

Episode: *Ethics Talk: Are the “3 R’s” Enough to Express Respect for Nonhuman Animals in Human-Centered Research?*

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[bright, plucky theme music]

[00:00:01] TIM HOFF: Welcome to *Ethics Talk*, the *American Medical Association Journal of Ethics* podcast on ethics in health and health care. I’m your host, Tim Hoff. The idea that nonhuman animals have some kind of moral status that deserves our regard and our respect is not new to most of us. As far back as the late 1700s, English philosopher Jeremy Bentham suggested that nonhuman animals’ ability to suffer is a foundation for our ethical obligations to care about their experiences. About half of all US adults oppose using nonhuman animals in human-centered research, according to a 2018 Gallup poll, and that’s up from only 32% in 2004. And you probably know somebody who considers a nonhuman animal a member of their family.

Debate about whether and to what extent nonhuman animals can suffer, are sentient, should be categorized as persons, have dignity, these all grow from our moral intuitions that our obligations to nonhuman beings stems from an overall regard for life, and not just human life, as precious and worthy of respect. The growing number of ways we have to talk about the moral worth of animals is one sign of the increasing nuance in this conversation.

DR DAVID DEGRAZIA: In the past, it wasn’t needed so much because there was more agreement about who counted. And now there’s more disagreement about how far to expand who counts.

HOFF: This month’s issue of the *Journal* focuses on uses of nonhuman animals in human-centered research. Many of this month’s articles rely on the so-called 3 *R*’s: that’s replacement, finding alternative to nonhuman animals; reduction, using strategies to limit the number of nonhuman animals needed for research; and refinement, altering research methods to reduce pain and distress when nonhuman animals are used. Joining us to discuss why the 3 *R*’s of nonhuman animal research might not be sufficient to promote good science, ethics, and nonhuman animal welfare, is Dr David DeGrazia, the Elton Professor of Philosophy at George Washington University in Washington, DC, and coauthor of *Principles of Animal Research Ethics*. Dr DeGrazia, thank you so much for being here.

DEGRAZIA: Tim, thank you so much for having me. It’s a great opportunity. [music fades]

[00:02:26] HOFF: Many of the articles in this month's issue rely, either implicitly or explicitly, on the 3 *R*'s of nonhuman animal research. That's replacement, reduction, and refinement, for those of our audience who are not familiar. Your recent work suggests that these should be rethought and that we should instead adopt a framework that relies on three principles of social benefit and three principles of nonhuman animal welfare. So let's start there. What are these principles, and why do you think these are the important values that a revised framework for thinking about nonhuman animal use should incorporate?

DEGRAZIA: Certainly. So, the three principles of social benefit all have to do with the core value that serves as the end or the purpose of animal research. And the three principles of animal welfare have to do with making sure that the means taken to pursue that important end are permissible. So, I'll walk us through the six principles, starting with social benefit.

The first is called no alternative method, and it's very similar to the *R* of replacement in the 3 *R*'s and says that if it's possible to get the knowledge that you seek without using animals, then that is the way to go. The principle of no alternative method is intended as a requirement, whereas it seems that replacement is sometimes thought to be something to be considered, but not so much of a requirement. So there might be that difference there.

Now all animal research has costs. So, to ask whether the costs are justified, you have to consider the possible benefits. The second principle's called expected net benefit. And it requires that the prospect of benefit exceed the anticipated costs to human beings. And the prospect of benefit is a function of both the value of good results, if you get them, and the realistic likelihood of actually getting those results. So the question then is not knowing whether you'll get the good results, whether their prospect is valuable enough to justify the cost to human beings in terms of financial costs and opportunity costs. So that's the beginning of a cost-benefit analysis. But we haven't mentioned animals' interests yet.

[00:05:03] So the third principle is called sufficient value to justify harm. And it asks this: Assuming the first two principles have been met, and there is the prospect of a unique net benefit to human society, is that valuable enough to justify the anticipated harm to the animals, to the animal subjects? And if so, then the three principles of social benefit have been met.

Importantly, with the principle of expected net benefit, we should bear in mind some concerns about translation from successful animal studies to clinical use in humans, and not just assume that anything that looks like it might be very valuable is valuable enough in prospect to justify all the costs and the harms to the animals. In any case, if the principles of social benefit have been met, then there looks like there's a valuable project to attempt, then the details of how the animals are treated become more important. And so, we focus on animal welfare.

And we begin with a principle with an obvious sounding name: no unnecessary harm. Shouldn't cause harm unless it's necessary given justified scientific purposes. This is somewhat obvious, but perhaps it's not so obvious that it should apply not only to scientific procedures, but to anything that affects the animal subjects' quality of life: how they're housed, how they're handled, the temperature in the room, and so on, of the laboratory.

[00:06:54] The second principle of animal welfare is called basic needs, and it states that animal subjects' basic needs should be met—and our book proposes a list of basic needs—unless failure to meet a particular basic need is justified by, and necessary for, achieving scientific purposes. So, in a way, this principle takes the idea of unnecessary harm and expands it to incorporate all the factors that give an animal a chance to have a decent life or make it impossible for an animal to have a decent life.

The third and final principle is called upper limits to harm. It has something in common with an EU directive, a requirement that really comes to almost the same thing. And what this principle requires is that animal subjects not to be forced to endure severe suffering for an extended period of time. As with the EU requirement, it's a little vague in defining severe suffering and extended period of time. That's okay, we think. It's better to have the principle in place and allow smart people working closer to the ground to try to operationalize it. But there is the idea here that sentient animals matter, and there are some limits to how much harm we should impose upon them, even for scientifically important research. So those are the basic principles of the framework.

[00:08:35] HOFF: Hmm. Interesting. So, do you think it would be helpful to think of this framework as supplementing gaps that exist in the current 3 *R*'s or just sort of expanding the scope of them? The first thing you mentioned, the no alternative method, seemed like a replacement, for lack of a better word, of the replacement value. But then the no unnecessary harm, you say that's sort of a standard approach to animal ethics.

DEGRAZIA: Yes.

HOFF: But this framework expands that to housing, how animals are treated outside the lab, etc.

DEGRAZIA: I wouldn't call it a replacement. There's definitely overlap. So, you could think of it as an expansion of the 3 *R*'s or a more comprehensive framework that sort of absorbs the 3 *R*'s. So, no alternative method is like replacement, but it's trying to have teeth. Much of refinement, I think, is captured in no unnecessary harm. Certainly, it adds some new things to the 3 *R*'s. Setting an absolute—absolute's a strong word—but setting limits to how much harm can be caused to animals is something that you just don't find in the 3 *R*'s themselves. And the analysis of how valuable the experiment seems to be is something that the 3 *R*'s doesn't touch at all. So that whole, all those questions that go into social benefit are now made explicit, rather than being something extraneous to the content of the 3 *R*'s.

[00:10:05] HOFF: Mmhmm. Right, right. You talk about giving these principles teeth, so to speak, and I think for many people that calls to mind the idea of some kind of regulating body. So how might regulations governing the use of nonhuman animals for federally funded human-centered research change if regulators adopt this updated framework?

DEGRAZIA: Interestingly, the Animal Welfare Act actually excludes mice and rats, the most commonly used research animals, and birds, from its provisions.

HOFF: Hmm.

DEGRAZIA: On the other hand, PHS policy rightly includes all vertebrates, so it takes care of that problem, but it's only as good as its scope of the PHS policy.

HOFF: PHS, for listeners who are unfamiliar, is a public health service. Sorry to interrupt.

DEGRAZIA: No problem. I think maybe other government agencies have adopted the same requirements, but I'm not positive about that. One thing I would add, though, it should also include, among invertebrates, at least cephalopod mollusks such as the octopus, because these animals are clearly sentient, and not just sentient, but actually intelligent. So there should be some expansion of the animals covered by the regulations or the relevant policy. Also, regulations and policies should require some kind of rigorous evaluation of animal studies in terms of their social benefit. So, hopefully, the principles of social benefit could be helpful. And that would mean that financial costs have to be considered. If the public's paying for research, they should be getting good value, and the likelihood of producing valuable knowledge should be considered as well. As far as animal welfare goes, the regulations or policies should go beyond the 3 R's and more explicitly acknowledge animal subjects' basic needs and then also set limits to how much suffering they'd be asked to endure in any experiment.

[00:12:11] HOFF: Can you, for the large portion of our audience who are clinicians or health professions students and trainees—and this might be a tall order—but give a brief definition of sentience that they can work with?

DEGRAZIA: Oh, yes, yes, absolutely. Very good question. By sentience, I mean the capacity to have pleasant or unpleasant experiences, which means that an animal has an experiential welfare or quality of life. Which means that the animal has interests which can be taken into account, and should be taken into account, ethically.

[00:12:46] HOFF: That's perfect. Thank you. One really interesting point you made, I think it was in *Principles of Animal Research Ethics*, is that ethics review committees often require investigators to carefully document the scientific, but not the ethical, dimensions of the protocols for which they're seeking review or approval. Can you help our listeners understand why it's not enough to just evaluate protocols based on that scientific merit alone, and why we need that ethical grounding as well?

DEGRAZIA: Oh, sure. Yes. Well, scientific merit is really important. It's necessary, but it's not sufficient for the permissible conduct of research. Again, all research has costs, and you have to ask whether the costs are being justified by the prospect of benefit. And if the research involves harms to animal subjects, or even risks in the case of human subjects research, we're clearly not in value-neutral territory anymore. So that means that we have to consider values. And our framework tries to help an analysis of the relevant values, namely an analysis of the prospect of some unique net benefit that justifies the various costs and harms to animals, and then whether the value, anticipated value, of the study justifies the means, how animals are treated.

[00:14:17] HOFF: I'd like to broaden the discussion now from this particular framework and ask what challenges do students face when you ask them to examine the moral worth of animals?

DEGRAZIA: I find my students very receptive to the idea that animals have moral status, at least once they understand that moral status just means whatever value animals have in their own right and for their own sake, and not just as tools for us.

HOFF: Mmhmm.

DEGRAZIA: So they seem very receptive to that, at least for sentient animals, because sentient animals clearly have their own interests. What is a little bit difficult at times is if they mix up moral status—the idea that animals matter in their own right—and moral agency, which is a completely different concept. And it refers to the capacity to make moral judgments and to be morally responsible. So, ordinarily, mature—sufficiently mature—human beings are moral agents, but that you don't have to be a moral agent to have moral status. Human infants are not moral agents, but they have moral status. They count morally. They have human rights. And sentient animals also have their own value, and they matter morally, even though there is disagreement, including reasonable disagreement, about how much they matter.

HOFF: Mm. Yeah, let's talk a little bit more about that disagreement.

DEGRAZIA: Yeah.

[00:15:49] HOFF: So, a lot of our discussion so far has assumed at least some level of shared understanding about the moral worth of animals, namely that they have a moral status of their own. But differing views, as you note, certainly exist. So is there enough agreement on some level for a framework like the one that you propose to earn consensus?

DEGRAZIA: I think so. Interestingly, I used to be more skeptical. Tom Beauchamp had approached me a long time ago about collaborating on a project like this, and at first, I thought it would be thwarted by disagreements about animals' moral status. Later, as I tried to work out principles that I thought just about anyone would be able to accept, I realized it didn't make as much of a difference as I thought. So, even though there's reasonable disagreement about how much moral status sentient animals have in comparison to us, I think there's enough agreement that the sorts of principles that

we've laid out all are likely to strike you as reasonable, whether or not you're heavily invested in animal research, and you're a good-standing member of the biomedical community, or if you're in the animal protection community. I think the principles all make sense. The third one, though, is one in which there might be different judgments about a particular case in evaluating a proposed animal study that's sufficient value to justify harm. I could see how some disagreements about animals' moral status would translate into some differing judgments. But at least with this principle, we make that issue explicit and encourage people to talk about it intelligently, rather than just refusing to talk or getting mad at each other.

HOFF: Mm, mmhmm. Yeah. A recent term we've referenced on this podcast actually is a "boundary object," coming from, I think, sociology, which in this case would be an idea that's flexible enough to be adapted locally while still offering some high-level structure to guide that discussion.

DEGRAZIA: Right.

[00:17:53] HOFF: But to wrap up here, I wanted to look forward and ask what clinicians, researchers, health professions students and trainees, really anyone who relies on nonhuman animal research, should know about the regulatory future of the field over the next months, years, decades, however long these things take.

DEGRAZIA: [chuckles] Yeah, I can't tell you anything interesting about the upcoming months. I think one really interesting place to pay attention is on the alternative, the science of alternatives to animal research. I think as that science develops, there will be much more interesting discussion about whether a particular animal model is needed in order to pursue some scientific objective. And this is really good news in a way, because the more alternatives are used, the less social concern there is about the ethics. And also, the more drug companies can save money and get drugs out faster because they have despaired at how low their translation rates have been, from successful animal studies to getting through clinical trials successfully. And it takes, usually, it takes them many years. So, I think alternatives is one really important area of interest.

I also think that in recent years the public has, and to some extent, Congress, members of Congress, have expressed more concern about nonhuman primates. Maybe there will be more restrictions on the use of primates and not only chimpanzees. The Veterans Administration has done a lot of thinking about whether to continue to use dogs in research, and there was a study by the National Academies of that issue. And I had the sense that they took alternatives more seriously than they were usually taken. This was a few years ago. So, that's certainly one area. And I also think the term "moral status" is likely to become more of a familiar term as it's discussed more not only in this area, but also in connection with the abortion debate, embryo research, and the evolution of artificial intelligence. [theme music returns]

[00:20:20] HOFF: Dr DeGrazia, thank you so much for your time and expertise on the podcast this month.

DEGRAZIA: My pleasure, Tim, and thank you for having me.

HOFF: That's all for this month's episode of the podcast. Thanks to Dr DeGrazia for joining us. Music was by the Blue Dot Sessions. To read the full issue for free, head to our site, journalofethics.org. And you can follow us on social media, including X [@journalofethics](https://twitter.com/journalofethics). We'll be back next month with an episode on Sleep Stewardship. Talk to you then.