Non-human Primates in Biomedical Research

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Non-human primates remain essential for certain types of biomedical research

Although non-human primates (NHP) account for less than a fraction of one percent of all of the animals used for biomedical research, their many similarities to humans make them vital, and presently irreplaceable, models for humans for certain types of research (*Hau et al., 2000*). The most common areas of research in which NHP are used include microbiology (including HIV/AIDS), neuroscience and biochemistry/chemistry. Several of the Old World monkeys (*Chlorocebus aethiops, Macaca mulatta, M. fascicularis and Papio spp.*) are the most commonly used species for research (*Carlsson et al., 2004*). Based on all articles published in 2001, it has recently been estimated that the global number of NHP used in research, including those participating in more than one protocol, is in the vicinity of 100,000-200,000 animals annually (*Carlsson et al., 2004*). The authors of the present paper were invited to give evidence to the joint Academy of Medical Sciences/Medical Research Council/Royal Society/Wellcome Trust study into the use of non-human primates in research, and this article is therefore addressed to the joint committee.

An inability to satisfy the demand for certain primate species for biomedical research

There is a critical shortage (*Cohen, 2000; National Research Council, 2003*) of NHP for use in research in general, and for AIDS research in particular, where Indian-origin *M. mulatta* are the most desirable and appropriate model (*Bontrop & Watkins, 2005*). The inability of captive NHP breeding colonies in the US and Europe to satisfy the research demand for Indian-origin rhesus and other species, necessitates the importation of NHP from source countries in Asia, Africa and South America. Long distance transportation to North America and/or Europe is logistically difficult, and more importantly, is unfortunately likely to induce stress on the relocated animals (*Honess et al. 2004*). Changes in climate, housing, social circumstances, light/dark cycle, and diet, often adversely affect the constitution of the animals (*Honess et al., 2004*). For animal welfare reasons, as well as for scientific, collaborative, logistical, and financial reasons, the development of primate research centres in NHP source countries should be an integral component of any global NHP utilization plan (*National Research Council, 2003*).

Wild-caught NHP are typically not the best models for biomedical research (*Leroy et al., 2004*), potentially introducing confounding variability into experimental designs. The use of wild-caught NHP has been criticized and is prohibited in some countries, including the UK (*GB Home Office, 1998*). In some cases, however, the capture of wild-caught animals for use as breeders in source country breeding colonies may not only be justified, but may also be beneficial to the species, the country, and the research community (*Stanley, 2003*). This is especially true when non-human primates are considered pests and are subjected to authorized or unauthorized culling or extermination programs (examples include *M. fascicularis* in Mauritius and parts of Indonesia; *C. aethiops* in Kenya and the Caribbean; and *Papio spp.* in Kenya). Rather than

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simply eradicating these NHP, research-minded entrepreneurs have converted pests into valuable financial and research assets for the source countries (*Stanley, 2003; Ervin & Palmour 2003; National Research Council, 2003*). Recent advances in capture and translocation techniques (*Moinde et al., 2003*) have helped to minimize the stress, morbidity, and mortality (*Suleman et al., 1999, 2000*) associated with the capture and maintenance of wild NHP in captivity.

Ethical considerations

Although society recognizes and acknowledges the need to use animals in biomedical research (*Hagelin et al., 1999*), there is still considerable debate concerning many aspects of this need. This is particularly true for the use of NHP, with significant opposition to the use of NHP in research in many parts of the world, especially in certain countries in the European Union (EU) and in Japan (*Pifer et al., 1994*). Some (*Balls, 2000*) have even called for a complete ban on the use of NHP in Europe. Despite these efforts to stop primate research, the scientific community (*Hau et al., 2000; National Research Council, 2003*) and the EU (*Scientific Steering Committee 2002*) continue to emphasize the importance of the appropriate use of NHP in biomedical research.

In the UK, the Netherlands and Sweden, the use of Great Apes for biomedical research is now prohibited. To single out and ban these few species from study may represent both unscientific thinking and speciesism. It is clearly important to evaluate the actual use of these NHP in research, specifically whether they are participating in trivial or harmful (causing pain, suffering or distress) experimentation. But, instead of proposing a ban on certain species, it would be more logical to ensure that procedures associated with pain and suffering would be closely monitored and absolutely minimized for these animals of high sentience and considerable self-awareness. By including this type of supervision as part of the ethical review process (as is, in fact, done in virtually every country), scientific and medical progress could continue without legally banning research on certain species and without causing unjustified harm to the animals participating in the research.

It is clear that the high degree of similarity between NHP and humans makes them both a high-fidelity model for human conditions and an ethically problematic model. In addition to this theoretical conundrum, there are also practical issues related to the maintenance and use of NHP, species that are basically undomesticated, wild animals that have spent relatively few generations in captivity. This is in contrast to the vast majority of laboratory animal species, many of which have a long history of coexistence with humans, either as pests (mice and rats), or as pets or farm animals subjected to generations of selective breeding for traits related to enhanced manageability in environments created by humans (e.g., docility and agreeableness). Balls (*2000*) suggests that the satisfaction of the minimum needs of NHP is difficult under laboratory conditions. While we agree that exact duplication of natural conditions is difficult, functional simulations of many aspects of the environment that satisfy the critical needs of NHP are relatively easily achieved in the laboratory (*Hau & Schapiro, 2004*). Many of these functional simulations address behavioural issues and there would seem to be considerable justification for the maintenance of "behavioural health records" that would be similar to the physical health records or medical records that are currently maintained for virtually all primates living in laboratory settings.

The use of NHP in multiple protocols – ethical and conservation considerations

Perhaps one of the most interesting and most illustrative issues for the committee to consider is the issue of re-use of NHP in multiple protocols. In a recent global survey of NHP use in 2001 (*Carlsson et al., 2004*), information concerning subject re-use was provided in 14% of the more than 2,900 published articles that were analyzed. Approximately two-thirds of all of the NHP represented in this

subset of the analyzed articles (>400) were used in more than one protocol. The question of whether NHP should be re-used or not is fascinating, multifaceted, and absolutely critical to the analysis of the need for NHP in research. It involves issues related to ethics, conservation, economics, and the quality of science. While it is neither possible nor desirable for us to attempt to solve the problem of re-use in this "paper of evidence", we can make a useful statement or two. First and most obviously, re-use of NHP in additional protocols should only occur when earlier protocols are deemed to have no negative effects on the subject's suitability for later protocols. [In a few instances, participation in, and the cumulative effects of, a first protocol (tests of a vaccine for Hepatitis C virus) actually make subjects more suitable for additional protocols (studies of therapeutics for Hepatitis C virus; *Thimme et al*., 2002)]. Scientific review and/or ethics committees, including Animal Care and Use Committees, are among those best qualified to evaluate the cumulative impact of participation in previous protocols. Second, practical considerations, including those related to limited funds for research and limited availability of the specific primates necessary for studies, suggest that re-use could help conserve both investigator funds and the animals themselves. In fact, the NIH of the United States supports the Primate Supply Information Clearinghouse, an entity with a worldwide user-base whose primary goal is to "…make the best possible use of available research primates in the United States by facilitating their sequenced use in biomedical research…"
(http://www.wanprc.org/psic/). Clearly, this would not be a strategy that would be strongly supported by those who feel that the individual animal and the manipulations it is subjected to are the critical data points for evaluation. As we mentioned above, analysis of the ethical, practical, and scientific issues related to re-use of NHP in multiple protocols may be among the most critical tasks for the committee to perform.

The way ahead

Rather than simply summarizing what we have written above, we would prefer to present our (hopefully) scientifically based opinions on what we think the committee should consider when evaluating the future use of NHP in research. It is gratifying to see that this committee is gathering the data necessary to generate a coherent, empirically-based, long-term plan for the maintenance and research use of NHP.

First, we believe that the establishment and support of primate research centres in countries with natural populations of NHP should be a major component of any global NHP plan. This would be especially true in countries where proper management of NHP resources could be used to convert the animals from pests to valuable assets. Second, we feel that there are numerous behavioural management techniques available that can reduce the amount of stress experienced by NHP during capture, transport, maintenance, and/or research use. These techniques, including the establishment of behavioural records, should always be used, and should be supported and enforced by Ethics and Animal Care and Use Committees during the protocol approval process. And finally, we feel that an analysis of the ethical, scientific, financial, and conservation issues related to the re-use of NHP in multiple research protocols must be performed. If these three tasks can be accomplished by the committee, then we are certain that they will be able to establish a sustainable plan for non-human primates to contribute to the scientific community's efforts to improve the health and welfare of all primates, human and non-human alike.

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