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Scientific Issues and Regulation of Primate Use

Andrew N. Rowan*

Abstract

Some of the patterns of use of nonhuman primates in the USA and Europe are outlined and a few specific examples of inappropriate and/or unnecessary use are described. The primate research resources program in the USA is examined and some suggestions as to how the program could be made more responsive to humane and conservation concerns are presented.

The National Primate Plan (U.S. Dept. of Health, Education and Welfare, 1980) opens with these words: "A severe and long-term shortage of nonhuman primates threatens the continuation of many essential health activities." It is certainly true that the supply of nonhuman primates has been disrupted over the past few years in India, Bangladesh and Malaysia. However, it is by no means clear that the continuation of *essential* health activities is threatened.

The National Primate Plan specifically notes that the use of nonhuman primates in lifetime testing of steroid contraceptives is so critical that it is required with a force equivalent to that of law (Food and Drug Administration, 1969). However, the steroid metabolic patterns of the primates used in this testing are sufficiently different (Shackleton and Mitchell, 1975) to prevent meaningful extrapolation of results to human beings. Data gleaned from studies on

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animals involving chronic administration of a new steroid contraceptive for several years are virtually useless for regulatory purposes. Therefore, in terms of health hazard evaluation for humans, these chronic tests are a waste of time, money and animals.

Similarly, the National Primate Plan notes that between 5,000 and 6,000 macaques are required annually for vaccine production and testing, mostly for poliomyelitis vaccine. This represents a considerable reduction over the late 1950's when hundreds of thousands of rhesus macaques were used every year in the development and production of polio vaccines (LeCornu and Rowan, 1979). This reduction has occurred, in part, through the development of better methods of harvesting monkey kidney cells. In Denmark, for example, these methods have resulted in a reduction in the number of monkeys required from 400 to 40 (Fennestad and Petersen, 1979). However, it is now technically possible to eliminate the present demand for macaques without jeopardizing human safety.

Currently, two types of polio vaccine are produced: the live, attenuated (Sabin) vaccine and the inactivated (Salk) vaccine. The virus for both types can be grown in human cell culture although the yield from a given quantity of diploid human cells is lower than in early generation monkey cell cultures (Beale, 1979). Only small amounts of virus are needed for immunization with the Sabin vaccine (the virus grows in the vaccinee), but larger quantities of the Salk vaccine are required, thus making it more expensive than the Sabin. The price of the Salk vaccine could, however, be reduced by using cell-suspension cultures or microcarrier techniques to produce a larger virus yield from a given volume of culture fluid (Petricciani *et al,* 1979). The technology is being developed and thus the economic need for monkey kidney cell cultures could possibly be eliminated. This would have health advantages since monkey kidney cell cultures are notorious for their contamination by extraneous agents, and up to 50% of monkey kidney cell cultures may have to be discarded because of viral contaminants (Beale, 1979).

Both vaccines are tested in several animal species, including monkeys. It is difficult to envisage a total replacement for monkeys in Sabin vaccine neurotoxicity testing, but one could certainly eliminate the monkey test for the Salk vaccine. The cell culture test for live virus particles is more sensitive (safer?) than the monkey test (Beale, 1978) and the World Health Organization (WHO) is considering a recommendation for a suitable cell culture test as a replacement method (F. Perkins, personal communication). Therefore, with a few technical modifications, and a change of attitude among regulators one could eliminate the need for monkeys to test the inactivated vaccine. However, memories of the Cutter disaster, when over 200 children contracted paralytic poliomyelitis after receiving an inadequately inactivated batch of Salk vaccine, still loom large in many minds despite our much greater understanding of the manufacturing process and our ability to guard against a repetition of such a disaster.

Almost twenty percent of the projected U.S. demand for primates is accounted for by the polio vaccine program. A switch from the Sabin to the Salk vaccine, the use of cell lines (human?) and microcarrier culture techniques, and dropping the requirement for the monkey test in Salk vaccine production could virtually eliminate this need. There are a few minor technical problems to be solved and much economic, political and bureaucratic inertia and resistance to overcome. Finally, it should be noted that there may still be some need for the

Sabin vaccine to deal with polio outbreaks since even Salk acknowledges that the Sabin vaccine is more effective under these circumstances (Boffey, 1977). The respective proponents of the Salk and Sabin vaccines are involved in a bitter argument over which is better in terms of effectiveness and safety (Editorial, 1977; Salk and Salk, 1978). Where one has a well-disciplined community (as in Sweden), there is no doubt that the inactivated Salk vaccine is effective, but there are questions as to whether it can provide the same level of protection in Third World countries. The testing issue has also not yet been decided by the World Health Organization and even if the WHO does produce a new recommendation, inertia will militate against authorities replacing the old monkey test. Nonetheless, it is clear that the use of nonhuman primates is not an *essential* requirement for the production and testing of polio vaccine.

While the use of monkeys in polio vaccine and oral contraceptive testing is a story of conflicting scientific data, conservative attitudes and inertia, the laboratory chimpanzee situation is a catalogue of mismanagement in which the chimpanzees come out a very distant last. In 1977, the National Institutes of Health (NIH) circulated a draft primate plan in which an annual need for 180 chimpanzees was estimated (Interagency Primate Steering Committee, 1977). However, in 1978, the Interagency Primate Steering Committee (IPSC) published a report of a task force on chimpanzees which estimated a total annual demand of about 700 chimpanzees (Table 1).

TABLE 1 — IPSC Task Force Estimate of the Number of Chimpanzees Being Used in or Required for Biomedical Programs.

Field of Research	Current Use	Projected Future Annual Demand
Behavioral Sciences	(not given)	50
Infectious Diseases		
Hepatitis	156	314
Other	46	46
Neurological Diseases	(not given)	45
Hematology, immunology & immunogenetics	150	50
Toxicology&pharmacology	200	100
Reproductive biology	85	50
Other (aging, aerospace, etc.)	25	80
TOTALS	662+	735

Not only was this projection vastly inflated, but the reasons given for why the chimpanzees were so necessary were gross overstatements (Rowan, 1979). It is now commonly (if privately) accepted among laboratory primatologists that

this report exaggerated the demand, presumably to make a case for additional importation from the wild as well as for more support for domestic breeding programs. There are currently 1100+ chimpanzees in laboratory and/or breeding facilities in the United States. These animals produce between fifty and seventy offspring annually, but a number of the infants die before reaching maturity. Little concerted action is being taken to improve this state of affairs and, in fact, one of the most successful breeding colonies has been broken up (and may well be destroyed) as the result of inadequate coordination and bad planning by funding agencies.

Several years ago, the Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP) was awarded a contract for chimpanzee breeding for a hepatitis study program by the National Heart, Lung and Blood Institute (NHLBI). When the contract came up for renewal, it was put out for competitive bids and another three year contract awarded to the Southwest Foundation for Research and Education (SFRE). The stated reason for moving the contract was that SFRE had quoted a price that was half LEMSIP's projection of $1.1 million. This judgment has been challenged, and New York University has sued NIH on the grounds that the issuing of the RFP (Request for Proposal) and review of the submissions had been mismanaged. Meanwhile, the chimpanzees still had to be moved. Over a period of two months, 73 animals were trucked from New York to Texas under conditions which, at best, could only be described as highly stressful. It is not particularly surprising that nine animals have subsequently died and that the breeding program has been totally disrupted. It is pertinent to note that LEMSIP's 1978 breeding success rate of 35% (J. Moor-Jankowski, personal communication) was among the best (if not the best) in the country.

This particular saga has been related in order to illustrate how the animals come off second best, especially when the situation is highly politicized, as in the LEMSIP-SFRE-NHLBI dispute. The chimpanzees were treated as chattel, to be picked up at a moment's notice and hauled thousands of miles across the United States without regard to anything more than mere survival. It was predicted that the move would disrupt the colony and that it would never achieve the stated goals of the contract, namely, ten offspring per annum. This prediction has, unfortunately, been borne out by subsequent events, and SFRE looks as if it will be hard-pressed to maintain the colony numbers, let alone increase the colony by thirty healthy offspring by June, 1982. However, NHLBI staff responsible for managing this contract have indicated that this does not concern them since they anticipate that they will no longer need a special chimpanzee colony after another year or two. It is not clear what will happen to the remaining animals when the contract expires.

Apart from the problems surrounding the long-term maintenance of the colonies of great apes (and most are kept in facilities which are grossly inadequate considering the animals' social and psychological needs [cf. McGrew, 1981]) there are other aspects of primate research in the United States which give cause for concern. It has been stated that the seven primate research centers around the country fail, with one or two exceptions, to provide adequate value for the money and top class research (NIH, 1976; Hobbs and Bleby, 1976). By contrast, LEMSIP, which, ironically, is on the verge of closing down, has been acknowl-

edged to provide excellent value for the money (Hobbs and Bleby, 1976). One of the main problems is that the Primate Research Center (PRC) program has become a self-perpetuating oligarchy within the Animal Resources branch of NIH's Division of Research Resources. In 1975, the PRCs received $12.5 million for core support out of a total of $17.1 million allocated to laboratory animal resources. They have since maintained this dominant role within the funding program. Because of the financial muscle behind the PRC program any efforts to reform the program have resulted in cosmetic changes rather than the necessary major overhaul. The Bolt, Beranek and Newman (BBN) consultant panel (NIH, 1976) came out with some relatively hard-hitting proposals for reform, but a subsequent review of the PRC program (NIH, 1979), stimulated by the BBN report, either undercut many of the BBN proposals or was so general and vague as to be virtually useless. According to a member of the second review, the panel did not feel free to entertain any proposals which would have resulted in radical changes in the extent or scope of the primate center program (L. Rosenblum, personal communication). However, the panel did note that the quality of the scientists in the PRCs was below par and that the centers do not have the reputation of being "the place to be."

The undermining effect of the second review was most unfortunate since one of the BBN proposals could be developed to provide answers to many of the problems which currently plague the primate research effort. The BBN panel suggested that a Primate Utilization Authority be established to oversee all primate breeding and use in the United States. This concept is, however, somewhat limited. It needs to be expanded to incorporate conservation questions and to include representation from humane and conservation groups. After all, the Endangered Species Scientific Authority has research community representation. Also, the name should be changed to the National Primate Study Authority (NPSA). There are other precedents for such an organization; for example, the National Toxicology Program is essentially a consortium of federal agencies involved in bioassays and the development of new methods.

The NPSA should include adequate representation from user groups such as NIH and the Department of Defense, as well as from conservation and humane organizations. The NPSA should have oversight for the immediate primate breeding and research programs as well as for the long-term fate of the animals. It should look carefully at the proposed needs for primates and determine just how essential some of the research really is. For example, a European Economic Community task force (Committee on Medical and Public Health Research, 1979) identifies the *essential* primate research needs (Table 2) in a more limited manner than the National Primate Plan (Dept. of Health, Education and Welfare, 1980). In addition, greater attention needs to be focused on primate housing and on some of the research techniques, especially in behavioral studies. If a primate really is a good model of human behavior patterns (such as addiction, depression, antisocial activity), then it presumably has very similar needs to human beings which should be acknowledged and met. If it is not a good model of the human psyche then we should question whether such research should be done at all.

For the great apes, we need to reassess our priorities completely. If the use of these animals is to be justified, then we consider that the following *minimum*

conditions should be met: First, the animals should be kept under conditions which, as far as possible, meet their physical *and* social requirements. Second, breeding programs should be established to obviate *any* current or future importation from the wild. Third, the research project must not be terminal. Fourth, adequate provisions should be made for the lifetime of the animals being used, and it must be recognized that great apes cannot be moved around as though they were pieces of machinery. It must be stressed that these are minimal conditions; ideally, we should accord the great apes the same quality of facilities and respect that we accord human subjects.

In conclusion, we accept that there are some legitimate and essential uses of primates in biomedical programs, but we do not consider the present level necessary or the current controls adequate. The conservation and humane concerns must be given adequate consideration and the primate program totally re-evaluated. The Primate Research Centers currently receive over $16 million in core support. It is arguable that far better use could be made of all or a portion of this money if it were allocated to the development of other types of biomedical technology. The development of primate research models appears to have high prestige and yet there is no clear reason why it should. One can only speculate that such prestige stems from an anthropomorphic bias derived from the fact that primates are our close evolutionary relatives. If this is indeed the case, then we need to consider their interests much more closely.

TABLE 2—Primate Use for Biomedical Research and Health Care (EEC, 1979)*

Species	Research or Other Activity for which Availability of Primate Species is:	
	Essential	**Highly Desirable**
Chimpanzee	Hepatitis B (vaccine testing); Hepatitis "non-A-non-B."	Hepatitis A; Certain cardiovascular diseases; Antifertility; Production of antisera.
Macaque (Rhesus and Cynomolgus)	Production and testing of vaccines (mainly polio); Toxicology and teratology.	Reproductive physiology and antifertility; Endocrinology; Diagnostic virology; Immunology and transplantation.
New World Monkeys	Hepatitis A (marmosets); Hepatitis "non-A-non-B" (marmosets); DNA and RNA tumor viruses; Hematopoietic chimaerism (marmosets); Malaria (owl monkeys).	Teratology, reproductive physiology and antifertility; Cardiovascular diseases (mainly squirrel monkeys); Pharmacology and toxicology (mainly squirrel monkeys); Immunology and transplantation; Slow virus diseases.
Baboon		Cancer virology; Reproductive physiology.

*From Reports and Memoranda of the Working Group on the Use and Supply of Non-human Primates for Biomedical Purposes. Committee on Medical Research Commission of the European Communities, Brussels, 1978.

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