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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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