer to humans than are rats increases the probability that predictions from monkey experiments will be correct. But this closeness also makes their use of greater concern. At some point after enough research has been done in monkeys, humans also have to be studied to find out the potential benefits and harms of the treatment. The fact that this is so does not diminish the importance of what is learned from the animal experiments. Far more harm would be done to humans if the animal experiments were not done first. When, exactly, enough preliminary research has been done to move to human trials is often a controversial point, and scientists tend to argue for more animal and safety studies.

***How should the research be conducted?*** When animal use is necessary, it should be carried out humanely and with concern for the comfort, general health, and well-being of the animals by scientists and staff who are qualified and trained to do the work successfully. These concerns have been codified in the *Animal Welfare Act and the Guide for the Care and Use of Animals* in the United States and in similar documents in other countries. Scientists, physicians, and veterinarians drafted these regulations not only for the well-being of the animals, but because they are necessary to ensure that research with the animals is valid. Animals are provided with veterinary care, cages that are large enough for them to move about, adequate food and water, an environment free of pain and with minimal stress, and conditions that are as natural as possible for their species. Proper anesthetics are used for procedures that might cause pain, along with analgesics thereafter. At the end of experiments, animals often must be killed to harvest tissues such as brain specimens that provide critical outcome measurements. These "sacrifices" are done humanely, using the same drugs that a veterinarian uses to put cats and dogs to sleep. If there are exceptions to any of these guidelines, such as research on pain, or the withholding of palliative treatments, these must be justified scientifically. The study plan and procedures must be reviewed and approved by an independent committee of experts for each institution that is constituted and operates according to rules that eliminate conflict of interest to ensure that the plan is properly carried out and the animals are cared for.

The best experimental designs should be used, with random assignment of treatment groups, controls for as many variables as possible, and blinding of evaluations to eliminate investigator bias. The fewest animals should be used that are necessary to accept or reject the study hypothesis according to the method that modern science uses to make progress.[8] The reality is that most experiments conducted in accordance with the scientific method could be described as failures, but this does not mean that they are without value. They rule out important negatives that lead to incremental knowledge and then, often after many years, to a successful new treatment. When new discoveries are made, they have to be replicated. That is not a "waste of animals" or duplication of effort, but how modern science works. Independent replication is how we confirm what is true. I have summarized the conditions for the use of monkeys in the table.

***Moral and ethical issues.*** The morality and necessity of medical research with animals are linked with the ethics of human research and medical practice. The ethical prescriptions and proscriptions as outlined in the Declaration of Helsinki in 1964 (and modified through 2008)[9] require a number of practices, many of which have been codified into the laws of many countries and are regulated in the United States by the Food and Drug Administration. These guidelines prescribe that humans should not be exposed to unknown risks or to risks without potential benefits. This usually requires that substances and potential treatments be tested in animals for efficacy and safety. It is certainly true that animal research does not predict human responses perfectly. This depends upon how accurate the animal model is and how similar or identical the particular animal system used is to humans. So research on human subjects is also always necessary. It is often necessary to do new animal experiments after human clinical trials to improve understanding or resolve problems before arriving at the most successful therapy.

***Could "alternatives" lead to the same or better results?*** Groups opposed to animal research often argue that computer models and other alternatives to animals could make animal experiments unnecessary. Alternatives to animal use

## Conditions for Using Monkeys for Biomedical Research

1. The research should address a significant basic science or potential therapeutic question for humans or monkeys.
2. Preliminary research should be done to support and justify the experimental approach proposed.
3. Some research should have been done in nonprimate species to gather preliminary data and, if possible, to test the experimental design.
4. There should be research findings to support differences between other potential animal models and monkeys or humans that would therefore support the study of monkeys and the inferiority of other animal models or alternatives to animals.
5. The potential benefits of the research should be evaluated against the potential risks to the primate subjects.
6. The species of monkeys used should be justified, and the use of endangered or threatened populations avoided without special justification.
7. The number of monkeys used for the research should be justified and minimized.
8. All animal welfare regulations should be followed, with special importance placed upon species-typical behaviors and environments unless exceptions are scientifically justified.

are clearly desirable and researchers eagerly adopt them when they become available. But at this time we do not have good alternatives to replace the animal models in use. A computer might be able to model a disease in some respects if we knew everything possible about it, and if the computer had all of the necessary capacities of an animal (the ability to move and to simulate the abnormal movement in Parkinson disease). But we do not have that knowledge, and to get it requires that we study animals.

The drug industry and academic and government scientists are highly motivated for economic and ethical reasons to replace animal research if possible. Animals are expensive, experiments often take a long time, and the necessary sample of animals that must be studied is often not clear. Finally, the experiments often fail to predict the results in humans. New strategies are being adopted that are an improvement over animal experiments, such as gene arrays for toxicology studies (see "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," in this volume) or stem cells taken from humans with a disease to be studied in cell cultures ("disease in a dish"). None of these advances, however, resulted from targeted efforts to find "alternatives," but from excellent basic science. Many of these alternatives depended upon animal experiments for their development or will depend on them for validation of results.

The suggestion by critics of animal research that scientists persist in animal experiments despite valid and viable alternatives is an ill-informed and intellectually and ethically insulting attack on the major scientific professional organizations, the National Institutes of Health, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, and most research universities and institutes. I do not know a single scientist who takes pleasure in inflicting pain or injury on animals. I, for one, have known and cared about all kinds of animals starting with my childhood experiences on my grandmother's farm with cows, horses, sheep, pigs, chickens, and other domestic animals (that are often treated horribly with today's industrialized farming conditions). I have been very attached to pet dogs and cats, and I had a monkey living in my house with my family for two years. I also have observed and interacted with numerous other animals in their native habitats and work for their conservation and protection. I have great empathy and respect for them, but I also accept the fact that the careful selection and use of animals in experiments to understand biology or to improve medicine is justified, even though this often represents a significant harm to them.

***Moral status of animals.*** I do not accept the idea that all living creatures have equal moral status, but rather that they have graded value according to their genomic similarities with us. In this view, highly intelligent, sentient creatures such as great apes, monkeys, dolphins, whales, and elephants have relatively high moral status. We have responsibilities because of our intelligence and power to interact with all animals with kindness and compassion. We also have the responsibility to understand and cure disease in our own species and others if possible, while inflicting the least amount of harm to both humans and animals. Basic science and research for new treatments are both essential for this process. Research with monkeys aided in the development of deep brain stimulation, with benefits for some Parkinson disease patients so far, but we have more work to do for the cure.[10] If the use of monkeys leads to the cure of Parkinson disease for the 500,000 people in the United States (and millions more around the world), some of whom suffer, suffocate, and die each year, it is an acceptable moral price to pay. These are your parents, grandparents, brothers, sisters, and possibly yourself. And Parkinson disease is *just one of many* horrible and incurable diseases that remain to be conquered with the aid of research with animals, including monkeys.



1. Foundation for Biomedical Research, http://www.fbresearch.org/TwoColumnWireframe.aspx?pageid=128, accessed September 30, 2012.
2. Ibid.
3. J.H. Comrow and R. Dripps, Jr., "Scientific Basis for Support of Biomedical Science," *Science* 192 (1976): 105-111; P.M. Conn and J.V. Parker, "The Animal Research War," *Federation of American Societies for Experimental Biology Journal* 22, no. 5 (2008): 1294-95; N.E. Miller, "The Value of Behavioral Research on Animals," *American Psychologist* 40, no. 4 (1985): 423-40; N.E. Miller, "The Morality and Humaneness of Animal Research on Stress and Pain," *Annals of the New York Academy of Sciences* 467, (1986): 402-4; D.L. Ringach, "The Use of Nonhuman Animals in Biomedical Research," *American Journal of the Medical Sciences* 342, no. 4 (2011): 305-313.
4. M.E. Emborg, "Nonhuman Primate Models of Parkinson's Disease," *Institute for Laboratory Animal Research Journal* 48, no. 4 (2007): 339-55; J.R. Taylor et al., "Behavioral Effects of MPTP Administration in the Vervet Monkey: A Primate Model of Parkinson's Disease," in *Toxin-Induced Models of Neurological Disorders,* A.J. Nonneman and M.L. Woodruff, eds. (New York: Plenum Press, 1994), 139-74.
5. Emborg, "Nonhuman Primate Models of Parkinson's Disease," 339-55.
6. A. Björklund and U. Stenevi, *Neural Grafting in the Mammalian CNS* (Amsterdam, the Netherlands: Elsevier Science Publishers, 1985); L.M. Björklund et al., "Embryonic Stem Cells Develop into Functional Dopaminergic Neurons after Transplantation in a Parkinson Rat Model," *Proceedings of the National Academy of Sciences U.S.A.* 99, no. 4 (2002): 2344-49; D.L. Choi-Lundberg et al., "Dopaminergic Neurons Protected from Degeneration by GDNF Gene Therapy," *Science* 275 (1997): 838-41; H. Lui et al., "Generation of Induced Pluripotent Stem Cells from Adult Rhesus Monkey Fibroblasts," *Cell Stem Cell* 3, no. 6 (2008): 587-90; I. Mendez et al., "Dopamine Neurons Implanted into People with Parkinson's Disease Survive without Pathology for 14 Years," *Nature Medicine* 14, no. 5 (2008): 507-9; M.J. Perlow et al., "Brain Grafts Reduce Motor Abnormalities Produced by Destruction of Nigrostriatal Dopamine System," *Science* 204 (1979): 643-53; D.E. Redmond, "Cellular Replacement Therapy for Parkinson's Disease—Where Are We Today?" *Neuroscientist* 8, no. 5 (2002): 457-58; D.E. Redmond, Jr., et al., "Cryopreservation, Culture and Transplantation of Human Mesencephalic Tissue into Monkeys," *Science* 242 (1988): 768-71; D.E Redmond, Jr., et al., "Behavioral Improvement in a Primate Parkinson's Model Is Associated with Multiple Homeostatic Effects of Human Neural Stem Cells," *Proceedings of the National Academy of Sciences U.S.A.* 104, no. 29 (2007): 12175-80; E.Y. Snyder et al., "Multipotent Neural Precursors Can Differentiate toward Replacement of Neurons Undergoing Targeted Apoptotic Degeneration in Adult Mouse Neocortex," *Proceedings of the National Academy of Sciences U.S.A.* 94, no. 21 (1997): 11663-68; M. Wernig et al., "Neurons Derived from Reprogrammed Fibroblasts Functionally Integrate into the Fetal Brain and Improve Symptoms of Rats with Parkinson's Disease," *Proceedings of the National Academy of Sciences U.S.A.* 105, no. 15 (2008): 5856-61.
7. Redmond, Jr., et al., "Behavioral Improvement in a Primate Parkinson's Model Is Associated with Multiple Homeostatic Effects of Human Neural Stem Cells."
8. Ringach, "The Use of Nonhuman Animals in Biomedical Research."
9. World Medical Association Declaration of Helsinki—Ethical Principals for Medical Research Involving Human Subjects, October 2008, http://www.wma.net/en/30publications/10policies/b3/.
10. T. Wichmann et al., "Milestones in Research on the Pathophysiology of Parkinson's Disease," *Movement Disorders Journal* 26, no. 6 (2011): 1032-41; "Parkinson's Patient Speaks Up," http://www.youtube.com/watch?v=uMaCiuapAW0, uploaded April 29, 2010, and accessed September 30, 2012.

# The Utility of Basic Animal Research

BY LARRY CARBONE

I am a comparative medicine veterinarian, mostly a mouse and monkey doctor; I started my professional life as a zookeeper. My entire career has relied on applying what we know about one species of animal to the care of another. Faced with diarrhea in a vampire bat, itchy skin in a hedgehog, or cloudy eyes in a monkey, I have reached for the diagnostic and treatment options I would choose for a dog or cat to supplement what is known about these less-studied species. If I find fungi in the itchy hedgehog's skin, I work on the assumption that the fungus is causing the itch, and will treat the hedgehog as I would a dog with fungal ringworm. As a monkey vet, I may go beyond the monkey medicine books and look to the available information on dogs, as well as to the advice of my colleagues who practice human medicine. My treatments could fail at any point—the fungus could be nonpathogenic; the medicine could be toxic—but this comparative approach is a starting place that I believe serves my patients and me well.

Cross-species extrapolation fits with evolutionary theory. Evolutionary continuities in anatomy, physiology, and biochemistry suggest that humans and nonhumans have medical continuities as well: similar diseases and similar responses to medicines and surgeries. Too much or too little glucose can cause health problems, and ancestral mammals bequeathed mice, dogs, and humans homologous pancreatic islets, producing homologous insulin and glucagon, that regulate blood glucose levels. It therefore seems plausible that studies of canine or murine diabetics will yield important information about their not-so-distant human relatives.

This cross-species extrapolation in clinical veterinary medicine buttresses the rationale for animal research for human health. In research, we seek to generate new knowledge that may indirectly benefit many patients. But this is a matter of significant moral weight: in that worthy goal, we may inflict great suffering on our animal subjects. An unexamined acceptance of cross-species extrapolation may be good enough as a veterinary clinician's starting point; is it good enough to drive time and resource allocation, and the infliction of animal suffering?

For animal research that causes sentient nonhuman animal suffering to be justifiable, I believe that two conditions must be met. First, harming animals for human benefit must be morally justified; this is the *speciesism* justification. Second, animal research must have utility—that is, it must produce useful, empirically valid knowledge that successfully increases our understanding of human illness and treatments and that could not reasonably be obtained through other means; this is the *utility* justification. In other words, (some) animals must be sufficiently *different* from humans in morally relevant ways to allow the morality of speciesism, and (some) animals must be sufficiently *similar* to humans biologically for cross-species extrapolation to have utility.[1] Both conditions are necessary, and neither by itself is sufficient to justify animal experimentation.

I focus exclusively on the utility justification. I do not defend the morality of using animals in experiments, nor do I review the alternatives and refinements that can minimize laboratory animal suffering, which remains an active area for inquiry and discussion.[2] (See "From the Three Rs to One: An Ethical Critique of Animal Experimentation" in this volume.) I do not defend the proposition that all Western allopathic, science-based medicine has utility, a paradigm that finds value in vaccines, antibiotics, surgeries, and cancer chemotherapeutics that outweigh whatever problems they present. Within that paradigm, I will argue here that I and the medical scientists with whom I work have a sound rationale to continue the work we do.

Larry Carbone, "The Utility of Basic Animal Research," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S12-S15. DOI:10.1002/hast.101



*All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility.*

## In Defense of Animal Research

Few defenses of the utility of animal research go beyond exhaustive lists of success stories, and few critiques go beyond listing failures. History is informative, but not conclusive. To say that dogs were vital to the discovery of the role of the pancreas in diabetes in the 1920s is not to conclude that other approaches could not have worked then, or that the dog studies would be necessary in the twenty-first century. Thalidomide, rofecoxib (Vioxx), and other drugs caused human health problems after having been tested on animals; these apparent failures do not show that animal research is useless.

C. Ray Greek and Jean Swingle Greek, as well as Hugh LaFollette and Niall Shanks, have published extensive critiques of the utility of animal models.[3] Their critiques focus mostly on the later stages of clinical research, when specific drugs and drug dosages are being investigated in humans for safety and efficacy. Greek and Greek begin their critique with a case study. A physician prescribes an antibiotic to a patient, Susan Knickerbocker, with no known drug allergies or sensitivities. The patient's severe drug reaction is fatal. The unnamed antibiotic would certainly have been tested extensively in animals and humans before it was available to this patient. What the authors highlight is that Knickerbocker's identical twin sister had taken the same antibiotic with no adverse reaction. "With difference in response so dramatic in two individuals who have virtually identical genetic profiles," they write, "what does this portend about attempting to extrapolate data on human response based on studies in rodents, monkeys, dogs, cats, and other species? Disaster." And so, they would end animal studies, which they find misleading to the point of danger—a "scientific failure."

Greek and Greek make important errors concerning how scientific biomedical knowledge is generated and applied. They err by misrepresenting how *generalized* biomedical knowledge is applied to individual patients. Medical practitioners cannot tell a patient the precise outcome of her medical condition, treated or untreated. Rather, they apply population-based, statistical, probabilistic information to each unique situation, hoping for the best while watching for the worst. One hundred percent safe, effective antibiotics do not exist. Nor are genes 100 percent predictive of outcomes; no one should expect twins to have identical medical outcomes any more than they live identical lives in other regards.

Greek and Greek write as though we should expect a one-to-one predictive correspondence between a subject (a patient's twin perhaps, or a laboratory mouse) and a given patient. But the truer depiction of the theories driving science-based medicine is one where data from many "subjects"— whether they are animals, humans, cells in culture, or computer simulations—are put together to build a body of knowledge that is general and probabilistic. Many animals, cells, and people are studied through a lens of statistical analyses applied to detect patterns from individual variation. Perhaps one mouse in a laboratory received that antibiotic for a lab-induced pneumonia and reacted as Knickerbocker had; perhaps not. Perhaps someone in the clinical trials on the drug met that fate as well; perhaps not. What matters is how their experiences were put with all the other subjects' experiences to identify a drug with certain odds of success and certain risks of failure. I believe that Greek and Greek err in overlooking this complicated middle piece. They do not just misrepresent how *generalized* biomedical knowledge is applied to individual patients, but they also oversimplify how biomedical knowledge is *generated*.

LaFollette and Shanks's is the stronger and more theoretically interesting challenge to animal research. They note a "shotgun effect." Given the amount of animal research performed and the evolutionary continuities among human and nonhuman animals, it is likely that at least some animal studies accurately produce knowledge about humans. But how often, and how can we know which ones are likely to do that? They argue that evolutionary differences that arise seemingly without explanation severely undermine our confidence in extrapolating from nonhumans to humans.

The assumption that what we learn in one species will be true in another often breaks down when we examine the particulars. Yes, mammalian livers generally occupy themselves with processing various foods, toxins, and medicines that we consume, but species differ in the particulars of the bio-

chemical processes. As LaFollette points out, cat, rat, swine, and human livers all metabolize phenol to an easily excreted metabolite by some combination of processes. Two of these processes are glucuronidation and sulfation. Human livers favor sulfation, though not exclusively. If you study phenol metabolism in pigs, which only glucuronidate, or cats, which don't glucuronidate, you might produce data that are dangerously misleading if applied to people. Worse, there seems to be no evolutionary explanation why the three omnivores in the group process phenol differently or whether being a carnivore explains the cat's approach to phenol metabolism. We share an ancestor who had its own way(s) of detoxifying phenol, but no theory to guide us on why or how twenty-first century pigs, cats, and people differ. It would be folly to blindly trust evolutionary continuity, and to underestimate real species differences, in choosing an animal model of phenol metabolism or possibly any other aspect of human biology.

The theory of LaFollette and Shanks is compelling, but I believe they misread actual practice in two important ways. First, they err in *underaccounting for the cumulative nature of biomedical knowledge*. How does a scientist start a research project into phenol metabolism? She does not start by buying whatever animal species meet her budget or her available housing; she reads the literature. A well-trained physiologist is not throwing darts at the wall in an unlit room. She already knows that there are species differences in phenol metabolism. She will call upon layers of scientific knowledge in the complicated task of choosing the animal model(s).[4] No biomedical researcher who is unfamiliar with this kind of literature should receive grant funding. The accumulated knowledge may lead to choosing different models for different applications.

The second error of LaFollette and Shanks is that they misunderstand the *dialectical* quality of research. Choosing an animal research model is not like choosing a racehorse: buy one chance and win or lose. Knowledge produced in a set of animal experiments is built on what has gone before and is then tested further; apparent failures (for example, not to see in humans what was seen previously in mice) need not mean that the initial work, much less the research enterprise, is bankrupt.

Consider one example from my institution. Stem cells of various sources hold the exciting potential to regenerate damaged tissue in the heart, other muscles, and central nervous system, which generally heal poorly. After surviving a major heart attack, the human heart has residual areas that never heal well, leaving the patient at risk of fatal heart disease. We can model this abrupt loss of blood to a region of heart muscle in pigs, mice, and rats and see similar structural and functional effects. And we can partially restore function by injecting bone marrow-derived stem cells into the damaged heart muscle. It seems plausible, then, that taking stem cells derived from the bone marrow of a human heart attack patient and transplanting them into the person's heart could save that person's life.

Unfortunately, mouse stem cells have been better at repairing damaged mouse hearts in the laboratory than have human stem cells in human clinical trials. So, one could put mouse models of heart attack on the scrap heap, one more example of animal studies failing to produce useful human medical knowledge. Or, one can go back to the laboratory, see how the mouse model studies differ from the human medical experience, and find out what the failure of extrapolation can teach us. In this case, genetic differences between mice and humans could be less important than the source of the cells and the timing of their collection. The mouse model at first used marrow cells from other, healthy mice of the same strain (an allograft from a near-twin), but human cells are harvested from someone who has had a heart attack right after it occurs and implanted into the patient's own heart. Wang and colleagues reworked the model and found that a heart attack can decrease the therapeutic potential of the mouse's marrow cells.[5] Rather than write the mouse model off as misleading, it can now be refined in culture and in animal studies to better explore how a heart attack can affect distant marrow cells, and to target the chemicals responsible for this effect.[6] The "failure" of the mouse model may in fact point to important, body-wide inflammatory processes—knowledge that may lead to improved management of post-heart-attack patients.

## In Search of the Perfect Model

Antivivisectionists are not alone in publishing critiques of animal studies; researchers do, too. Some bemoan the lack of animal models for particular conditions. Some argue over why some models are good and others not. Others explain the relative utility of different models depending on the particular question under investigation. No animal is a perfect replica of humans—not monkeys and apes, not "humanized" mice with human immune cells. Animals are chosen to model some aspect of human biology. The limitations of extrapolation must be recognized, and findings in humans that do not match the animal studies call for reexamination of the animal data, not its wholesale rejection.

Animal studies do not exist in a vacuum. They are conducted and interpreted with studies in cell and tissue culture, in human populations, in human volunteers, and in computer models. When that complex edifice leads to important discoveries and drugs, it is difficult to tease out the relative contribution of each research methodology. It is impossible to determine how much slower these discoveries would have been without animals, if they could have happened at all. It is even harder to look forward to as-yet-unknown knowledge and what studies will be most productive in its discovery. An enormous concern is about what we miss by overreliance on animal models. But that concern surely applies to overreliance on any of the research methodologies mentioned here, and even to the interwoven edifice of multidisciplinary research.

Animal research is similar to studies involving human volunteers, in vitro assays, epidemiological investigations, and computer simulations. All attempt to derive probabilistic knowledge in one context that will generalize to all people everywhere who will ever live. All are forms of modeling—even the longitudinal studies of tens of thousands of human participants—that will map onto all of humankind with less than 100 percent precision. They will predict with even less precision the fate of any individual human. All require learning from the models' apparent failures and comparing how the knowledge generated informs or is informed by data from other research modalities. All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility, in theory and in practice.

The utility that scientists claim for animal research does not in itself make the practice morally acceptable. It does not establish animal research as worth the time, money, and animal suffering it entails. But since animal research is justifiable only if the claims to utility are strong and accurate, those claims and the claims of its critics must be carefully examined. Lists of the apparent successes and failures of animal research do not alone establish or demolish claims to its utility. Scientists who think carefully about modeling should see both the successes and failures as sources of knowledge to guide future studies, always triangulating and testing knowledge gained in one system against information derived from other sources.


## Acknowledgments

Thanks to David Takacs, Elizabeth Boyd, Susan Gilbert, Lee-Ronn Paluch, Diana Bauer, Krista Lindstrom, and Monika Gramckow for their insightful comments on this manuscript.



1. H. LaFollette, "Animal Experimentation in Biomedical Research," in *The Oxford Handbook of Animal Ethics,* ed T.L. Beauchamp and R.G. Frey (New York: Oxford University Press, 2011), 797-825; L. Carbone, "Pain in Laboratory Animals: The Ethical and Regulatory Imperatives," *PLoS One* 6, no. 9 (2011): e21578.

2. Carbone, "Pain in Laboratory Animals"; L. Carbone, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy* (New York: Oxford, 2004), 291; A.N. Rowan, *Of Mice, Models, and Men: A Critical Evaluation of Animal Research* (Albany: State University of New York Press, 1983), 323; W.M.S. Russell and R.L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen and Co. Ltd, 1959), 238; J. Silverman, M.A. Suckow, and S. Murthy, eds. *The Institutional Animal Care and Use Committee Handbook* (Boca Raton, Fla.: CRC Press, 2000), 538; E. Kaliste, ed., *The Welfare of Laboratory Animals* (Dordrecht, the Netherlands: Springer, 2007), 358.

3. LaFollette, "Animal Experimentation in Biomedical Research"; J.S. Greek and C.R. Greek, *What Will We Do If We Don't Experiment on Animals?* (Victoria, Canada: Trafford Publishing, 2004); H. LaFollette and N. Shanks, *Brute Science: Dilemmas of Animal Experimentation* (London: Routledge, 1996), 286.

4. F. Quimby, "Animal Models in Biomedical Research," in *Laboratory Animal Medicine,* eds J.G. Fox, B.J. Cohen, and F. Loew (New York: Academic Press, 2002), 1185-1219.

5. X. Wang et al., "Donor Myocardial Infarction Impairs the Therapeutic Potential of Bone Marrow Cells by an Interleukin-1-Mediated Inflammatory Response," *Science Translational Medicine* 3, no. 100 (2011): 100ra90.

6. C.A. Springer and X. Wang, "Blunting Half of the Double-Edged Sword: Potential Use of Interleukin-10 to Protect Bone Marrow-Derived Cells after Myocardial Infarction," *Circulation Research,* 109, no. 11 (2011): 113-119.

# Accept No Substitutes:
## *The Ethics of Alternatives*

BY JOEL MARKS

*Any model system which moves down the phylogenetic scale from the generally acceptable animal model will be considered an alternative.*

—B. Taylor Bennett[1]

It is common to argue that animal experimentation is justified by its essential contribution to the advancement of medical science. But note that this argument actually contains two premises: an empirical claim that animal experimentation is essential to the advancement of medical science and an ethical claim that if research is essential to the advancement of medical science, then it is justified. Neither premise *looks* weak; the first premise is an article of faith for most biomedical researchers, and the second is usually considered so obviously true that it goes unstated. In fact, however, both are open to challenge. In the logic of the case, only one of the premises needs to be shown false or moot in order to refute the argument. A number of other commentators have questioned the first,[2] but it is the ethical premise that I find particularly wanting.

I think there are at least two ways to question it. The first depends on articulating the ultimate point of medical science. One can plausibly maintain that the justifying purpose of medical science is the health of humanity, or even more generally, the welfare of humanity. But if so, then medicine should be concerned as much as possible with *preventing* disease and injury, rather than with developing treatments and cures. Furthermore, as some have argued, we already know enough about the causes of most serious diseases to go a long way in preventing them. Our finite medical resources would therefore be far better spent on basic health care and public health education and campaigns than on further medical research.[3] Animal experimentation would likely be radically reduced, if not eliminated, in the bargain.

The second objection to the ethical premise of medical research is about whether the ends of medical science are overriding. For even if a given research regime showed great promise to eradicate cancer, society would not necessarily approve it. That is why we have animal experimentation in the first place. Cancer and all other major human ailments would probably yield their secrets far more rapidly if we performed various grisly and fatal experiments on human subjects instead of on other animals. Yet it is surely the consensus of modern medicine and society that we would never perform such experiments on humans, not even with their consent.

So then the question arises: Why do we perform them on other animals? If we would not conduct lethal experiments on humans in order to advance medical science, then there is no absolute *necessity* to cure or prevent cancer.[4] Yet one hears continually that we *need* to use animals in biomedical experiments, that animal experimentation is *necessary*. It is not.[5] It is a choice made by human beings for their own benefit.

When we think about the costs and benefits of animal experimentation, it is natural—unfortunately— to assume that only the costs and benefits for human beings are relevant. But of course, there are other sentient beings whose welfare is affected, namely, the animals on whom the experiments are performed. For all sorts of reasons, this fact has been largely overlooked for most of the history of medicine. In the starkest form of the argument in favor of animal research, even the bare capacity of nonhuman animals to feel pain has been denied by both biomedical researchers and philosophers.[6]

Joel Marks, "Accept No Substitutes: The Ethics of Alternatives," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S16-S18. DOI: 10.1002/hast.102



*It is really only full replacement of animals in biomedical research that merits the name "alternative." Any alternative to that understanding of "alternatives" is unjustified, not only in word but in deed.*

Of course, that view is by no means the contemporary consensus of the medical community. In the meantime, ethologists and others—including, indeed, animal experimenters—have confirmed what any pet owner already knows: nonhuman animals experience not only pain, but also distress and many other emotions.[7] Plainly, then, whatever benefits accrue to human beings from animal experimentation must be weighed against not only the costs to humans (including the *opportunity* costs of rejecting promising treatments because of their inefficacy or harm to other species and diverting scarce resources from effective preventive regimes), but also the costs to animals. Arguably, too, assessing these costs means more than just tallying up the experiences of the animals in laboratories; *interests* that transcend these costs are also relevant. Most salient would be the interest in continuing to live,[8] since the vast majority of laboratory animals are killed.[9]

In the calculation of all of these kinds of costs to these animals, we must consider not only the quality and magnitude of their suffering and thwarted interests, but also the number of animals affected. These figures are difficult to compile with precision because there are no uniform reporting requirements for all animals used in biomedical experiments. However, the number is certainly in the tens of millions, and of these a significant subset are subjected to "unrelieved pain and distress of varying severity."[10] Against this "cost," therefore, we are to weigh the benefit to human (and to animal) medicine in the long haul.

How is such a calculation to be carried out? There are two main problems here. First is that an actual cost—the animals' suffering and thwarted interests—is being balanced against a speculative benefit, such as a cure for cancer or the discovery of a new analgesic drug. The greater the gap between the certainty of the former and the uncertainty of the latter, the less does the latter justify the former. The second problem for this sort of calculation is that a common measure is needed in order to compare the various values. In particular, one wants to know how pain and distress and lost opportunities are to be assessed across species.

Here one must be alert to the inevitable bias human beings apply in their assessments of other animals' welfare and interests. The bias sometimes works to the apparent benefit of the animals, as when we treat pets as if they were members of our own human families. But in many other cases, we completely shut out of our mind what the animals must be experiencing. When animals are utilized for human purposes, such as providing food, clothing, and medicine, we simply fail to consider their actual suffering or denied freedom and so forth; we see these effects as somehow not measuring up to what a human being would experience in similar circumstances.

Absent from this way of thinking is an appreciation of the nonhuman animal's own valuation of his or her way of experiencing the world. If each of us, whatever kind of animal we may be, has but this one life to live, might we not conclude that a rat's life has as much value for him or her as a human's for him or her? Indeed, might not the much shorter life expectancy of a rat be an argument that the rat's few remaining years have greater, rather than lesser, value?[11] On whom does the burden of proof rest with this kind of issue? Is the issue even resolvable? And if it is not, then should we give the benefit of the doubt to those over whom we have absolute power and in whose exploitation we have a strong interest?

Thus, the various considerations that bear on the ethics of animal experimentation. Can any conclusion be drawn? I would say yes. One is that the only sure reason we can give for animal experimentation is that we have the power and the desire to do it for our own human purposes. This is not really a justification; it is that "might is right."[12] (Some experimentation on animals is done to promote animal welfare. However, not only does it typically "sacrifice" the individual for the sake of the species, but also typically does so in service to the broader human purpose of exploiting the animals, as when seeking a way to maintain the health of animals who are penned in close quarters and then slaughtered for food.)

The two most commonly given alternative rationales are that other animals experience *less* suffering or loss than we would under analogous circumstances and that their suffering or loss *matters* less than ours would. But any such attempt to justify promoting our good by imposing "bad" on other creatures must be immediately suspect, given that it is self-serving.

A second conclusion is that anything short of abolishing animal experimentation altogether risks leaving the status quo virtually intact. Consider the position of rodents in the laboratory. Rats and mice constitute the overwhelming ma-

jority of animals used for biomedical research—certainly over 90 percent.[13] Yet their welfare is systematically overlooked not only by animal users,[14] but even by some animal protectionists. The most in-your-face manifestation of the former is the explicit exclusion of research rodents from the definition of "animal" by the federal Animal Welfare Act.[15] But we find that even the so-called alternatives movement commonly contains a fatal loophole. For while a layperson may assume that the term "alternative" refers to the use of some wholly nonanimal method of research, testing, teaching, or training, in fact, it often means an animal "down the phylogenetic scale."

Thus, developing alternatives to the use of animals can mean simply using a *different* animal. (To stretch this point to absurdity, all animals used in animal experimentation can be thought of as alternatives, since they are alternatives to *human* animals.) Furthermore, the characterization of the other animal—usually a rodent—as "lower" on a phylogenetic "scale" is arbitrary and disputed.[16] The alternatives movement is therefore at risk of becoming a bait-and-switch con.

And it is even worse than that, for the very same animal (both species and individual) can be used as an "alternative." This is due to two additional ambiguities. One of them is between an experiment on a whole animal and an experiment on tissue taken from an animal of the same species. The latter can be considered an "alternative," but of course the animal is still bred, confined, and subject to various procedures. The other ambiguity is that "alternative" can refer to any attempt to reduce the number of animals in research, refine the procedures performed on them, or replace an animal subject with some other model.[17]

But it is really only full replacement of animals in biomedical research that merits the name "alternative." Any alternative to that understanding of "alternatives" is unjustified, not only in word but in deed.

1. B.T. Bennett, "Alternative Methodologies," in *Essentials for Animal Research: A Primer for Research Personnel*, 2nd ed., eds. B.T. Bennett, M.J. Brown, and J.C. Schofield (Beltsville, Md.: United States Department of Agriculture Library, 1994).

2. See, for example, R. Bass, "Lives in the Balance: Utilitarianism and Animal Research," in *The Ethics of Animal Research: Exploring the Controversy*, ed. J. Garrett (Cambridge, Mass.: MIT Press, 2012); P. Pound et al., "Where Is the Evidence That Animal Research Benefits Humans?" *British Medical Journal* 328 (2004): 514-17.

3. D.L. Katz, "Genomic Research Argument Overlooks Something Much More Obvious," *New Haven Register*, June 21, 2010.

4. H. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," *Philosophical Essays: From Current Creed to Technological Man* (Chicago, Ill.: University of Chicago Press, 1980), 105-135.

5. G.L. Francione, "The Use of Nonhuman Animals in Biomedical Research: Necessity and Justification," *Journal of Law, Medicine and Ethics* 35, no. 2 (2007): 241-48.

6. P. Carruthers, "Brute Experience," *Journal of Philosophy* 86, no. 5 (1989): 258-69. Carruthers's views have since evolved.

7. L.U. Sneddon, "Can Animals Feel Pain?" The Wellcome Trust, at http://www.wellcome.ac.uk/en/pain/microsite/culture2.html, accessed December 13, 2011; M. Bekoff, *The Emotional Lives of Animals* (Novato, Calif.: New World Library, 2007).

8. J.W. Yeates, "Death Is a Welfare Issue," *Journal of Agricultural and Environmental Ethics* 23 (2010): 229-41.

9. L. Carbone, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy* (New York: Oxford University Press, 2004), 22.

10. Ibid., 28.

11. A. Linzey, "Why Animals Deserve Special Moral Solicitude," *AV Magazine* 117, no. 4 (2009): 8-10.

12. Ibid.

13. Carbone, *What Animals Want*, 25-26.

14. I make this point in "On Due Recognition of Animals Used in Research," *Journal of Animal Ethics* 1, no. 1 (2011): 6-8.

15. S.A. Leary and C. Schaeffer, "Making History: Birds, Rats, Mice, and the AWA," *AV Magazine* 119, no. 2 (2011): 6-7.

16. A.L. Rosenberger, "Charles Darwin III: Descent with Modification," *Visionlearning* BIO-2, no. 5 (2004), at http://www.visionlearning.com/library/module_viewer.php?mid=112, accessed December 13, 2011.

17. A.M. Goldberg and J. Yager, "Replacement," Lecture 11 of "Enhancing Humane Science, Improving Animal Research," Center for Alternatives to Animal Testing, Johns Hopkins Bloomberg School of Public Health, http://ocw.jhsph.edu/courses/humanescience/PDFs/CAATLecture11.pdf, accessed December 13, 2011.



# Training the Next Generation

BY SUSAN KOPP

As an educator in an urban veterinary technology program, I often encounter students beginning their professional studies who are passionate about their commitment to a career working with animals. Typically, they have also firmly decided that they will never accept a job in the animal research field. They object to animal research in general because of what they assume is the abject mistreatment of animals housed in laboratories.

Chatting again with these students two years later as they prepare for graduation, however, I am increasingly finding that many reconsider those firm convictions. In fact, even in a strong job market for veterinary technicians, some of these graduates are actually choosing to enter the laboratory animal care field.

What is causing such an about-face? Listening to their experiences, I have noted that this change is due, in no small part, to the impact of working with and learning from deeply caring professionals during their required summer externships at major research institutions. Students see for themselves what actually takes place in a biomedical research facility. And the more supervisors take time to involve students in ensuring high standards of humane animal care in the laboratory, the more these soon-to-be graduates understand the vital role they can play in improving animal welfare. Students often return from these externships profoundly changed: more serious about their chosen profession, more attentive to the subtle needs of animals in their care, and with a deeper consciousness of the responsibilities involved in safeguarding animals. Several of these alumni are now budding leaders in laboratory animal welfare, presenting at national conferences and sharing their own projects and ideas to improve animal care.

Ten years ago, my responsibilities as both program director and the attending veterinarian for the institutional animal care and use committee at LaGuardia Community College (part of The City University of New York) caused me to delve deeper into student training in laboratory animal care and handling. Since that time, I have been edified by the level of commitment and caring I have encountered in the laboratory animal care professionals with whom I have collaborated. Much of their focus today is centered on the ongoing search for new and better alternatives to longstanding ways of handling and caring for animals. (I use the term alternatives here as it relates to the three Rs: *replacement* of animals with nonanimal research models, *reduction* of total animals needed by a given study, or *refinement* of current procedures to minimize distress and improve well-being.) Given the challenges and ethical conflicts surrounding work in the laboratory animal care profession, this is no small feat.

Teaching animal care personnel about the replacement, reduction, and refinement of animal use in medical experiments is a work in progress. It is important to acknowledge that this effort was fueled, as Bernard Rollin notes in his essay in this volume, by the key 1985 amendment to the Animal Welfare Act and related legislation, such as the Health Research Extension Act in 1985. Now, the animal research community itself is very much at the forefront in crucial efforts to improve care and welfare of animals in laboratories. This movement is evident, for example, in recent revisions to the *Guide for the Care and Use of Laboratory Animals*. First published in 1963, the eighth edition, in 2010, goes into more detail than ever regarding species-specific social housing needs, animal welfare, and the crucial role of staff education and training.[1]

Susan Kopp, "Training the Next Generation," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S19-S22. DOI: 10.1002/hast.103

A key means to improving animal care and welfare is to train those working with animals in the most current information about species-specific behaviors and needs and their varying expressions of both distress and pain. Conferences, webinars, and internal facility training are increasingly focused on improving overall animal well-being. "Twenty years ago, we rarely spoke of enriching an animal's environment or species' needs, or the necessity of identifying potentially stressful procedures," said Leticia Medina, a laboratory animal veterinarian at Abbott Laboratories, "but now these [topics] are always at the center of conversations and are among the most sought-after sessions at conferences." This was my own experience when asked to present animal ethics lectures for laboratory caretakers and researchers during this past year. Attendance exceeded expectations, and interest among session participants was keen.

Despite the costs, institutions are creating staff positions directly related both to the three Rs and to the teaching of best practices in animal care and assurance of animal welfare. Typically, three Rs "specialists" work closely with technicians and other experienced members of animal care teams to evaluate and refine current procedures and implement alternative approaches that are potentially capable of reducing stress and improving an animal's quality of life both with regard to standard husbandry procedures and in the actual research techniques themselves. In New York City, for example, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, and The Rockefeller University collaborate to run a tri-institutional training program in laboratory animal science.

A number of training modalities are currently being used and developed among institutions nationwide. Aside from training mannequins and models, Web seminars, simulated laboratory training sessions, and contracting with outside experts for in-house training are becoming increasingly common. The Laboratory Animal Welfare Training Exchange established in 1994 by a small group of laboratory animal care professionals, for example, provides a forum for exchanging best practices in laboratory animal care training and welfare. With limited resources at many facilities, the availability and exchange of high-quality training materials, particularly relating to species-specific care and handling refinements, can positively affect animal welfare. "It is no longer acceptable to just put an animal in a cage and get our research results," one veterinarian told me recently. "It's about acting responsibly, about doing what is right ethically in order to ensure humane care *for every animal*."

Until the last two decades, training included little information on animal distress or on the recognition and treatment of animal pain. As Rollin and others have discussed, this was due to a number of factors, including a lack of appreciation in the scientific community for the ethical importance of alleviating animal pain and distress. But the scientific community has become more attuned to this issue because of increased public awareness and concern for animal welfare, advancements in understandings of the physiological and behavioral complexity of animals, and greater availability of suitable pain relief protocols for animals, to name a few factors.[2]

## Training and Animal Welfare

Laboratory animal veterinarians, with support from technicians and caretakers, oversee disease surveillance, facility rounds, and care for sick animals. Veterinarians and animal welfare specialists are usually involved in the training and education of researchers and staff, drafting standard animal care procedures for husbandry and establishing medical and surgical protocols. Veterinarians are directly responsible, as members of institutional animal care and use committees, for approval of new and existing research studies. Because of this, they can have a tremendously positive impact on animal welfare considerations related to a given study.

Technicians are also crucial members of animal care teams because they are responsible for a large majority of daily, hands-on animal care and direct observation. Thus, training personnel to minimize animal stress through housing changes and environmental enrichment can markedly impact the quality of life for animals entrusted to their care. It is recognized, for example, that laboratory rats demonstrate a preference for cages that provide nest boxes that allow them to seek darker and more protected refuge.[3] Proper training of technicians and caretakers would include education in the correct placement of the nest boxes and in their cleaning and upkeep.

Similarly, in order to minimize distress, some researchers and technicians are now taking significant amounts of time to train higher functioning animals to cooperate for quick procedures like blood collection by using paired rewards such as treats, play sessions, petting, and other positive-reinforcement approaches. This serves both to decrease the need for animal restraint or sedation and to provide animals with additional enrichment during the course of research studies.

Good training also involves recognizing pain and distress in laboratory animals. While a general benchmark is that any procedure that would be painful to humans should be considered painful to animals, different species demonstrate pain differently. Signs of pain in mice will differ from those observed in cats, and certainly from those seen in zebra fish.

Pain is now considered to be much more complex than just the acute, sensory components of physical pain. More attention is being given to the emotional aspects of pain, which include fear, anxiety, depression, inability to express species-specific needs, and the long-term, systemic effects on an animal's overall well-being. A 2008 National Research Council committee publication, *Recognition and Alleviation of Distress in Laboratory Animals*, issued a call to the scientific community for better collaboration, communication, and adherence



*Chatting again with my students as they prepare for graduation, I am increasingly finding that, even in a strong job market for veterinary technicians, some of them are actually choosing to enter the laboratory animal care field. What is causing such an about-face?*

to the growing body of information regarding minimizing distress in animals housed in laboratories.[4] Strengthened language in the 2010 *Guide for the Care and Use of Laboratory Animals* also states that all persons involved in the care and use of animals are to be "adequately educated, trained, and/or qualified in basic principles of laboratory animal science to help ensure high-quality science and *animal well-being*."

Personnel who are able to recognize signs of animal pain and distress can represent a crucial link in improving animal welfare. A recent article in the *Journal of the American Association for Laboratory Animal Science*, written by veterinary staff at the M.D. Anderson Cancer Center in Houston, Texas, describes the implementation of an intensive training program for technicians and husbandry staff working with the center's rodent colony. After learning about early recognition and treatment of diseases in the animals, the staff felt empowered to be more proactive. They were able to notify veterinary staff of the animals' diseases earlier and to begin preliminary treatment for ill animals. This resulted in a decrease in illness-related animal deaths.[5]

## Supporting Efforts to Develop Alternatives

Several pharmaceutical companies and academic research centers have instituted programs to encourage employees to come up with ideas for reducing and replacing animals used in research and for refining how animals are treated. Abbott Laboratories, which has a strong institutional animal welfare policy, established a Global Animal Welfare Award in 2009 to honor employee efforts toward new and innovative ideas in caring for laboratory animals. A voluntary, company-wide committee provides a forum for pursuing new alternatives. Interdepartmental cooperation and collaboration among Abbott researchers in 2010, for example, allowed revisions to microsampling blood collection techniques that resulted in a 50 percent decrease in the number of mice required for one research study.[6]

Efforts in recent decades to improve animal welfare and generate needed alternatives have not, however, been well communicated to the general public. Due to strong sentiments about animal research, open discussions and transparency have historically been avoided, if not feared, by the scientific community. Timothy Blackwell and Bernard Rollin, in a 2008 article in the *Journal of the American Veterinary Medical Association*, suggest that the resulting void of information has ultimately risked increasing negative public opinion towards animal research.[7] Temple Grandin, a Colorado State University animal sciences professor, makes a similar argument when she suggests that it is necessary to "open the doors electronically" to the public. In a December 2011 interview at the University of Washington Health Sciences Center, where she was speaking to researchers, she commented, "If you don't show what you do, then people are going to imagine and it's going to be even worse."[8]

Similarly, in the 2010 Animal Welfare Institute (AWI) book, *Caring Hands*, editor Viktor Reinhardt chronicles 1,900 electronic comments and suggestions for improving animal care and welfare contributed by technicians, caretakers, veterinarians, and other participants in an ongoing AWI Laboratory Animal Refinement and Enrichment Forum. In his introduction to the book, Reinhardt eloquently speaks of the book's twofold purpose: it is both for persons "genuinely concerned about the welfare of animals kept in laboratories" *and* for those in the animal rights community "who don't know that most animal caretakers and technicians, many veterinarians and some researchers do their very best to refine the traditional, often inadequate housing and inhumane handling practices so that the animals experience less distress."[9] A concrete example of efforts by caretakers to develop refinement alternatives, the book is filled with pictures, explanations, and discussion threads around recommendations for husbandry and handling. One part of the book, for example, contains detailed responses to the question of how best to prepare enrichment materials for pigs that allow foraging and rooting activity. Photos speak volumes about the energy and compassion of many of those generating these ideas.

The Foundation for Biomedical Research and similar organizations use various media to communicate the important role of animal research in the search for cures for serious diseases. The foundation did this recently with a television

documentary on breast cancer research, which was nominated for an Emmy Award in 2011. Academic institutions such as the University of Wisconsin and Penn State University's Animal Resource Program have public Web sites about their animal research work, training, and facilities, with Penn State offering a virtual laboratory tour. In addition, several major companies, including Charles River Laboratories and Novo Nordisk, are sharing information on their Web sites about their animal welfare standards and practices. "There is an important story to be told," reflected Theresa Cunningham, director of the Center for Laboratory Animal Services at the Hospital for Special Surgery in New York. "The more we work at training and refining standards for animal care and communicating with the public on our current humane care and use of research animals, the more it can build trust and understanding for the work we do—and it also supports us in finding possible alternatives to using animals."

Even with improvements in animal welfare, invasive research on animals can be emotionally distressing to research staff. Humans form relationships with the animals in their lives. Evidence of this bond stretches back to prehistoric times. No matter how firmly a person believes in the value of medical research and the necessity of experimenting on animals (at least for now), there is no getting around the reality that animals pay a huge price. The death of a lab animal can cause veterinarians, lab technicians, and others who have worked with and become attached to it to grieve. Furthermore, as technicians, researchers, and others in animal care teams are encouraged to show ever-greater compassion and care for the animals entrusted to their care, the bond between the animals and their caregivers deepens. Recognizing this, labs have started conducting commemorative events in gratitude to their laboratory animals.[10] These events have their roots in religious and secular rituals performed around the world to pay tribute to animals for the many roles that they play in humans' lives—as companions, in military and police service, and in agriculture.

The Center for Laboratory Animal Services at the Hospital for Special Surgery, for example, has prepared two such tributes over the past four years that were supported at all levels of the hospital. Researchers, physicians, and hospital staff and administrators were present at these tributes, which were extremely well received. "Animal use to bring ahead medical progress is a privilege, not a right," one participant told me, "and something that everyone, at every level of an institution, needs to be reminded of."

1. National Research Council Committee for the Update of the Guide for the Care and Use of Laboratory Animals, *Guide for the Care and Use of Laboratory Animals,* 8th ed. (Washington, D.C.: National Academies Press, 2010).
2. J.S. Gaynor and W.K. Muir, *Handbook of Veterinary Pain Management* (St. Louis, Mo.: Mosby Elsevier, 2009).
3. E. Hutchinson, A. Avery, and S. VandeWoude, "Environmental Enrichment for Laboratory Rodents," *Institute for Laboratory Animal Research Journal*, 46, no. 2 (2005): 148-61.
4. National Research Council Committee on the Recognition and Alleviation of Distress in Laboratory Animals, *Recognition and Alleviation of Distress in Laboratory Animals* (Washington, D.C.: National Academies Press, 2008).
5. C.R. Lockworth et al., "Training Veterinary Care Technicians and Husbandry Staff Improves Animal Care," *Journal of the American Association for Laboratory Animal Science*, 50, no. 1 (2011): 84-93.
6. N.A. Bratcher and L.V. Medina, "Use of a Full-Time 3Rs Scientist/Alternatives Coordinator to Promote Refinement, Reduction, and Replacement in a Drug Discovery and Development Paradigm." Paper presented at the annual meeting of the American Association of Laboratory Science Association, San Diego, Calif., October 4, 2011.
7. T. Blackwell and B. Rollin, "Leading Discussions on Animal Rights," *Journal of the American Veterinary Medical Association*, 233, no. 6 (2008): 868.
8. K. Sienfeld, "Animal Expert Temple Grandin Says Fear Can Be Worse Than Pain," KPLU National Public Radio, December 8, 2011, at http://www.kplu.org/post/animal-expert-temple-grandin-says-fear-can-be-worse-pain.
9. V. Reinhardt, ed., *Caring Hands: Discussions by the Laboratory Animal Refinement and Enrichment Forum,* vol. II (Washington, D.C.: Animal Welfare Institute, 2010).
10. S.A. Iliff, "An Additional 'R': Remembering the Animals," *Institute for Laboratory Animal Research* 43, no. 1 (2002): 38-47.



# No Animals Harmed:
## *Toward a Paradigm Shift in Toxicity Testing*

BY JOANNE ZURLO

The original Food and Drugs Act, passed by the United States Congress in 1906, did not require any premarket testing of products.[1] In the ensuing years, however, several events led to passage of a stricter version of the law. In one case, a permanent mascara called Lash Lure caused blisters and ulcers in several women using the product and the death of one woman from a resulting infection. In another case, a drug preparation called Elixir Sulfanilamide was created by mixing an antibacterial sulfa drug with a sweet-tasting liquid to make it more palatable for children. The sweet liquid was actually diethylene glycol, a component of antifreeze, which is toxic to the kidneys. This drug claimed 107 lives, mostly children.[2] Thus followed the passage of the federal Food, Drug, and Cosmetic Act (FDCA) in 1938, which extended the power of the federal government to oversee the marketing of cosmetics and medical devices and mandated that drugs be tested for safety prior to marketing.

Over the course of the twentieth century, the creation and marketing of tens of thousands of new chemicals led to ever-growing concern about toxicity. The federal Insecticide, Fungicide, and Rodenticide Act, passed in 1947, required the registration of pesticides before they could be marketed on an interstate or international basis.[3] The Miller Pesticide Amendment to the FDCA in 1954 identified methods for setting safety limits for pesticide residues in food. In 1976, the Toxic Substances Control Act addressed the control of new and existing industrial chemicals not regulated by other laws. As of 2005, there were 82,000 chemicals in commerce, with approximately seven hundred new chemicals being introduced per year.[4] There is little publicly available safety data for most of these chemicals, and many of them are produced in quantities of a million pounds or more per year.

As this brief history demonstrates, the lack of safety information about the chemicals to which humans and animals—both domestic and wild—are exposed is a serious public health problem. But the prospect of generating the data for these numerous compounds presents other practical, scientific, and ethical challenges. Animal models have traditionally been used to test for toxicity, but animal testing cannot generate all the toxicity data we now need. To continue using animals for this purpose would lead to the killing of many millions of them. Moreover, animal models are not perfect substitutes for humans. It is true that much valuable information has been gleaned from animal research, and that the information has contributed to our knowledge of the mechanisms of many human diseases. On the other hand, it is not clear how often animal models have led research down a wrong path simply because results from animal studies were not applicable to humans.

Fortunately, advances in science have led to a new vision for toxicity testing based on human cell systems that will be more predictive, have higher throughput, cost less money, be more comparable to real-life exposures in humans, while using many fewer animals. This vision, embraced by leading scientific and regulatory groups, is a paradigm shift from animal-based to human-based testing that signals a major change in focus and promotes the development of new approaches to understanding the toxicity of chemicals in humans. Information gained from these new approaches will likely affect other areas of research as well, leading to less reliance on animals in the future.

Joanne Zurlo, "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S23-S26. DOI: 10.1002/hast.104

## A Call for Change

Since its inception, the mainstay of toxicity testing has been administering high doses of test compounds to animals and looking for adverse effects. While the methods of analysis have become more sophisticated, the premise has remained the same. There are numerous disadvantages to this approach. First, human exposures to environmental chemicals typically occur at low concentrations. However, if testing strategies were based on these low concentrations, many more animals, time, and money would be needed to detect adverse health effects in humans. Therefore, in order to maximize the detection of toxicities, animals are treated with very high doses of chemicals. Even so, the studies take years to complete, and only very low numbers of compounds can be tested in a given period. These studies also require large numbers of animals. In addition, in order to relate the test conditions in these high-dose animal studies to realistic human exposures, scientists must extrapolate the results to lower doses in order to determine safe levels of exposure for humans. Such extrapolations are fraught with difficulties because high-dose exposures may cause adverse effects through processes that may not occur at low doses.

Second, inbred strains of animals are routinely used for testing chemicals. Again, this strategy is employed to improve the detection of adverse effects. Inbred strains exhibit less genetic variability, which can affect an animal's response to a chemical agent. However, humans are not inbred—we are quite heterogeneous genetically and thus potentially exhibit considerable variability in susceptibility to adverse effects from a chemical. Yet the toxicity test data reflect only the effects of a chemical in a genetically restricted population.

The third major problem with the current animal-testing strategies is that the results are obtained primarily from rats and mice, and though rats and mice exhibit many of the same responses to chemicals as humans, there are also many differences. Toxicity tests of pharmaceuticals in rodents predict human toxicity only 43 percent of the time.[5] Interestingly, the results in the rat predict the results in the *mouse* only 57 percent of the time. If a chemical is shown to cause adverse effects in an animal species by a process that is known to be irrelevant to humans, the data from those studies are not used for risk assessment. But since the differences among species are not all known, an uncertainty factor must be applied even to the animal data that are used.

Thus, there are several major scientific issues with the current toxicity testing approaches: the necessity for high-to-low dose extrapolation, the limitations of genetically homogeneous animal strains, and the uncertainty of interspecies comparisons. The practical problems are the cost and time requirements and the inability to test large numbers of chemicals. The ethical concerns are the number of animals that would be required to undertake a full testing regimen of all chemicals, and the fact that the testing protocols typically involve some pain, distress, or both to the animals, making the whole scenario a major animal welfare issue.

Recognizing these shortfalls, the Environmental Protection Agency in 2003 requested that the National Academy of Sciences review existing strategies and develop a vision for the future of toxicity testing. After four years of toil, a committee of twenty-two experts in toxicology, epidemiology, environmental health, risk assessment, and animal welfare, representing academia, industry, and nongovernmental organizations, produced two reports: *Toxicity Testing for Assessment of Environmental Agents: Interim Report*[6] and *Toxicity Testing in the 21st Century: A Vision and a Strategy* (Tox21c).[7] The second report proposed a major change in toxicity testing—from charting the effects on animals to mapping toxic pathways in human cells with minimal use of animals.

A pathway of toxicity is a cellular mechanism that, when sufficiently perturbed, is expected to result in an adverse effect at the cellular level and may lead to an adverse health effect for the organism. So rather than the "black box" approach of dosing an animal with a chemical and looking at the end result (death, cancer, or organ failure, for example), the new approach would involve measuring changes in the molecules of the cell in response to a chemical. With low concentrations of chemicals, these changes might be reversible and the cells might recover through adaptive responses; with higher concentrations, the changes might be irreversible and would begin a cascade of cellular events that eventually lead to impaired function or death of the cell. As more information is derived from the study of these pathways, researchers would identify early cellular changes that, in years to come, cause catastrophic effects.

While the vision seems straightforward, in reality it describes an extremely ambitious task likely to take years, if not decades. Mapping the pathways of toxicity requires a concerted effort among many scientists and agencies. Recognizing the effort required to implement the vision, the committee outlined a plan to guide the development of the scientific basis for the new paradigm. In the first phase, scientists will work on elucidating the pathways of toxicity. Since this research will produce a large amount of data, massive data storage and management systems will be needed. Guidelines for assay performance and reporting of results will have to be developed as well. The first phase will also include creating a strategy for collecting data from human populations that have been exposed to chemicals already found in the environment. Population-based studies can provide information on toxicity pathways and health risks not revealed by traditional toxicity testing. Information gathered from population-based studies will also contribute to knowledge about susceptible populations including children, the elderly, and immune-compromised individuals.



*Advances in science have led to a new vision for toxicity testing based on human cell systems that will be more predictive, have higher throughput, cost less money, and be more comparable to real-life exposures in humans, while using many fewer animals.*

The second phase of the plan calls for developing a suite of representative human cell lines that can be used for assessing toxicity. At the same time, emphasis will be placed on developing high- and medium-throughput assays. The goal of these assays is to screen large numbers of chemicals in human cells and then follow up with limited, targeted testing in whole animals for chemicals that need further characterization.

In the third phase of the plan, scientists will assess the relevance and validity of the new assays. First, they will compare the results from new tests with historical information obtained from traditional animal tests. In particular, information from chemicals that have large datasets from traditional tests will be valuable in determining the benefit of new assays. It should be pointed out, however, that comparing the results from new assays with old tests may not be an "acid test," since the animal tests are considered less than perfect in predicting human toxicity. New methods for validation will also be needed. The new tests will screen many chemicals that have never have been tested, generating a large bank of valuable data. Surveillance of human populations will also be part of this phase and will provide data to support the validation of the new assays. Data from human populations will also be valuable in postmarket assessment of chemical toxicities because they will show adverse effects that occur in the population. In the final phase, a suite of validated tests will be proposed by the regulatory agencies for use in place of selected traditional methods.

## Putting the Plan into Place

The vision and implementation plan are grand, and yet to achieve these goals the committee identified many other elements that must fall into place. There must be institutional changes in attitudes and expectations. The scientific community must foster and accept the ideas put forth in the vision and collaborate to move the science forward. It is also imperative that scientists in academia, industry, and government regulatory agencies work together to identify goals and milestones. These collaborations should also inform policy changes that recognize the value of the new tests and facilitate incorporating them into regulation.

In the years since the publication of the Tox21c report, progress has been made to ensure this vision is implemented. The National Toxicology Program (NTP) set out its vision in a document called "NTP Roadmap—Toxicology in the 21st Century: The Role of the National Toxicology Program." Soon after the Tox21c report was published, a Memorandum of Understanding was drawn up among the EPA's National Center for Computational Toxicology, the National Toxicology Program, the National Institutes of Health Chemical Genomics Center, and the Food and Drug Administration's Center for Drug Evaluation and Research. This collaboration, called Tox21, commits these agencies to pursue together the goals put forth in the report.

Commitment to the goals set in the vision has expanded. In 2008, Francis Collins, now the director of the NIH, proposed "a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments." In 2009, the EPA published its "Strategic Plan for Evaluating the Toxicity of Chemicals,"[8] which serves as the agency's blueprint to take a leadership role in implementing the Tox21c vision. And at the 2011 annual meeting marking the fiftieth anniversary of the Society of Toxicology in Washington, D.C., Margaret Hamburg, director of the FDA, embraced the vision by declaring that, "With an advanced field of regulatory science, new tools, including functional genomics, proteomics, metabolomics, high-throughput screening, and systems biology, we can replace current toxicology assays with tests that incorporate the mechanistic underpinnings of disease and of underlying toxic side effects."

Work to implement the vision of toxicology testing without animals is progressing. The EPA's ToxCast Program is using 650 state-of-the-art rapid tests using mostly human cells to screen over two thousand environmental chemicals for potential toxicity.[9] In phase I of the program, ToxCast screened 309 chemicals (primarily pesticides) whose toxicity had been profiled over the last thirty years using animal tests. This phase was meant to provide the proof of concept for the approach. Currently in phase II, the investigators are screening

one thousand chemicals that include industrial and consumer products, as well as food additives and drugs that failed in clinical trials, in order to validate, expand, and apply predictive models of toxicity. In addition, the Tox21 collaboration has begun testing ten thousand additional chemicals. Data obtained from these testing efforts will be shared publicly to encourage reproduction and validation of the results.

Thomas Hartung, the director of the Johns Hopkins Center for Alternatives to Animal Testing, has spearheaded a related joint effort to begin to map the entire human pathways of toxicity (the "human toxome"). Through a grant from the NIH director's Transformative Research Award program, Hartung is collaborating with investigators at Johns Hopkins Bloomberg School of Public Health, Brown University, Georgetown University, The Hamner Institute for Health Sciences, Agilent Technologies, and the EPA ToxCast program to use integrated testing strategies in combination with computational models to study the pathways of toxicity for endocrine-disrupting chemicals. CAAT has also become the focal point and secretariat for the Evidence-Based Toxicology Collaboration, a group of individuals from government, industry, academia, and nongovernmental organizations formed to develop guidelines to validate new tests.

These new approaches to assessing the hazards of environmental chemicals essentially forecast the eventual end for the need for animals for toxicity testing. While the vision put forth in the Tox21c report still includes limited use of animals, the numbers will be dramatically reduced from those currently used. The advances in technology that can be applied to toxicity testing also serve as a bellwether for the future of animal use for biomedical research. The information gathered over the next several decades to inform regulatory decisions about environmental chemicals will vastly contribute to the body of scientific knowledge in other fields. Since much of biomedical research is focused on human health and disease, data obtained from studying the pathways of toxicity in human systems can be used to fill gaps in our knowledge of human biology and shed light on the differences between humans and the animals used to model humans.

There are potential drawbacks to any model system used to study disease. Certainly at this point, cell cultures cannot answer every scientific question. But it is likely that animals will eventually become obsolete for research to benefit humans. The paradigm shift in toxicology testing is the most significant force to date leading to the ultimate elimination of animal use for biomedical research and testing.


### Acknowledgments

I would like to thank Alan Goldberg and James Yager for their critical review of this manuscript.



1. U.S. Food and Drug Administration, "Milestones in Food and Drug Law History," at http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm081229.htm.
2. National Research Council, *Science, Medicine, and Animals: A Circle of Discovery* (Washington, D.C.: National Academies Press, 2004).
3. J. Zurlo, D. Rudacille, and A.M. Goldberg, *Animals and Alternatives in Testing: History, Science and Ethics* (New York: Mary Ann Liebert, 1994).
4. National Research Council, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (Washington, D.C.: National Academies Press, 2007).
5. H. Olson et al., "Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals," *Regulatory Toxicology and Pharmacology* 32, no. 1 (2000): 56-67.
6. National Research Council, *Toxicity Testing for Assessment of Environmental Agents: Interim Report* (Washington, D.C.: National Academies Press, 2006).
7. National Research Council, *Toxicity Testing in the 21st Century*.
8. U.S. Environmental Protection Agency's Science Policy Council, "The U.S. Environmental Agency's Strategic Plan for Evaluating the Toxicity of Chemicals," EPA 100/K-09/001, March 2009, http://www.epa.gov/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf.
9. U.S. Environmental Protection Agency, "ToxCast: Screening Chemicals to Predict Toxicity Faster and Better," http://www.epa.gov/ncct/toxcast, accessed October 2, 2012.






# Raising the Bar:
## *The Implications of the IOM Report on the Use of Chimpanzees in Research*

BY JEFFREY KAHN

I had the privilege of chairing the Institute of Medicine Committee on the Necessity of Chimpanzees in Biomedical and Behavioral Research in 2011, an effort that has lessons not only about the questions presented to it, but also about the policy and practice of the use of chimpanzees in research and about animal research policy in general. In this essay I will assess the impact and implications of the committee's work and at the same time clarify what I see as its limits.

The National Institutes of Health chartered the committee in response to public concerns over the proposed move of a small colony of chimpanzees from Alamagordo, New Mexico, where they had lived for approximately ten years. What prompted the proposed move was the end of a contract with a private company (Charles River Laboratories) to care for the animals, which the NIH had obtained after their original owner could no longer properly maintain them. The NIH planned to increase efficiency by moving the animals from Alamagordo to another colony of chimpanzees owned and supported by the NIH in San Antonio, Texas. The move, in addition to uprooting the Alamagordo chimpanzees from the environment they had been in for a decade, would also have returned them to the active research population (they had not been used in research while at Alamagordo). Animal welfare and animal rights advocates called for the decision to be reconsidered. The advocacy included appeals to both U.S. senators from New Mexico, as well as then-Governor Bill Richardson and Senator Tom Harkin from Iowa. The result was a letter to NIH Director Francis Collins signed by the senators requesting an in-depth analysis by the National Academies of the current and future need of chimpanzees in research. The Institute of Medicine, in collaboration with National Research Council, was awarded a contract by the NIH to perform the study.

The committee was multidisciplinary, with the expertise among the members representing a broad range of topics: virology, immunology, infectious disease, vaccinology, cancer, primatology, veterinary medicine, patient advocacy, and bioethics. It held its first meeting on May 26, 2011, and met two other times—once for a one-and-a-half day public workshop in August 2011, and the last time in a private session in October 2011. After the peer review process, the committee's report and recommendations were issued on December 15, 2011. The committee's most important and lasting contribution was the articulation of the criteria for justifying the use of chimpanzees in research, with separate criteria for biomedical and behavioral studies.

The committee recommended that the NIH limit the use of chimpanzees in biomedical research to those studies that meet the following three criteria:

1. There is no other suitable model available, such as in vitro, non human in vivo, or other models, for the research in question;

2. The research in question cannot be performed ethically on human subjects; and


Jeffrey Kahn, "Raising the Bar: The Implications of the IOM Report on the Use of Chimpanzees in Research," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S27-S30. DOI: 10.1002/hast.105

3. Forgoing the use of chimpanzees for the research in question will significantly slow or prevent important advancements to prevent, control, and/or treat life-threatening or debilitating conditions.[1]

The committee also recommended that the NIH limit the use of chimpanzees in comparative genomics and behavioral research to those studies that meet the following two criteria:

1. Studies provide otherwise unattainable insight into comparative genomics, normal and abnormal behavior, mental health, emotion, or cognition; and

2. All experiments are performed on acquiescent animals, using techniques that are minimally invasive, and in a manner that minimizes pain and distress.[2]

For both sets of criteria, the animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats. Comparative genomics and behavioral research using stored samples are exempt from these criteria.

When the committee examined the existing areas of biomedical research involving chimpanzees funded by the NIH, it concluded that nearly every one of them failed to meet the criteria for necessity. There were only two exceptions. One of them was research in the pipeline for developing monoclonal antibodies that rely on the chimpanzee model, though such ongoing research will be completed within a few years. The other exception was the development of a prophylactic vaccine for hepatitis C, on which the committee was evenly divided between those who felt such research satisfies the criteria and those who felt that it does not. The sticking point in the hepatitis C vaccine debate centered on whether a challenge trial is necessary before undertaking the first efficacy trials in humans. Challenge trials, in which vaccinated individuals are intentionally exposed to the infectious agent, cannot be performed ethically in human subjects. First trials of efficacy in humans can be, and are, performed without prior challenge trials in animals—HIV vaccine trials in populations known to be at risk of HIV are a prime example. Some members of the committee felt that while early-phase efficacy research without challenge can indeed be carried out ethically in human trials, challenge studies are required to identify appropriate candidate vaccines. The other members felt that challenge trials could be important but were not necessary. Even for that single area of disagreement there was consensus that rapid advances in the development of nonprimate animal models (so-called humanized mouse models, in particular) would mean that chimpanzees would be unnecessary within a few years. On the other hand, a substantial proportion of behavioral research did meet the committee's criteria. This included noninvasive research performed on acquiescent chimpanzees, as long as the animals are maintained in ethologically appropriate environments.

At the conclusion of the report's release briefing, Francis Collins, the NIH director, held a teleconference to announce his endorsement of its findings and the immediate implementation of its recommendations. NIH halted future funding of research involving chimpanzees pending the creation of a process for reviewing new applications for such research. It also instituted a process for review of all current NIH-funded projects involving chimpanzees to assess whether they met the new criteria.

## Lessons from the Committee

The most common and, in my view, most important question I have been asked since the release of the committee's report is one or another version of the following: Since it came so close, why didn't the committee recommend a total prohibition on research involving chimpanzees? Some versions were not so much questions but criticisms that the committee had not gone far enough in its recommendations. This question, or criticism, is about more than the will of the committee, raising important and challenging issues about the moral status of chimpanzees, the charge to the committee, and the policy landscape related to animal research in general and for great apes in particular.

Any substantive discussion or debate about a potential prohibition on the use of chimpanzees was limited by the charge to the committee, which stated that it should "explore contemporary and anticipated biomedical research questions to determine if chimpanzees are or *will be* necessary for research discoveries and to determine the safety and efficacy of new prevention or treatment strategies" (my italics). The key phrases are related to whether there are anticipated *future* uses that would satisfy the committee's criteria. The committee quickly acknowledged that since it is impossible to predict the future, it could not recommend a prohibition on all future research given the remote but possible emergence or reemergence of an infectious disease for which research would satisfy the committee's criteria. That said, the committee's strongly held view is that establishing strict criteria that include high standards for justified use will go a long way toward limiting any foreseeable future use.

The analyses and critiques of the committee's report started almost immediately upon its release and continued in a steady stream. That was hardly surprising given the high level of interest in the issue and the careful attention the committee's deliberations received from across the full spectrum of stakeholder perspectives. What is more surprising is the near consensus on core aspects of the committee's work, the report, and its implications: (1) that the report was fair, balanced, and accurate, (2) that the report paid insufficient attention to and did not adequately explain the ethics of research involving chimpanzees, (3) that the report and its recommendations will have a significant policy impact, and (4) that the adoption and implementation of the recommendations represent a watershed in animal research policy. While heartening to receive generally positive assessments, there are a number of aspects that deserve explanation and explication, and then there is the criticism regarding the paucity of ethics in the report. I briefly address each of the four areas below.



*The rapid implementation of the committee's recommendations by Dr. Collins ushered in a sea change in the criteria used to assess the necessity of the use of chimpanzees in research.*

***The report was fair, balanced, and accurate.***

The IOM process works to assure that committee members have the expertise relevant to the committee's task, and IOM staff are expert at accessing and collecting information as required. The chimpanzee committee was especially well served by the IOM process, which identified a group with the relevant mix of expertise that functioned remarkably well together and was committed to reaching consensus in its efforts. These were key characteristics for a committee presented with a highly contentious charge whose members clearly understood the policy implications of their recommendations. Along with its aim to reach a consensus, the committee was committed to undertaking its task with an open mind—it held no preconceptions about the need for using chimpanzees and was willing to review the information it found and make whatever recommendations the findings supported. The staff compiled the large amounts of information relevant to the committee's task, and the evidence supporting the committee's conclusions was clear and ample. Finally, the committee felt that it was very important to operate in public to the extent possible and to make its process transparent, both of which contributed to stakeholder trust in the process and the outcome.

All these features together created a process and an outcome that I believe are rightly perceived as fair and accurate. The fact that so much of the committee's work was performed in public or with public access allowed the full range of interested stakeholders to assess the perspectives sought and considered. These factors led to a process and a report perceived—I believe rightly—as balanced.

***The report paid insufficient attention to ethics.***

While the majority of the responses to the report's recommendations were positive, one consistent and significant criticism focused on the limited discussion of ethics. This criticism argues that it is odd for a report assessing the use of chimpanzees to have paid so little attention to what seems to be among the core questions motivating the appointment of the committee in the first place: Is it ethically acceptable to conduct invasive research on chimpanzees, given their close genetic relationship to humans? The criticism holds that answering this fundamental question is primary to any discussion of when chimpanzees are scientifically necessary for research, if ever.

Two factors help explain the committee's limited discussion of ethics in its report. First of all, the charge to the committee omitted any mention of the ethics of research on chimpanzees. As a result, the committee did not include the relevant expertise to assess that issue; in fact, I was the only scholar of bioethics on the committee. Second, the charge to the committee did not allow it to recommend a prohibition. In spite of these limitations, the committee made clear, both in public sessions and in its report, that ethics is at the core of any consideration of the necessity of the use of chimpanzees. Specifically, it recognized "that any assessment of the necessity for using chimpanzees as an animal model in research raises ethical issues" and that "the chimpanzee's genetic proximity to humans and the resulting biological and behavioral characteristics not only make it a uniquely valuable species for certain types of research, but also demand greater justification for their use in research than is the case with other animals." So while it did not assess whether it was ethically acceptable to use chimpanzees for research, the committee made its recommendations with a clear sense that they raised the bar for justification of the use of chimpanzees, and did its best to articulate a rationale for that position.[3]

***The report will have a significant policy impact.***

Those of us in bioethics working on national-level committees hope that our efforts will make an impact—on practice, policy, or at least on the thinking of those who read the results of our work. The fact that Francis Collins endorsed the committee's recommendations and implemented them on the day the report was released represented the sort of policy impact that we all aim for but rarely realize. The reasons for the rapid implementation will be debated, but I expect they include a combination of strong findings in support of clear recommendations that confirmed a trajectory that has been underway for some time, and an endorsement of a change

in policy that will institute a clear process for reviewing any proposed future use of chimpanzees. In addition, there is vocal public and government sentiment to support restrictions.

***The policy changes represent a watershed in animal research policy.***

The rapid implementation of the committee's recommendations by Dr. Collins ushered in a sea change in the criteria used to assess the necessity of the use of chimpanzees in research. Among the most surprising of the committee's findings was that there were no documented criteria for assessing the necessity of proposed chimpanzee use in NIH-funded research. The process internal to the NIH was apparently ad hoc and performed by a committee without membership from outside NIH. Similarly, the review process at the four primate centers lacked written criteria or guidelines. Thus, the decision to halt future NIH funding of research involving chimpanzees until the criteria recommended by the committee could be implemented represented a significant departure from past policy. The criteria, once implemented, will impose the strongest restrictions to date on the use of any animal species for research in the United States, a major change in animal research policy in general. And the committee's inclusion of a criterion that human subjects must be ruled out on ethical grounds as part of the justification for the use of chimpanzees turns the traditional presumption regarding the use of research animals on its head—again, a major change in animal research policy.

All in all, I believe it is fair to say that the committee's recommendations and the process of its work represent a success for bioethics-related consensus committees. The combination of topic, timing, and public stakeholder sentiment may have aligned in unique ways that contributed to that success. But even if it turns out to be a special case of sorts, there are lessons to be learned for the future.

1. Institute of Medicine, Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, D.C.: National Academies Press, 2011), 6.
2. Ibid., p. 6.
3. Ibid.



# The Case for Phasing Out Experiments on Primates

BY KATHLEEN M. CONLEE AND ANDREW N. ROWAN

Whether they realize it or not, most stakeholders in the debate about using animals for research agree on the common goal of seeking an end to research that causes animals harm.[1] The central issues in the controversy are about *how much* effort should be devoted to that goal and *when* we might reasonably expect to achieve it. Some progress has already been made: The number of animals used for research is about half what it was in the 1970s, and biomedical research has reached the point where we can reasonably begin to envision a time when it could advance without causing harm to animals. With some effort and aggressive development of new biomedical research technologies, full replacement of animals in harmful research is within our grasp. The goal will not be reached all at once, however, and phasing out invasive research on all nonhuman primates should be the priority.

Approximately 70,000 nonhuman primates are used for research in the United States each year, according to the U.S. Department of Agriculture, and another 45,000 are held or bred for research. They include macaques, baboons, marmosets, and other monkeys, as well as some chimpanzees. Moreover, these numbers are increasing in the United States and Canada. The rise is driven in part by the "high-fidelity" notion (supported by very little careful scientific justification) that primates are likely to be better models than mice and rats for studying human diseases, and partly by the sheer availability of primates.

The availability factor is a result of historical accident. In the 1960s, the United States invested in a significant infrastructure for primate research through creation of the National Primate Research Centers. The primate center program was the result of two unrelated occurrences. First, in the 1950s, hundreds of thousands of wild primates were captured and imported to support the race to develop a poliomyelitis vaccine. By 1960, with polio vaccines in use, this "race" was essentially over, but laboratories still had tens of thousands of primates. Then, they became swept up in another kind of race. The Russians had beaten the United States into space by launching the first satellite, creating panic that Russian science was outpacing U.S. science. American scientists made the argument that, because the Russians had a big primate research center, the United States should also have one or more primate centers. Seven facilities, formally recognized as government-supported institutions, were set up to provide support for and opportunities to do research in nonhuman primates.

The centers did not produce the hoped-for results. Three federal assessments found that the research conducted by the centers fell far short of expectations in terms of quality, and many deficiencies were also noted.[2] In the early 1980s, these centers were "rescued," in a sense, by the discovery that primates at the California Regional Primate Research Center were suffering from a simian version of AIDS. Suddenly, there was renewed focus on research in nonhuman primates. There are now eight National Primate Research Centers, the objective of which continues to be "to provide support for scientists who use NHPs in their research."[3]

Primates are used for a wide variety of research purposes. An analysis of one thousand federally funded studies that involved nonhuman primates found that research on HIV accounted for about 27 percent of the funding, followed by colony maintenance (likely because caring for primates is

Kathleen M. Conlee and Andrew N. Rowan, "The Case for Phasing Out Experiments on Primates," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S31-S34. DOI: 10.1002/hast.106

costly) at 15 percent, neurological research at 14 percent, and developmental research at 10 percent.[4]

### Arguments for Phasing Out Primate Research

Phasing out primate use should be a priority for ethical, scientific, and economic reasons. The ethical concerns fall into two categories. One of them is the nature of the primates themselves. They are well known for their cognitive and emotional abilities. Studies demonstrate that they have mathematical, memory, and problem-solving skills and that they experience emotions similar to those of humans—for example, depression, anxiety, and joy. Chimpanzees can learn human languages, such as American Sign Language. Primates also have very long lifespans, which is an ethical issue because they are typically held in laboratories for decades and experimented on repeatedly. The other category of ethical concern is how primates are treated. Each year, thousands are captured from the wild, mostly in Asia and Mauritius, and transported to other countries. For example, China sets up breeding colonies, and the infants are sold to various countries, including the United States and European countries. The animals experience considerable stress, such as days of transport in small crates and restrictions on food and water intake. Studies show that it takes months for their physiological systems to return to baseline levels,[5] and then they face the trauma of research, including infection with virulent diseases, social isolation, food and water deprivation, withdrawal from drugs, and repeated surgeries.

Providing for the welfare of primates in a laboratory setting is very challenging. According to the Animal Welfare Act, each facility must develop and follow a plan for environmental enhancement to promote the psychological well-being of nonhuman primates. The plan must address social grouping; enriching the environment, with special consideration for great apes; caring for infants, young juveniles, and those primates showing signs of psychological distress; and ensuring the well-being of those primates who are used in a protocol requiring restricted activity.

Social companionship is the most important psychological factor for most primates. Federal law requires institutions to house primates in groups unless there is justification, such as debilitation as a result of age or other conditions, for housing them alone. But a recent analysis of documents from two large facilities obtained by The Humane Society of the United States demonstrates that primates spent an average of 53 percent of their lives housed alone. In many instances, a metal shape hung for a month on the bars of a metal cage was deemed to constitute adequate "enrichment."[6]

There have been only a few detailed examinations of the scientific value of primate use, and most were undertaken in Europe.[7] While there has been no general review of the usefulness of primate research in the United States, chimpanzee research has recently come in for very careful evaluation and serves as a case study for how all primate use should be examined. The Institute of Medicine's landmark 2011 report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity,* concluded that "most current use of chimpanzees for biomedical research is unnecessary."[8] (See "Raising the Bar: The Implications of the IOM Report on the Use of Chimpanzees in Research," in this volume.) Most countries have banned research on chimpanzees, and there has been great pressure in Europe to end other primate use. A group chaired by Sir Patrick Bateson, current president of the Zoological Society of London and professor of animal behavior at Cambridge University, as well as former secretary of the Royal Society, published a report in 2011 that reviewed research using nonhuman primates in the United Kingdom. It is important to note that around 70 percent of all primate use in the United Kingdom is conducted to satisfy legislative or regulatory testing requirements and not necessarily because primates are essential for satisfying scientific goals.

The Bateson report recommended that all proposed primate studies be assessed using the following parameters: scientific value, probability of medical or other benefit, availability of alternatives, and likelihood and extent of animal suffering.[9] The report indicated that if a proposed use would cause severe suffering, it should be allowed only if there is a high likelihood of benefit. The report considered approximately 9 percent of the studies it examined to be of low importance and to inflict high levels of suffering.[10] The report was critical of some of the neuroscience research, which represented nearly half of the research surveyed. It found that half of the thirty-one neuroscience studies took a high toll on animal welfare, although most were also considered to be of high scientific value. Two of the studies were of concern because they posed a "high welfare impact," but moderate-quality science and little medical benefit.[11] The report recommended that more consideration be given to alternatives to nonhuman primates, including brain imaging, noninvasive electrophysiological technologies, in vitro and in silico techniques, and even research on human subjects.[12] The report recommended other ways of reducing the number of primates needed for research, including data sharing, publication of all results, and periodic review of outcomes, benefits, and impact of the research. "Researchers using NHPs have a moral obligation to publish results—even if negative—in order to prevent work from being repeated unnecessarily," the report states.[13]

In addition to the ethical and scientific arguments for ending research involving primates, there are economic reasons. Primates are very expensive to maintain. The eight National Primate Research Centers alone receive $1 billion of the National Institutes of Health's total $32 billion budget. The care and upkeep of primates other than chimpanzees is twenty to twenty-five dollars per day, compared with twenty cents to about $1.60 per day for small rodents. We argue that much of the research with nonhuman primates is either of questionable value or has not been carefully evaluated and justified. Therefore, these funds might be better spent on other research models, including several technologies that could replace nonhuman primates and other animals. Francis Collins, director of the NIH, argued in 2011 that new high-throughput approaches could overcome the drawbacks of animal models—they are slow, expensive, and not sufficiently relevant to human biology and pharmacology.[14]

Several such technologies are available. The U.S. Army recently announced that it would end the use of monkeys for chemical casualty training courses and replace them with alternatives such as simulators that mimic the effects of nerve gas on victims.[15]

*As we have done with chimpanzees, we need to critically analyze uses of other nonhuman primates. A good starting point would be the formation of a working group of diverse stakeholders who agree that ending primate research is a worthwhile goal.*

### Following Chimpanzees

The process that culminated in the phasing out of invasive research on chimpanzees in the United States in 2011 can and should be applied to all other nonhuman primates. Public opinion and ethical challenges drove that process. Even before the 2011 IOM report, scientists in the United States were having difficulty justifying why they should perform experiments on chimpanzees when their colleagues in other countries had stopped doing so. Unlike nonhuman primates in general, the number of chimpanzees in U.S. labs has been declining since reaching its peak in the late 1990s.

The main drivers for efforts to phase out research on chimpanzees are their genetic, biological, and behavioral similarities with humans.[16] Chimpanzees are humans' closest relative. Chimpanzee cognition has been studied extensively, and their capabilities are considerable. As with other primates, the impact of laboratory life—including barren housing and social isolation—on chimpanzees can last decades due to their long lifespan and thus raises significant welfare concerns. There is evidence that some chimpanzees used in research suffer from a form of posttraumatic stress disorder similar to that of humans. In their 2008 article, Gay Bradshaw and colleagues described the plight of a chimpanzee named Jeannie who endured invasive research and social isolation for over a decade. She exhibited abnormal behavior, including self-injury, bouts of aggression, and, according to laboratory documentation, a "nervous breakdown." When retired to a sanctuary, she recovered partially, but was ultimately diagnosed with complex PTSD. The paper concluded: "The costs of laboratory-caused trauma are immeasurable in their life-long psychological impact on, and consequent suffering of, chimpanzees."[17]

As we have done with chimpanzees, we need to critically analyze current uses of other nonhuman primates, the viability of alternative models, and the economic issues involved to forge the best way forward. A good starting point would be the formation of a working group of diverse stakeholders who agree that ending primate research is a worthwhile goal. Such a working group—possibly organized by the NIH and the National Academies—would analyze the necessity of primate use and identify existing and potential alternatives.

The stakeholder group could develop a concrete plan to work on common-ground issues. This would involve developing priorities, short-term outcomes, and related activities. The ongoing Human Toxicology Project Consortium's work to ultimately replace all animals for toxicity testing is a good example of this approach. (See "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," in this volume.) The mission of the consortium is to "serve as a catalyst for the prompt, global, and coordinated implementation of '21st Century' toxicology, which will better safeguard human health and hasten the replacement of animal use in toxicology."[18] Because science is ever-changing, there must be an ongoing analysis of new technologies and challenges, and regulatory authorities must adjust regulations accordingly. In the United States, many stakeholders express frustration with the fact that the Food and Drug Administration, for example, favors data from outdated tests, including those that involve primates and other animals.

Phasing out invasive research on all nonhuman primates would take courage on the part of leaders in science and policy. It is a formidable task, but similarly transformative changes in how we conduct biomedical research have been

achieved. At various points in the past century and a quarter, restrictions have been placed on particular kinds of human and animal research because of ethical issues, despite objections that such restrictions would slow scientific progress; think, for instance, of the Helsinki Declaration to protect human subjects in research and the animal welfare laws in the United States and the European Union. However, these laws have not slowed the pace of discovery about biology and disease processes. If anything, there has been an acceleration of such discovery in the half-century since these restrictions went into effect.

In the early 1950s, Sir Peter Medawar pressed the Universities Federation for Animal Welfare to develop a report on how laboratory animal welfare could be improved and how distress and suffering in the research laboratory might be reduced. That initiative led to publication of a volume on humane experimental approach that is now regarded as the foundation for the concept of the Three Rs of replacement, reduction, and refinement of animal studies.[19] Ten years later, in 1969, Medawar correctly predicted that laboratory animal use would peak within ten years and then start to decline. He argued that animal research would allow researchers to develop the knowledge and understanding that would lead, eventually, to the replacement of animal use in laboratories. In 2010, forty years after Medawar's prediction, laboratory animal use is approximately 50 percent of what it was in 1970. Francis Collins has pointed to the down sides of animal-based research—that is "time-consuming, costly, and may not accurately predict efficacy in humans."[20] He has also suggested that nonanimal technologies might be quicker and more effective in new drug discovery programs. Given the trends and political will, we believe that we could reach Medawar's prediction of complete replacement by 2050.

Now is the time for an internationally coordinated effort to define a strategy to replace all invasive research on primates. At the very least, we need to move quickly to reverse the increase in laboratory primate use in the United States and Canada. Until replacement is a realistic option, we must reduce the number of primates used and refine studies to reduce their suffering, for the sake of both animal welfare and science.

1. C. Blakemore, "Should We Experiment on Animals? Yes," *Telegraph,* October 28, 2008.
2. A.N. Rowan, *Of Mice, Models and Men* (Albany: State University of New York Press, 1984).
3. Department of Health and Human Services, Funding Opportunity for the National Primate Research Centers, http://grants.nih.gov/grants/guide/pa-files/PAR-11-136.html, accessed July 7, 2011.
4. K.M. Conlee, E.H. Hoffeld, and M.L. Stephens, "A Demographic Analysis of Primate Research in the United States," *Alternatives to Laboratory Animals* 32, suppl. 1A (2004): 315-22.
5. P.E. Honess, P.J. Johnson, and S.E. Wolfensohn, "A Study of Behavioural Responses of Non-Human Primates to Air Transport and Re-Housing," *Laboratory Animals* 38, no. 2 (2004): 119-32; J.M. Kagira et al., "Hematological Changes in Vervet Monkeys (*Chlorocedub aethiops*) during Eight Months' Adaptation to Captivity," *American Journal of Primatology* 69, no. 9 (2007): 1053-63.
6. J. Balcombe and K.M. Conlee, "Primate Life in Two American Laboratories," presentation to the Eighth World Congress on Alternatives and Animal Use in the Life Sciences, held in Montreal, Quebec, Canada, on August 21-25, 2011.
7. P. Bateson, *A Review of Research Using Nonhuman Primates: A Report of a Panel Chaired by Professor Sir Patrick Bateson, FRS* (London and Wiltshire, U.K.: Biotechnology and Biological Sciences Research Council, Medical Research Council, and Wellcome Trust, 2011) http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008083; J.A. Smith and K.M. Boyd, eds., *The Use of Non-Human Primates in Research and Testing* (Leicester, U.K.: British Psychological Society, 2002); D. Weatherall, *The Use of Non-Human Primates in Research: A Working Group Report Chaired by Sir David Weatherall FRS FmedSci* (London: Academy of Medical Sciences, 2006), http://www.acmedsci.ac.uk/images/project/nhpdownl.pdf.
8. Institute of Medicine, Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, D.C.: National Academies Press, 2011), 4.
9. Bateson, *A Review of Research Using Nonhuman Primates*, 2.
10. Ibid., 1.
11. Ibid., 12-13.
12. Ibid., 4, 5, 16.
13. Ibid., 3.
14. F.S. Collins, "Reengineering Translational Science: The Time Is Right," *Science Translational Medicine* 3, no. (2011): 1-6.
15. B. Vastag, "Army to Phase Out Animal Nerve-Agent Testing," *Washington Post,* October 13, 2011.
16. G.W. Bradshaw et al., "Building Inner Sanctuary: Complex PTSD in Chimpanzees," *Journal of Trauma and Dissociation* 9, no. 1 (2008): 9-34; J.A. Smith and K.M. Boyd, eds., *The Boyd Group Papers on the Use of Non-Human Primates in Research and Testing* (Leicester, U.K.: British Psychological Society, 2002).
17. Bradshaw et al., "Building Inner Sanctuary," 31.
18. Human Toxicology Project Consortium Web site, http://htpconsortium.wordpress.com/about-2, accessed February 13, 2012.
19. W.M.S. Russell and R.L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).
20. F.S. Collins, "Reengineering Translational Science," 3.



# U.S. Law and Animal Experimentation: *A Critical Primer*

BY STEPHEN R. LATHAM

Every country's law permits medical experimentation on animals. While some countries protect particular kinds of animals from being subject to experimentation—notably great apes and endangered species—very few place concrete limitations on what researchers may cause animals to suffer, given sufficient scientific justification. What laws do, instead, is establish standards for the humane treatment and housing of animals in labs, and they encourage researchers to limit or seek alternatives to the use of animals, when doing that is consistent with the scientific goals of their research. The result, of course, is that no existing regulatory scheme is satisfactory to opponents of animal research. The law, in their view, does nothing more than make the animal research scientist into a sort of James Bond villain: superficially polite, offering fine housing and well-prepared cuisine even to those whom he intends, eventually, to kill.

Of course, the goals of animal experimentation law seem much more reasonable if one accepts that research on animals is both important for medical progress and morally permissible. On those assumptions, it makes a great deal of sense for the law to aim primarily at limiting unnecessary animal suffering even as it licenses scientifically justified experimentation. U.S. law accepts those assumptions and adopts that aim.

The system that has evolved in the United States combines elements of sometimes competing regulatory philosophies. The result is a complex, multilayered system that addresses the most important concerns, but, partly because of historical accident, also leaves some gaps. Even proponents of medical research on animals can see obvious ways in which the regulatory structure could be changed to benefit animals. Perhaps more important, though, is the fact that the existing regulatory structure, imperfect though it may be, is elastic enough to accommodate substantial changes that could reduce unnecessary animal suffering.

Stephen R. Latham, "U.S. Law and Animal Experimentation: A Critical Primer," *Animal Research Ethics: Evolving Views and Practices*, *Hastings Center Report Special Report* 42, no. 6 (2012): S35-S39. DOI: 10.1002/hast.107

## Multiple Regulatory Approaches

Animal welfare laws must address three main ways in which unnecessary animal suffering can occur in the context of medical experimentation. First, such suffering can occur when a given research protocol is not well justified scientifically. An experiment that was so badly designed that it could never generate any useful scientific knowledge would never warrant animal suffering. Harder cases result when the amount of suffering is ratcheted down, or the experiment's potential to generate useful knowledge is ratcheted up. A legal regime concerned with avoiding this kind of unnecessary suffering can opt to trust in the judgment of each individual research scientist, or empower someone besides the researcher to make at least some baseline assessment of the scientific value of each new animal research protocol. It can also provide information and guidance to researchers or overseers to improve their decisions.

Second, unnecessary suffering can occur when the amount of animal suffering induced by an experiment is not strictly required to conduct the experiment—perhaps because more animals are used than are necessary; or because less sentient animals could be substituted for more sentient ones, or computer or tissue models substituted for animals entirely; or because crude experimental procedures are producing avoidable stress or pain. A legal framework seeking to avoid these kinds of unnecessary suffering will encourage or require researchers to use the three Rs: *reduce* (the number of animals used in experiments), *replace* (animals with nonanimals, higher-order animals with lower), and *refine* (experimental procedures causing pain or distress).[1]

Third, unnecessary suffering can occur outside the actual research protocol yet still in the research setting because of inappropriate animal handling, housing, and feeding practices. A legal regime seeking to avoid this kind of suffering will dictate humane standards for animal housing and care.

Given these goals, what sort of regulatory scheme would be best at realizing them? One can imagine a variety of available approaches, from strong, centralized state regulation and monitoring of all experimentation to a hands-off reliance on professional self-regulation among laboratory researchers. On the world stage, the United Kingdom is closest to taking the former approach, Japan to the latter. U.S. law falls somewhere in the middle, in part because U.S. law in this area is in fact the result of a gradual, decades-long merging of the government regulatory and professional self-regulatory approaches.[2]

The government regulatory approach is embodied in the sprawling, strange, and often amended Animal Welfare Act of 1966. In its original form, the AWA was designed to control pet breeding and sale practices; it was passed, in part, as a result of public outcry about the mistreatment of dogs sold to laboratories. As amended, it governs the treatment of animals in a wide range of settings, from pet shops to circuses and from zoos to laboratories. Its enforcement is delegated to the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, whose inspectors make unannounced site visits to research facilities. Violations uncovered on such visits can result in fines and even, in extreme cases, criminal prosecution. The most common complaint about enforcement under the AWA is that it is rigid and mechanistic.

Because of its historical roots in concern for pets, the AWA's reach is confined to warm-blooded animals, and it contains special regulations addressed to certain animal favorites: dogs, cats, rabbits, and monkeys. Its animal experimentation regulations apply to any school or research facility that purchases or transports live animals in interstate commerce or that receives federal funding. But in fact the law has never reached the bulk of warm-blooded animals actually used in research. Concern about high regulatory costs—and about possible delay in creating guidelines for other, more popular animals—led the USDA to exclude laboratory rats and mice from its oversight from as early as 1970. In spite of lobbying efforts in the 1980s by proanimal groups, a congressional amendment to the AWA in 2002 legally formalized the agency's longtime practice, excluding rats, mice, and birds from the definition of "animal."[3]

In general, the law and its implementing regulations have focused on setting demanding, detailed standards for animal housing and basic standards for pain control. It supports only minimal review of the scientific merit of research protocols, but it requires researchers to make efforts to "reduce, replace, and refine."

The self-regulatory approach to animal research regulation is embodied in the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*.[4] The *Guide* has existed in some version since 1963, when it was introduced as a voluntary set of professional standards for laboratory animal research. Today, the *Guide's* standards are mandatory for all research facilities receiving federal funds. The *Guide* covers the treatment of all vertebrates, which means that, at least in federally funded research, it closes many of the gaps left open by the AWA. Not only are rats, mice, and birds covered, but also cold-blooded vertebrates like zebra fish—currently the go-to animal for laboratory studies of pain and nerve function.

The change in the *Guide's* status to a rulebook has altered its content somewhat. Earlier editions' expansive aspirational goals have given way in later editions to more readily applicable rules. There has also been considerable pressure to get the AWA's regulatory requirements and the *Guide's* standards to match, since all federally funded researchers are bound by both. Indeed, today, the two sets of standards are, if not identical, at least compatible with one another. But in general, where the AWA regulations are more rigidly prescriptive, the *Guide* permits lab veterinarians to use their professional judgment in applying general standards to particular species or protocols.

Since the 1980s, both the AWA and the *Guide* have attempted to assure oversight of animal research primarily by mandating the establishment, at each research institution, of an institutional animal care and use committee. The law mandates that each IACUC include among its members a veterinarian who will attend to the needs of the animals on site, an expert in the scientific use of lab animals, a person (from within the research institution or outside it) without such scientific expertise, and a community member who is unaffiliated with the research institution and can represent the views of the public. The IACUC is charged with reviewing all proposed animal research protocols, with ensuring that researchers make efforts to employ the three Rs, with overseeing and reporting on laboratory compliance with regulations relating to animal housing and care, and with answering complaints about the treatment of animals. Each IACUC is also empowered to require changes to experimental protocols or to laboratory animal care procedures and even to suspend research activities.

Federal standards are full of specific requirements for different kinds of studies, but in general, it is fair to say that they offer the most concrete guidance on questions of animal housing and care. The regulations include detailed discussions of square footage, exercise requirements, room temperature, and more. Considerably less guidance is offered on issues of protocol evaluation and implementation of the three Rs.

Of course, this is exactly what might be expected given the incredible volume and variety of animal research in the United States. A central authority can say a lot about how to house and feed monkeys, mice, and zebra fish, and expert advice on those issues will apply to all monkeys, mice, and zebra fish in every lab, no matter what protocols they are being used for. But questions about the other possible sources of unnecessary animal suffering—the scientific justification of a given protocol, or the ways in which animal suffering connected to a given protocol might be avoided or reduced—are too numerous and varied to be answerable in advance by a central authority. With regard to those highly fact-specific questions, U.S. law relies on the expert judgment of local IACUCs.

*Clearly there is room for reform. If the AWA were amended to include rats, mice, and birds, for example, that would be a major step toward ensuring the humane treatment of all animals in public and private labs.*

It is no coincidence that this kind of reliance on decentralized expert committees is also the salient feature of U.S. law governing research on human subjects. The federal Common Rule,[5] faced with a similar diversity of research protocols to evaluate, regulate, and modify, uses the same tactics as the AWA: it mandates creating research oversight committees (institutional review boards), specifies that their membership should include both relevant expertise and community representation, and empowers them to make and enforce a range of judgments about particular experimental protocols.

While the many IACUCs are expected to exercise independent judgment with regard to the scientific issues brought before them, the U.S. government does its best to inform the judgment by providing them with educational resources. The Public Health Service and the Department of Agriculture Web sites are full of guidance documents and educational resources for laboratory researchers and for IACUC members. There are documents, for example, with specific ideas about how and when to substitute lower-order animals for higher-order animals, and other documents providing up-to-date scientific news about newly developed computer models that can substitute, in some cases, for animal experimentation.

Finally, just as in the human subjects research world, federal regulations are quite commonly supplemented by private education and accreditation. Many research facilities seek accreditation by the Association for the Assessment and Accreditation of Laboratory Animal Care, a professional association of veterinarians and laboratory scientists. AAALAC provides education and does prearranged site inspections of labs once every three years. Educational and inspection standards are built largely around the requirements of the *Guide*, and the NIH accepts AAALAC accreditation as prima facie evidence of a facility's compliance with the *Guide's* requirements.

## Toward Reform: Accountability, Uniformity, Balance

The system of decentralized oversight by local IACUCs has several obvious advantages: it permits oversight by people with knowledge of the local researchers and laboratory facilities; it allows IACUCs to develop specialized knowledge, well tailored to the research being done at their facilities; and it is likely more speedy than any alternative program of centralized governmental research oversight would be. On the other hand, the decentralization of oversight has given rise to a number of problems—which, not surprisingly, are similar to those that beset the IRB system in human subjects research.

First, there is a problem of transparency and accountability. IACUCs are for the most part fairly anonymous. Hardly anyone not directly involved in animal research knows that they exist, much less who their members are. And of course, their members are not elected or in any other way publicly accountable for the decisions they make. Most IACUC decisions do not take the form of opinions or any other form of substantive, publishable decision, but of recommendations to researchers for piecemeal alteration of protocols. A central repository of IACUC minutes, and of policies adopted by different IACUCs, might both increase accountability and stimulate new ideas by creating cross talk between IACUCs. But any such repository would have to be created with an eye toward preserving researchers' intellectual property.

Second, decentralization almost necessarily gives rise to a lack of uniformity in decision-making and in quality of research oversight. One IACUC may conclude that a protocol involves unnecessarily harsh treatment of animals or presents an opportunity for substitution of nonanimal models; another may view the original protocol as unproblematic and requiring no amendment. A number of studies have shown that similar protocols are treated quite differently by different IACUCs.[6] It is unclear what the implications of such findings are. Do they reveal that IACUCs have differing standards relating to animal welfare? That they judge similar protocols

differently when they are presented by different researchers? Or some combination of these factors? In any case, enforced uniformity across IACUCs is a dangerous solution to propose for the problem of varying standards, in the absence of clear knowledge about whose standards are appropriate—and whose would be enforced.

A third complaint about the decentralized approach to animal-research regulation involves the perception that the U.S. government is too deferential to local IACUCs and does not take the task of auditing labs sufficiently seriously. In the early 2000s, there were some high-profile allegations made by whistleblowers from the USDA's Animal and Plant Health Inspection Service (APHIS) that audit findings were deliberately being watered down to be less critical than the field officers originally intended them to be.[7] U.S. audits of APHIS confirmed allegations of lax auditing in some regions of the country.[8] The obvious reform here is to better fund and train both the regulatory overseers and those who audit their performance.

There are other important criticisms of the U.S. regulatory regime not directly connected to its choice of decentralized decision-making. First, there is the question of scientific justification for animal suffering. The AWA does not ask IACUCs to balance animal suffering against the scientific merit or promise of any given experiment. Instead, it asks IACUCs to ensure only that any given protocol has scientific merit and that any animal suffering the protocol induces is strictly necessary to that science. The result is that any study that will advance science, even in a very small way, can be used to justify tremendous amounts of animal suffering, as long as the suffering is necessary to the advance. Though they do seek to modify studies via use of the three Rs, IACUCs almost never reject protocols.

Finally, and most importantly, there is the issue of which animals are protected. As already mentioned, the hundreds of thousands of rats, mice, and birds used in private, nonfederally funded labs are not subject to any federal regulation. (Some individual states' anticruelty statutes may apply in some cases, but there is very limited case law in the area.) Excluded, also, are cold-blooded animals. This means that there is no federal legal pressure on private firms such as drug companies to reduce or refine animal use, or to replace animals with computer or tissue models—a strategy that may be particularly feasible in studies of toxicology or drug metabolization.

Even in federally funded facilities, the living conditions of rats, mice, and birds are not subject to the USDA's APHIS inspection; only in AAALAC-accredited facilities is there oversight beyond self-reporting, and AAALAC does scheduled inspections only once every three years. Rats and mice, it should be stressed, are the most commonly used laboratory animals. In addition, U.S. law offers no protection for invertebrate, cold-blooded animals such as cephalopods. By contrast, Europe has recently moved to protect cephalopods in light of their manifest intelligence and sentience. Nor does U.S. law prevent research on great apes, or ban (though it does regulate) the use of wild-caught animals. And the United States is one of only two governments in the world that still permits invasive research on chimpanzees, though the scope of federal funding for chimp research has recently been sharply limited.[9] (See "Raising the Bar: The Implications of the IOM Report on the Use of Chimpanzees in Research," in this volume.)

Clearly there is room for reform. Some needed reform involves stepping up research oversight. If the AWA were amended to include rats, mice, and birds, for example, that would be a major step toward ensuring the humane treatment of all animals in public and private labs. In addition, the inspection rate for facilities could be more frequent. Publicly funded U.S. labs are inspected by APHIS about once a year, by their own IACUCs twice a year, and by AAALAC (if they choose to be AAALAC-certified) once every three years. Compare this to the U.K. system of inspecting about once a month. Other reforms could involve improving rigid and not-terribly-useful existing regulations, like cage-size requirements currently based on animals' body size rather than on their behavioral needs. Most significantly, the law could be reformed to permit a more explicit balancing of harms to animals (including both suffering and death) against the scientific gains at which the research aims. Empowering IACUCs to engage in such balancing is hardly radical; IRBs, for example, are already empowered to engage in such balancing in the human subjects research area, and this has not caused research to grind to a halt. Such a reform would require us to confront directly the question of how much suffering humans can impose on other species in return for small but real gains in knowledge.

Finally, a great deal can be accomplished even within an unchanged legal regime. The most urgent need is for more to be done to implement the three Rs. The familiar calls for better education about replacement techniques and more aggressive IACUC intervention on behalf of reduction and refinement are, of course, well justified. But even more dramatic reduction might be achieved if the goal of reduction were pursued not only within but also across protocols. There might be significant gains from putting animal-sharing procedures in place at the institutional level. At the moment, animals are commonly euthanized whenever the particular research project they're involved in comes to an end, without regard to the animal's age or health status. If a protocol involves attempts to breed, for example, mice with particular genetic traits, the pups born without those traits are routinely euthanized. If research facilities could work with researchers to use healthy animals from one study in another, rather than default to their euthanization, then fewer animals would need to be bred for suffering.

1. The widely accepted "Three Rs" terminology was first introduced into the animal research literature in W.M.S. Russell and R.L. Burch, *The Principals of Human Experimentation Technique* (London: Methuen, 1959).

2. A detailed account of the confluence of these two streams of regulation (to which my brief discussion here is heavily indebted) is provided by L. Carbone, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy* (Oxford, U.K.: Oxford University Press, 2004), p. 34ff.

3. Wild-caught rats and mice are included in the regulations. For more detail, see Carbone, *What Animals Want*, p. 69ff.

4. National Research Council, *Guide for the Care and Use of Laboratory Animals*, 8th ed. (Washington, D.C.: National Academies Press, 2011).

5. U.S. Department of Health and Human Services, 45 CFR 46.

6. See, for example, S. Plous and H. Herzog, "Reliability of Protocol Reviews for Animals Research," *Science* 293 (2001): 608-9.

7. See, for example, the statement of Dr. Isis Johnson-Brown, USDA whistleblower, alleging regulatory inaction on her report criticizing cage conditions at the Oregon Primate Center, at http://www.all-creatures.org/saen/articles-statementofijb.html, accessed October 2, 2012.

8. USDA Office of Inspector General, Western Region, "Audit Report: APHIS Animal Care Program Inspection and Enforcement Activities," Report No. 33002-3-SF, September 2005, p. i, http://www.usda.gov/oig/webdocs/33002-03-SF.pdf.

9. See Institute of Medicine, *Committee on the Use of Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, D.C.: National Academies Press, 2011); B.M. Altevogt et al., "Guiding Limited Use of Chimpanzees in Research," *Science* 335 (2012): 41-42.

# AUTHORS

**Larry Carbone** holds doctorates in veterinary medicine and in history and philosophy of science, both from Cornell University. As a veterinarian, he specializes in the care of laboratory animals and has specialty certification with the American College of Laboratory Animal Medicine. As a scholar, he conducts scientific studies of animal welfare and animal pain management, along with policy and ethical examinations of laboratory animal use. His book, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy*, was published by Oxford University Press in 2004.

**Kathleen M. Conlee** is vice president for animal research issues with The Humane Society of the United States. She worked for several years at a primate breeding and research facility and also worked with great apes in a sanctuary setting. Her current work focuses on the long-term goal of replacing the use of animals in harmful research and testing, the ongoing development of nonanimal alternatives, and the short-term goals of ending invasive chimpanzee research and retiring chimpanzees from laboratories to sanctuaries.

**Jeffrey Kahn** is the Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy in the Johns Hopkins Berman Institute of Bioethics. He is also professor in the Department of Health Policy and Management in the JHU Bloomberg School of Public Health. His most recent book is the forthcoming eighth edition of *Contemporary Issues in Bioethics* (Cengage Publishing), edited with Tom Beauchamp, LeRoy Walters, and Anna Mastroianni. His research interests include the ethics of research, ethics and public health, and ethics and emerging biomedical technologies.

**Susan Kopp** is a veterinarian and professor of health sciences in the veterinary technology program at LaGuardia Community College, City University of New York, where she teaches courses in veterinary nursing and ethics. A scholar at Yale Interdisciplinary Center for Bioethics, she also coconvenes the Center animal ethics study group and teaches a summer seminar in animal welfare and veterinary ethics.

**Stephen R. Latham** is director of the Interdisciplinary Center for Bioethics at Yale University. He has published on a broad range of issues at the intersection of bioethics and law. He is a former board member of the American Society for Bioethics and Humanities, a former graduate fellow of Harvard's Safra Center on Ethics, and a former research fellow of the University of Edinburgh's Institute for Advanced Studies in Humanities. His current research includes a project funded by the Robert Wood Johnson Foundation to create a database of state statutes and cases criminalizing HIV exposure and a project on a legal framework for newborn whole-exome screening.

**Joel Marks** is professor emeritus of philosophy at the University of New Haven and a bioethics center scholar at Yale University. His books include *Ethics without Morals* (Routledge, 2013) and *Ought Implies Kant* (Lexington Books, 2009). His main areas of scholarly interest are theoretical and applied ethics, which have most recently converged on animal ethics.

**D. Eugene Redmond, Jr.,** is professor of psychiatry and neurosurgery at the Yale University School of Medicine. He has published extensively on his team's effort to cure Parkinson disease using cell replacements, beginning with fetal brain cells and more recently using stem cells in monkeys. His research interests are in restoring the damaged brain and spinal cord, using cellular replacements, and gene therapy. He has worked extensively with nonhuman primates on studies of anxiety, drug addiction, schizophrenia, cognition, Parkinson disease, spinal cord injury, and amyotrophic lateral sclerosis.

**Bernard E. Rollin** is university distinguished professor, professor of philosophy, professor of animal sciences, professor of biomedical sciences, and university bioethicist at Colorado State University. His scholarly interests include both traditional philosophy and applied philosophy. In addition to numerous articles in the history of philosophy, philosophy of language, ethics, and bioethics, he has written many books, including, most recently, *Science and Ethics* (Cambridge University Press, 2006), and *Putting the Horse Before Descartes* (Temple University Press, 2011). He has also edited, with M. Lynne Kesel, the two-volume *The Experimental Animal in Biomedical Research* (CRC Press, 1990 and 1995). He is one of the leading scholars in animal rights and animal consciousness and has lectured over 1,500 times all over the world.

**Andrew N. Rowan** is chief scientific officer at The Humane Society of the United States and chief executive officer of The Humane Society International. He has written numerous books and peer-reviewed publications regarding animal research, including a book titled *The Animal Research Controversy: Protest, Process and Public Policy* (Center for Animals and Public Policy, Tufts University School of Veterinary Medicine, 1995). He is a biochemist in training, and a focus of his career has been promotion of the three Rs in animal research: replacement of nonhuman animals, reduction in number of animals used, and refinement to decrease animal suffering.

**Joanne Zurlo** is a senior scientist in the Department of Environmental Health Sciences and director of science strategy for the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health. Previously, she was the director of the Institute for Laboratory Animal Research at the U.S. National Academy of Sciences, where she oversaw the publication of numerous reports related to the humane use of laboratory animals. Her interests lie in laboratory animal welfare and the application of new technologies to toxicity testing.

# GLOSSARY OF ANIMAL RESEARCH ETHICS TERMS

*Debates about using animals in research rest on the special, sometimes contested interpretation of key terms. Several of them are provided here. In the interest of fostering clear and civil discussion of the ethical controversies, The Hastings Center invites further discussion and development of the glossary at http://animalresearch.thehastingscenter.org.*

**Alternative:** This word is used in different ways. (1) Sometimes it refers to nonanimal models (that is, an alternative *to animals*), but sometimes (2) it refers to another, less objectionable animal model (an alternative to the original animal), and sometimes (3) to any approach that reduces, refines, or replaces research methods using animals (an alternative to the original research method).

**Animal:** (1) In common parlance, an animal is any multicellular but nonhuman member of the kingdom Animalia. (2) In the Animal Welfare Act, however, an animal is "any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm blooded animal, which is being used or is intended for use for research, testing, experimentation, or exhibition purposes or as a pet. This term excludes: Birds, rats of the genus *Rattus* and mice of genus *Mus* bred for use in research." Thus more than 95 percent of the (taxonomic) animals used in biomedical research *are not defined as animals* in the act. (3) In the *Guide for the Care and Use of Laboratory Animals,* which sets mandatory standards for all research facilities receiving federal funds, meanwhile, an animal is "any vertebrate."

**Distress:** A typical definition is found in *Merriam-Webster's Collegiate Dictionary:* "a pain or suffering affecting the body, a bodily part, or the mind." The Animal Welfare Act requires research facilities "to ensure that animal pain and distress are minimized, including adequate veterinary care with the appropriate use of anesthetic, analgesic, tranquilizing drugs, or euthanasia." The account is open to interpretation, and the relationship of pain and distress to cognition is a key issue.

**Humane:** The Animal Welfare Act describes the humane treatment of laboratory animals this way: "minimum requirements with respect to handling, housing, feeding, watering, sanitation, ventilation, shelter from extremes of weather and temperatures, adequate veterinary care, including the appropriate use of anesthetic, analgesic or tranquilizing drugs . . . and separation by species." This definition excludes enrichment and other efforts to meet species-specific needs, such as companionship.

**Necessary:** In the context of biomedical research, "necessary" refers to what is needed to carry out an experiment *and* what is needed for the humane handling, care, or treatment of laboratory animals. The word sometimes also refers to whether an experiment is itself needed to attain some medical or scientific goal.

**Not Tested on Animals:** This phrase, found on some product labels, does not necessarily mean that the product involved no animal testing. It can mean that (1) the final product was not tested on animals, although ingredients were; (2) the manufacturer or distributor did not test the product on animals, although someone else did; (3) the animal tests were done more than five years ago; or (4) the final product and its ingredients really were not tested on animals.

**Pain:** According to the International Association for the Study of Pain, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain control in laboratory animals is challenging and controversial—whereas acute pain is relieved with short-term use of analgesics, the answer to chronic pain tends to be euthanasia.

**Reduction:** One of the "three Rs" (along with *refinement* and *replacement*) often taken to guide the use of animals in biomedical research, *reduction* refers to efforts to use fewer animals to perform an experiment or test. Reduction can be achieved, for example, by using research methods that allow comparable amounts of data to be obtained with fewer animals or that allow more data to be obtained with a given number of animals.

**Refinement:** This term refers to the use of techniques and procedures that minimize pain and distress in research animals.

**Replacement:** The primary meaning is the use of research methods that do not involve sentient animals. Examples include computer modeling and research on tissue culture, microorganisms in culture, or human volunteers. *Replacement* also sometimes refers to research conducted on tissue taken from an animal instead of on the whole animal.

**Welfare:** Animal welfare is concerned with assuring humane treatment of animals: maintaining good health, minimizing negative states such as pain, enhancing positive states, and giving animals the freedom to behave in ways that are natural to the species. What constitutes humane treatment is open to interpretation.

## About The Hastings Center

The Hastings Center addresses fundamental ethical issues in the areas of health, medicine, and the environment as they affect individuals, communities, and societies. With a small staff of senior researchers at the Center and drawing upon national and international experts, The Hastings Center pursues interdisciplinary research and education that includes both theory and practice. Founded in 1969 by philosopher Daniel Callahan and psychoanalyst Willard Gaylin, The Hastings Center is the oldest independent, nonpartisan, interdisciplinary research institute of its kind in the world. From its earliest days The Hastings Center has understood that the moral problems arising from rapid advances in medicine and biology are set within a broad intellectual and social context. The Center's collaborations with policy-makers, in the private as well as the public sphere, assist them in analyzing the ethical dimensions of their work.

## Ordering Information

For copies of this or other *Hastings Center Report* Special Reports, write or call:

Customer Service
John Wiley and Sons
800-835-6770 or cs-journals@wiley.com.

Full text of this Special Report and additional resources are available at **http://animalresearch.thehastingscenter.org**

ON THE COVER

*The Fate of the Animals,* by Franz Marc, 1913, oil on canvas, 77 x 105 inches. Photo: Art Resource.

WILEY-BLACKWELL