HHS Public Access

Author manuscript

Theor Med Bioeth. Author manuscript; available in PMC 2017 July 24.

Published in final edited form as:

Theor Med Bioeth. 2014 April ; 35(2): 157–173. doi:10.1007/s11017-014-9285-5.

Should protections for research with humans who cannot consent apply to research with nonhuman primates?

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Abstract

Research studies and interventions sometimes offer potential benefits to subjects that compensate for the risks they face. Other studies and interventions, which I refer to as "nonbeneficial" research, do not offer subjects a compensating potential for benefit. These studies and interventions have the potential to exploit subjects for the benefit of others, a concern that is especially acute when investigators enroll individuals who are unable to give informed consent. US regulations for research with human subjects attempt to address this concern by mandating strict protections for nonbeneficial research with subjects who cannot consent. Typically, humans who cannot consent, such as children, may be enrolled in nonbeneficial research only when it poses low risks and has the potential to gather information of sufficient value to justify the risks, an appropriate surrogate gives permission on the individual's behalf and the individual agrees (assents). In contrast, US regulations for nonbeneficial research with nonhuman primates do not include these protections, even though it too involves subjects who cannot consent and who face risks for the benefit of others. Is this difference in regulatory protections justified? Or does the principle of fairness—treat like cases alike—imply that regulations for nonbeneficial research with nonhuman primates should include protections similar to those that apply to nonbeneficial research with humans who cannot consent?

Keywords

Nonhuman primates; clinical research; risks; informed consent; assent

Introduction

Research with nonhuman primates and research with human beings who cannot consent are similar in two important ways: both involve subjects who can be harmed and who are unable to consent. Recently, commentators have asked whether these two similarities imply that research with nonhuman primates should be governed by protections similar to those that apply to research with human beings who cannot consent [1].[1]

The author has no conflicts of interest with respect to the present work.

[1]Much of the present analysis applies to research with all nonhuman animals. However, consistent with the theme of the present collection, I will focus on research with nonhuman primates. The proposal from Pascal Gagneux, James Moore, and Ajit Varki [1] involves research with great apes.

Current US regulations include very different protections for research with these two groups. US regulations mandate strict protections for research with humans who cannot consent; US regulations for research with nonhuman primates do not include these protections [2, 3]. This difference in regulatory protections is clearest with respect to research studies and interventions that pose risks to subjects but do not offer them a compensating potential for benefit—what I will refer to as "nonbeneficial" research. For example, humans who are unable to consent typically may be enrolled in nonbeneficial research only when the risks are "minimal" and justified by the value of the research. These limitations are based on the fact that human beings who cannot consent are unable to authorize their enrollment in research that poses risks to them for the benefit of others.

Nonhuman primates also cannot authorize their enrollment in research that poses risks to them for the benefit of others (I will assume, unless otherwise specified, that nonbeneficial research with nonhuman primates is designed to benefit human beings).[2] Yet, US regulations do not mandate an upper limit on the risks allowed in nonbeneficial research with nonhuman primates. They also do not mandate that the risks to which nonhuman primates are exposed must be justified by the value of the study in question.

For present purposes, I will assume that existing protections for humans who cannot consent are largely appropriate and consider the question of whether nonbeneficial research with nonhuman primates should be subject to similar protections. I will try to answer this question in a way that is consistent with the lack of consensus at the level of moral theory regarding the comparative moral status of human beings and nonhuman primates. This disagreement makes it difficult to identify the conditions under which it can be acceptable to expose nonhuman primates to risks for the benefit of human beings [4]. However, this debate notwithstanding, I argue that modified versions of several existing protections for research with humans who cannot consent are appropriate for research with nonhuman primates.

This conclusion is based on a general principle and five related considerations. The general principle holds that individuals who are unable to consent should be enrolled in nonbeneficial research only when, at the very least, there is sufficient reason to believe that the potential benefits of the research justify the risks it poses and the harms it causes.[3] The five related considerations are: (1) It is frequently unclear (to us) to what extent a given study poses risks/harms to nonhuman primates; (2) The chances that any given nonbeneficial study with nonhuman primates ultimately will benefit humans (even in combination with other studies) is uncertain and likely low; (3) Uncertainty regarding the comparative moral status of humans and nonhuman primates makes it especially difficult to determine what level of potential benefits for humans is necessary to justify a given level of risk/harm to nonhuman primates; (4) Nonbeneficial research involves investigators acting as the proximate cause of the risks subjects face and the harms they experience; (5) In general, no

[2]The standard benefits to human beings involve improvements in human health and well-being. Research studies also sometimes offer financial benefits for funders, and gains in knowledge per se.

[3]In the research context, *risk* is a term of art that refers to harms that may occur, as well as to harms that are certain to occur; the inevitable pain of a blood draw constitutes a 'risk' of research participation. I will follow that usage here, although when it seems important to be particularly clear, I will specify both risks and harms. Also, it is worth noting that this terminology does not assume that being exposed to risks is per se harmful to subjects.

justification has been identified for enrolling individuals who cannot consent in nonbeneficial research to benefit others.

The first three considerations establish that it frequently will be unclear whether a given nonbeneficial study with nonhuman primates satisfies the general principle that the potential benefits for human beings should justify the risks and harms to subjects. I argue that in this context—where it is frequently uncertain at the level of individual cases whether there are sufficient potential benefits to justify the risks and harms—policies should be based on normative caution. Specifically, the policies that cover the individual cases should include requirements to minimize serious harms, and allow them only following sufficient review to ensure that the harms are justified in the particular case. This policy approach is supported by the fact that harms to subjects do not simply occur but are *caused* by investigators (the fourth consideration), and by the uncertainty regarding the appropriateness of nonbeneficial research with those who cannot consent (the fifth consideration). I end by considering the extent to which five existing protections for humans who cannot consent—social value; subject selection; acceptable risks; independent review; assent/dissent—might help to implement normative caution in the context of nonbeneficial research with nonhuman primates.

The interests of nonhuman primates

Strict protections for research with nonhuman primates would be unnecessary if it turned out that the interests of nonhuman primates, unlike the interests of humans who cannot consent, do not possess any moral significance, at least any moral significance that we have reason to respect. There also would be no need for strict protections if it turned out that the interests of nonhuman primates have so much less moral significance that, in practice, their interests are essentially irrelevant to determining how we ought to act and the policies that we ought to adopt. If this were the case, essentially any potential to benefit human beings would justify essentially any and all risks to nonhuman primates.

A great deal has been written on the interests of nonhuman animals, and I will not attempt here to canvass the many views, nor evaluate their implications for the present discussion. As an alternative, imagine that a competent human adult willfully causes a nonhuman primate to suffer excruciating pain for months on end in order to realize some negligible benefit that could not otherwise be realized, such as developing an exotic shade of lipstick that minimally improves the lives of a few human beings.[4] Further imagine that the only individual who is affected negatively by the agent's actions is the nonhuman primate. No additional details are needed to conclude that the agent is acting unethically. This conclusion does not depend, for example, on whether his treatment of the nonhuman primate has detrimental consequences for him, or for any other humans. The severity of the suffering, together with the paucity of the benefits, implies that the agent is acting unethically. In other words, his actions are unethical because they are not consistent with the aforementioned

[4]The qualifier to 'willfully' causing the suffering is intended to refer to the conditions, whatever they might turn out to be, that are sufficient for it to be the case that the agent is morally responsible for his actions.

principle on the treatment of individuals who are unable to consent, namely, that the potential benefits of our actions must justify the risks/harms they pose.

This conclusion has several important implications. First, the agent's actions are unethical because the harms clearly and significantly outweigh the potential benefits. And given, I am assuming, that the nonhuman primate is the only individual affected negatively, it follows that the nonhuman primate is harmed when made to suffer excruciating pain. This implies that nonhuman primates have interests. At a minimum, nonhuman primates can be harmed—their lives go worse for them—when they suffer excruciating pain.

Second, the fact that the agent willfully causes the nonhuman primate to suffer is relevant to a moral evaluation of his actions. This suggests that at least one interest of nonhuman primates (i.e., their interest in not experiencing excruciating pain) is of moral significance. Put generally, the impact that a given course of action, including nonbeneficial research studies, has on at least one of the interests of nonhuman primates is relevant to determining whether that action (on our parts) is morally appropriate. Causing nonhuman primates to suffer harms them and, absent sufficient justification, is morally wrong.

This conclusion suggests that contractarian-inspired views, according to which the interests of an individual are morally relevant (to us) only if the individual (implicitly or explicitly) has entered into a social contract with us or lives in some fairly rich degree of cooperation with us, are false. This conclusion also suggests that appeal to individuals' rights will not be sufficient to reject strict protections on nonbeneficial research with nonhuman primates. Specifically, this example establishes that there are some things that are morally wrong for us to do to nonhuman primates. It follows either that nonhuman primates are the bearers of at least some morally relevant rights or that possessing rights is not a necessary condition for it being possible to act wrongly toward another being. The latter possibility could be explained by the fact that nonhuman primates have interests and the possession of these interests is sufficient to establish moral boundaries on how we ought to treat them.

The conclusion that nonhuman primates have at least some morally relevant interests, while important, does not provide any way to estimate how many interests they have, nor the extent to which their interests are of moral relevance (for us). To this point, I have shown only that nonhuman primates have an interest in not suffering that is relevant to how we ought morally to act. This conclusion does not determine whether, to take an example of particular relevance, painlessly killing nonhuman primates sets back their interests and, if it does, what degree of potential benefit is needed to justify this harm.

Third, in at least some cases, promotion of our interests does not justify setting back the interests of nonhuman primates. Put differently, there are at least some courses of action we should not pursue because the benefits they produce for us do not justify the harms they cause to one or more nonhuman primates. Although this conclusion does not identify when the promotion of human interests might justify harming nonhuman primates, it does suggest that, in principle at least, there will be some nonbeneficial research studies that we should not conduct because the potential benefits they offer to human beings do not justify the risks they pose and the harms they cause to nonhuman primates. The case of the individual

causing a nonhuman primate to experience excruciating pain suggests, for example, that we ought not to conduct a research study that causes excruciating pain to nonhuman primates for months in order to develop an exotic shade of lipstick that benefits a few human beings. This conclusion leaves the challenge of determining when nonbeneficial research with nonhuman primates is justified.

Moral status

The prior section reveals that there are some combinations of human interests and nonhuman primate interests such that promotion of the human interests does not justify setting back the nonhuman primate interests. It follows that nonbeneficial research with nonhuman primates cannot be justified simply by claiming that how the research affects them is morally irrelevant. Granting this conclusion, most nonbeneficial research with nonhuman primates is not designed to realize negligible benefits. It is devoted to promoting significant human interests, such as finding better treatments for cancer and hepatitis. To determine when these studies are acceptable, it is not enough to know that nonhuman primates have morally relevant interests. We need to know how the interests of human beings that may be promoted by the research compare morally to the interests of the nonhuman primates that may (or will) be set back.

For present purposes, I am assuming a relatively weak condition on the moral acceptability of nonbeneficial research with individuals who are unable to consent: individuals who are unable to consent should be enrolled in nonbeneficial research only when, at a minimum, there is sufficient reason to believe that the potential benefits of the research justify its risks. Determining whether this principle is satisfied is relatively straightforward when the interests set back are trivial and the interests that might be promoted are significant. Presumably, there would be little moral objection to a study that requires some nonhuman primates to experience the equivalent of 15 minutes of boredom in order to perform a noninvasive test that has the potential to identify the first effective treatment for a disease that afflicts millions of human beings.

Easy cases like this one, however, are rare. In the process of attempting to promote important human interests, most studies set back important interests of nonhuman primates, such as their interest in not suffering. Not only do some studies pose significant risks to nonhuman primates, but conducting research with nonhuman primates typically requires activities prior to and following the research that pose additional significant risks and harms. They may require the nonhuman primates to be caged and isolated and transported long distances under stressful conditions. These more common and difficult cases raise the question of when studies to collect data that have some potential to benefit human beings in important ways, typically in conjunction with data collected from previous and future studies, can justify significant risks to nonhuman primates.

To answer this question definitively, we would need some estimate for the comparative moral status of human beings and nonhuman primates, which, for the present discussion, we can understand as a multiplier on the moral significance of the interests of individuals [5]. On this understanding, the claim that human beings have greater moral status than

nonhuman primates implies that human interests are more important morally than the (otherwise comparable) interests of nonhuman primates, where the degree of difference in the moral significance of the interests is a function of how much greater humans' moral status is. For example, the view that the moral status of humans is *significantly* greater than the moral status of nonhuman primates might imply that human interests on average are, to take a figure somewhat at random and to assume such claims are sensible, two or three orders of magnitude greater than the comparable interests of nonhuman primates. This view would imply that a nonhuman primate experiencing some level of suffering provides much less reason to avoid the activity in question than the fact that a human being would experience the same level of suffering.

The previous conclusion that promoting a negligible human interest does not justify causing profound harm to nonhuman primates (e.g., causing them to suffer excruciating pain for months) establishes, in effect, that human interests are not of so much greater moral significance that any interest of a human being always outweighs (in the sense of providing more reason to act) any number of interests of any number of nonhuman primates. This conclusion can be summarized in terms of the claim that the moral status of human beings is not *dramatically* (to pick a somewhat vague term for a necessarily vague concept) greater than the moral status of nonhuman primates.

This conclusion is consistent with many other options: the moral status of human beings and nonhuman primates is roughly equal; the moral status of human beings is slightly greater than the moral status of nonhuman primates; the moral status of human beings is moderately, but not dramatically, greater than the moral status of nonhuman primates.[5] And these different possibilities have very different implications for the present question of the extent to which regulatory protections for nonbeneficial research with nonhuman primates (which is designed to benefit human beings) should be similar to regulatory protections for nonbeneficial research with human beings who cannot consent.

Does it follow that currently there are no reasonable grounds on which we can determine appropriate policy for nonbeneficial research with nonhuman primates? Is it simply that those who believe the respective interests are of equal moral significance are justified in thinking that the protections should be roughly similar, whereas those who believe human interests have much greater moral significance are justified in thinking that we should not adopt strict protections for research with nonhuman primates? In the next section, I identify some grounds for developing a rational policy despite continuing uncertainty and ongoing disagreement at the level of moral theory regarding the comparative moral significance of the interests of humans and the interests of nonhuman primates.

Setting policy in the setting of uncertainty

I am assuming that individuals who are unable to consent should be enrolled in nonbeneficial research only when, at the very least, there is sufficient reason to believe that the potential benefits of the research justify its risks. For example, it is widely regarded as

[5]There is also the theoretical possibility that nonhuman primate interests have greater moral significance.

unethical to conduct nonbeneficial research with children when the risks and burdens that the research poses on them are greater than the potential benefits that the research offers to others. As the metaphorical nature of the included terms suggests, it is difficult to determine when the risks and burdens faced by subjects are justified by the potential benefits to others. Because there is no way to provide numerical estimates for these calculations, reviewers, i.e., Institutional Animal Care and Use Committees (IACUCs) or others charged with evaluating the ethics of particular protocols, must rely on intuitive judgment to determine when this condition is satisfied. These decisions, difficult enough in the case of research with human subjects, are even more difficult in the case of research with nonhuman primates that is designed to benefit human beings.

Limited epistemological access

In the case of human subjects research, the reviewers, like the subjects, are humans. This similarity provides reviewers with insight into the impact of various research interventions on human subjects, which, in turn, provides a basis to estimate the risks of the interventions. They have a general sense for how much of a burden it is for humans to undergo a lumbar puncture. Human reviewers have much less insight into the impact of various interventions on nonhuman primates. What is it like for a nonhuman primate to undergo a lumbar puncture? Given our limited epistemological access to the experiences of nonhuman primates, reviewers must assess the impact of research interventions by appeal to proxy measures, such as blood pressure, facial expression, body posture, and information on how the research in question would affect humans. Reliance on these proxy measures to assess the experiences of nonhuman primates, together with the fact that the nature of the experiences of sentient beings is central to their interests, implies that there is frequently a good deal of uncertainty regarding the risks and harms that nonbeneficial research poses to nonhuman primates.

The chances of future benefit are uncertain and likely low

The chances that any given nonbeneficial study with nonhuman primates will lead to improvements (even as a necessary but insufficient part of a series of studies) in health or well-being for human beings are low [6]. It is estimated that only approximately 8% of interventions that enter phase 1 studies in human beings are eventually approved and marketed [7, 8]. Because testing in nonhuman primates precedes phase 1 testing in humans, the percentage of interventions tested in nonhuman primates that are eventually approved and marketed is likely even lower, possibly much lower.

For present purposes, we can assume that studies that are true positives (i.e., studies that are successful in nonhuman primates and then successful in human beings) yield benefits for human beings. However, a full evaluation of the level of benefit here would have to take into account the extent to which interventions that are successful in human beings are ultimately approved and marketed (e.g., the sponsoring company does not abandon the intervention for financial reasons), and also how the benefits derived from conducting the preliminary studies in nonhuman primates compare to the benefits that would be derived from conducting the preliminary studies in other ways (e.g., using in vitro models). Human beings also benefit to some extent from studies in nonhuman primates that turn out to be true negatives in the

sense that the intervention fails in nonhuman primates, and this failure accurately predicts that the agent would fail in humans. These studies provide the benefit of not testing the intervention in humans and, thereby, allowing humans to avoid the associated risks.

The overall potential benefit for humans of nonbeneficial research in nonhuman primates is a function of the benefits for humans minus the harms that result for humans from this form of research. This discounting is necessary because some nonbeneficial studies in nonhuman primates end up being false positives: the intervention succeeds in nonhuman primates, but fails during human testing due to excessive toxicity or insufficient benefits. We can assume that these studies have negative value to the extent that they expose human beings to research risks in the process of testing interventions that are never adopted. (A full estimate of these costs requires some comparison to the costs that would be realized by relying on alternatives to testing with nonhuman primates.)

Perhaps more importantly, some nonbeneficial studies in nonhuman primates are false negatives in the sense that testing in nonhuman primates predicts that the intervention would be overly toxic or ineffective in humans (and the intervention is therefore abandoned), even though it actually would have been safe and effective in humans. An accurate assessment of the percentage of studies for which this is the case is crucial to determining the net benefits for humans of nonbeneficial research in nonhuman primates (and similarly for nonbeneficial research with nonhuman animals in general). However, I am not aware of any estimates for the percentage of false negatives with respect to nonbeneficial research with nonhuman primates.[6] In the absence of data, one can say only that the possibility of false negatives discounts to some extent the benefits for human beings of nonbeneficial research with nonhuman primates.

Uncertainty regarding comparative moral status

In the case of human subjects research, the beneficiaries and the subjects are human beings. As a result, reviewers can assume that the interests of the subjects have similar moral significance as the analogous interests of the beneficiaries. Given uncertainty regarding the moral status of human beings compared to the moral status of nonhuman primates, this assumption of comparability does not apply in the present context. This adds an additional level of uncertainty when evaluating whether the potential benefits for human beings of a given nonbeneficial study justify its risks to nonhuman primates. Even if it were possible to accurately estimate the risks/harms to nonhuman primates, and to accurately estimate the potential benefits to human beings, there would remain uncertainty regarding whether the potential benefits justify the risks/harms.

The assumption that the moral status of nonhuman primates is not greater than the moral status of human beings offers a possible baseline for these assessments. Nonbeneficial

[6]A large part of the problem here is that these data would be difficult to collect. The most straightforward, albeit ethically problematic approach, would be to take a range of interventions that fail in nonhuman primates and test them in human beings. An alternative approach would be to take interventions that are known to be effective in human beings, but have never been tested in animals (e.g., interventions that were adopted before animal testing was required) and test them in nonhuman primates. Interestingly, this latter option offers one example of nonbeneficial research with nonhuman primates that might benefit other nonhuman primates (by possibly showing that research with nonhuman primates is counterproductive for the purposes of improving human health and well-being).

studies with human beings who cannot consent that are acceptable on risk-benefit grounds are likely to be acceptable on risk-benefit grounds in nonhuman primates.[7] For example, it is widely agreed that nonbeneficial research that exposes children to two blood draws can be ethically acceptable. This suggests that such a study would also be acceptable in nonhuman primates (assuming the study offered at least the same level of potential benefits). In contrast, uncertainty enters when reviewers consider to what extent it might be acceptable to allow nonhuman primates to face greater risks in the context of nonbeneficial studies than human beings who cannot consent.

To summarize briefly the argument to this point, I am assuming that individuals who are unable to consent should be enrolled in nonbeneficial research only, at a minimum, when there is sufficient reason to believe that the potential benefits justify the risks. Three considerations reveal how difficult it can be to determine whether this principle is satisfied in particular cases. Specifically, it is difficult to estimate accurately the risks that most interventions pose to nonhuman primates; it is difficult to estimate the potential benefits for humans of testing interventions in nonhuman primates; it is unclear what level of potential benefits for human beings is needed to justify a given level of risks/harms to nonhuman primates. It follows that, in most cases, it will be difficult to determine whether a proposed nonbeneficial study in nonhuman primates satisfies even this minimal condition of ethical acceptability.

I shall argue that in particular cases in which it is certain whether there will be sufficient future benefits to justify present harms, policies should be based on normative caution. To this end, governing policies should adopt protections for subjects to minimize the chances of serious harms and to allow serious harms only when there is compelling reason to believe that they are justified. But, first, two additional considerations provide further support for normative caution.

Investigators as proximate causes

One way to characterize the minimal principle governing nonbeneficial research with those who cannot consent is in terms of the claim that the potential benefits to others should *outweigh* the risks/harms to the subject. Metaphorically, this process involves placing the potential benefits on one side of a scale and placing the risks/harms on the other side, and comparing them. The first three considerations reveal how difficult it is to make this assessment in actual cases. The fourth consideration concerns the fact that this essentially consequentialist assessment fails to take into account a factor that is central to the ethical acceptability of our actions. In particular, the determination of whether a given course of action is acceptable depends on more than whether it poses net risks. It also depends on the source of the risks.

Clinical research typically involves the investigator acting as the proximate cause of the harms that subjects experience [9]. To get some sense for this aspect of the relationship between investigator and subject, and to assess briefly its normative implications, consider

[7]Although I will not consider them here, there are some reasons to think that the limitations on research with nonhuman primates should be stricter than the limitations for human beings who cannot consent.

whether it would be acceptable to torture an innocent and very young child in order to gather valuable information (e.g., by compelling a third party who cares about the child to divulge some information).[8] To make the example analogous to research, imagine that the torture involves repeatedly sticking the child with needles. It seems clear that the ethical acceptability of this course of action is not determined solely by the balance of potential benefits to others versus the risks/harms to the child. Put simply, this course of action is not acceptable whenever the expected value of the information to be obtained is greater by any extent than the harm inflicted. One also needs to take into account the source of the risks/harms.

In the present case, the risks/harms are not simply happening to the child, they are being inflicted on the child. Hence, a full moral assessment needs to go beyond the impact on the child and others to include what it is morally appropriate for one *to do* to other beings. For present purposes, a full assessment of the constraints on what it is acceptable for one to do to other beings need not be developed. Instead, the important point is that there is a moral cost to inflicting suffering on uncomprehending others. Hence, the potential benefits of such an act do not need simply to outweigh the costs understood in terms of the negative experiences of the victims. The potential benefits also need to outweigh the moral costs of inflicting suffering on uncomprehending others. Put differently, the requirement that the potential benefits to human beings must justify the risks to nonhuman primates involves more than the potential benefits outweighing the risks by any degree. Instead, ethical justification in this case requires something like the potential benefits significantly outweighing the risks.

One way to begin to get a sense for the magnitude of this added moral cost is to consider when it might be acceptable to inflict suffering on uncomprehending individuals for the benefit of others. It seems that inflicting excruciating and prolonged suffering is unacceptable no matter what the compensating potential benefits. In contrast, while these cases are likely to be controversial, it seems that it might be acceptable when the suffering is mild and the value of the information to be gained is significant. This suggests that the moral costs of inflicting suffering on uncomprehending individuals are significant, but not absolute.[9] And this conclusion points toward an analysis in which there is not a complete moral proscription on our inflicting suffering on uncomprehending individuals, but there are effectively upper limits on the suffering that we may inflict.

For present purposes, the important point is that the reasons against conducting nonbeneficial studies involve more than just the harms subjects experience. In addition, there is the fact that the investigators inflict these harms on the subjects. Hence, determining when it is acceptable to expose nonhuman primates to risks and suffering for the benefit of human beings is not simply a matter of balancing the costs incurred by the subjects and the benefits

[8]Readers who assume that the fact most children will become competent is relevant to this example can regard the child as one who does not have the capacity to develop competence.

[9]A complete analysis here would need to consider the relevance of the moral status of the subjects in question. It might be morally worse to inflict suffering on uncomprehending individuals who have higher moral status compared to uncomprehending individuals who have lower moral status. If this is right, and human beings have higher moral status than nonhuman primates, the moral costs of inflicting suffering on them would be lower to some extent. Making this determination would require an analysis of the extent to which the moral costs of inflicting suffering on uncomprehending individuals depends only on the amount of the suffering and the moral status of the subject, and to what extent it also takes into account the moral status of the agent.

realized by others. One also needs to take into account the fact that research involves actively inflicting the suffering on the subjects [10]. This consideration provides additional reason to adopt policies that promote normative caution. In particular, these considerations support protections that place an upper limit on the allowable harms and allow greater than minimal harms only when there is compelling reason to think that the harms are justified by the value of the research.

No extant justification for nonbeneficial research

The previous section considered the fact that nonbeneficial research with nonhuman primates involves investigators inflicting harms on individuals who cannot consent. The present section emphasizes the fact that this is being done for the benefit of others. As far as I am aware, no one has developed an ethical justification for inflicting harm on nonhuman primates for the benefit of others. The absence of a justification, and the attendant uncertainty over whether and when this category of research is morally acceptable, provides additional reason to adopt policies that minimize the chances that we allow seriously unethical studies to be conducted. This suggests that the relevant policies should allow nonbeneficial research with nonhuman primates only when the risks are sufficiently low, or there is compelling reason to believe that the risks and harms are justified by the potential benefits of the study. The following subsections consider to what extent five existing regulations for research with humans who cannot consent can help realize this goal of normative caution with respect to nonbeneficial research with nonhuman primates. Full analysis of each of these options would require at least a paper on its own. Here, I will try only to sketch the relevant considerations as a hopeful prelude to future work.

Social value

The minimal principle that I have been assuming, namely, the potential benefits of individual studies should justify their risks, is suggested in a number of regulations governing research with nonhuman primates. However, to my knowledge, this condition is not currently stipulated in US regulations. For example, the National Research Council “Guide” states that IACUCs are “obliged to weigh the objectives of the study against potential animal welfare concern” [2, p. 27]. The *US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training* mandates that studies “should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society” [11, p. 1]. Requiring that reviewers weigh and give due consideration to the benefits and the risks does not seem to require that the potential benefits of the research must justify the risks. To realize this protection, guidelines should adopt an explicit statement that nonbeneficial research with nonhuman primates should be approved only when there is sufficient reason to believe that the value of the information to be gained justifies the risks/harms.

Selecting subjects for nonbeneficial research

All things being equal, it is better to conduct nonbeneficial research with individuals who can consent and, thereby, authorize their exposure to risks for the benefit of others, rather than individuals who cannot consent. This requirement suggests, at a minimum, that review committees should evaluate whether it is better to conduct a given nonbeneficial study in

humans who can consent rather than in nonhuman primates [12]. When making this determination, review committees should take into account the fact that some studies pose substantially lower risks and burdens to individuals who can understand and consent. Being placed in a narrow metal tube and subjected to loud noises can be terrifying for individuals who do not understand what is happening or how long it might last [13]. This experience can be enjoyable and educational for individuals who understand that they are undergoing an essentially risk-free MRI. Conversely, individuals who can consent sometimes face greater risks. The ability to consent presupposes many other abilities—to understand, to reason, to remember. These abilities are associated with broad and deep interests that may be placed at risk by enrollment in nonbeneficial research that would be significantly less risky to individuals who lack these abilities.

Many guidelines and commentators assert that individuals who cannot consent should be enrolled in nonbeneficial research only when it satisfies the additional requirement of being designed to benefit "the population represented by the potential subject" [14]. For example, one might argue that nonbeneficial research with adults who cannot consent due to Alzheimer's disease may be acceptable in some cases, but only when it has the potential to benefit individuals with Alzheimer's disease. This requirement suggests that it may be acceptable to enroll nonhuman primates in nonbeneficial research to benefit other nonhuman primates, but nonhuman primates should not be enrolled in nonbeneficial research designed to benefit human beings.[10] I have argued elsewhere that this requirement does not offer an additional protection for individuals who cannot consent [15]. Briefly, one might endorse this requirement based on an assumption that individuals are willing to face risks for the benefit of other members of their in-group, but not for members of other groups. The primary problem with this argument is that it is not clear that it makes sense when applied to individuals who have never been competent. For example, it is not clear that there is any morally relevant sense in which chimpanzees are more willing to help future chimpanzees than future human beings.

Acceptable risks

Determining what levels of risk are acceptable in the context of nonbeneficial research with individuals who cannot consent requires an understanding of why such research is justified. Put generally, to determine the levels of risk to which we can expose individuals who cannot consent, one needs to know why they can ethically be exposed to risks for the benefit of others. For example, to consider one justification that has been offered for nonbeneficial research with children, if it is acceptable to expose individuals who cannot consent to risks for the benefit of others because doing so teaches them important lessons, then the value of these lessons would provide a measure for what level of risk is acceptable. This suggests that until a justification is identified for nonbeneficial research with individuals who cannot consent, one needs to rely on estimates of acceptable levels of risk.

[10]One of the challenges with implementing this requirement is identifying the relevant class to which the individual belongs. Does this requirement imply that rhesus monkeys may be enrolled in research to help other animals, other primates, other monkeys, other rhesus monkeys, other rhesus monkeys of a similar age, with a similar health profile?

A standard approach in human subjects regulations is to estimate acceptable risks based on the risks allowed in other contexts. The most widely endorsed approach here is to define an acceptable level of research risk based on the risks individuals ordinarily encounter in daily life. For example, IRBs may approve nonbeneficial research in healthy children only when the risks do not exceed the risks healthy children face in daily life, such as the risks of riding a bicycle to school. The similarities between nonbeneficial research with children and nonbeneficial research with nonhuman primates—absence of a compelling justification, lack of consent, possibility of harm—suggests that we might use the same level to define acceptable risks for nonbeneficial research with nonhuman primates.

One way to implement this approach would be to apply the qualitative standard—risks in daily life—to research with nonhuman primates. The problem with this approach is that the risks of daily life do not seem to provide an appropriate normative standard. As with the analogous standard for children [16], the fact that individuals face certain risks in daily life does not imply that those risks are acceptable. Why should the risks nonhuman primates face in the wild or in sanctuaries from predators, disease, status conflicts, and the like, determine the levels of risks to which they can be exposed in the context of research designed to benefit humans?

A more promising approach would be to use the quantitative levels of risk that are allowed in nonbeneficial research with humans who cannot consent. For example, the probability of moderate harm allowed for nonhuman primates could be based on the probability of moderate harm allowed for children. While this approach makes somewhat more sense, it would yield very restrictive risk limits. For example, investigators may cause only very low levels of pain to children, such as the pain produced by a few needle sticks. Even moderate anxiety that lasts several hours is prohibited. Adoption of this standard would allow very little nonbeneficial research with nonhuman primates.

Recognizing the restrictiveness of the minimal risk standard, US regulations include a category that allows special review and approval of pediatric studies that do not satisfy the requirements for IRB approval. This category replaces many of the substantive protections included in the categories eligible for IRB approval with a number of procedural requirements. For example, this category does not include any explicit upper limit on risks. Instead, it stipulates that the research must be conducted in accord with sound ethical principles, and then mandates procedures for realizing this protection, including consultation with a panel of experts, opportunity for public review and comment, and approval by a government official. One way to address concern that a minimal risk standard would be overly restrictive for research with nonhuman primates would be to adopt a similar category for special review.

An alternative approach would be to prohibit the studies that seem clearly unacceptable. As noted, it seems inappropriate to cause those who cannot consent prolonged and significant suffering for the benefit of others. This protection might be realized by establishing a risk standard that precludes nonbeneficial research with nonhuman primates that poses greater than moderate pain or suffering, in terms of both its magnitude and duration. One way to implement this approach would be to define three levels of risk: minimal, moderate, and

high. Minimal risk studies would require few safeguards and only minimal independent review, such as expedited review by one person. Moderate risk studies would be permitted following full committee review. And high risk studies would be allowed only after special review. Future research will be needed to assess whether one of these, or some other approach, offers appropriate protection for nonbeneficial research with nonhuman primates.

Finally, implementing a risk standard in practice will require understanding both the interests of nonhuman primates and the ways to measure in practice the extent to which their interests are set back by research involvement. Importantly, this evaluation should take into account the activities prior to and following research that are necessitated by research on nonhuman primates, such as caging prior to and during the study. To what extent is it a harm to be kept in a laboratory, away from one's species-typical environment, to be separated from conspecifics, or to be held in a cage after the research? Does painless and unanticipated killing harm nonhuman primates? A good deal of research is needed to identify the interests of nonhuman primates and also to identify ways to assess the impact of different research interventions on those interests.

Independent review

To ensure that subjects are not exposed to excessive risks, review committees need to include members who can appreciate the impact that the study interventions will have on the subjects. For this reason, US regulations stipulate that at least one member of the committee that reviews and approves research with prisoners "shall be a prisoner, or a prisoner representative." The Office for Human Research Protections (OHRP), the group that oversees the US regulations, recommends that this individual should have a "close working knowledge and understanding and appreciation of prison conditions from the prisoner's perspective" [17]. This requirement is based on the assumption that many individuals are not in a position to adequately judge how participation in research might affect prisoners. Since the impact on nonhuman primates of participation in research is likely to be at least as unfamiliar to many human beings, it seems reasonable to mandate that review of research with nonhuman primates should include someone who has the experience and knowledge to judge how the research in question is likely to affect nonhuman primates. It seems unlikely that the current requirement that Institutional Animal Care and Use Committees (IACUCs) include a veterinarian is sufficient for this purpose.

Assent/Dissent

Allowing individuals who do not have sufficient capacity to consent, but who can nonetheless express their preferences, to decide what happens to them can protect their interests in two ways. First, even individuals who cannot consent often are in the best position to judge how a given experience or activity affects them. Children who cannot consent can indicate that a given procedure is causing them pain. Second, many individuals prefer to decide what happens to them. In this regard, a recent Institute of Medicine report on research with chimpanzees states that behavioral and biomedical research should be conducted only on acquiescent animals [12].

There are two ways to respect the expressed preferences of research subjects who cannot consent. One is to require that they give an affirmative agreement to participate based on what they can understand regarding the study in question (i.e., they assent). Future research will be needed to determine whether an assent requirement makes sense in research with nonhuman primates. Even if individuals cannot assent, taking their objections (dissent) seriously offers an important way to protect them from inappropriate harm. This does not imply that animals must be removed from research at the first sign of distress or dissent. Instead, investigators should be required to evaluate signs of dissent and distress in nonhuman primates and determine whether they indicate that the animal is suffering. Suffering that can be alleviated without undermining the validity of the study should be alleviated. Suffering that cannot be alleviated should be permitted only to the extent that it does not exceed the allowable risk level for the study. Future work will be needed to identify measures that can be used to make these determinations.

Conclusion

Nonhuman primates, like children and adults with severe dementia, cannot consent but can be harmed. These similarities raise the question of whether nonbeneficial research with nonhuman primates should be subject to regulations similar to those that apply to nonbeneficial research with humans who cannot consent. I have considered existing regulations and related moral requirements governing nonbeneficial research with human beings who cannot consent. This analysis suggests that several of the existing protections for research with humans who cannot consent are appropriate for research with nonhuman primates. However, extensive work will be needed to determine precisely how these requirements should be specified for research with nonhuman primates and, thereby, promote the goal of ethically acceptable research involving nonhuman primates.

Acknowledgments

Thanks to Tom Beauchamp, John Gluck, Leslie DeRenzo, Sam Garner, John Phillips, Hope Ferdowsian, and Tina Rulli for helpful discussion and suggestions on earlier versions of the manuscript. This work was completed as part of the author's official duties as an employee of the US NIH Clinical Center. However, the views expressed are the author's own. They do not represent the position or policy of the NIH, DHHS, or US government. The NIH had no role in the analysis, writing of the manuscript, or the decision to submit it for publication.

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