COMMENTARY

The ethics of research on great apes

In the wake of the chimpanzee genome publication, **Pascal Gagneux**, **James J. Moore** and **Ajit Varki** consider the ethical and scientific challenges for scientists who work on captive great apes.

Most captive great apes were born in captivity and returning them to the wild is not feasible.

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Publication of the draft sequence of the chimpanzee genome is an exciting event; it opens the door to learning a great deal about our closest evolutionary cousins — and about ourselves in the process. But unlike the human genome project, the chimpanzee sequencing effort was not accompanied by studies addressing ethical, legal and social issues[1]. Meanwhile, there is continuing debate over the future of captive 'great apes' (chimpanzees, bonobos, gorillas and orang-utans)*.

What does the publication of the chimpanzee genome mean for the thousands of great apes in captivity in the United States? Some fear the potential for increased invasive research on these individuals. Others are concerned that our limited knowledge of chimpanzee physiology and biology will constrain the usefulness of the chimpanzee sequence for understanding both humans and great apes. For example, critical resources required for comparative genetic and biological studies, such as messenger RNA or complementary DNA libraries, are almost non-existent for great apes. Here, we advance a proposal that addresses these and related issues, to lead, we hope, to a mutually beneficial outcome for all, including the great apes (see Box for a summary of proposed goals and objectives). We emphasize that this article relates only to great apes, and not to other primates, nor other animals. Also, this piece is not about animal 'rights' but about ethical and scientific challenges specific to great apes in captivity.

Born in captivity

Opinions and attitudes regarding captive great apes span from the view that they are just expensive research animals to the idea that they should be accorded equal 'rights' with humans. Such views are in the minority, but there is need for continued dialogue among the majority spanning the middle ground.

The current ethical status of the great apes also varies among nations. US research on great apes is regulated by local 'animal-subjects' committees. And although national guidelines for breeding and long-term care have been proposed[2,3], there is still much disagreement. Some believe that our close similarity to the great apes means that they should never be kept in captivity, but for the ones now living in US facilities, it is too late.

While great ape numbers in the wild have fallen to tens of thousands, captive populations have expanded, especially in the United States, where past government support for breeding programmes was aimed at producing subjects for research into the human immunodeficiency virus (HIV). Today the United States is

*Footnote: 'Great apes' is used here in its colloquial sense. In the commonly used classification, these species are grouped alongside humans in the family Hominidae, and humans belong to the tribe Hominini, along with chimpanzees and bonobos.

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home to roughly 3,000 captive great apes (mostly west African chimpanzees) in research institutions, sanctuaries, zoos, private hands or the entertainment industry. Most of these individuals were born in captivity and never learned how to forage for survival or avoid predators. Thus, with few exceptions, attempts at returning captive great apes to the wild have proven extremely demanding — logistically and financially.

Regardless, we agree with those who say the biomedical-research community has special ethical responsibilities towards captive great apes. In our view, the great apes share traits — including, but not limited to, their genetic similarity to humans, the ability to use and modify tools and a sense of 'self' — that collectively justify this special status. (Individually, such traits are not unique to great apes; for example, bottle-nosed dolphins may also have a sense of self.)

Pause for thought

But there are other reasons to re-evaluate the situation for captive great apes. Their current medical care often assumes physiological and pathological identity with humans. But despite genetic and biological similarities, humans and apes differ markedly in their susceptibility to some major diseases, including AIDS (ref. 3). Working out the reasons for such biomedical differences will benefit all concerned, including the great apes, by allowing more species-appropriate medical care. Understanding how our genetic differences give rise to these and other biological differences has been a long-term interest of some researchers.

Sequencing of the chimpanzee genome is likely to motivate many further studies of ape biology and physiology. But how such research should proceed needs careful thought. Given the diversity of opinions (including among the three of us), it is impossible to define a single clear-cut principle that can guide this discussion. We do suggest, however, that the study of great apes should follow ethical principles generally similar to those currently used in studies on human subjects who cannot give informed consent. Of course, many complex questions arise, such as who acts as the advocate for a great ape in agreeing on what are appropriate studies? And there are many grey areas. For example, is it acceptable to do reversible harm, such as causing a mild treatable infection (as is done with adult human volunteers), or to sedate a chimpanzee (as you would a child) to allow a therapeutic or research procedure?

"Our ability to care for wild populations could benefit from an increased understanding of great ape medicine."

Captive great apes have been subject to experimental procedures with the potential for irreversible damage or death, such as infections with human pathogens, vital-organ biopsies, multiple inoculations for vaccine testing, transfections for virus production and so on. Development of the widely used hepatitis B vaccine and understanding of the hepatitis C virus would not have been possible without the use of captive chimpanzees — and may still not be possible using other technologies. In retrospect, however, many of these expensive studies (for example, on HIV/AIDS, *Plasmodium falciparum* malaria and influenza A) turned out to have limited benefits for improving human health.

We suggest that alternatives to the use of whole chimpanzees be sought as soon as possible, and that substantial new funding be directed towards finding such alternatives. And, as with humans, we believe that the newly emerging genomic data should never be used to attempt germline genetic modifications in great apes (to produce 'transgenic' apes, as is routinely done with mice). Additionally, we recommend that any new biomedical studies on great apes be carried out in a manner that supports further improvements to their care.

The time has come to establish broadly accepted guidelines for systematic, humane and ethical studies of captive great ape populations. These studies should be carried out at all levels, from genetics to biochemistry to physiology to behaviour and culture. A previous US National Research Council report[2] addressed many issues regarding the care of captive chimpanzees, and a follow-up 2005 Federal Register Notice emphasized that they deserve the best and most humane care possible. For example, they should be maintained in groups that respect existing social bonds, with opportunities for physical, intellectual and social activities. Moreover, euthanasia is specifically excluded as a means of population control[2]. Although opinions vary about the benefits of contact with human caretakers, there is generally wider agreement regarding human intervention for the control of escalating aggression within or between groups.

Precious resource

There is currently a moratorium on the breeding of chimpanzees at facilities funded by the National Institutes of Health (NIH). Although this may seem inhumane to some, it must be remembered that each birth in captivity can represent a 50-year or longer commitment on the part of human society. Facilities that do allow great apes to breed should avoid large numbers of births, as well as inbreeding and the mixing of subspecies.

As long as great ape facilities provide a safe, healthy and humane environment, it seems reasonable that captive great apes should remain a source of basic knowledge — which, in turn, may benefit both them and us. Understanding the normal biology, physiology and behaviour of the great apes provides a unique approach to understanding ourselves, even if we do not suffer from all the same diseases. Much of this can be accomplished through simple observational studies and by giving high-quality medical care to diseased individuals, as occurs routinely in human medicine. Experiments involving physical intervention with no long-term consequences could also be considered, provided that there is due consideration to the individual personalities of each ape, and that comparisons to normal humans are made wherever possible.

When a captive ape dies of natural causes (or is humanely killed to end incurable suffering), a thorough autopsy and rapid collection of organ samples for genomic, transcriptomic (gene expression), proteomic, biochemical and histological studies should be done, to generate an extremely valuable and sorely needed resource. There is also much to learn by careful preservation and analysis of the

A summary of proposed goals and objectives

Community issues

- Promote funding for an ELSI (ethical, legal and social issues) component of the chimpanzee genome project, as was done with the human genome project.
- Encourage dialogue on ethical standards and guidelines for research on great apes, following principles generally similar to those used in research on humans.
- Promote institutional and individual recognition of, and support for, the connection between the care and use of captive apes and their conservation in the wild.

Research issues

- Encourage exploration of genetic, biological and medical similarities and differences between great apes and humans, especially in the context of providing medical care.
- Promote development of standardized databases of individual genotypic and phenotypic information about all captive great apes.
- Encourage funding for standardized collection and banking of tissues, fluids, imaging and biometric data obtained during medical care and autopsies. And make such data available to the scientific community for genetic, biochemical, histological and morphological studies.
- Encourage funding for the production of high quality cDNA libraries.
- Encourage funding for expanded programmes focused on understanding cognitive functions in great apes.
- Encourage development of mechanisms for sharing data, while respecting individual and institutional privacy concerns.

Care issues

- Encourage greater fiscal support to ensure optimal living conditions for captive great apes.
- Suggest mechanisms to ensure and support the best possible medical care for captive great apes.

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remaining musculoskeletal system. Partly due to inadequate funding, personnel, and facilities, many great ape deaths now occur without such analysis, translating into numerous wasted opportunities to learn more about their biology. Being responsible for great ape captivity, we must maximize the information from them, rather than treating them as single-use, disposable tools. Likewise, body fluid and tissue samples that are collected during routine medical care are often discarded or inadequately archived. Such detailed studies of living and deceased humans have long benefited our species by providing valuable medical and scientific knowledge. Indeed, some humans approve postmortem donation of their entire bodies to science.

Mutual gains

In 2000, the US Congress passed a Chimpanzee Health Improvement, Maintenance, and Protection Act mandating the establishment of the NIH Chimpanzee Management Program[4] (ChiMP) and federal funding of sanctuaries for chimpanzees from research institutions, such as Chimp Haven (www.chimphaven.org). We suggest that these and many other ongoing efforts be bolstered by a federally and philanthropically supported collaborative network in which facilities housing captive great apes could choose to participate.

This would generate interactions among interested scientists from fields such as comparative biomedicine, psychology or biological anthropology. Already, leaders from US institutions holding most chimpanzees have come together to establish a National Chimpanzee Resource Committee, which meets regularly to discuss issues of mutual interest. The increased cost of supporting all such facilities will be more than justified by the knowledge gleaned from the study of healthy, socially integrated great apes — information that could potentially contribute to the ultimate survival of some of these species in their natural habitat.

Such a national network could also help train and support scientists interested in the standardized accumulation of all relevant biological information on healthy captive great apes. Each great ape should continue to be accounted for, by a name and unique identifier. Complete medical records should be collected in a standardized fashion into electronically searchable databases, in a way that maintains the privacy of researchers and institutions. Samples, such as body fluids, taken from live apes during routine physical examinations should also be collected and archived. In this way, we can create a great ape tissue bank of flash-frozen and archived samples for use by the scientific community — which could eventually result in (among other payoffs) the production of high quality cDNA libraries.

In some cases, therapeutic medical care could be extended to include data collection for research purposes (for example, standardized brain magnetic resonance imaging protocols appended to diagnostic imaging procedures). Increased funding will be needed to enhance existing medical facilities and expertise, and the ability to perform complete autopsies with tissue collection.

J. BALOG/GETTY

Fast learner: tool use is one of the traits that sets the great apes apart from most other research animals.

As for newly proposed research studies on live great apes, we suggest that these be reviewed and approved by specialized ethical oversight groups that incorporate appropriate aspects of the separate human-subject and animal-subject committees found at most institutions. Cooperation by the great ape research subjects will be critical for many studies, and will only be possible if there is also adequate funding for behavioural training of the animals.

We fully recognize that our proposal is unlikely to please everyone interested in great apes, and that this is only an initial contribution to a much-needed dialogue among all interested parties. Many changes and adjustments will be required to develop a mutually acceptable solution for all concerned, including the great apes.

Meanwhile, there is a deep irony in the fact that the sequencing of the chimpanzee genome coincides with the potential demise of great apes in the wild. We urge all scientists studying great apes, or tissues and samples derived from them, to contribute not only to the care of captive apes, but also to develop mechanisms by which studies of captive great apes would help generate a revenue stream to support the conservation of populations in the wild. While recommending improved care of captive great apes, we recognize that the remaining wild great apes may end up living in strictly managed reserves, depending on increased human intervention for their survival. In the long run, even our ability to care for wild populations could benefit from an increased understanding of great ape cognition, behaviour, physiology, biology, pathology and medicine. ■

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