Guest Editorial

Reassessing Animal Research Ethics

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Animal research has long been a source of biomedical aspirations and moral concern. Examples of both hope and concern are abundant today. In recent months, as is common practice, monkeys have served as test subjects in promising preclinical trials for an Ebola vaccine or treatment[1,2,3] and in controversial maternal deprivation studies.[4] The unresolved tension between the noble aspirations of animal research and the ethical controversies it often generates motivates the present issue of the *Cambridge Quarterly of Healthcare Ethics*.

As editors of this special section, we hope that these original and timely articles will push the professional discussion of animal research ethics in a positive direction that will benefit research scientists and others interested in moral problems in animal research. We also look forward to a day when animal research will genuinely meet both appropriate scientific and appropriate ethical criteria—criteria that themselves can be improved by critical scrutiny.

Animal research—that is, the use of live animals as experimental subjects in biomedical and behavioral fields of learning—has been deeply entrenched for well over half a century. One signal development was the enactment in the late 1930s of federal product safety legislation in the United States and other nations that *required* animal testing of food, drugs, and medical devices prior to use by human subjects or consumers.[5] Another development was the publication of codes of research ethics that called for animal research prior to human research. The Nuremberg Code, published by an American military tribunal in 1947–48 after scrutiny of Nazi medical atrocities, stated that experiments involving the use of human subjects should be "based on the results of animal experimentation."[6] The Declaration of Helsinki, first published in 1964, reaffirmed this assumption and added, rather imprecisely, that "the welfare of animals used for research must be respected."[7]

Against the background of such statements, the institutionalization and widespread acceptance of animal research in the twentieth century rested on two basic assumptions, one factual and one moral. The *factual assumption* was that animal research is sufficiently reliable as a basis for predicting the effects of drugs, products, and other materials on human beings that animal trials can be expected to yield significant scientific conclusions and medical benefits to humanity.

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Animal research was viewed as protecting human subjects from unnecessary research risks and providing information vital to the advancement of biomedical science. The *moral assumption* was that the moral status of animals is inferior to the moral status of human beings—a thesis commonly expressed in the language of "human dignity."

This moral assumption helps explain why many have thought it relatively easy to defend the involvement of animal subjects in conditions and procedures that often seriously harm them and where anticipated benefits are nearly always for the sake of humanity rather than the animal subjects. Significantly harmful, nontherapeutic research on human beings without their consent is a paradigm of unethical research, as exemplified by the Nazi medical atrocities. Thus the moral acceptability of such research involving animal subjects requires the assumption that their moral status is exceeded by the moral status of human beings—or requires some related assumption such as the claim that humans have rights or dignity, whereas nonhuman animals do not.

Both of the above-mentioned pivotal and widely believed assumptions are now increasingly called into question. Several of the articles in the present volume attempt to illuminate some aspect of animal research ethics without taking a definite stand on either of the contested assumptions. But other articles criticize some aspect of these and related assumptions.

The package of articles commences with Hope Ferdowsian and John Gluck's "The Ethical Challenges of Animal Research: Honoring Henry Beecher's Approach to Moral Problems." With his 1966 article "Ethics and Clinical Research," Henry K. Beecher significantly advanced the cause of human research protections by exposing multiple ethical deficiencies in human subjects research.[8] His influential contribution was to demonstrate that unethical practices were far more common than was generally appreciated at the time. Ferdowsian and Gluck argue that numerous problems with animal research as currently practiced, including a dearth of rigorous ethical evaluation, are analogous to the problems in human research to which Beecher called attention. These authors describe cases that illustrate what they believe to be sobering ethical shortcomings in the conduct of animal research. They conclude by offering a set of recommendations that address some of the deficits on which they focus.

In the second article in this special issue, "The Flaws and Human Harms of Animal Experimentation," Aysha Akhtar bluntly challenges the factual assumption that animals provide reliable models for human responses, disease, and biology. She points to a growing body of scientific literature that critically examines the performance of animal modeling (and of animal experimentation more generally) and raises concerns about its value for predicting human outcomes and for insights into human physiology. She argues that empirical studies of the unreliability of animal experimentation across a wide range of types of research undermine scientific arguments in support of this work. Akhtar also argues that animal experimentation often imposes significant harms on human beings through misleading safety studies, abandonment of potentially effective therapies, and diversion of resources away from more effective testing methods. The picture she presents is one in which the collective harms and costs to human beings from animal research generally outweigh potential benefits. She concludes that resources would be better invested if redirected to the development and use of human-based testing methods.

In the third article, "Necessary Conditions for Morally Responsible Animal Research," David DeGrazia and Jeff Sebo present a nuanced position with respect to the pivotal moral and factual assumptions undergirding the mainstream justification of animal research. First, they assume that the moral assumption that human beings have higher moral status than animals is true. This assumption permits them to address proponents of animal research who make the same assumption and are also disposed to take seriously the ethical issues generated by animal research. From this common ground, the authors argue that several conditions are necessary for animal research to be morally justified. The first condition, the expectation of sufficient net benefit, effectively incorporates the pivotal factual assumption that animal testing is reliable and productive. Remaining agnostic on the truth of this assumption, the authors argue that the expectation of sufficient net benefit is not particularly controversial but must be satisfied. DeGrazia and Sebo also defend what they call a worthwhile-life condition and a no-unnecessary-harm/qualified-basic-needs condition for justified animal research. They argue that, whether or not these necessary conditions are *jointly sufficient* for justified animal research, they are demanding, with the implication that much animal research as currently practiced may fail to satisfy them.

Another arguably necessary condition of morally responsible animal research is the placement of an upper limit on the pain, distress, or suffering that animal subjects may undergo. If such a limit is appropriate, then animal trials that exceed it are morally unjustified. In "The Upper Limits of Pain and Suffering in Animal Research: A Moral Assessment of the European Union's Legislative Framework," Tom L. Beauchamp and David B. Morton propose that a ceiling be placed on experiential harm. They assess the merits of perhaps the most important statement in the current literature on upper limits, namely, the European Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes. The authors contend that this legislation governing animal research in the European Union shows considerable promise but also needs improvements. Beauchamp and Morton offer a moral rationale for the incorporation of upper-limit guidelines and legislation and then address the complicated problem of whether exceptions to this necessary condition should be allowed. They advance several reasons why revision of the EU directive is needed while maintaining that this European legislation, suitably revised, could have a substantial and salubrious influence on the conduct of animal research worldwide.

Animals are used as research subjects for a variety of purposes, most falling under one or more of four categories: basic biological research; the study of human disease; the search for effective medicines; and safety testing of medicines, chemicals, cosmetics, and other products. In "Ending the Use of Animals in Toxicity Testing and Risk Evaluation," Andrew Rowan focuses on safety testing, with special attention to recent and future developments in toxicology. He provides a history of developments in safety testing technology and explores the implications of several developments in industry, public policy, public health, economics, and ethics. A striking feature of Rowan's analysis is its evidence-based challenge to the factual assumption underlying the justification of animal research—namely, that animal models are reliable. Rowan maintains that the predictive value of animal testing appears to be, typically, in the range of 50–60 percent accurate,[9] but the predictive value in rodent-only studies appears to fall below 50 percent (less accurate than a coin toss).[10] More positively, he describes the Environmental Protection

Agency's ToxCast program,[11] an alternative to animal testing, as comparable in accuracy to the animal tests that have emerged after 80 years of attempted improvements. He finds good reason to believe that this and other nonanimal testing programs will continue to improve, allowing the discontinuation of animal testing and resulting in savings in time, money, and animal welfare, without cost in predictive power.

In the final article, "Is There a Role for Assent or Dissent in Animal Research?," Holly Kantin and David Wendler start with the fact that in the context of pediatric research, children who presumptively cannot provide *informed consent* (or *refusal*) may nonetheless have preferences about participation that matter morally. If they have any significant capacity to understand what participation involves, their *assent* must be solicited. If they balk at participating, their dissent must be respected unless entering a protocol is in their medical best interests. Like children, animals are incapable of providing informed consent but often have preferences regarding participation in research. Kantin and Wendler then consider whether animal subjects can nonverbally assent or dissent in a meaningful way. They find welfare-based reasons for investigators to consider and in some cases respect the dissent of animal research subjects who behaviorally express dissent. They also find empirical grounds for believing that agency-based reasons apply to chimpanzees, and supply a rationale for the U.S. Institute of Medicine's ground-breaking recommendation that comparative genomics and behavioral research with chimpanzees should be conducted only if they "acquiesce" to participation.[12]

As the articles in this special section indicate, scholars in bioethics from several disciplines have come to regard various problems of animal research as resolvable either by tailoring existing human research requirements to fit the animal research context or by creating new protections for animals that satisfy what are arguably necessary conditions of morally justified animal research. The importance of this work has finally gained recognition in bioethics, where it had stirred up little notice for decades. We hope the contributions in this journal issue will continue the trend to ethical analysis of animal research, thereby bringing animal research a notch closer to the more settled domains within bioethics and research ethics.

Notes

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William de Morgan (1832–1917), *Monkey Looking at Reflected Moon*. Tile design. Location: Victoria and Albert Museum, London, Great Britain. Photo credit: V&A Images, London / Art Resource, NY. Reproduced by permission.