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Illuminating the Art of Medicine

Nonhuman Animal Research

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FROM THE EDITOR IN CHIEF

Fiat Lux

Audiey C. Kao, MD, PhD

Alabaster, oyster white or gypsum? Favorite jeans, revel blue or down pour? For many DIYers, choosing a paint color for a room or house can feel downright daunting. In deciding on a shade of white or blue, experts advise painting a swatch in the actual space because the way that light illuminates a space affects one's perception of its "true" color.

Such advice is aptly applied to the celebration, in September 2024, of the 25th anniversary of the *AMA Journal of Ethics* and its predecessors.[1] From its beginning as an ethics section within *msJAMA*, the *AMA Journal of Ethics* has grown into a distinct, editorially independent, peer-reviewed publication that has striven to publish content—much offered with continuing education credit—that sheds light on topics of ethical relevance and importance in health and health care. In each monthly issue, which is freely available to all, cross-disciplinary experts, scholars, and artists aim to illuminate complex questions and ideas often overlooked in traditional ethics curricula. Take, for example, this month's issue, which examines, through insightful commentaries, engaging podcasts, and provocative artwork, *What do good science and ethics require of human-centered research using nonhuman animals?*

In motivating the journal's long-standing mission to "illuminate the art of medicine," we see it as our ongoing editorial responsibility to help readers and listeners gain a deeper appreciation and truer understanding of ethics in the often fraught and complicated enterprise of caring for patients and the public. Given the climate of social and political polarization and rampant misinformation and disinformation in which health care is practiced today, the *AMA Journal of Ethics*' illumination of the shades of ethics is needed more than ever—and may it continue to be a source of insights to make health care better.

Let there be light.

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FROM THE EDITOR

Why Should We Care About What Using Nonhuman Animals in Human-Centered Research Suggests About Our Characters?

Bethany M. Erb

As a scuba diver, I am routinely confronted by what happens when we humans ignore the reality that the health of our ecosystem affects the health of our species. For example, the shark population in Mexico's territorial seas has dramatically decreased in part because of illegal shark finning—removing fins from sharks and releasing the sharks back into the ocean.[1,2] The fins are widely prized as the main ingredient in shark fin soup—a stewed delicacy served in parts of Taiwan and Southeast Asia—and in several Eastern traditional cures.[3,4] In seas where shark populations have decreased secondary to overfishing, lower-level predators multiply unchecked, no longer the prey of sharks that have historically regulated their numbers.[5,6] Groupers—large-bodied, wide-mouthed fishes—decimate populations of smaller reef fish, such as parrotfish,[7] that locals depend on for food and income.[6,7] "*No nos preocupamos por los tiburones, y ahora no pueden protegernos*," my dive master José told me last year. "We did not concern ourselves with the sharks, and now they cannot protect us."

In other words, protecting other species can be one of the most paradoxically powerful ways to protect our own species.

Nonhuman animals have long been and continue to be routinely used in biomedical and behavioral research to promote human health. When SARS-CoV2 infections triggered a race to develop and scale global access to vaccines in 2020, 2 key innovations happened that affected the supply chain of animals created for science: experiments and trials regarded as essential were prioritized, and governments and researchers shortened vaccine production timelines.[8] As a result, the pandemic led to accelerated vaccine production processes requiring fewer research animals.[9,10]

During the same period, organs-on-chips (OoCs)—"engineered or natural miniature tissues grown inside microfluidic chips"[11]—showed potential to better reproduce the physiologic environment of human organs relative to in vivo models.[11,12,13] Nonhuman animal models have come under scrutiny, given mounting evidence that metabolic differences between species can leave translatability—the applicability of animal research to humans—subject to chance.[14,15,16] Moreover, preclinical laboratory animals experience significant and repeated stress that may affect the reliability of experimental data.[17]

More than ever, it is time to reevaluate the utility of nonhuman animal-based research as it is currently practiced. Reasonable people can still disagree about when, why, and how nonhuman animals should be sacrificed for human health, but we now know that we reap lifesaving benefits even when we sanction fewer nonhuman animals' cultivations and deaths for science.

This theme issue of the *AMA Journal of Ethics* is an investigation into what this revelation means for the future of human-centered science. Contributors share their expert opinions on clinical, ethical, legal, and policy questions raised by animal experimentation in human-centered research. They also make the case for why and how to model regard for animals in laboratories; and they interrogate current decision-making principles and societal values that govern treatment of nonhuman research animals, while outlining the philosophical underpinnings of animal rights. Questions about power, hierarchy, and consciousness are interwoven in this issue: What do we owe other species relative to our own and why? What definition of consciousness should we use to decide the value of a life? This issue ends on a hopeful note, highlighting advancements in disease and biological modeling that foreshadow a more evidence- and value-driven medical science pathway.

For some readers, nonhuman animal use in human-centered research may seem too far removed from the primary care clinic or operating theater to be of import. Yet the patients of tomorrow rely on the quality of research done today. Many of medicine's great breakthroughs, from Louis Pasteur's germ theory of disease to the Pfizer-BioNTech COVID-19 vaccine, have emerged from the laboratory.

As my dive master José recognized, our instinct is to see our ecosystem as a metaphorical pantry stocked to meet our needs and wants. However, building mutually beneficial relationships with other life forms is a way to ensure that humanity adapts and thrives in today's changing environment. This issue is a critical examination of human-centered research and a conversation about why and how to channel such research into ethical and technological evolution.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Should Clinician-Researchers Model Regard for Nonhuman Animals Bred for and Used in Human-Centered Science?

Rebecca L. Walker, PhD

Abstract

If we assume that nonhuman animals experience pain or distress, then ethically justifying human-centered research with only nonhuman animals as subjects likely requires that the research's benefits to humans must, at least, outweigh harms suffered by the nonhuman animals. Yet this reasoning does not seem to account well for the ethical view that nonhuman animals are morally valuable in their own right. This commentary on a case considers this ethical tension and discusses how clinician-researchers should navigate it. This commentary also suggests why clinician-researchers' reasoning about the nature and scope of their obligations to nonhuman animals extends beyond governing regulations and federal oversight, which is silent on or ambiguous about nonhuman animals as morally valuable in their own right.

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Case

Dr Q is a clinician-scientist who studies brain tumor growth. The clinical utility of Dr Q's work has grown in importance over the decades, and Dr Q's team has contributed to many improvements in human brain tumor diagnostics.

Over the years, Dr Q's team has responded to many changes required by the Code of Federal Regulations (9 CFR §§1-4.11)[1] and the Health Research Extension Act of 1985,[2] which augments the Animal Welfare Act of 1966.[3] Evolution in social and cultural thought, attitudes, and activism also demand Dr Q's lab staff members' consideration and reconsideration of their roles in creating a market for laboratory animal cultivation and in using live mice in human-centered research. Dr Q seeks advice from Dr A, a veterinarian member of their organization's Institutional Animal Care and Use Committee (IACUC), to more carefully consider the team's short- and long-term efforts to minimize suffering among the live mice needed to carry out Dr Q's protocols.

Dr Q mentions to Dr A, "I'd like to model thinking carefully about whether and when our efforts to minimize our animals' pain and suffering is enough to meet our obligations to

the animals we use for human clinical science applications. I suspect that orienting ourselves to these questions and concerns will be key to the future of our lab and work."

Dr A considers how to respond, how to continue the exchange of ideas, and how to advise Dr Q.

Commentary

Dr Q is interested in "thinking carefully" about the broader moral question of when the lab's efforts sufficiently meet its obligations to nonhuman animals. This query calls for more than a regulatory approach, since it asks basic moral questions that are typically not addressed within nonhuman animal research oversight. A take-home message from this commentary is thus the importance of using moral reasoning to address complex ethical issues in laboratory practices. Because oversight is also integral to the conduct of ethical animal research, I additionally consider how US nonhuman animal research oversight relates to some of the points raised from the perspective of moral reasoning. After all, the researcher in this case consults with a veterinarian member of the IACUC, and it is the job of the IACUC to oversee application of the regulatory structure, not necessarily to address broader moral concerns.

Identifying common biases is key to this endeavor. Regardless of their purposes or origin stories, mice are individual creatures with their own subjective welfare, which is undermined by pain and distress, and whose value is independent of their usefulness. Thus, when we are asked to "model" regard for nonhuman animals bred for and used in human-centered science, we must distinguish between what we owe these creatures themselves and how we might support their interests only for the sake of some other important purpose.[4]

To illustrate, we might treat nonhuman animals well in research merely because doing so is good for the science—healthy animals lead to better data.[5] Or we might treat nonhuman animals well in research merely because this "models" care that mentees should learn to perform or helps to curb public "attitudes … and activism" about nonhuman animal use. All of these reasons for treating the mice well in these studies, important as they are, are consistent with the idea that the mice themselves have no independent value. Thus, if it turns out that nonhuman animal welfare is not consistent with the goals of a particular protocol, then there remains no independent reason to support animal welfare. Or if it turns out that the public doesn't care about nonhuman animal welfare or that students can learn to perform good animal care in other ways than direct modeling of such care, then again there is no independent reason for supporting the welfare of the nonhuman animals in question. For these reasons, if we want to take seriously what the case refers to as "our obligations to the animals," then we must assume from the outset that the nonhuman animals themselves matter, morally speaking—meaning that our obligations are directly to them and not merely to further some other goal.[6]

Justifying the Research

The idea that mice have some value independent of their purpose-bred status has implications for how we should think about what does or does not justify their use. By using the term *human-centered science*, the case seems to refer to animal research that, like most research of its kind, aims at human health or human welfare benefit. For such research, the only moral justification available, once we assume that animals themselves are morally valuable—and once we also agree that they are harmed by the

research—is that the human benefit outweighs, in some morally appropriate sense, the animal harm.[7]

Are nonhuman animals in this case harmed? The case study focuses on tumor growth, an area of nonhuman animal research in which pain and distress are expected.[8] The researcher, moreover, is wondering if efforts to "minimize" these harms are sufficient, which indicates that they are present in the research. Looking beyond the specifics of the studies in question, mice are typically killed at the end of experiments,[9] and, even if they are not killed, they must live their entire lives in vivarium confinement. Such confinement includes restricting the types of food, space, and cohabitants available to the mice and subjecting them to the prescribed lighting and temperature settings of the human-controlled space.[9,10] There is reasonable debate regarding whether and how mice are harmed through being killed or living in vivariums; however, it is important to recognize these potential sources of nonhuman animal harm as well as those imposed by the study protocol itself.

From a moral reasoning point of view, then, the use of mice in studies like those of Dr Q could only be justifiable if it leads to human benefit that is greater than the harms they experience. To say that the use of mice could *only* be justified in this way is not to say that it necessarily *can* be justified in this way. For example, if mice have rights not to be used in these ways, these rights would preclude their use even if the balance of benefit and harm would support their use.[11] Let us stick nevertheless with the idea that such use could only be justified if the human benefits outweigh the nonhuman animal harms. The case states that the clinical utility of the work in question "has grown in importance," which indicates that this research has a generally promising trajectory. From the point of view of justifying animal protocols, however, the question is whether each study gives a reasonable trajectory of benefit and whether this benefit is greater in some morally suitable sense than the harms caused to the animals.[12] As a moral justification for an individual study, then, it is not enough that the research program in general is beneficial for humans. Dr Q's research team should ensure that each one of its studies is assessed for the potential value of the research in comparison with nonhuman animal harms that cannot be alleviated, including pain and distress experienced in the study, any potential environmental stressors, and death.

If we suppose that a study can be justified by being, overall, more beneficial for humans than harmful for the nonhuman animals involved, it might still be the case that some kinds of harms to nonhuman animals are out of bounds, morally speaking, because the levels of pain and distress are too great. This is an evolving area of consideration in nonhuman animal research, but ethically it seems right that there are some harms that are wrong to inflict on other sentient beings even if the benefits could be significant. Thus, Dr Q should consider establishing parameters on the types of tumor-related harms studied in the lab. Doing so not only is a matter of humane end points, but also rules out types of studies in which the burden of nonhuman animal harm is too great to be conscionable.

Ethics and Oversight

How does the US oversight regime, as reflected in IACUC standards for animal care and use, relate to these points gained through moral reasoning? On the specific question of if animals have independent moral value, US oversight does not take a definitive stance,[13] although it does appeal to obligations to uphold animal welfare for all who work in animal science.[9] Regarding the obligation to balance harms to animals against

specific benefits of a protocol, US regulations are ambiguous about how or if IACUCs are to balance benefits and harms,[14] unless unrelieved pain and distress are necessary to meet scientific goals.[9] Finally, there is no established upper limit to animal pain and distress, with researchers relying instead on scientific justification, searches for alternatives, and refinements to any research methods that cause unrelieved nonhuman animal pain and distress.[15] Given that US oversight does not dictate an approach to some of these important moral issues under consideration, it stands to reason that the regulatory structure itself will not guide Dr Q on how to meet a sufficient standard in fulfilling moral obligations to the animals. At the same time, meeting regulatory obligations is itself a necessary (though not sufficient) condition for the conduct of ethically sound research. In other words, ethical research must at minimum meet regulatory standards, but meeting such standards does not guarantee that a project is ethically sound.

Beyond justifying Dr Q's research, crucial ethical considerations arise during the research itself. For example, researcher obligations of care for these dependent nonhuman animals require more than merely monitoring overt signs of health and welfare and following minimal housing standards dictated by oversight regimes. Instead, teams should be aiming to support the highest level of species-specific animal flourishing possible for the animals in their care.[16] For example, the study team should consider how housing, food, vivarium space, and cohabitation can be implemented to best support mice as mice. Furthermore, in managing tumor burden for these animals, the team may be able to better support their animal subjects by thinking creatively about analgesic interventions.[17] Finally, it is important in this case that Dr Q is concerned about the use of nonhuman animals and is looking for outside advice from Dr A. Taking this step shows character traits important for being a practically wise researcher.

Conducting nonhuman animal research in an ethical manner requires much effort and thought. Being motivated by compliance with regulations and public concern for nonhuman animals are both important ways to spur ethically better practices. However, the willingness to look beyond regulatory requirements and public perception to engage questions of broader moral justification and deeper ethical practice is an important feature of the practically wise researcher. The researcher in this case wants to meet ethical obligations to the nonhuman animals themselves and that requires taking a moral reasoning approach.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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CASE AND COMMENTARY

According to Which Criteria Should We Determine Whether and When IACUCs Are Sufficient for Protecting the Welfare of Nonhuman Animals Used in Research?

Peter John, MD, PhD

Abstract

Nonhuman animals used in biomedical research frequently suffer and are harmed as part of their use as experimental models. The Institutional Animal Care and Use Committee (IACUC) of a given institution is meant to ensure that research protocols follow federal guidelines, but research protocols such as those described in this case can generate unnecessary suffering; this problem suggests limitations of IACUCs' capacity to protect nonhuman animals' welfare. This commentary on the case considers how to more fully protect nonhuman animals used in scientific research and identifies barriers to more comprehensive protection of nonhuman animals' welfare.

Case

Cardiologist and scientist Dr J oversees a federally funded cardiac antiarrhythmic pharmacologic research lab in a well-known academic health center. Dr J teaches in many of the health sciences programs of the university and is often invited to lecture on topics ranging from research ethics to animal research protocol design to pharmacology and cardiac pathophysiology. Dr J is especially known among students for their lecture on how mid-21st-century animal rights campaigns informed passage of the Animal Welfare Act of 1966.

Dr J's team's protocols have always adhered to federal animal care and use guidelines, and Dr J served for many years on the university's Institutional Animal Care and Use Committee (IACUC). Dr J's team's research remains a controversial point of tension, however, between animal rights activists and patient advocacy groups, whose presence is always visible to students.

Dr J's team's research requires induction of cardiac arrhythmias in source-bred dogs. Antiarrhythmic pharmacologic agents are then administered to the dogs, and those agents' cardiac effects in the dogs are observed over time, sometimes until their deaths. Over the course of a typical study, many dogs experience cardiac arrest and painful gastrointestinal and pulmonary side effects of the pharmacologic agents.

Protesters, usually animal rights activists, and counter-protestors have long gathered with signs, pamphlets, and bullhorns outside the campus's known research facilities. Counter-protesters are usually patients and patient advocates, including children and parents of children with congenital heart conditions that predispose them to cardiac arrhythmias. Protesters' signs often show photographs of live mammals, presumably animals just like those used in research on campus, connected to invasively placed tubes and devices. Slogans like "Research is not 'care'! IACUCs are sham federal covers for animal cruelty!" are commonly seen on signs.

Students in Dr J's lectures sometimes ask Dr J about protesters' messages and question whether IACUC requirements are enough protection for research animals' welfare.

Dr J considers how to respond.

Commentary

Use of nonhuman animal models in biomedical research is, by its nature, utilitarian in its approach to reducing suffering. A goal of such research is to advance knowledge and thereby reduce human suffering and death from disease, but this goal is met at the cost of suffering to nonhuman animals used in experimental settings. If we acknowledge this sacrifice is necessary, we recognize that our next obligation is to reduce suffering in experimental animals. Although a given research institution's IACUC is critical in enforcing practice guidelines that minimize suffering in nonhuman animals, scenarios that lead to avoidable pain or distress reveal potential limitations in the capacity of IACUCs to protect animal welfare.

For the discussion here, I will focus entirely on vertebrate animals, particularly mammals such as the dogs used in Dr J's experiments, as these animals are most frequently used to model human diseases and have perceptions of pain and stress most like ours.

In the seminal 1959 publication that has become the landmark for modern laboratory practice, *The Principles of Humane Experimental Technique*, W. M. S. Russell and R. L. Burch describe the treatment of nonhuman animals with the terms *humanity* and *inhumanity*.[1] These terms are meant to be descriptive and not normative, to contrast actions that uphold the ethical goal of protecting animal welfare (ie, humane treatment) with actions that do not. *Inhumanity* is a term used by Russell and Burch to encompass several concepts, such as pain, fear, and distress.[1,2] It carries many of the same connotations as suffering, as will be described in this work. Suffering may be subdivided into a few discrete categories. First is pain, the inherently undesirable sensation transmitted by the nervous system of vertebrates as a result of physiological or physical trauma. Second, stress is a mental state that may be associated with fear or anxiety due to the perception of being in a hostile environment. Lastly, there are negative sensations that occur due to inadequate fulfillment of bodily needs, such as hunger in the absence of food.[3] Identifying specific modes of suffering is helpful for creating actionable targets for humane experimental design. Moreover, the successful protection of animal welfare necessarily indicates the absence of such suffering.

Minimizing Suffering

Laboratory animals are frequently exposed to painful or stressful stimuli, which may be inseparable from certain disease states or experimental interventions. However, not all suffering is necessary or justifiable. In their discussion of inhumanity, Russell and Burch contrast direct inhumanity—that which is an integral and inseparable aspect of the

experiment—with contingent inhumanity, which is "incidental and inadvertent" and not necessary for the success of a given experiment.[1] This distinction is critical to analyzing Dr J's experiments. In Dr J's experiments, cardiac disease and complications are likely unavoidable, as their purpose is specifically to study antiarrhythmic drugs. Unfortunately, these experiments are continued until the death of the animals. An essential aspect of humane experimental design is to define not only experimental endpoints but humane endpoints. *Experimental endpoints* refer to when the data required to fulfill the aims of the study have been obtained. In contrast, *humane endpoints* identify when an experimental animal experiences severe and irreversible suffering, requiring the affected animal to be removed and euthanized. In Dr J's experiments, it is necessary to induce arrhythmias in the experimental animals to initiate the experiment, but since it is not clear whether these arrhythmias need to be sustained until the death of the animal to obtain the relevant data, inducing persistent arrythmia should be discouraged. A compelling argument for this practice would be expected to justify why arrhythmias must be sustained until the death of the animal. Furthermore, the case states that "many dogs experience … painful gastrointestinal and pulmonary side effects of the pharmacological agents," which may lead to irreversible, life-threatening debility with associated severe pain and distress.[4] This debilitated condition is described as a moribund state, a commonly used humane endpoint in nonhuman animal experiments.[5] Since these adverse effects are seen in many experimental subjects, they should be anticipated, and the clinical findings should be clearly described and included as humane endpoints in Dr J's protocols. From a scientific perspective, if the tested pharmacologic agent is obviously toxic in nonhuman animals, then it would not be desirable for use in human trials either. Therefore, terminating experiments early due to the toxicity of the agents is not only humane but practical.

Identifying occurrences of contingent inhumanity (ie, avoidable suffering) is thus critical and a key criterion of whether an IACUC is adequately protecting animal welfare. A great deal of expertise is needed to determine the degree of pain and stress necessary and is the reason why IACUCs are mandated to have at least one member with experience in nonhuman animal research.[6] However, there is no guarantee that the IACUC members have adequate experience in a particular field of research. It is possible for protocols that unnecessarily expose nonhuman animals to harm to slip past IACUC review should the members lack the relevant experience. In Dr J's case, there may not be an IACUC member who is knowledgeable about experimental design for cardiac electrophysiology research using canine models, and, as a result, this IACUC would be limited in identifying unnecessary harms to the dogs used in the study. Therefore, the IACUC should seek out and recruit researchers who are subject matter experts to review the proposal. Taking this step may require looking for reviewers outside of an IACUC's home organization, particularly if the field of research is small or highly specialized.

Identifying Limitations in IACUC Review

Russell and Burch are best known for proposing 3 guidelines for preventing unnecessary pain and distress in animal research: replacement, refinement, and reduction.[1] *Replacement* refers to the replacement of animals with either inanimate models or with phylogenetically simpler nonhuman animals that may have less capacity for fear or pain. *Refinement* refers to the modification of animal protocols to reduce unnecessary suffering, as described in the above discussion on contingent inhumanity. *Reduction* is the practice of using as few nonhuman animals as needed for an experiment and maximizing the data gained from the animals used. However, the 3 *R*'s have been

criticized as being insufficiently comprehensive for the purpose of preventing unnecessary pain and distress in animals.[7,8] Curzer et al argue that the 3 *R*'s are framed to focus entirely on the improvement of existing research protocols on the presupposition that the proposed research will occur. Therefore, there must exist a fourth *R*, *reject*, to constrain research when anticipated harm to nonhuman animals clearly outweighs the knowledge that might be gained.[8] While this fourth *R* acts as a general ethical guide, it is also a practical mandate for all IACUCs. IACUCs may be reluctant to make such nuanced decisions if their members do not have sufficient expertise, as the criteria for excessive harm would vary greatly depending on the scientific field. As described previously, IACUCs should recruit subject matter experts with relevant experience to identify proposals for research in which the knowledge to be gained would not be enough to justify the harm posed to the animals in the study. Such proposals should be rejected at an early stage to prevent unnecessarily inhumane experiments from occurring.

We assume that IACUCs act as impartial and unbiased reviewers, but this assumption should not be taken for granted. Federal regulations expressly forbid members of an IACUC to have financial, personal, or professional conflicts of interest.[6] Nevertheless, bias may be subtle and difficult to eliminate entirely. Dr J is a highly successful and influential researcher who is likely well-known throughout the research institution, not to mention a former IACUC member. While these achievements in the field confer a great deal of credibility on Dr J's work, they do raise the concern that IACUC review may be less critical of Dr J than of a less influential investigator. This potential for partiality indicates another key criterion for IACUC reliability: members of the IACUC must perform impartial and unbiased review to ensure the protection of animal welfare. Instituting a standardized system of blinded proposal review, whereby the IACUC reviewers are not aware of the principal investigator for a given proposal, might help promote impartiality and reduce bias.

Conclusion

For IACUCs to perform their role as overseers of animal welfare in laboratory research, they must be able to identify and minimize occurrences of avoidable suffering, reject research in which suffering clearly outweighs the potential knowledge gained, and act impartially without undue influence. Yet while there will invariably be gaps in the ability of IACUCs to perform their duties, their role as impartial third-party reviewers is critical to prevent research protocols from breaching ethical guidelines. We must strive for analysis, refinement, and improvement of IACUC function, although thus far there is sparse literature on objective analyses of IACUC performance metrics.[9] By improving IACUC performance, we might better navigate the ethical terrain of using sentient nonhuman animals in laboratory research while ensuring their welfare.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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IN THE LITERATURE: PEER-REVIEWED ARTICLE

Roles of Randomized Controlled Trials in Establishing Evidence-Based Gender-Affirming Care and Advancing Health Equity

Theodore E. Schall, PhD, MSW, MBE, Kaitlyn Jaffe, PhD, and Jacob D. Moses, PhD

Abstract

This article reviews the design of a recently published randomized controlled trial (RCT) on immediate vs delayed access to gender-affirming hormones for transgender and gender-diverse (TGD) people and outlines key learning points that clinicians should know about how RCTs can and cannot contribute to advancing health equity for TGD people.

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Questioning the Evidence Base

In recent years, transgender and gender-diverse (TGD) Americans and their clinicians have faced increasing political backlash against gender-affirming care modalities. While attacks on TGD medicine initially targeted youth, adult access to care is now also threatened.[1,2] One tactic used by critics has been to assert that the quality of evidence for gender-affirming care is low[3] and to call for a moratorium on such care until randomized controlled trials (RCTs) are conducted.[4] Calls for additional evidence might seem reasonable on their face: who could object to better evidence? But opponents of TGD health care leverage these calls to justify denying, obstructing, or criminalizing access to such care. And while RCTs are often portrayed as the "gold standard" in evidence-based medicine, a range of logistical and ethical objections make them inappropriate for answering many important questions about TGD medicine. It is critical to understand what researchers and clinicians should know about how RCTs can—and cannot—contribute to advancing health equity for TGD people.

The Nolan et al RCT

Several limitations of RCTs can be discerned by examining the conditions that made a recent RCT of gender-affirming care possible. In September 2023, *JAMA Network Open* published "Early Access to Testosterone Therapy in Transgender and Gender-Diverse Adults Seeking Masculinization: A Randomized Clinical Trial" by Nolan et al,[5] which examined the effects of testosterone therapy on depression, suicidality, and gender dysphoria (a diagnosis associated with clinically significant distress resulting from

incongruence between one's assigned sex and one's gender identity, which some TGD people object to on the basis that it implies distress is intrinsic to TGD identities) in a sample of 64 Australian TGD adults. The RCT was designed as an open-label study; participants in the study knew whether they had been assigned to an intervention group, which received immediate initiation of testosterone, or to a control group, which received no treatment during a waiting period of 3 months prior to initiation of testosterone—mirroring real-world conditions. The study found a statistically significant decrease in gender dysphoria and a clinically significant decrease in suicidality among the intervention group.

The Nolan et al study was reported as a novel comparative study and the first RCT for gender-affirming hormones.[6] To investigate procedural improvements, the study took advantage of existing structural deficiencies: namely, that Australian TGD patients who seek gender-affirming care often face long wait times at state-funded endocrinology and gender clinics.[7] This context allowed Nolan et al to describe a 3-month waiting period between initial assessment and initiation of testosterone therapy as "standard care." As such, there was no need to assign patients to a nonintervention control group, which would have been ethically untenable.

Nolan et al's explicit project was to develop an evidence base for reimbursement of transition-related costs under the evidentiary standards of the Australian national health system.[6] The authors described their study as a phase 4 efficacy trial[8] because of their intent to extend permitted on-label prescribing of testosterone to TGD people. As in Australia, in the United States prescribing of testosterone for TGD people is always off-label; there is no Food and Drug Administration (FDA) indication for testosterone use in TGD people,[9] so studies such as this one provide an important pathway to improved access. Nolan notes that transgender patients were willing to participate because the 3-month waiting period did not, in this case, constitute an additional burden, as it was already standard care.[6] Other studies designed similarly—to exploit weaknesses in existing procedures and policies—might indeed be a valuable addition to the evidence base for TGD health, but they must be designed to ensure access to affirmative health care with established benefits.

Limitations of RCTs

Given that it is only ethically permissible to use RCT designs in TGD health research within narrow circumstances and that a robust evidence base of observational studies consistently shows the benefits of affirmative models for TGD adults,[10,11] access to gender-affirming care should not be denied on the basis of an evidence base lacking RCTs. The evidence for gender-affirming care for children and youth is not as strong as that for adults, but the need for research in this population still ought to be met without randomizing pediatric patients to non-intervention groups. Instead, as with adult studies, pediatric researchers should exhaust alternative study methods that explore the potential benefits of access to care and the harms of existing structural barriers (without reinforcing them), at least until such barriers fall away. Nor should researchers underestimate the potential harms of RCT designs on individuals or communities that might depend on research for access to the standard of care. Many TGD people's access to gender-affirming care is severely curtailed by underinsurance, poverty, and medical discrimination[12]; if research participation offers the only accessible path to gender affirmation, decisions about participation may become less voluntary and more coercive.

Furthermore, that this one RCT was possible does not mean that TGD medicine should be subject to critics' contention that only RCTs provide evidence of sufficient quality to justify care. In a 2023 review article in the *International Journal of Transgender Health*, Ashley et al describe a set of problems with RCT study designs that make them inappropriate for TGD mental health research,[13] including the impossibility of masking to which study group a research participant has been assigned due to physiologically evident effects of gender-affirming care, risks of participant nonadherence and withdrawal due to unmasking, and samples of willing participants not being representative of the broader population. Another challenge for RCTs in both the United States and Australia arises from the common practice of self-directed (or "DIY") treatment; recruiting sufficient study samples of treatment-naive participants is resource-intensive, even for established research programs.

Perhaps the most significant challenge to conducting RCTs in TGD health research is the lack of clinical equipoise[14] and expected scientific value: gender-affirming care for adults has been the clinical standard for decades.[15,16] Reviews of observational studies show associations between access to gender-affirming care and improved health outcomes, including reduced suicidality, improved subjective quality of life, decreased incidence of psychiatric diagnoses, and decreased suffering associated with gender dysphoria.[12] RCTs on the pharmacokinetics of testosterone have long since established its safety and effectiveness.[17] Few researchers (or institutional review boards) would consider study designs that deny TGD patients access to widely used, often lifesaving care to be ethical.[18] Similarly, ethics boards may question the time, cost, and risks of study participation to address research questions previously answered.

A Path Forward

None of this is to suggest there is not a need for research. There are still many things to be learned about TGD medicine, including long-term effects of hormones, hormone blockers, and surgeries; health beyond gender affirmation and throughout the lifespan; and reproductive health care.[19] The broad exclusion of vulnerable populations from research opportunities only further compounds health disparities; clinicians need high-quality research to guide evidence-based medicine. When RCTs can be structured appropriately, they have a place in expanding the evidence base for gender-affirming care. However, other study designs, such as longitudinal observational cohort studies and case-control studies, may be more appropriate for answering many important research questions, given the limitations of RCTs. Good-faith calls for more research should include calls for these other designs, not just RCTs.

Nolan et al cleverly devised a key to fit in the lock of the Australian regulatory system. However, that RCTs are practical and ethical in only some cases renews questions of how regulatory bodies can promote equity in access to care for gender and sexual minorities by accommodating a wider variety of evidence. For example, the FDA could clear a path to expand the list of indications for testosterone therapy by accepting data gleaned from non-RCT studies and other clinical sources such as registries, electronic health records, and claims data sets—so-called "real-world evidence" (RWE).[20] In 2022, the FDA announced an expansion of its program to improve the quality and acceptability of RWE in approval decisions,[21] signaling agency interest in data sources beyond conventional RCT designs and hopefully new opportunities to expand indications for TGD medicine.

Conclusion

The Nolan et al study delimits both the possibilities and the boundaries of possibility of RCTs in informing TGD health policy. RCTs can be most helpful for studying process improvements and advancing goals of quality improvement. Yet RCTs are unlikely to resolve the underlying ethical tensions between the availability of evidence and the justifications for providing care or to remedy the social conditions that undermine TGD health equity. And they are certainly unlikely to resolve questions raised to stoke political controversies.

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HEALTH LAW: PEER-REVIEWED ARTICLE

How Might Corporations' and Nonhuman Animals' Personhood Compare Under the Fifth and Fourteenth Amendments?

Richard L. Cupp Jr, JD

Abstract

The Fourteenth Amendment to the US Constitution prohibits states from depriving any person "equal protection of the laws," and the Constitution's Fifth Amendment has been interpreted as applying this prohibition to the federal government. This article considers whether constitutional equal protection should apply to some nonhuman animals in light of corporations having gained such protection and concludes that expanding equal protection personhood to nonhuman animals is improbable in the present legal landscape.

Corporations and Nonhuman Animals

A common argument for extending legal personhood to at least some nonhuman animals is that courts grant legal personhood to corporations, and that, if lifeless corporations are legal persons, then equality principles and justice demand granting legal personhood to sentient or at least particularly intelligent nonhuman animals.[1] Legal personhood would enable legal standing for such nonhuman animals to bring or participate in legal proceedings implicating their interests through legal guardians, akin to how human children may be parties in legal proceedings represented by guardians. Corporations' legal personhood[2] has enabled corporations to bring lawsuits for alleged violations of their constitutional rights, including the constitutional right of "equal protection of the laws." Constitutional equal protection requires that the government protect rights equally for similarly situated persons. For example, if courts extended equal protection rights to animals, statutes and regulations allowing medical research on nonhuman animals for the benefit of humans without consent of an appointed guardian could be challenged as unconstitutional. These challenges would likely note that laws and regulations protect humans with less autonomy than some animals (eg, humans in a vegetative state and human infants) from medical research without consent of a guardian acting in the humans' best interests and thus that research on nonhuman animals merits equal protection of the laws.

This article begins by explaining the background of the constitutional guarantee of equal protection of the laws. It then addresses the courts' application of legal personhood to corporations and the common position of many advocates that sentient or intelligent nonhuman animals are at least as deserving of legal personhood and constitutional

equal protection as corporations. The paper next analyzes challenges to this argument for animal legal personhood, highlighting the connections courts have made between personhood and a norm of capacity for responsibility within humans' legal system. The paper concludes that courts are unlikely to accept the analogy between corporate personhood and animal personhood in the foreseeable future and that they are unlikely to assign constitutional equal protection rights to nonhuman animals in the foreseeable future. Thus, although extending equal protection rights is a timely issue, as views of animal protection have evolved, courts are unlikely to find in the foreseeable future that using an animal for human-centered medical research without consent of an appointed guardian acting in the animal's best interests violates constitutional equal rights protections.

Equal Protection for "Persons"

As mentioned, US courts apply the constitutional guarantee of equal protection of the laws to corporations, but they do not apply this protection to nonhuman animals. The Constitution's Fourteenth Amendment, which embodies the equal protection clause, was ratified in 1868 in the aftermath of the Civil War.[3] The amendment was inspired by the need to address racial injustice and to protect former slaves from unlawful discrimination. The Fourteenth Amendment applies only to action by states and does not govern action by the federal government. However, during the Civil Rights Movement in the 1950s, the Supreme Court of the United States (SCOTUS) interpreted the due process clause of the Fifth Amendment ("no person shall be … deprived of life, liberty, or property, without due process of law"[4]), which was part of the Bill of Rights, as requiring equal protection of the laws by the federal government as well.[5]

The most prominent application of the equal protection guarantee was the 1954 case of *Brown v Board of Education*.[6] *Brown* overruled the infamous 1896 decision in *Plessy v Ferguson*, which held that "separate but equal" accommodations based on race did not violate the Fourteenth Amendment.[7] *Brown* held that segregating school enrollment by race violates the Fourteenth Amendment's equal protection clause.[6] It led to significant societal changes by illegitimizing the formal racial segregation that was commonplace at that time. *Brown* is widely viewed as one of the most important and broadly respected judicial decisions in US history, leading one prominent scholar to opine that "an approach to constitutional interpretation is unacceptable if it entails the incorrectness of *Brown v Board of Education*."[8]

Extending Equal Protection

In 1886, a headnote (not an official part of the court's ruling) in a case before SCOTUS, entitled *Santa Clara County v Southern Pacific Railroad Company*, stated that the court's justices were in unanimous agreement that corporations are entitled to the Fourteenth Amendment's equal protection guarantee.[9] Later decisions cited *Santa Clara County* as precedent for treating corporations as legal persons under the Fourteenth Amendment, and SCOTUS has affirmed corporations' right to constitutional equal protection in many cases. SCOTUS has also extended some other constitutional protections to corporations. For example, in the controversial case of *Citizens United v Federal Election Commission*, SCOTUS held that corporations have a constitutional right of freedom of speech that allows them to make unlimited political donations.[2] Some advocates of "strong" animal rights challenge the courts' assignment of legal personhood and constitutional rights, such as equal protection, to corporations while denying legal personhood and constitutional rights to sentient or highly intelligent animals.[1] In contrast with typical existing legal protections of nonhuman animals that

are described by some as "rights," strong animal rights may be understood as rights that, if recognized, would enable legal standing for at least some animals, with the animal's rights asserted by a human representative acting on behalf of the animal.[10] Asserting constitutional or other legal rights through a representative is routine for humans who lack legal competency, such as children or adults with significant cognitive limitations. As living beings that can suffer pain or experience pleasure, sentient or highly intelligent nonhuman animals are in some respects closer to human beings than are lifeless corporations; corporations are artificial entities and sentient nonhuman animals are, like humans, biological creatures.[11]

Challenges to a Legal Personhood Comparison

Although arguing that sentient nonhuman animals should have equal protection rights if such rights are granted to corporations has been appealing to many advocates, a growing body of judicial decisions has firmly rejected animal-corporation comparisons regarding legal personhood. For example, in 2022, New York State's highest court dismissed a lawsuit seeking a writ of *habeas corpus* in the name of an elephant kept at a zoo.[12] The lawsuit demanded that the elephant be moved to a sanctuary, which the plaintiff believed to be a better environment for the elephant. *Habeas corpus* means "produce the body" and is used to bring a detained or imprisoned person to court for a challenge regarding the lawfulness of the person's confinement.[13] While listing reasons that the lawsuit must fail, the court stated "[n]or does any recognition of corporate and partnership entities as legal 'persons' lend support to petitioner's claim. Corporations are simply legal constructs through which human beings act and corporate entities, unlike nonhuman animals, bear legal duties in exchange for legal rights."[12] In a similar animal personhood lawsuit rejected in 2019, a Connecticut appellate court stated: "We note that entities to which personhood has been ascribed by law are formed and governed for the benefit of human beings."[14] In 2014, another New York State appellate decision rejecting animal legal personhood held that "[a]ssociations of human beings, such as corporations and municipal entities, may be considered legal persons, because they too bear legal duties in exchange for their legal rights."[15]

These courts' emphasis on corporations' status as proxies for their human owners has a strong foundation in legal precedent and in the dominant scholarly theories regarding the nature of corporate personhood. Under all of the major corporate personhood theories, corporate personhood is anchored in the interests of humans.[16] Asserted animal legal personhood, by contrast, is focused on the interests of animals. The former stance does not imply that human society's legal systems should not protect animals but that nonhuman animals are not proxies for the interests of individual humans or groups of humans.

A Norm of Capacity for Responsibility

A growing body of legal precedent rejecting animal legal personhood assertions in recent years has emphasized that personhood and a norm of capacity for legal responsibility are intertwined. As one of these courts put it, "collectively, human beings possess the unique ability to bear legal responsibility."[12,14,15,17] Although some humans, such as infants, lack this ability, these humans' personhood may be viewed as anchored in their membership in the human community rather than in their individual capacities. For example, legally incompetent persons often were—or in the future likely will be—deemed legally competent, and they typically are tightly interconnected with humans capable of bearing legal responsibility (eg, parents, children, siblings, caretakers). Thus, our legal system recognizes legally incompetent people as rights-bearing humans, rather than

defining them as less than human due to their legal incompetence. Furthermore, as addressed above, the legal personhood of entities such as corporations is grounded in the interests and duties of humans, and thus courts have deemed treating corporations as responsible actors with some rights within our legal system as appropriate. No animals possess sufficient capacity to hold them morally responsible under our legal system.

Textualism, Originalism, and the Living Constitution

Three of the most influential approaches to interpreting the US Constitution are textualism, originalism, and the living constitution approach. Although definitions of all 3 approaches may be nuanced and debated, in general terms textualism reflects a strong focus on the text of the constitutional statute or provision under consideration—sometimes referred to as the "plain text" —in determining its meaning.[18] Originalism focuses on seeking to determine and abide by the original intent of the constitutional provisions' drafters.[19] The living constitution approach holds that the Constitution should be interpreted in accordance with "changing circumstances and, in particular, with changes in social values."[19]

Textualism and originalism have played a significant role in modern constitutional jurisprudence, and the concept of applying constitutional equal protection to nonhuman animals fares poorly under either interpretive approach. The Fourteenth Amendment's text states that it applies to "persons." The plain text meaning of *person* in 1868 would seemingly be a human being or, at the furthest plausible stretch, human beings and their proxies, such as corporations. Even more plainly, the original intent of the Fourteenth Amendment's drafters could not have been to include nonhuman animals in the definition of persons. Rather, "[a]s everyone knew when it was ratified in 1868, the amendment's guarantees of equal protection . . . were designed to secure the rights of the newly freed slaves and protect them from discrimination by the states."[3] Both textualism and originalism may be subject to flexible interpretation, but a level of abstraction well beyond the toleration of most jurists would be required to shoehorn them into supporting constitutional equal protection for animals.

Although it champions interpretive flexibility, the living constitution approach is also unlikely to persuade courts to apply constitutional equal protection to nonhuman animals in the foreseeable future. Multiple decisions by influential appellate courts agreeing on an issue with no appellate courts disagreeing creates precedent that even living constitution jurists view as significant. Furthermore, judicial decisions often shed light on societal values. The living constitution approach is highly unlikely to be employed by SCOTUS—the ultimate arbiter of all constitutional law issues—to make a fundamental change to equal protection doctrine that not only is inconsistent with the Constitution's text and original intent, but also does not appear to represent widespread changes in social values regarding whether nonhuman animals should be considered persons. The growing body of judicial decisions rejecting animal legal personhood addressed in this paper reflect the commonsense reality that US society has not changed sufficiently to broadly view nonhuman animals as legal persons, and only persons may assert equal protection rights. Put another way, society's evolution toward caring more about protecting animals does not represent a substantial societal shift toward embracing animal legal personhood. Every additional legal decision rejecting animal legal personhood strengthens the precedent against widespread acceptance of the concept in the foreseeable future.

Writ of *Habeus Corpus*

Several highly publicized lawsuits have been filed in recent years seeking legal personhood for intelligent nonhuman animals such as chimpanzees and elephants, and it is notable that these lawsuits have avoided pleading violation of the Fourteenth Amendment as the basis of their claims. Most of these lawsuits have instead focused on seeking a writ of *habeas corpus* under state common law[12,14,15] (ie, law derived from judicial decisions rather than the Constitution or statutes),[13] perhaps reflecting recognition of the particularly exceptional challenge of convincing courts to apply the Constitution to animals. Courts have rejected all of the *habeas corpus* lawsuits thus far, and the possibility of prevailing in a constitutional claim, with its attendant focus on text and the framers' intent, is even more remote.

Society is evolving to demand greater protections for sentient animals, and the US legal system is increasingly providing stronger protections. However, assigning constitutional personhood to nonhuman animals under the Fourteenth Amendment or under any other constitutional provisions would be highly problematic (eg, a 2022 appellate decision noted that allowing an elephant to invoke *habeas corpus* protections—analogous to personhood in the scope of its implications—"would have an enormous destabilizing impact on modern society"[12]) and is quite unlikely, given the approaches to constitutional interpretation that are currently dominant in US courts.

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HEALTH LAW

Should Nonhuman Animals Be Recognized Legally as Persons?

David Favre, JD

Abstract

This article explores the legal status of nonhuman animals used in biomedical research. While acknowledging that, presently, nonhuman animals in research settings hold no personal legal rights, this article explores what a legal person is and proposes that it is possible for nonhuman animals to become legal persons and receive better protections under the federal Animal Welfare Act.

Introduction

Many readers of this article might have a strong sense of the importance of the ethical treatment of nonhuman animals in scientific experimentation. How might that ethic be reflected within the legal system? Since the publication of Peter Singer's book, *Animal Liberation*, in 1975,[1] the ethical discussion about the status of nonhuman animals has become increasingly robust on a global basis.[2,3,4] This article focuses on a possible expansion of this concern about nonhuman animal rights by considering the concept of legal personhood.

What Is a Person?

Beginning as early as the Greeks, society accepted a hierarchy of status, with human men at the top and plants at the bottom, and the presence of rationality as a key factor in determining position in the hierarchy: free men, free women, children, slaves, animals, and plants in descending order.[5] Moreover, from an early time, some nonhuman animals—those that were useful and had financial value—were given the legal status of personal property. The law's focus at this point was not on the nonhuman animal at all but on the animal's financial value to the human owner.[6] Accordingly, legal rules about human conduct toward nonhuman animals as property developed within criminal law—but not rules related to nonhuman animals themselves. All legal systems have long held that nonhuman animals are things and domestic nonhuman animals are personal property, not legal persons.

So, what does it mean to be a legal person? Can a nonhuman animal be included under this definition? It is not a biological definition; it does not require 2 legs and big brains. Instead, a legal person is a category created by the political process of lawmaking for the purpose of designating who or what has the capacity to hold and exercise some legal rights. Historically, in the United States, human slaves were not legal persons. As

individuals, they held no legal rights and had no capacity to seek relief in court.[7] Today, all humans are legal persons, but not all have the same rights. Children and undocumented immigrants have very limited rights under the laws of the United States, but all are legal persons. Yet legal persons need not be humans. Consider that corporations are legal persons in the United States.[8] This means that when harm, usually financial, exists for a corporation, it can be a plaintiff in a lawsuit (or, if causing the harm, a defendant). It can seek legal relief for some harms.

Can these standards be applied to nonhuman animals? The animals have only modest personal financial interests: that which is necessary to provide food and shelter. So, let us consider the possibility of physical harm and mental pain and suffering as a focus point for endowing animals with personhood and legal rights. Should nonhuman animals have personhood and a right to be free from "unnecessary" pain and suffering? Yes, but defining *unnecessary* is the trick.[9]

Consider the situation of a cat, Tom, the human owner of the cat, Jerry (Tom is Jerry's property), and a bad human, Wolf. If Wolf beats up Jerry with a baseball bat, Jerry, being a legal person with the right to be free from intentional infliction of harm, may sue Wolf for the harm inflicted. If Wolf beats up Tom, the cat, Tom is not a legal person and therefore has no legal remedy available to sue Wolf (Wolf may be criminally liable under state anti-cruelty laws). Jerry can recover from Wolf the financial value of harm to Tom, but in a majority of jurisdictions he cannot receive compensation for his grief, pain, and suffering for what happened to Tom.[10,11] If an entity is not a legal person, it can have no rights. If it is a legal person, then some rights can be conferred, but not all harms are recognized by the law.

The Animal Welfare Act

What if, at Big University, a professor wishes to do spinal experiments on cats; the cats will necessarily experience some level of pain. The professor is sure his experiment will add to the knowledge of the operation of the brain. Some organizations oppose any such experiment.[12,13,14] Others might ask about the necessity of using cats or the possibility reducing the number of cats and the degree of pain. The cats themselves have no voice in this debate.

These difficult and complex questions were addressed by the US Congress in 1966 when it adopted the Animal Welfare Act (AWA) with a focus on stolen companion nonhuman animals and nonhuman animals in experimentation.[15] In the 1985 amendments to the federal AWA,[16] Congress adopted a more complex regulation scheme for nonhuman animal experimentation. The new law allowed that some pain and suffering of nonhuman animals is acceptable for the advancement of science. However, Congress created a system of controls to ensure that the pain and suffering of nonhuman animals used in research is in fact necessary and minimized. First, the decision to proceed is not left solely to the researcher, as the Institutional Animal Care and Use Committee at the researcher's institution must also agree that the researcher's assessment of the need for practices involving pain to nonhuman animals is correct. Second, any experiment with a listed nonhuman animal must show that all precautions have been taken to reduce pain and suffering to a minimum.

Does the AWA provide any legal rights for nonhuman animals? No, not at this time. What happens if the professor at Big University does not comply with the law? Assuming that he does follow the procedures required, there may be no one in the room of the

experiment to observe or measure the degree of pain and suffering a specific animal may experience. It is very difficult to objectively measure nonhuman animals' perceived pain[17] and also very difficult to decide if a procedure likely to cause pain is unnecessary. But, even if a case can be made that the pain-inducing procedure either will be or was unnecessary, there would only be modest possible consequences for the professor. Mistreatment of research animals is not a crime under the AWA. State anti-cruelty laws tend to exempt actions within science.[17] Perhaps the professor will be at risk of having funding withdrawn from his National Institutes of Health grant. Or perhaps the professor's institution will impose a sanction, or his peers will shun him. Clearly a cat has no specific remedy.

Would it be possible to give cats a legal right? Yes, Congress could adopt an amendment that acknowledges all animals under the jurisdiction of the AWA to possess a cause of action to stop, by injunction, any action that would clearly violate the existing protections provided under the law. So not all cats, but laboratory cats, would have a cause of action against the professor to stop an experiment or to provide the necessary care. With the granting of this legal right, a cat would become a legal person. If an experiment violated the cat's right to be free from unnecessary pain and suffering, a judge would see the cat as an individual deserving the consideration and protection of the law; this is, by definition, a legal person.

Should All Nonhuman Animals Be Recognized as Persons?

If a legislature makes nonhuman lab animals legal persons for limited purposes, does that mean that the chicken in the pen or the dogs on the couches of the United States are now also legal persons? No. While many individuals seek legal rights for all nonhuman animals, that will not happen or should not happen. Given the extraordinary complexity of all human-nonhuman animal interactions and nonhuman animal uses—and the billions of dollars some of those interactions represent—obtaining such legal personhood for nonhuman farm animals from those holding political powers would be nearly impossible in the near term. Additionally, the uniform adoption of rights for all animals should not happen, as rights will have to be crafted for animals in different categories. Legal rights for companion animals will be separate from those for zoo animals or the cows in the field. Legal rights will have to accommodate the nature of the human-nonhuman animal context.

How Could It Happen?

A constitutional amendment might be drafted that would allow nonhuman animals to hold legal rights. The following model language might be considered: *As animals have interests apart from humans, Congress shall have the power to adopt laws providing personhood for all primates (all mammals? all vertebrates?)*. This possibility, however, does not seem realistic in the near term—but in a hundred years, hopefully.

On the other hand, perhaps a Constitutional amendment is not necessary. In a 2018 case, the Ninth Circuit Court of Appeals ruled against a macaque named Narotu[18,19] for a claim under US copyright law.[20] The organization People for the Ethical Treatment of Animals (PETA) brought a legal action on behalf of Narotu. A picture that Narotu had taken of himself with the defendant's camera was being sold by the defendant. PETA claimed that, as Narotu took the picture (which is factually correct), he had copyright control over the use of the picture. The statute provides protection for any "person," and PETA wanted the court to declare that Narotu was a legal person. In declining to do so, the court said that the claim could be made by Narotu if Congress would simply change

the definition of person in that specific law to include primates. The court's reasoning suggests that Congress has the power to create personhood for nonhuman animals but must specifically do so.

At present, the federal protections provided for nonhuman animals in science labs are very weak. One way to enhance the level of protection in the law is to allow nonhuman animals to present their case directly to a court. As with all the trust laws in our 50 states, the law could allow any human or nonprofit corporation to petition the court for the right to represent the animals in question. Amending language could be as follows: *The provisions of this law providing protection for nonhuman laboratory animals may be enforced in federal courts with injunctive powers. Any human or nonprofit corporation may petition the court on behalf of specific nonhuman animals and, upon a showing of sufficient interests and resources, be granted permission to file an action.*

While a number of attorneys and nonprofit corporations are available to represent nonhuman animals in court, the real-world difficulty is that the public usually has no idea what is happening in science laboratories, so the lack of information would be a significant difficulty in bringing a case should the law be amended.

Conclusion

Ethical concern for nonhuman animals directs the actions of those who hold that ethical belief. If those who hold an ethical position about nonhuman animals also believe others should change their conduct, the path of the law must be taken in order for those beliefs to become legal standards of conduct. Nonhuman animals in science are a group for which ethical concerns, but no legal rights, presently exist. Both the Constitution and Congress represent paths available for legal change. The future will be interesting, as proponents of different ethical views seek resolution of this significant dilemma.

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STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE

With What Should We Replace Nonhuman Animals in Biomedical Research Protocols?

Mikalah Singer, JD, LLM and Aysha Akhtar, MD, MPH

Abstract

Historically, most discussions about nonhuman animal experimentation consider what has become known as the 3 *R*'s: refinement, reduction, and replacement. Refinement and reduction receive the most attention, but recent modeling advances suggest that suitable replacement of nonhuman animal testing would bolster human research and increase translatability to human health outcomes. This article discusses these modeling advances and advocates their use, especially as replacements to nonpredictive nonhuman animal protocols, and discusses growing momentum in biomedical research communities and federal agencies that favors replacement of animal testing.

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Three *R*'s

The principles known as the 3 *R*'s (*replacement*, or substituting animals for insentient, nonanimal models; *reduction*, or reducing the number of animals used to gain information; and *refinement*, decreasing the severity of pain-inducing procedures used on animals) have been a staple framework guiding the use of animals in biomedical research for more than 50 years.[1,2] Historically, however, emphasis has been placed on refinement and reduction, with less effort devoted to replacement due to the former being seen as more achievable than the latter.[3] Today, there is a worldwide call by scientists and animal advocates to shift to a 1-*R* principle: replacement.[4] This call stems not only from the increased global concern for nonhuman animal suffering, but also from the growing recognition of the lack of translatability of nonhuman animal research and recent technological advancements in human disease and biological modeling.

While the principles of reduction and refinement arguably lead to some reduction in harm to animals and improvements in medical research, they nevertheless remain rooted in a paradigm that perpetuates the use of nonhuman animals for biomedical research and drug development. Moreover, it is now well known that the lack of translatability of nonhuman animal research testing to human outcomes is causing failures in therapeutic development at an alarming rate. More than 80% of all drugs and

vaccines found safe and effective in preclinical trials, including those based on animal testing, fail during human clinical trials.[5] Much of this failure rate can be attributed to the physiological and pathological differences between humans and nonhuman animals.[5] Additionally, even with attempts to reduce the failure rate by changing nonhuman animal study design protocols, which can be costly and time-consuming, animal research has yet to translate reliably to humans.[6] This article discusses human-relevant models that can replace animal testing, the ethical questions spurring the growing momentum in biomedical research away from animal testing, and the federal actions that support this shift.

Human-Relevant Models

Research methods that more faithfully reproduce human biology and physiology than nonhuman animal models offer a path toward a new paradigm for biomedical research that is fundamentally more accurate, predictive, efficient, and effective.[4] Recent scientific developments have led to multiple "human-relevant" research models—those based on human biology—that have the potential to lead to improved understanding of human biology, disease pathophysiology, and therapeutic development.[7] Unlike traditional in vitro systems, these newer in vitro models utilize 3-dimensional architecture of human tissues and organs.[8]

Some of these in vitro models are referred to as microphysiological systems (MPS) or, more commonly, as organ-on-a-chip or organ chips. By combining human cell sourcing, organ-specific microenvironments, and tissue-relevant forces, MPS more closely emulate human biology than traditional 2-dimensional in vitro models. MPS can also be integrated into multi-organ and potentially full human-body systems.[8] Another alternative to traditional in vitro models is organoids, stem cell-derived, 3-dimensional culture systems or "mini organs" that are proving useful for closely examining organ-specific functions and diseases. Both MPS and organoids can be considered human-relevant models in that they are based on and represent human physiology as opposed to animal physiology.[9]

These methods more faithfully recapitulate human physiology than nonhuman animal tests and have the potential to predict human drug safety and effectiveness more accurately. Over the past few decades, improvements in these models have led to brain organoid screening systems that can help identify gene mutations, vulnerable cell types, and gene regulatory networks underlying autism spectrum disorders[10]; kidney-on-a-chip models that can be used to predict kidney-related toxicity of cancer drugs[11]; and lung tissue models than can revolutionize infection research.[12] Researchers in this space are working on organoid and organ chip models of nearly all major organs in the human system,[8] with certain specialists aiming to build full human-on-a-chip models.[13,14]

Additionally, the biological differences between humans and other animals, combined with the lack of diversity in nonhuman animals bred for research, lead to results that do not account for the genetic and ethnic diversity of humans.[9] Human-relevant models not only represent human physiology better than animal tests, but also can represent the physiology of specific populations, ethnicities, or individuals.[13,15,16,17,18,19] Models that better represent the diversity of human populations can lead to better predictions of clinical trial outcomes.[20] Thus, the future applications of human-relevant methods far exceed those of animal testing.

Critics of human-relevant models note that these models are not yet fully proven and are not at a point at which they can fully replace all animal testing.[21,22,23,24] This criticism, while fair, serves as an impediment to rather than a facilitator of the improvement of human-relevant methods. It reinforces the status quo in governmental funding instead of boosting government funding for improved human-relevant methods. Very little funding goes toward human-relevant methods currently,[25] but with government funding and support to validate their reliability and improve their complexity, they could flourish, as did the Human Genome Project.[26]

Is It Ethical to Keep Using Animals for Biomedical Research and Drug Development?

Despite rats, dogs, cats, and humans sharing many biological features, subtle differences in physiology, biochemistry, and genetic expression between humans and other animals can significantly mislead research and therapeutic development. Species differences result in drugs and vaccines that seem promising in animal tests failing when tried in humans. For example, thousands of drugs that worked in animal tests for stroke, HIV, immune system disorders, and other diseases failed when tried in humans.[6,27,28,29,30] These failures are primarily due to toxicities not predicted by animal tests or to a lack of efficacy.[6,27,28,29,30]

One of the main safety problems caused by drugs is liver toxicity.[31] A groundbreaking study found that, in a set of 27 drugs, human liver chip methods identified nearly 7 of every 8 drugs proven to be hepatoxic during clinical use after they were deemed safe by animal tests.[32] Twenty-two of these drugs were determined to be safe by animal tests but later caused the death of 208 patients and required liver transplants in 10 others.[33] The drugs were subsequently pulled from the market or given black box labeling.[33]

There is also strong reason to believe that many drugs that may be effective and safe in humans are prematurely delayed or discarded due to misleading results in animal tests.[6] Certain drugs, such as cyclosporine, are widely and successfully used but were initially delayed because of animal test results that did not apply to humans.[6]

Both the abandonment of potentially useful treatments and the numerous unsafe treatments that proceed to clinical trials after nonhuman animal testing call into question the opportunity costs of the current research paradigm. The continued costly focus on animal testing impedes the development of better, more accurate organ-on-chip and other human-relevant research methods. The lack of translation of nonhuman animal tests to humans is especially alarming, as there are no approved treatments for many diseases, including sepsis.[27] Additionally, the poor translatability from animals to humans leads to suffering in nonhuman animals that is disproportionate to any perceived knowledge gained. Therefore, a shift in focus toward the development and use of human-relevant research methods should be at the forefront of industry, academia, and governmental funding and priorities.

Human-Relevant Methods

In 2013, Francis Collins, then director of the National Institutes of Health (NIH), published his thoughts on the failures of animal testing and a need to move toward human-relevant methods.[34] Since that time, the US government has demonstrated interest in the pursuit of human-relevant testing methods. This interest comes in the form of agency actions and legislative initiatives.

Federal agency actions. While important steps have been made, agency actions have thus far been small in impact and have fallen short in essential ways. A more robust shift away from animal testing has yet to happen or to be determined as a goal for the future.[5] In the 2012 International Animal Research Regulations report, the National Research Council stated that almost half of NIH funding goes to testing that involves animal use.[35] Much of this funding is in the form of grants. Between FY 2008 and FY 2015, more than 70% of projects awarded NIH grants used mouse models.[25,36] However, the US government has a few initiatives that have the potential to support human-relevant research. Under the umbrella of the NIH, the Advanced Research Projects Agency for Health (ARPA-H) was founded on the idea that increasing direct federal funding of transformative and innovative research will drive—as well as quicken the application and implementation of—scientific breakthroughs to improve health. ARPA-H has shown an interest in more accurate human-relevant models by requesting research proposals using human cells to 3D-print organs.[37] Another center within the NIH, the National Center for Advancing Translational Science, is home to many programs focused on advancing human-relevant research methods. These programs include the 3-D Tissue Bioprinting Program and the Tissue Chip for Drug Screening Program.[38] Although these federal agency programs constitute a good start in funding research methods that are more accurate for human biology than animal testing, human-relevant testing methods are still not a top priotity.[25]

Legislative initiatives. In December 2022, the US president signed into law the FDA Modernization Act 2.0. The FDA Modernization Act 2.0 is a bipartisan-supported act that updated the Federal Food, Drug, and Cosmetic Act by lifting the legal requirement for animal testing and allowing drug applicants to use non-animal methods, such as organ chips, for therapeutic safety and efficacy testing.[39] While this new law does not end the use of animals in drug testing, it does establish that human-relevant methods, including organoids and organ chips, can be used to determine a drug's safety and efficacy for the purpose of gaining approval from the US Food and Drug Administration (FDA). In theory, this act opens the door for drug manufacturers to embrace human-relevant test models. However, by not mandating the use of more accurate human-relevant methods in place of animal testing, and by not making the replacement of animal testing a programmatic priority within the FDA, this new law may not lead to any practical changes within the drug development field in the near future.

While the FDA Modernization Act is the most significant bill supporting human-relevant research methods, other bills have been introduced in recent years, including the Humane Research and Testing Act of 2021 (HRTA) and the Humane and Existing Alternatives in Research and Testing Sciences Act of 2022 (HEARTS Act).[40,41] The HRTA would have established a center dedicated to human-relevant research methods within the NIH. This center would fund and incentivize scientists to develop novel, more effective methods to replace nonhuman animal testing.[40] While the HRTA has not been reintroduced in the 118th congressional session, its concept of a center was integrated into the HEARTS Act, which will require NIH to provide incentives for the use of nonanimal research methods.[41] Both the HRTA and the latest version of the HEARTS Act actively incentivize a shift away from animal testing in favor of non-animal, human-relevant methods.

Conclusion

The US federal government has recognized the importance of human-relevant research methods as ethical alternatives to the use of animals and as beneficial for medical

advancement. The poor translatability of nonhuman animal research and the high failure rate of drugs in development reflect the immense limitations of animal testing. However, the United States has yet to fully prioritize a shift away from animal testing, as reflected by its funding programs. To better support the discovery, development, and use of innovative human-relevant models, researchers, physician groups, and patient advocacy groups should demand that comprehensive governmental funding of such research be a priority. Not only is such a funding priority more humane for nonhuman animals, but it is also a necessity for human health.

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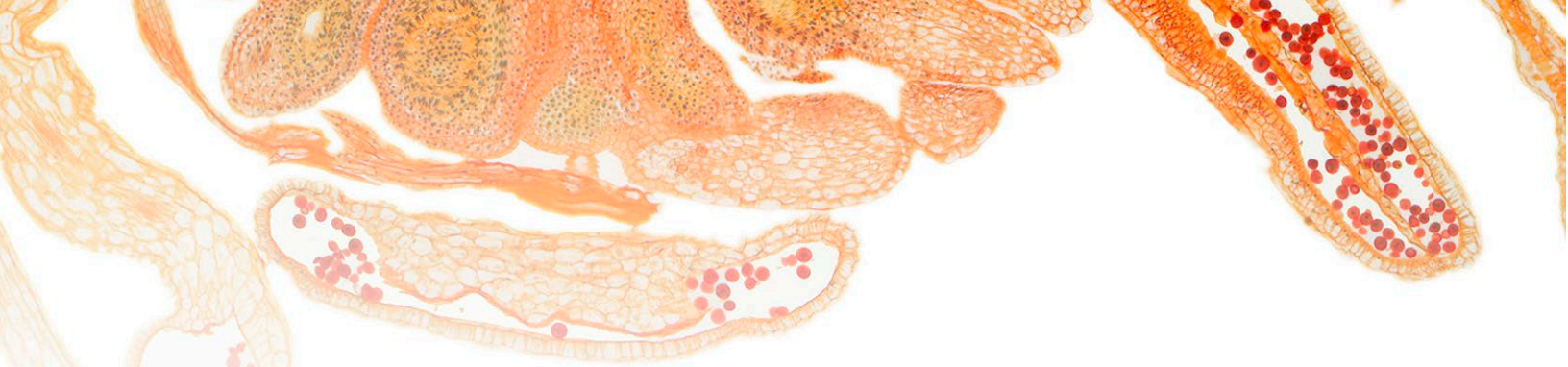

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POLICY FORUM

Which Concepts Are Key to Transitioning From Nonhuman Animal Models to Engineered Microphysiological Systems in Biomedical Research?

Erin Sharoni, MBE

Abstract

A transition from nonhuman animal models to engineered microphysiological systems (MPS), such as organoids and organ-on-a-chip technologies, would signal a paradigm shift in biomedical research. Despite MPS' potential to more accurately model human physiology, reduce high failure rates of drugs in clinical trials, and limit unnecessary animal use, widespread adoption is hampered by public opinion and lack of scalability, standardization, and current regulatory uptake. This article suggests how 5 key concepts (awareness, access, education, application, and rewards) could help address these barriers. These concepts are part of a framework that underscores a need to integrate MPS into mainstream biomedical research and to better promote ethical responsibility for the means of biomedical innovation.

Paradigm Shift in Research Modeling

We are approaching a tipping point in the burgeoning field of engineered microphysiological systems (MPS) as alternatives to nonhuman animal research models. MPS are in vitro platforms that mimic aspects of human and nonhuman animal physiology using tissue- or organ-specific cells. Microfluidic organ-on-a-chip (organ chip) technologies and organoids are MPS that have shown significant promise in research and drug development, as they continue to demonstrate physiological relevance. It has long been recognized that the physiological systems of nonhuman animal models do not sufficiently resemble those of humans, and, consequently, an estimated 95% of drugs fail in human clinical trials.[1] Humans may also be deprived of effective drugs that never reach clinical trials because they failed prematurely in animal models. Nevertheless, animal models are the de facto use case for validation studies.

Nonhuman animal models have remained the universal standard in translational research for several reasons: (1) traditional in vitro models cannot sufficiently replicate complex and dynamic human physiological systems; (2) animals can be genetically engineered to replicate various disease states; and (3) many necessary scientific experiments cannot be ethically conducted on human subjects. For decades, the scientific community has also debated whether such experiments can be ethically

conducted in nonhuman animal subjects.[2] This moral dilemma is compounded by the failures of nonhuman animal model systems in translational science that are widely recognized by academia and industry.[3] The transition towards MPS is thus grounded in both ethics and practicality. It highlights the empirical and normative challenges of the current animal research model paradigm and pushes us to consider our obligations to science, humanity, and other animal species.

Engineered Microphysiological Systems

The transition toward commercialization of MPS is underway but faces challenges in widespread adoption. Technical limitations, validation and standardization of MPS models, and regulatory hurdles are primary blockers. In December 2022, the bipartisan-supported FDA Modernization Act 2.0 removed the long-standing requirement for drug developers to conduct animal toxicity testing of novel drugs before human trials.[4] Although the act is a significant step forward in fostering the adoption of MPS, it does not mandate the reduction or replacement of animal use, nor does it explicitly incentivize the use of MPS. US regulatory agencies like the US Food and Drug Administration (FDA) have long-standing protocols that are based on animal testing. Incorporating MPS data in drug approval processes requires extensive historical evidence, which presents a barrier to rapid adoption of these technologies.

Importantly, MPS support the widely used "3 *R*" framework for nonhuman animal research. The 3 *R*'s represent the principles of replacement, reduction, and refinement—ie, the replacement of nonhuman animals in research with alternative tools, the reduction of animal use required to meet scientific aims, and the refinement of animal welfare conditions to alleviate or eliminate animal pain and distress. MPS make the principles of replacement and reduction more achievable.

As mentioned above, organ chips and organoids are MPS that offer advanced alternatives to traditional animal models. Organ chips, microfluidic devices that mimic whole-organ functions, can be linked to form multi-organ or body-on-a-chip systems, simulating organ interactions and fluid dynamics seen in vivo. While particularly effective in pharmacokinetic studies, they cannot fully capture an organ's complexity and require custom fit-for-purpose designs, limiting their scalability.[5] Organoids, on the other hand, are 3-dimensional, stem cell-derived tissues that model organ structure and function and are useful in organ development studies, disease modeling, and preclinical drug development. However, organoids have short lifespans and a lack of vascularization that limits their ability to recapitulate the in vivo transport of oxygen, nutrients, and chemicals to living tissues.[6] Despite these limitations, the accuracy of both technologies in certain research areas has been shown to be equivalent to or surpass that of nonhuman animal models, with ongoing reviews indicating their growing efficacy in clinical research.[7]

Given these technologies' promise, it is important to view regulatory and scientific challenges in context. When juxtaposed to the troubling physiological irrelevance of animal models in drug development, MPS draw our attention to critical ethical questions. Should we allow long-standing frameworks to impede scientific progress? Do scientific researchers have a moral responsibility to change course when confronted with the failure of existing systems? Is it ethically permissible to ignore the failures of standard animal models and deprive people of future solutions by restricting the development of lifesaving therapeutics facilitated by MPS?

Now is the time to address these ethical questions and practical considerations. MPS present us with novel in vitro human research opportunities. Failure to consistently replicate preclinical trial results is estimated to cost $28 billion USD per year, with a drug-to-market failure rate of 90%.[8,9] The most common causes cited for these failures are toxicity and inefficacy, both of which may be better addressed by MPS than by animal models. In light of these deficiencies—and following a global pandemic that underscored the importance of rapid medical innovation—it is clear that we ought to urgently pursue the transition away from animal models toward viable MPS alternatives.

Advancing the Transition to MPS

Many questions remain about how to deploy ethics in constructive ways that simultaneously advance state-of-the-art research and serve as the guardrails required in any medical field, given the tensions that exist between science, industry, and regulatory policy. Special attention should be paid to the multidisciplinary nature of MPS, the variety of stakeholders, and the basic human psychological aversion to paradigm-shifting change. We can consider how ethics might be practically applied to advance the transition from animal models to MPS using a framework comprising 5 actionable pillars: (1) awareness, (2) access, (3) education, (4) application, and (5) rewards.

Awareness. The field of MPS is multidisciplinary and sits at the nexus of science, engineering, and technology. Its numerous stakeholders include researchers, clinicians, regulators, journals, teachers, students, investors, and the general public. As a primary step in advancing the transition to MPS, all stakeholders have an ethical obligation to become aware of this existing technology because stakeholders are human first, and humans have a collective duty to support flourishing––the Aristotelian ideal of a holistically well-lived life.[10] This flourishing includes the pursuit of new, transformative knowledge that improves the lived experiences of human beings and, it can be argued, the lives of nonhuman beings. It is equally important to ensure that the pros and cons of MPS are clearly communicated so that people have a holistic rather than narrow awareness of their potential. Although MPS technologies have limited scalability because they are fit-for-purpose, animal models have clear technical, economic, and ethical limitations. All stakeholders need to be aware of those limitations as experts seek to overcome them with new options.

Access. The need for sufficient access to transformative technology is underpinned by cornerstone ethical principles such as equity, inclusion, justice, and fairness. It is broadly applicable to all MPS stakeholders, although the type of access required varies by role. Patients and clinicians require access to information about the treatments developed via MPS for decision-making, while academic institutions require access to the technology to conduct training and research. Access is also mediated by economic considerations. Industrial and academic pricing differs, as does the value MPS provide to academia and industry, where they can be used to narrowly or broadly advance medical research. Moreover, access is tied to different sets of responsibilities. The government should be responsible for training people who conduct grant reviews to accept nonhuman animal models; the FDA Modernization Act 2.0 paved the way for the actualization of this responsibility. Journals have a responsibility to promote scientific research by sharing transformative knowledge. Via the peer review process, journals function as gatekeepers to both legitimize scientific research and guide its future direction.[11] MPS access may be diminished when reviewers continue to require animal validation studies despite their well-known failures in translational research.[12] Without

sufficient access to MPS by regulators, grant reviewers, researchers, students, and other stakeholders, few will truly understand or seek to leverage the technologies' capabilities.

Education. A fundamental challenge to the widespread adoption of MPS is the basic human psychological resistance to change. Change is perceived as a threat, and, in response, the brain signals the release of stress hormones.[13] We are hardwired to avoid change as an evolutionarily protective mechanism. Like neural circuitry, the pathways of animal models in biomedical research are hardwired into scientific processes and reinforced the more they are used. However, like new neural connections, new scientific pathways can be developed through training and education. Stakeholders in the biomedical sciences, academia, and government have a social responsibility to explore new technologies that improve medical outcomes, even if it means accepting the fact that the methods they currently use are both subpar and unethical. Ethics both inform and evolve in response to technological advancement. Normalizing MPS through education can increase institutional uptake, support a new generation of researchers, and move science closer to realizing goals that benefit both humans and nonhuman animals.

Application. Ethics questions arising from the application of MPS are vast and worthy of a separate discussion. At a high level, protective guidelines concerning emergent medical technologies, such as genetic engineering of DNA and in vitro fertilization, have historical precedent.[14,15] MPS will remain bound by the ethical guardrails of the emergent technologies that came before it, and its evolution will generate new ethical challenges. Already, human sperm has been put on cervical organ chips, neuronal cells have been used in brain chips, and brain organoids can achieve some functionality.[16,17,18] While replicating fertility and brain function is technically plausible, these incomplete recapitulations require further ethical consideration. As the application of MPS evolve, ethical and regulatory guidance must evolve alongside them in real time rather than reactively and in retrospect.

Rewards. Ethical incentives might motivate stakeholders to take the risk of replacing animal models with MPS. Researchers working on toxicology studies, journal reviewers, and FDA representatives have historically relied on animal models, and, despite their well-documented deficiencies, there has been little incentive to move away from them. Yet there is historical precedent for the involvement of institutions in fostering technological adoption. As an example, the rise of transgenic mice in the 1980s was supported by Harvard taking advantage of changes in patent law and was promulgated by scientific journals.[19] It would be ethically permissible to do the same for MPS.

While there are grants supporting MPS and recent legislation allows for MPS adoption in drug development,[4,20] additional incentives are required to trigger a key tipping point in industry and academia's transition to MPS. One suggestion is to extend patents for the first companies to use MPS to bring a drug to market. The patent extension provides ample economic incentive and, if supported equitably with grant dollars, could facilitate a moonshot MPS race that triggers a new wave of research, development, and investment. Establishing a government-subsidized consortium of MPS-interested companies is another option; industry, the government, and the public can all benefit from advancements facilitated by MPS. Some pharmaceutical companies are already self-selecting subgroups of people open to taking risks on new technologies and creating programs to explore MPS.[21] However, such initiatives are expensive and may

not be equally available to all industry participants. In this case, a subsidized consortium could help distribute opportunities among a diverse set of participants.

Conclusion

Despite technical, regulatory, and educational hurdles, the need to transition away from animal models and adopt more accurate, humane, and efficient research models like MPS is clear. The described framework provides a lens through which to examine the ethical, practical, and scientific nuances of this shift, but it is important to supplement and build upon it. The journey toward fully integrating MPS into mainstream research and overcoming existing ethical tensions will be complex and multifaceted, requiring concerted efforts across disciplines. Nevertheless, the promise of MPS to advance clinical science, reduce unnecessary animal suffering, and unlock new avenues in drug development and disease understanding makes this journey not just necessary but essential for the future of ethical and effective biomedical research.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

How Should Treatment of Animals Beyond the Lab Factor Into Institutional Review?

Laurie Sellars, MA and Jeff Sebo, PhD

Abstract

Discussions of nonhuman research ethics tend to focus on what we owe nonhuman research subjects in laboratory settings only. But humans make critical decisions about these animals outside the lab, too, during breeding, transportation, and end-of-study protocols. This article reviews extra-lab risks and harms to nonhuman research subjects, focusing on the most commonly and intensively used animals like rodents and fishes, and argues that extra-lab risks and harms merit ethical consideration by researchers and institutional review.

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Beyond the Lab

Discussions of nonhuman research ethics tend to focus only on what we owe nonhuman research subjects in laboratory settings. But humans make critical decisions about these animals beyond the lab, too. We decide how these animals are born, how they live, and how they die. In the United States (US), we make these decisions about many animals each year. According to the US Department of Agriculture, 994 297 animals were held or used at US research facilities in 2021.[1] This figure excludes animals like fishes and rodents bred for research,[2] yet these animals account for the vast majority of research subjects.[3,4] For instance, researchers estimate that rodents account for between 93% to 99% of all US lab mammals, with between 10 to 115 million rodents used annually, depending on the methodology used.[5,6]

This paper surveys 3 contexts beyond the lab in which nonhuman research subjects are potentially vulnerable to harm: breeding, transportation, and end-of-study protocols. Because practices vary across and within species, this paper highlights case studies across species while focusing on some of the most intensively used animals in the US, namely fishes and rodents. It then notes that these impacts merit ethical consideration and institutional review and describes how different moral frameworks for assessing nonhuman subjects research might apply to current practices. It concludes that these practices raise serious ethical concerns and that more comprehensive discussion is needed to fully evaluate these concerns.

Three assumptions inform our analysis. First, we assume that sentient animals—that is, animals capable of consciously experiencing positive and negative states like pleasure and pain—have moral standing—that is, morally matter for their own sakes—and that we should therefore consider their interests when deciding how to treat them.[7,8] Second, we assume that fishes, rodents, and other animals discussed in this paper are sentient.[9,10] Third, we assume that, even if all sentient animals have moral standing, different animals merit different protections insofar as they have different interests and needs.[11,12] While not everyone will agree with these assumptions, our aim is to build upon rather than replicate work defending them.

Breeding

Lab animal breeding facilities create many animals who are not directly used in research, because these animals either are used for breeding or have unwanted characteristics.[13,14] In 2021, US research facilities held, without using, 166 322 animals covered by the Animal Welfare Act (AWA), approximately 17% of all AWA-covered animals held.[1] And since many animals—including fishes and rodents bred for research—are not covered by the AWA, the percentage of animals held and not used might be even higher. In 2017, for example, the European Union (EU) held approximately 14 million "surplus" lab animals, including fishes and rodents. Since the EU used approximately 9.4 million animals in experiments that year, surplus animals accounted for approximately 60% of the total research animal population. In other words, for every 2 animals used in experiments, 3 surplus animals were bred but not used in experiments.[13]

How breeding processes affect lab animals depends on which species and breeding facilities are involved. In general, the conditions in which breeding facilities keep animals and the procedures they use depend partly on anthropocentric concerns such as cost and research goals.[13,15,16] For example, to maximize output, breeding facilities often organize animals into group sizes and compositions that deviate from natural mating and rearing behaviors.[13,15,16] Breeding facilities also handle animals frequently, which can increase stress for animals who are not habituated to frequent handling or moving.[16] And when these facilities create animals with characteristics that make natural reproduction difficult or impossible, they often subject animals to invasive procedures, including ovarian transplants and in vitro fertilization, for breeding.[15]

Additionally, the breeding process often creates animals with harmful characteristics or "phenotypes."[17] For example, research mice and rats can develop atypical social behaviors, impaired locomotion, lethal syndromes, skin and coat disorders, and sensory organ, metabolic, reproductive, neurological, immunological, cardiovascular, hematological, respiratory, digestive, and renal diseases.[17] In the EU, 3.9% of genetically altered animals used in research and testing in 2020 possessed a harmful phenotype (313 937 animals).[18] Additionally, 27.3% of animals used to maintain genetically altered lines in the EU that year had a harmful phenotype (83 163 animals).[18] Since genetic modifications are common in intensively used species like mice and zebrafishes,[18] the number of US lab animals with harmful phenotypes is likely very high as well.

Transportation

Lab animals may be transported variable distances between breeding and research facilities when breeding and research are at different locations as well as between different research facilities.[19] In many cases, lab animals are transported not only between facilities but also between countries. For example, the US imports millions of animals for research annually.[4,20] Importation is the primary way in which US research

facilities obtain certain animals, particularly nonhuman primates (NHPs).[15,21] In fact, research threatens some wild NHP populations by driving up prices for laundered or smuggled wild-caught NHPs, raising questions about risks and harms of research for free-living as well as captive nonhuman populations.[21,22]

Lab animals are transported via ground and air.[23] For example, major US commercial rodent breeders use established land routes, either employing their own truck fleets or contracting with other companies.[19] Lab animals are also transported as air cargo, although many major airlines now refuse to carry animals—particularly NHPs—destined for research.[24,25] Travel durations vary, with most trips lasting a few days.[19] For example, ground transportation for rodents ranges from under 24 hours to multiple days: breeding facilities limit how long rodents can be in shipping containers—usually 5 days—due to welfare concerns.[19,26] International travel can require multiple days in transit and multiweek predeparture quarantines for some animals.[23,27]

Transportation is inherently and acutely stressful for many animals.[28,29,30,31] Indeed, transport stress is so common that many research facilities grant animals time to recover to preserve the apparent validity of scientific results.[19,27,32] Standard transport procedures can also compound this stress. For example, adult zebrafishes are typically denied food for 24 hours before transport, removed from their home tanks, and transported in polyethylene bags with high stocking densities, which, combined with long trip durations, can generate dangerous conditions.[33,34] These and other such procedures expose animals to disease, injury, and environmental extremes—risks that are especially pronounced for immunocompromised animals.[32] Of course, animals face ordinary risks associated with ground or air travel, including delays and crashes, as well.[21,23,26]

End of Study

Following their use in research, animals are typically killed.[35] Humans kill lab animals as part of experimental design, either because experiments are sufficiently painful or because the animals are no longer useful.[36] Humans also kill surplus animals who are no longer useful for breeding or have unwanted characteristics.[14,36,37] Regulatory and institutional guidance on killing lab animals recommends "humane" methods that minimize pain and distress while prioritizing study goals and other anthropocentric interests. For example, the AWA makes exceptions when investigators provide scientific justification for using painful or stressful killing methods,[2] and institutional guidance often does as well.[38,39] Other justifications for killing methods that do not minimize pain or distress include efficiency, convenience, and physical and emotional health and safety of humans.[36,40,41]

Lab animals are killed in numerous ways. According to the American Veterinary Medical Association (AVMA) *Guidelines for the Euthanasia of Animals: 2020 Edition*, "acceptable" methods for killing lab rodents include administering barbiturates or dissociative agents, while methods "acceptable with conditions"—which investigators might prefer on scientific or other anthropocentric grounds—include gassing them with certain chemicals, injecting them with certain chemicals, decapitating them, disarticulating their cervical vertebrae from their skulls, and heating their brains using focused beam microwave radiation.[39,41,42] Several of these methods are controversial, given evidence that they cause pain and distress.[40,41] Physical methods such as cervical dislocation depend on the skill of the human, thereby varying in their animal welfare impacts.[41]

As an alternative, some research organizations offer adoption programs for certain animals, including dogs, cats, and small mammals, and some US states legally require offering adoption when certain research animals are no longer needed.[43,44,45] Adoptions can be mutually beneficial, since they can provide companionship for humans and better lives for former lab animals.[46] Some research facilities also retire animals who cannot be privately adopted, such as NHPs, by partnering with sanctuaries to care for retired animals or potentially establishing their own.[47] True sanctuaries provide animals with excellent care and maximal agency throughout their natural lives in a nonexploitative setting.[48] However, these programs remain limited in the number and diversity of animals adopted or retired and are the exception rather than the rule.[44]

Extra-Lab Risks and Harms

These risks and harms clearly merit ethical consideration and institutional review. In the US, under the AWA, Institutional Animal Care and Use Committees (IACUCs) oversee animal use in research facilities. Generally, IACUCs focus on animal welfare concerns *within* rather than *beyond* research protocols.[49,50,51] For example, investigators may submit transportation plans in some cases, but IACUCs are not required to directly review or approve transportation.[52,53] Similarly, IACUCs review killing methods for alignment with AVMA guidance but do not generally require investigators to justify their decision to kill animals.[51] Comprehensive ethical review of animal research must fill these gaps by considering all risks and harms for sentient animals during breeding, transportation, and end-of-study procedures.

Of course, assessment of these risks and harms depends on which ethical framework one applies. In the US, IACUCs apply the "3 *R*'s" framework, asking whether researchers can *replace* animal subjects with nonanimal methods, *reduce* the number of animal subjects used, or *refine* protocols to minimize pain and distress for animal subjects.[53,54] Expanding this framework to include all relevant impacts would raise the bar for approval in many cases; for instance, reduction would require accounting for the number of lab animals *and* the number of surplus animals, and refinement would require accounting for harms in *and* beyond the lab. However, whether these factors alter the outcome of the institutional review process will depend on other factors as well, including the benefits of scientific research for humans and, arguably, the benefits of existence for some nonhumans.

Moreover, applying ethical frameworks that are more rigorous than the 3 *R*'s to assess beyond-the-lab risks and harms might have additional significance.[55,56,57] For example, Beauchamp and DeGrazia argue that animal research must meet 6 principles of social benefit and animal welfare to be acceptable, including meeting animals' basic needs.[57] These principles might forbid at least some beyond-the-lab practices. Similarly, the second author (J.S.) argues that nonhuman subjects research should embody principles of respect, compassion, and justice.[56] These principles would clearly forbid many beyond-the-lab practices. Moreover, when experimental protocols cause harm to animal subjects, these additional considerations might simply make the impermissibility of such animal research overdetermined. But when experimental protocols are deemed harmless, these additional considerations might make the difference in whether the research is allowed to proceed.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

How Should the 3 *R*'s Be Revised and Why?

Rebecca Critser, JD, LLM, MA and Paul Locke, JD, DrPH

Abstract

The Principles of Humane Experimental Technique established what many know today as the "3 *R*'s"—refinement, reduction, and replacement—when it was published in 1959. Since their formulation, these principles have guided decision-making for many about nonhuman animal subjects' uses in laboratory-based research. Discussion about how to amend or replace the 3 *R*'s is ongoing, driven mainly by philosophical ethics approaches to nonhuman animal rights and by scientific advancement. This article explores merits and drawbacks of possible updates to and interpretations of the 3 *R*'s.

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The 3 *R*'s

Russell and Burch published *The Principles of Humane Experimental Technique* in 1959, which established the "3 *R*'s" as key principles that govern use of nonhuman animals in a laboratory setting.[1] Today, the 3 *R*'s is the most well-known ethical framework for conducting scientific research using nonhuman animals. The 3 *R*'s—refinement, reduction, and replacement—are almost universally accepted by responsible scientists throughout the world and form the basis of many legal and regulatory systems that govern laboratory nonhuman animal use.[2,3,4,5,6,7]

However, it is no longer obvious that the 3 *R*'s as originally conceived represent a sufficient framework for the use of animals in research. Since the initial formulation of the 3 *R*'s, there has been considerable discussion about how to amend or replace them, driven in part by the writings of philosophers such as Peter Singer[8] and Tom Regan,[9] as well as by organizations that advocate for nonhuman animal rights. Furthermore, science and scientific methods have advanced in the past 6 decades, and the need for, and use of, nonhuman animals has changed. In addition, the translatability of animal models to human conditions has been called into question.[10] These factors raise the question about how to revise the 3 *R*'s for modern-day science.

Key Lessons

Several lessons have been learned since the implementation of the 3 *R*'s ethical framework in the mid-20th century. First, the integration of ethical principles into practice requires substantial time. The 3 *R*'s took over 30 years to take hold within the scientific community.[4] Therefore, it is unsurprising that the 3 *R*'s would warrant revision, given their long history. And yet there are many aspects of the 3 *R*'s that have endured; these aspects are a testament to the original wisdom and utility of the framework and help to account for its worldwide adoption.

A crucial pillar of the 3 *R*'s is the notion that humane science is necessary for both scientific and ethical reasons. Scientific results obtained from animals deprived of necessities or animals experiencing unmitigated pain, stress, or distress have little-to-no scientific merit.[11] Scientists must care about animal welfare so that their research can yield meaningful results. Fortunately, most scientists understand that the strength of scientific results is not independent of animal welfare and that good science comes from well-cared-for nonhuman animals.[11,12]

Yet, what is meant by humane treatment or well-being of nonhuman animals is less clear. The 3 *R*'s are premised on a pain-and-stress avoidance model that seeks first to avoid pain and stress by replacing animal models with nonanimal alternatives (which evolved from the original intent of replacing "higher-order" nonhuman animals with "lower-order" nonhuman animals), then to minimize total pain by reducing the number of animals, and finally to minimize individual pain by refining the pain-inducing procedure. The problem with this utilitarian model is that the consequence of the action cannot be known until the action is taken. Although an experiment may yield a very strong positive outcome that could warrant an animal's subjection to some pain, that outcome cannot be known before the experiment is conducted. Additionally, when applied, the principles can conflict with one another, giving rise to the need to better define each of the 3 *R* concepts.

Although the use of animal models under a 3 *R* ethical framework has yielded substantial scientific progress, there are instances in which animal models have not accurately predicted human responses. Some of these failures indicate that the animal model information cannot be relied upon when assessing toxicity of potential drugs in humans.[13] Furthermore, drugs for some disease types, such as Alzheimer's, have repeatedly seen successes in animal models and yet failed in human clinical trials.[14] Finally, although the extent of the problem is unknown, there are instances in which a drug could be fatal to nonhuman animals but a major success in humans (eg, aspirin).[13] A retrospective evaluation of the 3 *R*'s framework suggests that it is insufficient and that a different or modified ethical framework is needed.

Importantly, the particular ethical framework adopted by scientists is only one of the factors that influences scientists in their choice of methods. The 3 *R*'s may predispose a researcher to use a scientifically sound animal alternative, but that choice may be impeded by lack of regulatory approval. The regulatory state is an intermediary between what the scientific literature and ethical analysis support, on the one hand, and what is legally permissible, on the other. Vanda Pharmaceuticals tried to use the former to challenge the latter in filing suit against the US Food and Drug Administration in 2019.[15] This suit was unsuccessful but demonstrates a clear instance in which a drug product could not be brought to market without data from nonhuman animal subjects despite the scientific experts determining that animal models were unnecessary.

Finally, although the 3 *R*'s are codified in the laws of other countries, in the United States they are not explicitly required by law but only incorporated into guidelines by reference, such as through the National Research Council's *Guide for the Care and Use of Laboratory Animals*.[16] Some call for the codification of the 3 *R*'s, while others treat the *Guide* as synonymous with the law.[17,18] Regardless, it is clear that the 3 *R*'s are widely used by US-based researchers. Therefore, we can conclude that ethical mandates need not necessarily be enshrined in statutes or regulations but may be captured at a lower level, such as in guidance documents.

Systemic Changes to Modern Clinical Science

Changes are needed not only to the ethical framework but also to the system within which the ethical framework functions. Training is one of the most important gaps to address. The Animal Welfare Act (AWA) of 1966 requires animal care personnel to be trained in welfare practices.[19] However, Russell and Burch envisioned a far more expansive form of training, which remains an ideal.[1] A 2014 study found that 58% of scientists who had signed up to take a laboratory animal sciences course were not aware of the 3 *R*'s prior to the course.[20] This survey included career scientists who had been conducting animal research for years. Ethics training for scientists and everyone working with animals in research must occur regularly. Ethics training for personnel working with animals in the lab should include a survey of normative ethical theories (eg, utilitarianism, deontology, virtue ethics) and cover both how the laws and regulations have incorporated some of these ethical approaches, as well as ethical gaps in the legal framework like the failure to require facilities to report *all* nonhuman animal use numbers so that reduction can be assessed on a larger scale. Most importantly, the training must not be superficial but instead be substantive, employing appropriate pedagogical methods to ensure staff's engagement in the course, retention of the content, and application of the content in laboratory settings.

But training should not be limited to the 3 *R*'s directly. Rather, in order for the ideas of the 3 *R*'s to be fully accessible, it is necessary to address the knowledge gap between those actively conducting research and those developing innovative technologies. Currently, in the event that a painful procedure will be used, there is a requirement for researchers to search for an alternative and address why an alternative to nonhuman animal models cannot be used.[21] Yet, in practice, this requirement is met primarily pro forma.[22,23,24,25] This requirement can be satisfied by merely checking a box and writing a simple sentence on a form submitted to a local Institutional Animal Care and Use Committee (IACUC), but doing so often does not reflect a concerted effort to identify plausible alternatives. Part of the problem is that the dissemination of information concerning animal alternatives is lacking. The number of alternatives is exploding, but there is no clear pathway for regulatory acceptance of new methods in the United States. This is a major limitation for the adoption of alternatives. New methods will not be widely accepted in science and research without a clear regulatory pathway.

New Ethical Framework

Several ethical frameworks have been proposed to succeed the 3 *R*'s framework. Some propose a justice-based model that aims to end nonhuman animal testing completely.[26,27] Some proponents of this model omit an acknowledgement that this transition could not occur overnight or fail to provide a proposed plan for such a transition.[28] The absence of these 2 features is a major limitation of these approaches, particularly within the context of a discourse focused on practical application. For the

purpose of remaining grounded in the practical, the ethical framework described below focuses on filling a key gap in the 3 *R*'s model.

Experimental strength has been identified as a key missing component of the 3 *R*'s model.[10] This criticism is to some extent due to the shortcomings of the 3 *R*'s' utilitarian foundations. Interestingly, the IACUC—the body responsible for reviewing nonhuman animal research protocols under the AWA and the Public Health Services Policy—is implicitly instructed to refrain from this type of review.[29] Nevertheless, many may find it difficult in practice to avoid identifying this omission as a weakness of the system.

One proposal to incorporate experimental strength extends the 3 *R*'s to what has been coined the 3 *V*'s.[30,31] These additional elements comprise (a) construct validity, (b) internal validity, and (c) external validity. Each of these elements represents a unique aspect that, when taken together, provides a better assessment of overall experimental strength. *Construct validity* refers to the model's capacity to speak to the scientific objective of interest. *Internal validity* refers to design rigor (eg, sample size, statistical model, use of control groups). *External validity* refers to the extent to which the results are widely generalizable or only narrowly applicable. Taken together, the 3 *V*'s aim to reduce the occurrence of animal research that provides little-to-no meaningful information. The 3 *V* approach is also consistent with the evolution of science after the 3 *R*'s were first conceived by addressing the most pressing problems that confront animal models today.

Next Steps

Science advances when it respects and incorporates ethical principles. The introduction of the 3 *R*'s marked a fundamental shift in uses of nonhuman animal subjects.[32] However, reviews of the 3 *R*'s framework over the past several decades indicate room for improvement. For science to truly operate ethically, everyone involved must be taught—and express in their actions—the principles. Furthermore, the principles must be regularly reinforced. Knowing the 3 *R*'s is only one step, and that alone is insufficient. The 3 *R*'s can and should catch up with the scientific advances of the past few decades and seek to address some of the framework's limitations that have been uncovered. Efforts made to develop new replacement models must be given their full chance of success by identifying a clear regulatory approval pathway, and there must be systematic ways to disseminate information about newly available alternatives.

Finally, even with all this in mind, a revision of the 3 *R*'s is warranted. Russell and Burch provided a cornerstone of animal research practice. Yet the best models are refined over time as use and experience reveal gaps. The addition of the 3 *V*'s, which serves to address experimental validity, is one possible revision. The moment is ripe to implement changes and strengthen the 3 *R*'s so that they can continue to be a useful tool for 21st-century science.

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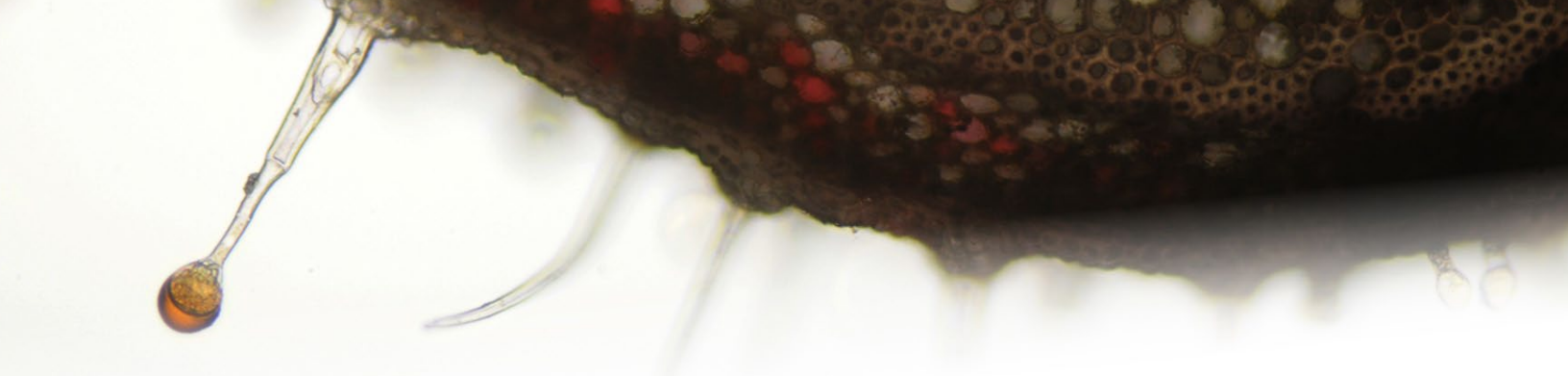

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HISTORY OF MEDICINE

The American Medical Association on the Ethics of Vivisection, 1880-1950

Jorie Braunold, MLIS

Abstract
The American Medical Association (AMA) was a major player in debates about vivisection in the late 1800s to mid-1950s. This article provides an overview of arguments and guidelines the AMA once offered in favor of the practice in 1909.

Vivisection and Allopathic Medicine

Live animal experimentation, or vivisection, has existed since ancient times, and debates over its ethical implications in health care were considered in the United States in the 1860s,[1] when allopathic medicine was becoming more popular but struggling to establish and maintain credibility. Medical professionalization happened to coincide with the rise of a burgeoning and controversial animal protection movement. The American Medical Association (AMA), as the face of organized, scientific medicine, was a major player in vivisection debates, especially from the late 1880s to the mid-1900s. Not only did the AMA argue in favor of vivisection, but it also created guidelines for ethical conduct in animal experimentation to promote human health.

"Blessed" Work?

An entirely new construct of the field of medicine and how it should be practiced was being created in the late 19th century on the basis of empirical evidence (which necessitated experimentation on animals), and, because the field of medicine was largely unregulated at the time (this was the era of the "snake oil" salesman), the public initially viewed these changes, and physicians who practiced vivisection, with concern.[2] The fact that vivisection, at a time of growing awareness of animal welfare, was a part of this professional transformation only added to the controversy. Antivivisection activists organized around the principle that cruelty to animals was immoral. They believed that the practice would lead to a slippery slope of cruel acts and would deform the moral character of not just the physicians performing experiments, but of society in its entirety.[2] As Bates has argued, "Vivisection was seen as different from other forms of cruelty, such as the mistreatment of farm and draught animals, partly because those responsible were linked with the healing and academic professions, whose morality was supposed to be beyond reproach, and also because it had implications beyond animal welfare: for the way society made ethical choices, for how science should be conducted, and for how humans saw themselves in relation to the rest of creation."[2]

The vivisection debate was the AMA's first real test: could it bring the public and the policy makers along on its journey to change the face of medicine with some degree of moral authority? By the late 19th century, antivivisection was a *cause célèbre*, bringing together disparate members of society to garner mainstream support, despite vivisection accounting "for only a tiny fraction of the vast amount of suffering inflicted on animals by human hands,"[2] a fact the AMA frequently invoked.

AMA's Ethical Defenses of Vivisection

Beginning in the 1880s, the AMA created numerous committees and councils devoted to defending the practice of animal experimentation from restrictions that would "be an injury and hindrance to the pursuit of medical knowledge and the improvement of the medical art."[3] In response to a particularly intense period of antivivisection activity beginning in 1908, the AMA formed the Council on Defense of Medical Research.[4] Its aim was "first, investigating the conditions of animal experimentation and the opposition to it; second, taking precautions against abuse of animal experimentation and against misconceptions of the conditions and purposes of medical research; [and] third, diffusing information regarding laboratory procedures and the results of laboratory study of disease."[5] In order to combat the claim that students were operating on animals in private places outside of proper supervision, it also advocated "that teachers of the medical sciences speak to students concerning the importance of the experimental method in medical research … the desirability that every care be taken to obviate discomfort and pain in using animals for research and instruction, and the urgent necessity that students avoid any act or word that would tend to rouse a feeling against the humane use of animals for educational and research purposes."[5]

In order to accomplish its third goal, the Council created a series of pamphlets on the importance of vivisection to various medical breakthroughs, such as "Vaccination and Its Relation to Animal Experimentation" (Jay Frank Schamberg, 1911) and "The Fruits of Medical Research With the Aid of Anesthesia and Asepticism" (Charles W. Eliot, 1910).[6,7] These pamphlets (as well as mainstream magazine and newspaper articles authored by members of the Council) also pushed back against the idea that vivisection was immoral and cruel. The documents focused primarily on the following points.

Western religions and customs allow for the belief that man's dominion over animals is absolute. A 1909 pamphlet says of Western religion, "Most widely prevalent—and sanctioned at one time or another by religious practices among all peoples—is the view that man is the overlord of the animals and may use them for his pleasure and profit, even to the point of robbing them of life."[8] The author posits that though Buddhists may believe in transmigration of souls, this is so uncommon a belief in the American context as to be "non-existent."[8] A 1949 *Hygeia* article is similarly explicit, stating: "Religion approves it. We are to use the beasts of the field."[9]

Animals themselves benefit from the practice. These "chain of being" arguments based on Christianity not only were used to defend the practice of vivisection but also were reflected in the language used by the AMA and other physicians when describing the benefits of experimentation to the animals themselves. In "The Role of Animal Experimentation in the Diagnosis of Disease," Dr M. J. Rosenau contends that in having a more exact knowledge of the causes and channels of infection and disease in "lower animals," we are also able to create more intelligent and humane efforts to conserve the health and comfort of our livestock.[10] The literature abounds with examples of animals saved by experimentation, from cows with bovine tuberculosis to dogs with rabies. An

example from 1941 asserts that "Animals which otherwise would have been left to roam the streets to starve and to be found, as they are often found, lying dead from motor vehicle accidents, make their contribution under ideal circumstances to the advancement of the science of care of animals and man."[11]

Laws and customs of the US allow for the use of animals for personal pleasure. The AMA argued that a society that fails to condemn meat eating, wearing leather, castrating farm animals, and so on would be hypocritical to deny using animals for the most valuable human purposes. A 1915 pamphlet states: "If experiments on animals must be prohibited let the same law prohibit castration of animals and the dehorning of cattle."[12]

A similar line of argument was that if one believes that choosing the life of a human over that of an animal is ever justified, then the moral argument is finished, and the only thing left to discuss is under what circumstances. The psychologist James Rowland Angell's pamphlet contends that while those who believe no animal life can or should be sacrificed to save a human life cannot be reasoned with, this belief is not shared by most people or even most antivivisectionists. Accordingly, the only problem remaining is "determining the circumstances and conditions which warrant particular forms of the method."[8]

Physicians are morally above reproach. The medical establishment also promoted the idea that medical practitioners have, by the very nature of their chosen profession, devoted their lives to easing suffering and are therefore assumed to be moral and compassionate. In 1896, the AMA adopted a resolution condemning legislation to restrict the practice of vivisection. In it, the delegates note that even to consider these laws "is an unjust reflection upon the humanity of those engaged in animal experimentation."[13] Physicians and their allies proclaimed that physicians are "normal men, not at all lacking in the ordinary feeling of humanity, quite as merciful as the average non-medical man of the educated class."[14]

It is not practical or desirable in medical practice to harm animals. It is not in the medical establishment's interest to harm the animals unnecessarily, both from a moral and a scientific perspective. In his 1910 pamphlet, Dr W. W. Keen states: "I have seen their experiments, and can vouch personally for the fact that they give to these animals exactly the same care that I do to a human being. Were it otherwise their experiments would fail and utterly discredit them."[15] Dr Samual S. Maxwell explains: "The experimenter, even if he were really cruel, would usually defeat his own ends by the infliction of pain."[15]

It is the duty of every American physician to save American lives. Not only did the AMA believe it was the responsibility of medical professionals to ensure the health of the human race using the best means at their disposal, but it also argued that during times of war it was downright unpatriotic to work against their efforts. In response to the American Red Cross' refusal to take a position on animal experimentation during World War I, the AMA reaffirmed its belief in the importance of vivisection and that "the necessity for such animal experimentation is greater and more urgent at this time than ever; and that those who interfere with it in any way, thereby interfere with the conduct of the war and fail in the gratitude owing to our defenders."[16]

In the 1940s, this argument was reused. Then-AMA President Herman Louis Kretschmer wrote an article in *Hygeia* essentially accusing antivivisectionists of hindering war

efforts. He wrote: “Several times, right in the midst of the war effort, some of the physicians of Chicago have had to interrupt their teaching and research work because of the pernicious activities of the antivivisectionists.” He went on to say that “many of the splendid results achieved in the treatment of casualties in this war would not have been possible [without vivisection].”[17]

Sacrificing a “lesser good for a greater good and encountering a moderate evil to escape a greater evil”[9] *is morally just.* A 1910 pamphlet, referencing pioneers in the field of medicine, put forth this question: “Who is the more cruel: Dr. Carrel, in devising this life-saving method of transfusion of blood by experimenting on two living dogs, and saving . . . already, and even thousands in the future; or the women who would shackle him, shut up the Rockefeller Institute and thrust these poor patients into their graves? Does not the work of Drs. Flexner, Jobling and Carrel and their assistants not only justify the existence of the Rockefeller Institute, but also bid us tell them Godspeed in their mission of mercy, and give them and those engaged in similar blessed work all over the world our confidence, encouragement and aid?”[15] The AMA thus viewed medical progress as an unalloyed good which could not be negated by occasional injury to “lesser animals.”

AMA Defines Ethics of Animal Experimentation

Although initially loath to put any restrictions on laboratories whatsoever, the AMA eventually came to believe in 1909 that it was important to disseminate a set of rules, drawn up by the Bureau for the Protection of Medical Research of the AMA, to convince opponents that the medical profession was taking their concerns seriously. Still hostile to the idea that men in the medical profession could be said to do anything unethical, the Council, in creating these rules, notes: “Although they probably do not change in any respect the already good conditions under which animal experimentation is conducted, they indicate to newcomers in the laboratories and to interested and intelligent people the intent of the investigators and the precautions which they take against suffering.”[5]

The rules were as follows:

I. Vagrant dogs and cats brought to this Laboratory and purchased here shall be held at least as long as at the city pound, and shall be returned to their owners if claimed and identified.

II. Animals in the Laboratory shall receive every consideration for their bodily comfort; they shall be kindly treated, properly fed, and their surroundings kept in the best possible sanitary condition.

III. No operations on animals shall be made except with the sanction of the Director of the Laboratory, who holds himself responsible for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems.

IV. In any operation likely to cause greater discomfort than that attending anesthetization the animal shall first be rendered incapable of perceiving pain and shall be maintained in that condition until the operation is ended. Exceptions to this rule will be made by the Director alone and then only when anesthesia would defeat the object of the experiment. In such cases an anesthetic shall be used so far as possible and may be discontinued only so long as is absolutely essential for the necessary observations.

V. At the conclusion of the experiment the animal shall be killed painlessly. Exceptions to this rule will be made only when continuance of the animal’s life is necessary to determine the result of the experiment. In that case, the same aseptic precautions shall be observed during the operation and so far as possible the same care shall be taken to minimize discomforts during the convalescence as in a hospital for human beings.[5]

AMA's Post-1950s Activism

Toward the second half of the 20th century, the AMA spent less of its time on defending vivisection. A *JAMA* article on the AMA's historical role in the use of animals in biomedical research states that, in the 1960s, "The AMA and the NSMR [National Society for Medical Research] recognized the need for uniform standards for the care of laboratory animals to convince the public and Congress that federal regulations were not necessary to ensure the humane treatment of research animals. In 1963, the AMA Board of Trustees organized the AMA Task Force for Laboratory Animal Care.[4] From that time, the AMA has occasionally reiterated its support for the practice of animal experimentation in medicine. Although the language may have changed, the general principles behind the AMA's ethical support of vivisection have remained. As recently as 2015, the House of Delegates reaffirmed its policy that "The AMA encourages medical school faculty who use animals in the education of students to continue instruction of students on the appropriate use and treatment of animals."[18]

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ART OF MEDICINE

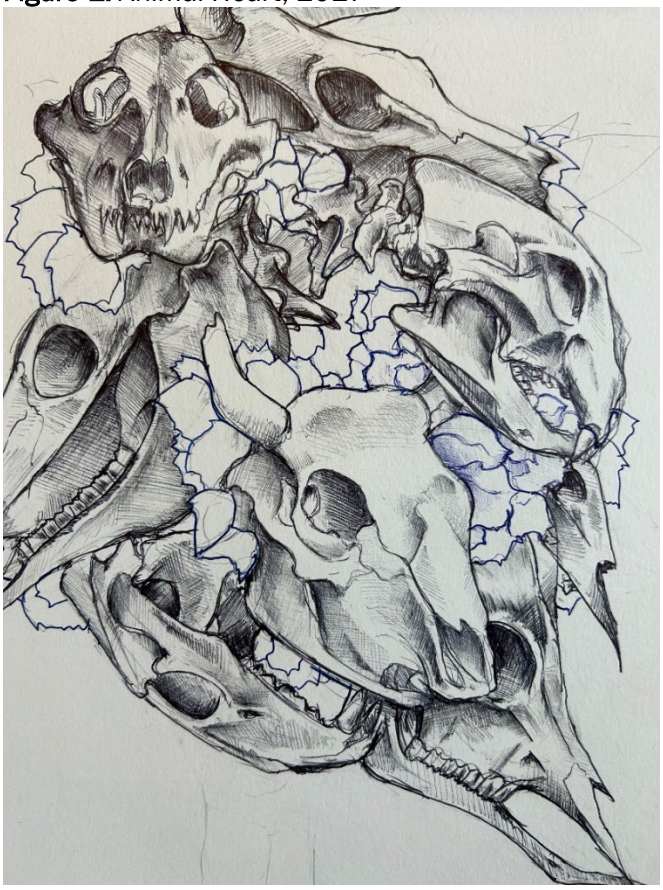
Does It Make Sense to Say Humans "Protect" Nonhuman Animals While Using Them to Promote Human Health Interests?

Christopher Lau, MD

Abstract

Nonhuman animal research has contributed to human health advancements but raises questions about the extent to which humans protect nonhuman animals during such endeavors. This series of drawings explores several ethics and empirical questions from a visual point of view.

Figure 1. *Animal Heart*, 2017



Media
Ink on mixed media paper.

Caption
Multiple animal skulls are assembled into the shape of a human heart, offering a visual interrogation of whether and to what extent potential benefits to human health of nonhuman animal research can express respect for the value of nonhuman animal life.

Figure 2. *Man & Animal No. 1*, 2023

Media
Graphite and pastel on mixed media paper.

Caption

The head of Aesculapius, the Greek god of healing, is represented as half human on the left and as half dog skull on the right. This drawing invites consideration of whether and when human health benefits outweigh nonhuman animal suffering that might promote them.

Figure 3. *Man & Animal No. 2*, 2023

Media

Graphite, ink, and watercolor on mixed media paper.

Caption

A half-human and half-dog skull is at the center of the drawing. Multiple history of art references (eg, the hand of man and God from Michelangelo's fresco *The Creation of*

Adam in the Sistine Chapel, the Monument to the Laboratory Mouse, the Aesculapian snake, and flowers in the style of *Dia de Los Muertos*) and syringes radiate from the skull. Empirical questions, in addition to ethical questions, prompt our consideration about whether and when nonhuman animal models accurately reflect human physiology and diseases and enable scientifically valid research. Is adherence to federal animal use and care guidelines[1] ethically sufficient to promote transparency and human stewardship accountability?

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Christopher Lau, MD is a second-year pulmonary and critical medicine fellow based in Phoenix, Arizona, who is interested in visually exploring health care ethics via multimedia art. He takes inspiration from the classic sculptures of Rome, surrealism, and contemporary graphic artists, particularly Yoji Shinkawa.

Editor's Note

This is a co-winning artwork of the 2023 John Conley Art of Medicine Contest.

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ART OF MEDICINE

Humanity and Inhumanity of Nonhuman Primate Research

Kaitlin R. Weed

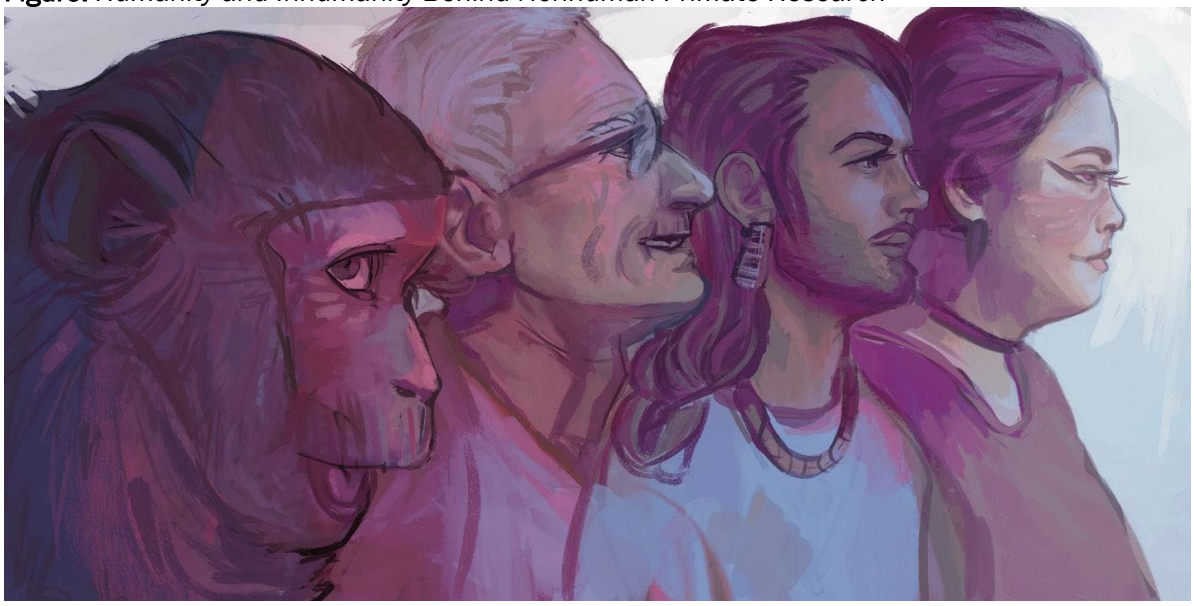
Abstract

This illustration depicts important biomedical advancements generated by nonhuman primate (NHP) research. NHPs' value in human-centered research is their unique evolutionary proximity to humans.

Primates in Human-Centered Health Research

Despite public hostility, nonhuman primate (NHP) research has contributed invaluable knowledge about disease states and drug therapies that have benefited underserved human communities.[1] This success further complicates ethical conversations about uses of NHPs[1,2]; the illustration represents a spectrum of human interest by visually elucidating interrelations among NHP research and advancements in human-centered health.

Figure. *Humanity and Inhumanity Behind Nonhuman Primate Research*



Media

iPad, Procreate.

NHP research has triggered widespread public outrage and activism. Notable instances include the infamous "pit of despair" experiment conducted by comparative psychologist Harry Harlow, which horrified the public by putting young rhesus macaques under extreme psychological distress.[3,4,5] A doctoral student of Harlow, Gene Sackett, said animal rights advocates' hatred was so intense that he personally believed it was Harlow and his experiment that started the modern animal rights movement.[3] In the 1980s, Edward Taub's Silver Spring monkeys sparked allegations of limb deafferentation, improper housing conditions, and poor veterinary care.[3] Taub had been using NHP deafferentation experiments to test his hypothesis of learned non-use and its applications to human stroke rehabilitation, which facilitated development of constraint-induced movement therapy.[3,6] NHP researchers have also been the target of attacks by animal rights groups, such as a string of attacks on California NHP researchers in the mid-to-late 2000s.[4] More recently, in 2020, the University of Wisconsin-Madison was fined $74 000 by the US Department of Agriculture for 28 violations of federal animal research standards, such as injuries requiring amputations.[7]

Human Interest Illustration

One subject, at left in the illustration, is the rhesus macaque, 1 of 2 preferred species in NHP research and the same species used in Harlow's experiments.[3] Each person to the right in the illustration represents the impact of NHP-derived medication on one particular difficult-to-treat or understudied human disease. The first subject, an older man, symbolizes the impact of new treatments for neurodegenerative diseases, such as Parkinson's (PD) and Alzheimer's disease (AD), on length and quality of life. NHP models for PD became critical after the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[8] After "identifying MPTP as the likely cause of permanent parkinsonism,"[8] early studies using MPTP with NHP models for PD emerged. NHP models gained prominence at this moment, as traditional rodent models showed moderate-to-severe resistance to neurotoxic effects of MPTP.[9,10] Even today, NHP models for PD help improve cell-based treatments[11] and serve as critical models for early-stage tau pathology in AD. (Rodents have little tau pathology, and early-stage tau phosphorylation is difficult to study in humans postmortem.[12])

The second human subject in the drawing, a young queer man, represents the impact that HIV/AIDS medication development has had on gay communities and survivorship. The extensive contributions of NHP research to HIV/AIDS treatment include evaluation of Tenofovir's toxicity and its efficacy in suppressing viral replication and testing its prophylactic use as early as 1996.[13]

The last person in the illustration has a malar rash, one of the most well-known symptoms of systemic lupus erythematosus (SLE), and represents the impact of new treatments for SLE on quality of life.[14] NHP models were critical in advancing SLE care: cynomolgus monkeys were used for toxicity testing and dosage testing of the biologic belimumab.[15] Before the US Food and Drug Administration approved belimumab in 2011, no new drug treatment specifically targeting SLE had been released in 56 years, and treatment options up to that point were often inadequate.[15]

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