# Experimental use of nonhuman primates is not a simple problem

**To the Editor:**

The recent *Nature Medicine* editorial on the use of nonhuman primates in research[1] presented some of the many sound scientific arguments for why such studies continue to be an essential component of medical research. The article also discussed some aspects of the ethical dilemma surrounding this work: such experiments may be scientifically justified, but is it 'right' that we do them?

On this issue, the editorial concluded that "the solid scientific case that can be made to support the use of monkeys and apes in research must take precedence over ethical arguments until the latter can be settled for good." This position is somewhat unrealistic—the history of both this debate and many others in medical ethics tells us that such a resolution is unlikely. Even if a resolution is reached within the scientific community, it may be more difficult to achieve one amongst the wider public, who, after all, are the principal stakeholders.

Furthermore, adopting such a position may give rise to a reality or at least a perception in which scientists are distanced from the ethical arguments. This is problematic, because the pivotal point for decisions over whether or not to use animals in research is a cost-benefit analysis, where the 'cost' is principally couched in terms of probable animal suffering. Ethical issues are therefore involved in decision making at every stage of the research process, from grant applications to local ethical review committees and specific experimental designs. Most importantly, as scientists, we must continue to have an active and vociferous presence in this debate. It is not that the scientific case should take precedence over 'unsettled' ethical arguments; rather, the scientific case must remain an inextricable part of the ongoing ethical debate.

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1. Editorial. *Nat. Med.* **14**, 791–792 (2008).

**To the Editor:**

Your recent defense of nonhuman primate research[1] rests on assumptions of its utility that have little supporting evidence and implies that critiques of it are selective and anecdotal. On the contrary, the only scientific analyses made to date have been critiques that have revealed nonhuman primate models to be of little relevance to human medicine.

Some of the most compelling evidence concerns the chimpanzee. Over 85% of chimpanzee studies published between 1995 and 2004 were either not subsequently cited or cited by papers not describing human medical progress[2,3]. The remaining 15% that were subsequently cited by human medical studies had not contributed to any reported advances in human clinical practice. A recent analysis of AIDS vaccine research showed that many of the 85 vaccines tested to date in almost 200 clinical trials had been previously tested in chimpanzees with positive results, only to fail in humans[4]. Hepatitis C represents another failed attempt at a vaccine, despite almost thirty years of effort, a lot of it in nonhuman primates.

Yet HIV infection does not cause AIDS and hepatitis C infection does not cause hepatitis in chimpanzees, reflecting the very different pathological processes of these viruses in chimpanzees as compared to humans. Even studies of why this is so have come up empty handed for the benefit of humans, and none of this informs nonhuman primate researchers who nevertheless persist in claiming they need to do more nonhuman primate studies, defying evidence of the lack of utility of chimpanzee research and ignoring increasing knowledge of the species differences between humans and chimpanzees underlying this evidence. For example, significant differences in the full gene complement and in gene expression and splicing have been shown in a variety of tissues and gene classes[5–9], and 80% of the orthologous proteins in these two species are different in terms of amino acid identity[10].

There is little evidence to support the assertion that other nonhuman primate species even more distantly related to humans than chimpanzees are valid research models. Many drugs fail in clinical trials despite promising results in preclinical nonhuman primate tests, and many that do reach the market cause human harm. Moreover, nonhuman primate use in toxicology is no more predictive of human response than the use of more evolutionarily distant species.

Further, the ethical perspective cannot be overlooked. For example, we have known for years that chimpanzees can acquire American Sign Language, demonstrating their complex nonverbal communication abilities. They are capable of reasoned thought, abstraction, generalization and symbolic representation and have a concept of self. They also show a broad range of emotions, experiencing mental, as well as physical, pain. Nonhuman primates in captivity show behavioral abnormalities and measurable signs of distress, which can result from separation of infants from mothers, sensory-motor deprivation or social isolation. Recently, one study reported post-traumatic stress disorder in chimpanzees that had been in captivity and used in multiple research programs[11], and there is unpublished evidence of psychological traumas that affect cross-fostered chimpanzees (G.A. Bradshaw, T. Capaldo, L. Lindner and G. Grow, unpublished data). Such ethical costs combined with little or no scientific worth represent serious concern. Combining the two, the argument for the replacement of nonhuman primate research with superior and more humane alternatives is formidable.

Alternatives cannot be dismissed using arguments such as 'whole-system' reasoning. The wrong system is the wrong system; whole animals may have similar complexities to the human body that cannot be accurately reflected *in vitro*, but it is these very complexities and their interspecies differences that, when combined, confound research results. A collective use of alternative, human-specific methods obviates this—methods such as three-dimensional human tissue culture, microarray-based elucidation of pathology and discovery of druggable targets, microfluidic systems, simulated human immune system cultures, human tissue bioassays, brain-scanning technologies and post-mortem examination for studies of brain function and neurological disorders, human microdosing for the derivation of human-specific pharmacokinetic properties of new drugs, and many others.

In summary, systematic study of nonhuman primate research and testing suggests that such research has delivered precious little to tangible human medical progress. Unless its advocates critically and scientifically

appraise this work, learn from past mistakes, accept the serious nature of its ethics and embrace all that new human-specific technologies deliver, medical progress against diseases affecting billions of people will continue to stall. Intransigence is unacceptable in a scientific world.

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**To the Editor:**

As your August 2008 editorial[1] pointed out, there are ethical and scientific issues when considering the use of animals in science. These are separate issues, as the implications of one position do not necessarily have an impact on the other. For example, one might oppose the use of nonhuman primates on ethical grounds while acknowledging that such use could advance science. Or one might have no ethical objections but may question the predictive value of using nonhuman primates as models for humans. From a scientific perspective, the arguments for and against using nonhuman primates in research are very different from the ethical arguments.

For example, 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[2–6]. HIV is a case in point; the use of nonhuman primates to predict the human response to HIV has been unsuccessful[7]. Vaccines that have protected nonhuman primates from HIV did not protect humans, and the mechanism of HIV attack varies among primates. Humans and nonhuman primates do share characteristics important to drug and disease response, but these shared characteristics are not quantitatively or qualitatively adequate to allow prediction in the scientific sense of the word.

The editorial appeals to the 'intact biological systems' argument to justify the use of nonhuman primates in research touted to predict human response. Most people would agree that *in vitro* and *in silico* approaches are not predictive of what a drug will do in an intact living human. But this invites the following question: does the use of nonhuman primates achieve positive and negative predictive values sufficient to claim that they are predictive of human outcomes? The answer is that they do not. Claiming that society should use nonhuman primates because *in vitro* and *in silico* approaches are not predictive is to commit the *ignoratio elenchi* (irrelevant conclusion) fallacy.

Basic research—research that is not goal oriented—in nonhuman primates can definitely increase our understanding of life's processes. It is almost tautological to say that we can learn things from studying nonhuman primates. If the scientific community wishes to use nonhuman primates in basic research, no educated person could argue that such use is scientifically illegitimate.

Jim Giles[8] put the use of animals in research in context: "In the contentious world of animal research, one question surfaces time and again: how useful are animal experiments as a way to prepare for trials of medical treatments in humans? The issue is crucial, as public opinion is behind animal research only if it helps develop better drugs. Consequently, scientists defending animal experiments insist they are essential for safe clinical trials, whereas animal-rights activists vehemently maintain that they are useless."

On the basis of the available evidence, we maintain that research on nonhuman primates, although valuable in the context of basic research, cannot be used to predict drug or disease response in humans. Before biomedical researchers continue to justify their use of nonhuman primates by appealing to the predictive nature of research in these animals, they should review the literature.

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***Nature Medicine* replies:**

We welcome the correspondence[1–3] we received on our August editorial[4] and would like to clarify some points raised by these letters.

First, we did not want to imply that ethical considerations in relation to the use of nonhuman primates should be dismissed. However, we are not persuaded by the argument that the ability for language, "reasoned thought, abstraction, generalization and symbolic representation and… concept of self"[2] gives nonhuman primates an ethical status equivalent to that of humans. There are indeed other animals—the celebrated parrot Alex[5] quickly comes to mind—for which such 'high-order' cognitive skills have been described, and critics don't seem to worry about experimenting on those species as much as they care about monkeys and apes. Furthermore, it seems arbitrary to invoke those particular cognitive skills to make a case for monkeys instead of choosing, say, the faithfulness of voles and parakeets to their mates or the navigational skills of ants and bees.

We think that the 'cognitive' argument aims to add scientific clout to a view that remains largely subjective, owing to our relative lack of understanding of the mental processes of human and nonhuman primates. Thus, the 'cognitive' argument would be more compelling if one could

show that the same mental processes take place in human and primate brains when solving the cognitive problems referred to above and that these processes are different from what goes on in, say, Alex's brain. In other words, do monkeys and humans use the same cognitive strategies during abstraction, generalization and symbolic representation, or does a monkey solve the problem the same way a parrot does? Although it can be argued that there are similarities between the neural systems that subserve some cognitive skills, scientists are not yet in a position to categorically answer this question. So, for the time being, the cognitive argument fares no better than the genetic argument, the arbitrariness of which we criticized in the editorial.

We also want to clarify our view regarding the use of nonhuman primates as preclinical models. It is true that the existing primate models of HIV and hepatitis C have been unsuccessful at predicting clinical response, but we don't subscribe to the view that this is a reason to abandon them. If anything, these failures should help researchers improve upon the models by, for example, looking for new readouts that may have predictive value.

Furthermore, the critics are too quick to conclude that if an AIDS vaccine hasn't emerged from the use of monkeys, it's because the model is flawed, something that (they go on to argue) is not surprising because the biological differences between human and nonhuman primates are too large[2,3]. But the differences between mice and humans are even larger, yet one cannot use the 'biological differences' argument to dispute the usefulness of experimental autoimmune encephalomyelitis as a model of multiple sclerosis or of collagen-induced arthritis as a model of rheumatoid arthritis (as imperfect as these models may be), because successful therapies have emerged from their use.

An alternative view, which we support, is that researchers don't understand enough of the pathophysiology of the diseases that they are trying to model in monkeys for the model to be as useful as it can be, something that can only be remedied by more research. As we wrote in the editorial, to advocate abandoning a model as a result of a translational failure ignores how difficult it is to develop new drugs. It is easy to forget, for example, that it took nearly half a century to develop the polio and measles vaccines. Why should anyone expect faster results for an HIV vaccine?

Again, a more compelling argument against the use of nonhuman primates for preclinical work would be the existence of a model in another species with the predictive value that researchers dream about. If, say, the recently developed humanized mouse model of hepatitis C leads to the development of a vaccine, it won't be necessary to advocate the cessation of experiments in nonhuman primates to study this pathology; the researchers themselves would gladly choose the cheaper, less problematic model.

Lastly, we agree that *in vitro* and *in silico* approaches could ultimately make experiments in monkeys and other species redundant. It must be acknowledged, however, that science is nowhere near that point. As we stated in the editorial, finding *in vitro* surrogate markers of drug efficacy is the Holy Grail for drug developers, and finding surrogate markers of toxicity is even more quixotic.

*In vitro* approaches ought to be pursued, but this fact doesn't negate the need for animal experimentation. Returning to the topic of nonhuman primates, their use for toxicological purposes needs to be examined with a view to replacing them with alternative species, and we stated as much in the editorial. But to argue that using *in vitro* and *in silico* approaches will be enough to propel molecular medicine at this stage is, frankly, unrealistic.

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