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Chimpanzees in AIDS research: A biomedical and bioethical perspective

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The present article represents a consensus view of the appropriate utilization of chimpanzees in AIDS research arrived at as a result of a meeting of a group of scientists involved in AIDS research with chimpanzees and bioethicists. The paper considers which types of studies are scientifically justifiable in this species, the conditions under which such studies should be carried out, and the conditions which should be encouraged for post-experimental retirement of these animals.

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Introduction

Chimpanzees have been found to be the only readily available nonhuman primates which are highly susceptible to HIV-1 infection; their use in AIDS research, however, raises difficult bioethical questions. Four years ago, a group of scientists addressed the issue of the supply of chimpanzees for AIDS research [17] and concluded that sufficient animals were already available in medical research facilities to satisfy reasonable needs for the foreseeable future, so that importing of additional animals from the wild could not be justified. This situation has not changed.

On August 8–9, 1992, a group of scientists representing animal welfare and AIDS research interests met at TNO in Rijswijk, The Netherlands, to discuss additional issues concerning the use of chimpanzees in AIDS research, in the light of recent developments. This document represents the consensus arrived at concerning the types of experiments considered justifiable, and the conditions under which animals should be maintained during and after experimentation. The opinions expressed are those of the authors, and do not necessarily reflect the opinion of others.

Utilization

At present, the chimpanzee, man's closest living relative, is primarily utilized in AIDS research for the development of vaccines [3,11], passive immunization strategies [10,14], and, to a lesser extent, in studies on experimental chemotherapy, immunotherapy, and immunopathogenesis. The group first considered issues concerning the necessity and appropriateness of the use of chimpanzees for such studies.

Vaccine development

Vaccine development research can be divided into safety evaluation, immunogenicity studies, and protective efficacy trials. Physiological safety tests can, in all except the rarest of circumstances, be conducted in other animals, including nonhuman primates. Immunogenicity determination with candidate vaccines which have been shown to be safe usually can be carried out in man. An exception would be tests on recombinant viral vectors carrying HIV genetic material, or attenuated strains of HIV, the safety of which could only be appropriately studied in the chimpanzee. For protective ef-

ficacy tests, chimpanzees offer the advantage that live virus challenges can be carried out, thus providing a preliminary estimate of efficacy by using a small number of animals, without requiring a large human vaccine trial.

When high-risk human populations suitable for vaccine trials are identified, it may be possible to simultaneously evaluate multiple vaccine candidates in such populations directly. Such tests would also provide assessment of protection against natural routes of transmission.

Passive immunization

Passive immunization studies directed toward the prevention of maternal–infant transmission or protection against accidental percutaneous exposures differ from vaccine studies, in that chimpanzees are necessary for preliminary safety evaluation [14]. These studies will be likely to also involve monoclonal antibodies, the safety of which needs to be established [10]. As HIV stocks titrated by subcutaneous or intradermal routes are not available, the chimpanzee model cannot be used at present to evaluate percutaneous exposure prophylaxis. Furthermore, it is not presently practical to carry out large scale studies on the prevention of maternal–infant transmission in chimpanzees, thus efficacy tests of passive immunization must be carried out mainly in man. Such studies are in progress.

Therapy

The use of chimpanzees already infected with HIV for evaluation of approaches to therapy is possible, since about 150 such animals already exist. No additional animals should be infected solely for use in such studies. Furthermore, there is no shortage of human subjects for such investigations.

Pathogenesis studies

HIV-1 has not been demonstrated to cause AIDS in any species other than man. Infection in chimpanzees has so far resulted only in infection, but not disease. Investigation of the mechanisms of this disease resistance is of obvious importance [8]. As numerous HIV-infected chimpanzees are already available, no new infections should be initiated for this purpose.

Virus titrations

HIV strains differ widely in nucleic acid sequence, antigenicity, and pathogenicity. It will be important to challenge chimpanzees which have resisted challenge with the current prototype vaccine strain, HIV/Lai, with different strains prevalent in human populations. At present, this is not possible since only HIV/Lai (IIIb) has been titrated in chimpanzees. Titrated stocks are essential for a minimal use of chimpanzees in challenge studies. Thus, the additional titration of prototype HIV stocks is desirable and is in progress.

Alternatives to HIV-1 studies in chimpanzees

Because of the special welfare and housing requirements of chimpanzees, alternative models have been sought for research into basic approaches to immunization and therapy. One widely used approach is the SIV-macaque model. This has provided important data on vaccination strategies [6]. It has recently been reported that *Macaca nemestrina* are susceptible to HIV-1 infection at high challenge doses [1]. The utility of this species for vaccine studies depends on the reproducibility of the data, and on the susceptibility of these monkeys to small challenge doses. Recent data indicate that approximately a 1000-fold higher dose of HIV/Lai is needed to infect *M. nemestrina* than is required to infect chimpanzees and that the infection may only be transient [2]. Another recently reported alternative is the use of recombinant SIV strains expressing the HIV-1 envelope genes [12]. The use of monkeys may accelerate research, and may also obviate the need for the involvement of chimpanzees in certain experiments. However, the welfare and social needs of other primates must also be considered. Unnecessary large numbers should not be used, caging of adequate size must be provided, and group housing should be used whenever possible.

Appropriate conditions for chimpanzees during and after experiments

Because of their near-human nature, chimpanzees require very special consideration in order to provide for their general welfare and to protect their psychological well-being. Whenever possible, these animals must be housed at least in pairs, or larger groups [15,16]. The fact that HIV is rarely, if ever, transmitted between animals caged together [reviewed in 16] supports the practicality of such a policy. Obviously, if adult animals were to be caged together it would be necessary that they have been resocialized together to avoid fighting. Furthermore, menstruation could provide a mechanism of transmission which must be guarded against. Cages should be of a size sufficient to permit exercise and normal play behavior, and a variety of enrichment articles should be provided to avoid boredom and facilitate recreation [4]. The housing

of chimpanzees involved in AIDS research singly in isolator cages which deny social interaction and companionship, as well as social interaction with human care-givers, is both unnecessary and unethical [5].

Retirement

It is now generally accepted that chimpanzees must be retired at the end of their involvement in research, to live under conditions which provide for their social and psychological well-being, for the remainder of their 40–50 year life span [16]. For this reason, no experiment should be carried out unless the supporting agency has guaranteed to provide the funds necessary for such retirement [9]. Such funds must be kept in a secure annuity account. At present, approximately $30,000–$60,000 per chimpanzee are standard charges for this purpose.

The provision of more dedicated retirement facilities is a matter of great urgency. They should be as free-ranging as possible, should provide access to the outdoors, and should include a relatively large group of resocialized animals [7,13,15]. Retirement facilities can be open to public view, as long as their design prevents any possibility of animal escape or inadvertent exposure of viewers to the risk of being bitten. Such facilities can convey an important message to the public concerning the ethical responsibility of the medical research community.

In summary, we have reviewed bioethical and biomedical aspects of the use of chimpanzees and other primates in AIDS research. The necessity of such research, in the light of the horror of the AIDS epidemic, seems to be unarguable. However, we point out that certain studies can be better carried out in other animals or in man. Chimpanzee studies should be limited only to those for which there is no available alternative. These should involve no more suffering than is caused by giving injections and collecting blood samples. No research should be carried out with chimpanzees unless financial support for life-long retirement is guaranteed.

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