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SCIENTIFIC CONTRIBUTION

Using non-human primates to benefit humans: research and organ transplantation

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Abstract Emerging biotechnology may soon allow the creation of genetically human organs inside animals, with non-human primates (henceforth simply "primates") and pigs being the best candidate species. This prospect raises the question of whether creating organs in primates in order to then transplant them into humans would be more (or less) acceptable than using them for research. In this paper, we examine the validity of the purported moral distinction between primates and other animals, and analyze the ethical acceptability of using primates to create organs for human use.

Keywords Primates · Research · Xenotransplantation · Personalized organs · IPS cells · Chimeras · Hybrids · Regenerative medicine · Stem cells

Animal research

Millions of scientific experiments are conducted on animals around the world every year. In the UK alone, over 4 million experiments were conducted on animals in 2012. The vast majority of research is conducted using mice (74 % of experiments in the UK), but larger animals and primates are also used, and over 50 % of experiments in the UK were on genetically modified animals (UK Government 2012). Increasing awareness of animal welfare issues among the public and professionals has led to increased regulation of the use of animals in research, with a particular focus on the 3 Rs: replacing, reducing and refining the use of animals in research (NC3RS 2013).

The 3 Rs are in turn based on two key principles: proportionality and subsidiarity. These state, respectively, that any use of animals for research must be proportional to the prospective benefit, and that animals should only be used when no reasonable alternative is available. But even these principles rest on the assumption that research on animals is acceptable in some circumstances. It is widely agreed that the use of animals for testing of medical products is justified, given that the alternative is to pose serious risks to humans. However, many animal rights activists believe than any experimentation on animals is wrong, whatever the benefits to humans. While most people believe that it is reasonable to use some animals for research, these activists would argue that it is wrong to do so regardless of the type of creature in question. If all animals were accorded equal moral status, this conclusion would indeed be correct. However, most people regard animals as being morally inferior to humans, and the question of exactly how to ascribe moral status to animals is a controversial one.

The 2012 Cambridge Declaration on Consciousness by three eminent neuroscientists focuses on the criterion of consciousness, stating that "the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Non-human animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates" (Edelman 2012). This would suggest that many more animals have the capacity for consciousness than is widely believed, and in turn that they should perhaps be accorded higher moral status. Using consciousness as the criterion for moral status appears to cast the net too wide, as it would include almost all animals.

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In contrast, most modern conceptions of the moral status of animals have tended to be linked to their capacity for personhood, which most animals are seen as lacking.

Indeed, one of the most widely used definitions of personhood is "humanism", which states that only humans are persons and reveals an implicit bias against non-human animals; this casts the net too narrow. A less anthropocentric definition is used by Peter Singer, who defines a person as a "rational and self-conscious being" (Singer 1993). This definition would include some animals, and particularly primates, Singer argues that there is more difference between an oyster and an ape than between an ape and a human, yet the important distinction is still mistakenly held by many to be between humans and other animals. Indeed, Singer has stated that "we are great apes" ourselves (Singer 2001).

Jeff McMahan offers a different account of why harming animals is less objectionable than harming people:

> The Time-Relative Interest Account offers an explanation of why the killing of animals is less seriously objectionable than the killing of persons. Because the psychological capacities of animals are significantly less well developed than those of persons, the range of goods accessible to them is narrower and the degree of psychological unity within their lives is less. They therefore have a weaker time-relative interest in continuing to live than a person normally does. (McMahan 2003, p. 204)

While McMahan's account could be seen as legitimizing animal research, it should be noted that the time-relative interests account would yield different conclusions regarding different species. For example, while mice have much less psychological capacity than humans, pigs may have more than mice, and primates may have more than any other animal (with the possible exception of cetaceans such as dolphins, which are not normally used as a model for humans in research). Whilst the time-relative interests account provides justification for worrying less about using some animals in research, its "sliding scale" nature cannot tell us whether the use for research of animals with slightly less psychological capacity than humans is justified. The question remains regarding where the "cut-off" should be—between mice and pigs, between pigs and primates, or between primates and humans.

Primate research

Many countries have taken steps to prohibit experiments on the most "human-like" animals, non-human primates. These include Norway, Austria, the Netherlands and New Zealand; (Wikipedia 2013) Spain has officially extended human rights to great apes (Glendinning 2008) In the UK, research on primates is permitted, but is only approved by the Home Office when there is no satisfactory alternative; 2,186 primates (mainly macaques) were used for research in the UK in 2012 (UK Government 2012). Research using great apes such as chimpanzees and gorillas is not currently licensed in the UK. Despite the claims by some activists that primate research is not necessary, many scientists maintain that key medical discoveries depended on such experiments. These include:

- polio vaccines, which have virtually eliminated the disease in the USA and Europe since the 1950s
- life-support systems for premature babies
- kidney dialysis
- anti-rejection drugs for organ transplant recipients
- deep brain stimulation to suppress the symptoms of Parkinson's disease
- surgical treatment for macular degeneration—an incurable eye disease that is the primary cause of blindness in older people
- new techniques in stroke rehabilitation therapy
- drugs to combat asthma. (Welcome/MRC 2006)

It should be noted, however, that the fact that primates *were* used in the research that led to these advances does not mean that these advances could not have been made without using primates; other animal models could have been used instead, or humans could have volunteered.

Today, primates are mainly used in research concerning six areas of medicine: Parkinson's disease, reproduction, cognition, vaccines, vision and stroke. The use of primates is necessary in some cases because they are the animals that are most like us, and provide the most accurate animal model. Given that the only alternative would be to use humans, the subsidiarity criterion is met, and given the substantial potential benefits of some of the treatments that may result, the proportionality test is also met. It should be noted, however, that to the extent that primates actually meet the criteria for personhood, they should be treated as persons rather than animals, making the proportionality and subsidiarity principles irrelevant. For the purposes of this paper, we will assume that the current consensus position is correct, and primates (with the possible exception of great apes) are not persons. The European Commission's Scientific Committee on Health and Environmental Risks (SCHER) has stated that "because non-human primates have close and sometimes unique similarities to humans, their use remains necessary in the safety testing of new pharmaceuticals and in several areas of biomedical research, such as research on infectious diseases and on the brain." (SCHER 2009) However, the fact that primates provide the best animal model does not mean that that model is actually of sufficient predictive power: it has been

argued that "studies comparing toxicity in animals, including nonhuman primates, consistently reveal positive and negative predictive values far less acceptable than those needed to substantiate the claim that they can be used to predict human response" (Shanks and Greek 2008). Nonetheless, the consensus remains that the use of animals, including primates, in research is necessary and justified. The Nuffield Council on Bioethics concluded that: "the concept of the Three Rs and the hybrid moral position underlying the Animals (Scientific Procedures) Act 1986 (some absolute limits, and a case by case weighing of the costs and benefits) could be accepted, or at least tolerated, by all those holding reasonable views." (Nuffield Council 2005) (Although some would question why those who believe in animal rights should tolerate what they cannot accept.)

This claim that research on primates is necessary because they are most like us represents the crux of the ethical dilemma: in a sense, it is an inevitable consequence of trying to find an accurate animal model that any such model will have similar intellectual and emotional capabilities to ourselves. However, animal rights activists would argue that the fact that primates are like us does not necessarily mean that we should treat other animals with any less respect than we accord primates. We empathize more with the pain of primates because their expression of suffering is so similar to ours. But the mere fact of this "unique similarity" does not mean that the suffering of pigs or even mice is any less acute; they may just express it in a less human way. It can be argued that our reluctance to use primates for research is itself a product of anthropocentrism:

> Empathy with animals most likely is a psychological side-effect of adaptive empathy among humans, and its expression is largely determined by the degree of similarity between animals and us in morphology and behaviour. As a result, compassion with animals is vulnerable to anthropocentric bias, prejudice, and deception, and animal protection based on compassion is likely to be unfair towards animals. (Wurbel 2009)

Here, the argument is that we should not overlook the possibility that we accord more moral weight to primates partially because they look and act more like us rather than because they embody characteristics that designate moral worth. As Thomas Nagel pointed out, we cannot imagine what it is like to be a bat (Nagel 1974). While we think we can easily imagine what it's like to be a gorilla, that does not mean our guesses are accurate; equally, our anthropocentric guess that other animals do not perceive suffering at the same level may also be mistaken. The point here is not that research on primates should not be conducted, but that it is not obviously true that doing so is much (or any) worse than conducting it on pigs, dogs or mice. Now let us turn to a novel potential use of primates that may be easier to justify.

Primates, pigs and organ creation

Recent advances in regenerative biotechnology have enabled scientists to grow rat organs in mice using induced pluripotent stem cells derived from rats and injected into mice embryos (Kobayashi et al. 2010; Isotani et al. 2011) The result is a rat/mouse chimera: a mouse with, for instance, a rat kidney. It is likely that this same technology will allow human organs to be grown inside pigs or primates within one or two decades, depending on which species is more suitable. The potential advantages of using this technology are tremendous: this would not only represent a new source of organs with which to reduce the number of people dying every day waiting for a transplant, but could also significantly reduce the rejection rate of transplants (Shaw 2014). All transplant recipients must take immunosuppressant drugs for the rest of their lives in order to prevent the organ being rejected, and the failure rate is relatively high despite these drugs. However, if the stem cells used to create the new organ inside an animal are derived from the recipient, the chances of rejection would be close to zero. Even if such autologous transplants prove too costly, IPS cell lines can be used to create allogenic human leukocyte antigen-matched organs; while not as ideal as autologous transplants, these are nonetheless less likely to be rejected than transplants from whichever donors die on a given day. This novel biotechnology does raise some safety and other ethical concerns in addition to those raised by using primates, which we discuss elsewhere (reference 1). To summarize, the risk of zoonosis (generation of new cross-species viruses) is close to zero. No humans have been infected with a retrovirus following traditional xenotransplantation of an organ from a pig (Boneva and Folks 2004), and any tiny risk would be reduced further by the use of fully human organs obtained from chimeras, although precautions would still have to be taken given the potential harm caused by any new virus Mattiuzzo et al. 2008). Furthermore, any risk of the animal developing human mental features or being able to produce part-human offspring could easily be avoided by "knocking out" genes for neuronal and gamete development in the human cells. While the chimera organs technique is still experimental and would have to undergo thorough clinical trials, it is quite possible that it will become a proven therapy within a decade. This paper proceeds on the assumption that those trials will establish the efficacy and safety of this regenerative technology, thus moving the

creation of chimera organs from the realm of experimental research to that of established treatment.

Proportionality

The key question is the same as that in the earlier xenotransplantation debate: whether it would be acceptable to use animals for the purpose of producing organs for humans. It seems reasonable to assume that most people would accept the use of pigs for this purpose. Unlike primates, pigs are routinely eaten by millions of people every day. (For many people, the fact that it is regarded as acceptable to eat pigs rests on the assumption that they are treated humanely until killed; while such humane treatment could be provided for GM chimera pigs, they would have shorter lives, as they will be sacrificed whenever the organ is large enough to be transplanted.) In terms of proportionality, using pigs for this purpose seems far less of a problem than using them for food or for research. While the use of pigs for this purpose might be acceptable, it is a distinct possibility that primates might have to be used instead because of the aforementioned greater similarity with humans. However, the use of primates is more ethically challenging. Even if it is generally wrong to use primates for research, could it be acceptable to sacrifice them for life-saving clinical purposes?

First let us consider the use of primates to create organs in terms of proportionality. Although it might seem callous to be willing to create and sacrifice a primate for its organs, the potential benefits of doing so should not be underestimated. It is not just about saving human lives and reducing future human suffering; if the primate option was used, people wouldn't need to wait several years for someone to die and donate a kidney (for example) as the organ could be grown from scratch. In the US patients wait an average of 2 years for a liver, and in Germany the wait for a kidney is 6 years. As such, the removal of suffering would be much greater than it might at first appear. (Of course, there are other objections to creating chimera organs: that it is playing God, or against human dignity. These points are considered in another paper.)

Another potential objection is that using primates for research is acceptable because only a few experiments are needed, and then the knowledge is obtained (or not); however, in the case of organ creation, we are essentially advocating the creation of primate factories that will be in operation for many years to come. This raises the question of how many primates would be needed each year. This basically equates to: how many people would require an organ each year? In the UK, 1,000 people die every year waiting for an organ, and more would need organs to improve quality of life, so maybe 2,000 primates would be needed per year. In contrast, 2,186 primates were used for research in the UK in 2012 (UK Government 2012) Therefore, a rough estimate is that roughly the same number of primates would be used each year for organ production as for experiments—a substantial increase, but perhaps justified given the greater direct benefit compared with their use for research. The fact that great apes might be necessary due for organ creation also raises the question of whether the distinction between lesser and great apes is relevant in this context. Most primates used in research, and all used in the UK, are smaller primates. While these could be used for organ production (especially for children), bigger primates are more likely to be appropriate donors.

Subsidiarity

While the creation of human organs inside primates appears to meet the proportionality criterion (with the possible exception of great apes), the subsidiarity principle raises further questions. One of the most common objections to using primates (and other animals) for research is that doing so is not necessary or useful even when scientists say it is. However, this objection is easily overcome in the case of using primates to create organs. If these organs are not created, people will die or continue to suffer. As such, proving that there is "no alternative" would be much easier for organ creation than for research that might never bring any benefit, at least under a permissive reading of the subsidiarity principle that would allow this use of primates if there is no proven non-problematic alternative. However, a more restrictive reading of the principle would be that using primates to create organs would not acceptable as long as there may be possible alternatives that are equally effective but less problematic. It could be argued that "no alternative" is never true in the case of organs because many people do not donate their organs after death, and there are other potential sources of organs than primates. This is true in a general sense, but for the specific people who will die soon without an organ there really is no alternative, suggesting that the restrictive reading of the subsidiarity principle is too strict. Therefore, using primates for this purpose appears to be more justified than using them for research, at least in terms of expected utility. Of course, if it becomes possible to create entire solid organs using scaffolds in laboratories at some point in the future, the subsidiarity principle would then yield the conclusion that the use of primates (or any animals) for this purpose would not be justified. Another interesting issue concerning subsidiarity arises from the possibility that creating organs inside pigs might be workable but less effective than using primates. In this context, it would be questionable whether even the more permissive reading of the principle would allow the use of primates.

Similarly, it could also be argued that primates should only be sacrificed to create organs when it's necessary to save life rather than to improve quality of life. While lessening the suffering of dialysis for kidney patients, for example, is a good goal, it is not clear that it is worth sacrificing a great ape for; in contrast, such a sacrifice seems more appropriate if a human will die without it. Furthermore, it could be argued that using primates for allogenic transplants would be more ethical than using them for autologous transplants. Most people who seek an autologous transplant will only need one organ, meaning that the others will go to waste unless they are used for allogenic HLA-matched transplants. (In allogenic organ creation, all organs from an animal can be used as the matching is not so specific, although this increases the risk of rejection.)

Finally, if the use of pigs or primates for this purpose was deemed inappropriate because of the suffering it would cause them, and the fact that there are other means of obtaining organs, there is one way in which all animal suffering could be avoided while still using them to grow human organs. It could eventually be scientifically possible to "knock out" the genes for major brain development in animals, enabling anencephalic pigs or primates being used to grow organs. While this would certainly avoid the possibility of any suffering (except perhaps that experienced by the mothers of the anencephalic animals), it might paradoxically be regarded as worse in some respects, as it would involve deliberately creating animals that would normally have moral status, but whose integrity has been seriously compromised (Nuffield Council 2005). However, given that this solution would cause no suffering and could save thousands of lives over several decades, concerns about integrity might not win the argument. If we really wished to avoid inflicting any suffering on animals, while also saving many human lives, the creation of organs in anencephalic ("brainless") pigs or primates might be the solution. Nonetheless, it is not obvious that the animals used to create chimera organs would suffer much more than those currently used in research, and those who wish to reduce suffering might actually be more troubled by the creation of anencephalic animals for integrity reasons.

Should only great apes be suitable for the creation of chimera organs, the same idea of avoiding major brain development might be considered as a way to avoid any possibility that using these animals would amount to using persons. This line of reasoning invites the thought that human anencephalics could be created for the same purpose as well. If there is no overriding objection to doing this in great apes, why indeed would things be different in humans? On the other hand, if the moral reluctance we feel with the idea of creating human anencephalics as organ sources has any ethical weight, the question arises why this would not also count against doing this in apes.

One last objection to creating human organs in primates is that many primate species are endangered, while humans are flourishing and consume increasing amounts of the Earth's natural resources; how can using endangered animals to create human organs be justified, given this context? This is a valid argument, but the same applies to using primates for research. It is sadly true that humanity operates on an anthropocentric basis. Furthermore, the people who would benefit from this biotechnology are likely to be wealthy citizens of developed countries, while less lucky people elsewhere in the world continue to starve. Again, it is sadly true that Western societies are somewhat self-focused. Of course, if access to chimera organs was also provided in developing countries, this concern would be addressed. These are problematic issues, but they are systemic and do not in themselves offer a decisive argument against using primates to create chimera organs.

Conclusion

In conclusion, we use primates for research because they are the animals that are most like us, despite the concern that they may not actually be biologically enough like us for such research to be useful. The problem posed by the fact that we may need to 'cannibalize' our closest primate relatives for organs parallels the problem that these relatives also constitute the best animal research model. While it would require initial research on primates, the use of primates for organ creation would represent a shift from their use in medical research, which is dwindling in any case, to their use as an essential resource for clinical medicine. This shift means that the question of whether a given research project will ultimately result in benefit is removed, as each sacrificed primate would save at least one life, and could improve several more. The criteria of proportionality and subsidiarity are likely to be met by the creation of organs inside primates, provided that no alternative artificial sources of organs such as "lab-grown" organs are developed, and that the creation of chimera organs in pigs or other animals is not viable. Currently, chimera organs appear to be the most promising new source of organs due to technical hurdles in creating bionic or lab-grown organs, but all such alternative sources should be actively pursued, as any success in creating organs via other means could avoid the ethical issues posed by using chimeras. While this preliminary analysis suggests that using primates to grow human organs should be more acceptable than using them for research, a public debate on the issues raised in this paper is clearly required.

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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