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Breeding and Use of Nonhuman Primates in the USA

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Abstract

Several species of nonhuman primates, each possessing specific characteristics of particular value, are used by the United States biomedical community in a wide variety of health-related activities. These animals are man's closest relatives and are indispensable in the effort to understand and control human health problems.

The destruction of primate habitats and embargoes on export of primates from source countries have decreased the supply of these animals. Continuation of many ongoing and new activities contributing to the improvement of human health is threatened by inadequate and erratic supply of these resources. In the U.S., a program has been developed to meet health needs for primates by: 1) ensuring the most effective use of primates; 2) developing domestic production of primates; and 3) contributing to conservation programs to ensure a stable supply and long-term availability of primates from their countries of origin.

Introduction

Nonhuman primates are indispensable in modern biomedical research, biologics production, and in testing compounds for toxicity. These animals are especially valued because of their evolutionary kinship to man, both in gross anatomical resemblance and behavior as well as in specific biochemical similarities. Because of this close relationship, biomedical and behavioral studies of nonhuman primates offer particular insight into parallel situations in man. Not only were nonhuman primates the key to development of antipoliomyelitis vaccine, but they also have contributed greatly to our knowledge and understanding of other entities such as malaria, yellow fever, measles, enteric diseases, tuberculosis, mental disorders, and viral oncogenesis, (Goodwin and Augustine, 1976). New biomedical discoveries can be expected to depend upon the availability of these animals. In addition, the actual application of the fruits of research depends to a large extent on nonhuman primates. Without preliminary testing in these animals, the risks may be too great to apply theoretical knowledge directly to humans.

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TABLE 1
U.S. Estimated Requirement for Nonhuman Primates by National Need (Interagency Primate Steering Committee)

Required by Law or Regulation		7,000
Production of Biologics		1,000
Testing		3,500
Research		22,500
	TOTAL	34,000

The United States biomedical community needs about 34,000 nonhuman primates each year (Table 1). Of these, approximately two-thirds are needed for research, and about one-fifth to fulfill regulatory requirements. In 1974, the Institute of Laboratory Animal Resources, a part of the National Academy of Sciences, surveyed nonhuman primate users and found that pharmacology and toxicology research together with vaccine production and safety testing accounted for 37 percent of the primates used (Committee on Conservation of Nonhuman Primates, 1975).

Based on past utilization, we have calculated that of the 34,000 primates needed, 24,000 have their origins in the Old World, and 10,000 in the New World. Altogether, about 35 different species are involved, each possessing specific characteristics of particular value in meeting national health needs. The relative importance of each of these species is continually changing. Some factors influencing this change are: an acceleration in the state-of-the-art of biomedical research resulting in an increasing need for a larger number and wider variety of animal models more closely related to man; the identification of characteristics not previously recognized which make a species particularly desirable as a model of human disease; and the substitution for species now in short supply. At present, less than a dozen of the total 35 species account for the great majority used.

Old World Primates

Of the Old World species used, over 80 percent (20,000) are macaques, with rhesus accounting for more than one-third of the total. The remainder consists mainly of African greens (2,100) and various species of baboons (1,200).

a) Rhesus monkey

The rhesus monkey, or *Macaca mulatta,* has always been considered the general purpose laboratory primate, apparently because it was relatively easy to obtain, a convenient size for most studies, and a hardy animal. The rhesus also is by far the most widely used primate for the production and testing of biological products such as poliomyelitis and other vaccines. As a result of a long history of its use and the data that have been developed with respect to the anatomy, physiology, and behavior of this animal, it is highly preferred for many experimental purposes.

Geographically, the rhesus monkey is found within India and neighboring countries. Unfortunately, the number available has decreased considerably in recent years. In 1972, an estimated 50,000 of these animals were exported from In-

dia, the primary source country. In 1974, the Government of India began restricting the numbers exported, and early in 1978 it imposed a ban on exports of all primates. Small numbers of these monkeys occasionally were exported from Bangladesh, but that country too has not permitted exports since early in 1979. Although the possibility remains of obtaining rhesus from other countries of southern Asia, the wild populations are relatively small and even at best would allow the withdrawal of only limited numbers of animals.

b) Crab-eating macaque

The *Macaca fascicularis,* commonly known as the cynomolgus, long-tailed, or crab-eating macaque, is second only to the rhesus in the numbers used for medical purposes in the United States. In the past, approximately 6,000 were required annually. This species also is considered to be a general-purpose primate, and for many uses, it is substituted for the rhesus. Moreover, for some purposes it is considered preferable, because it is more tractable and is slightly smaller. The trend of substituting the cynomolgus for the rhesus is accelerating as the supplies of rhesus have become more restricted. However, the cynomolgus has not yet been accepted in the United States as a substitute for the rhesus in the safety testing of vaccines, especially poliomyelitis vaccine.

The cynomolgus is available from Southeast Asian countries where it remains relatively plentiful. However, habitat destruction and other competition from man are causing a continuous reduction in the wild population of this species in its native countries. Thailand recently prohibited their export; the other source countries for the United States are Indonesia, Malaysia, and the Philippines.

c) Other macaques

It is estimated that at least 1,000 macaques other than *Macaca mulatta* and *M. fascicularis* are needed per year. These macaques are used almost entirely for research purposes, rather than biologics production or testing. The fields of research are numerous and, as a group, the neurosciences, including behavioral studies, seem to have the greatest need for them.

Recently, spontaneous diabetes mellitus was discovered in the Celebes ape, *Macaca nigra.* The use of this "other" macaque will add a new tool to the armamentarium of diabetes research, which should contribute greatly to the understanding and eventual control of this disease.

d) African green monkey

Approximately 2,100 African green monkeys, *Cercopithecus aethiops,* are used each year in the United States, primarily for the production of biological material and toxicology testing. Tissue cultures made from the kidneys of this animal are essential for the production of SV40 virus-free poliomyelitis vaccine. The National Heart, Lung, and Blood Institute also is developing this monkey as a model for the study of hypertension. The use of this animal for other biomedical purposes has been somewhat inhibited because of its association with the outbreak of a severe and fatal disease among laboratory workers in Marburg, Germany, who had contact with newly imported monkeys of this species.

The African green monkey is widely distributed throughout the African rain forest, woodland, and savannah and has been readily available from normal commercial channels. However, potential policy changes, including conservation measures in source countries, make the future availability of this species uncertain.

e) Baboon

Various species of baboons are used in biomedical research. These large, hardy primates are especially desirable for surgery, neurophysiology, and reproductive physiology research. Baboons are considered general-purpose primates, and approximately 1,200 are used in the United States each year. Baboons are found over a very wide range of Africa, south of the Sahara. Although these animals remain relatively abundant, they are being exterminated in many areas because of the damage they cause to agricultural crops. Supplies of wild-caught baboons probably will be available via existing trade channels for the next few years.

f) Other Old World primates

Various other Old World nonhuman primates are utilized in research for special purposes. The most important is the patas monkey, *Erythrocebus patas,* another African species recently found to be particularly promising for certain types of cardiovascular research. In addition, tree shrews, bushbabies, and occasionally other species are used in small numbers for special purposes in a wide variety of institutions.

The gibbon has attracted special interest because it has been identified as a model for the study of certain cancer viruses. However, this animal is virtually unavailable to biomedical research. It is found throughout most of southeastern Asia, including nearby islands of Indonesia. Since this animal is confined to areas of primary forest, clear-cutting lumbering practices and general deforestation have caused gibbon population reductions in some localities. In recognition of this situation, this animal has been identified as endangered, and steps have been taken to control international trade of this species.

The chimpanzee, which originates from West Africa, also is endangered. None have been imported into the United States from the wild for several years. However, some of these animals are available from established U.S. breeding colonies. The chimpanzee is the irreplaceable model for study of certain human health problems. The alternative subject for such studies is man, and research with human beings is less feasible now than ever before. The chimpanzee is in great demand for research in hepatitis, especially since it is the only animal other than man known to be susceptible to hepatitis B. This ape also is used for studies of various other human diseases and for psychobiological research. In total, approximately 180 chimpanzees are needed each year. As man's surrogate for evaluation of many health hazards and health protective measures, this animal is without equal.

New World Primates

Of the approximately 10,000 New World species needed each year, half are squirrel monkeys, a quarter owl monkeys, and the remainder marmosets and various other species.

a) Squirrel monkey

The squirrel monkey, *Saimiri sciureus,* is considered to be a general-purpose experimental primate and the primate second most widely used by the worldwide biomedical community. The numbers required within the United States rank third

after the *Macaca mulatta* and the *M. fascicularis*. The estimated 5,000 squirrel monkeys required each year are used for a wide variety of health research and testing purposes, including the major areas of nutrition and cardiovascular research, as well as neurophysiology, pharmacology, toxicology, and behavioral and stress studies.

Although the squirrel monkey is widely distributed in significant numbers throughout northern South America and Central America, each geographical group has differing characteristics. Those found in the regions near Leticia in Colombia and Iquitos in Peru are most in demand owing to the extensive baseline of data collected on these animals. However, they are no longer available through commercial channels.

b) Owl monkey

The owl or night monkey, *Aotus trivirgatus,* is the only suitable model currently known for human malaria chemotherapy and immunology studies, and is considered essential for these areas of research.

Investigators of viral oncology also are finding this animal to be of increasing value. In addition, the owl monkey holds special importance in vision research because of its unique eye structure.

c) Marmosets and tamarins

Numerous species of marmosets and tamarins have special value for biomedical research. *Saguinus mystax,* the mustached tamarin, is especially needed because of its susceptibility to hepatitis A virus. Other species are used in virology, immunology, dental studies, reproductive physiology, behavioral studies, and other research. Their potential use as test animals for hepatitis and for cancer research suggests that research demands for these species will increase and large numbers will be needed over a long period of time.

The cotton-top marmoset, *Saguinus oedipus,* is particularly important for work in viral oncology. This species, however, is endangered and only limited numbers are available from domestic breeding programs.

Although U.S. researchers have used the small Brazilian common marmoset, or *Callithrix jacchus* only infrequently, this animal is becoming a valuable model in Europe, especially in Great Britain, for a number of research and testing purposes. Some of the most notable of these are reproductive physiology (including testing of antifertility products), teratology, toxicology, infectious diseases, drug safety, and a variety of behavioral studies. Since export of this animal from Brazil is currently prohibited, those marmosets being used in Europe come from domestic breeding programs which have proved to be practical and cost-effective.

d) Other New World primates

Relatively small numbers of such other South American primates as capuchin and spider monkeys are used for special kinds of research. Demand for any of these animals could increase greatly since new discoveries can transform infrequently used species into highly desirable models.

Primate Supply

Unfortunately, many exciting research projects are impeded by the instability of supplies of nonhuman primates from all parts of the world. Most of these

animals are captured from wild populations in their native habitats and, until recently, were regularly available. Now, however, destruction of primate habitats for agricultural development or lumbering threatens the existence of many primate populations. The loss of primates to the demands of research is negligible in comparison with the enormous losses inflicted by the destruction of the natural habitat by urbanization, overcropping for the pet trade, and hunting in areas where these animals are eaten. As a result, several previously abundant species that have not been used in research or testing are now scarce.

Motivated by concern for conservation, some primate source countries have instituted measures to limit or prohibit exports. In addition to the virtual unavailability of the rhesus resulting from the Indian government's ban on primate exports, Brazil, Colombia, Peru, and other Latin American countries over the last decade decided to embargo the exportation of their New World primates.

Acknowledging the growing shortage of various species of nonhuman primates in the United States and the impact of these shortages on medical research, a National Institutes of Health (NIH) Interagency Primate Steering Committee (IPSC) was established in 1974 with representatives from government agencies concerned with human health and biological research. After consulting the academic community, the pharmaceutical industry, and private research institutions, the committee developed a National Primate Plan to ensure that the requirements for nonhuman primates for all essential health activities can be met now and in the future.

Three courses of action are recommended to meet these health needs:

i) Producing primates in the United States;

ii) Ensuring stable supplies of primates from their native lands;

iii) Making the most effective use of the available primates.

Domestic Breeding Projects

In the past, U.S. domestic breeding colonies were funded primarily for reproductive research; reproduction served experimental purposes rather than as a replacement source for animals used in other projects. This attitude was justified in the past when imports were available and inexpensive. However, this dependency on primates caught in the wild created major problems for the biomedical community when foreign supply sources proved to be unstable or discontinuous.

To date, the majority of our domestic breeding projects have centered around the rhesus monkey because of its high rate of utilization, irreplaceability for certain regulatory purposes, and past history of supply interruptions (Table 2). One of the earliest experiences of breeding rhesus monkeys in the United States occurred in the 1930's when a colony was established for behavioral studies on Cayo Santiago, 3 miles east of Puerto Rico. This island colony was originally established for behavioral studies, which continue to be its primary focus. This highly successful colony has been maintained at a population of approximately 800 with the daily supplemental provision of food and fresh water and killing of surplus animals. Since the quality of these animals has been outstanding and they are very well suited for many biomedical research projects, it was natural to look at island breeding as a way to expand our U.S. production. Island breeding col-

onies have also been established off the coasts of Florida and South Carolina.

The IPSC has encouraged the development of alternative breeding systems as well. One system is composed of large corrals from a quarter of an acre to two acres in size, permitting somewhat closer observation of the animals and greater ease of handling, accomplished by herding the animals into special chutes.

The California Primate Center at the University of California (Davis) has successfully utilized large enclosed ½-acre pens for production. These covered pens offer greater security as well as additional surface for the animals' use. Smaller enclosed pens which house a harem of one male with 10-12 females are used at some centers.

Corn cribs have become very popular for the harem breeding of rhesus. They can be built relatively inexpensively, and the round configuration allows animals to avoid being cornered by their cagemates. Corn cribs and other small pens accommodate smaller groups of animals and allow even closer observation and manipulation of the colony.

To ensure a continuous, stable, and long-term supply of nonhuman primates, the IPSC recommended that a series of general-purpose domestic primate production colonies and a large number of special-purpose colonies be designed and established. The National Primate Plan contains specific recommendations for the number of colonies by species and the desired productivity of each colony. As a general policy, multiple colonies dispersed over wide areas are preferable to a few very large colonies. This is intended to provide protection against loss from epidemic disease or other disasters.

Since future biomedical needs may require species not currently used in sufficient numbers to warrant general-purpose production, the committee will continually reevaluate the need for each species to determine annual requirements and adjust domestic production programs to assure future availability. In addition, the committee will review all breeding proposals and facilitate information exchange to ensure the development of a balanced, nationally coordinated breeding program.

TABLE 2 U.S. Rhesus Monkey Production

	Breeding Females as of 1/1/80	Production 1979	Production 1980 (Anticipated)
Federal Sector	7,947	4,321	5,015
Nonprofit Sector (includes Universities and Foundations)	602	293	403
Commercial for Profit	1,629	773	1,043
TOTALS	10,178	5,387	6,461

At present, these breeding colonies meet only a limited part of the nation's needs; domestic rhesus production supported by government agencies now meets only 25-35 percent of our requirements. Nonetheless, our remarkable accomplishments with this species in relatively few years have demonstrated the practicability of domestic breeding programs.

Although our breeding plans were initiated in response to international shortages, we recognize the long-term benefits of laboratory reared primates for biomedical research. By the turn of the 21st century, most primates used in research will be laboratory reared. The use of these animals will revolutionize research just as the use of laboratory reared rodents increased the sophistication of our current projects.

Hobbs and Bleby (1976) identified the following advantages of using domestically bred primates: First, laboratory reared animals will be of better *quality* since they are basically disease-free. The use of these animals will increase the validity of research and eliminate a variety of hazards to personnel. Second, the supply of uniform groups of genetically characterized animals will result in better *standardization,* more accurate work and lead to a reduction in the number of primates needed for a particular study. In addition, once animals are genetically characterized, we can measure the impact of other factors such as nutrition. Third, the problem of *availability* would be obviated by ensuring continuity of supply, which would save research time and money. In addition, domestic breeding of animals would eliminate the mortality loss we experience with imported animals. Fourth, the animals would be more *suitable.* With constant supply and knowledge of available stock, primate usage could be extended to include pregnant, fetal, and young animals. Fifth, some of the *ethical* objections to primate research would be removed since there would be less need to use captured wild animals.

Contrary to statements sometimes expressed, the biomedical community recognizes its practical as well as moral responsibility to protect wild primate populations in their natural habitat. Although we are increasing our domestic breeding capabilities, native populations are valuable natural resources that must be conserved. Of the approximately 201 species in 56 genera, only a small number have been studied sufficiently to warrant domestic production for research use. We must assure the continuation of gene pools for the over 90 percent not now being considered for research production. Some species not now used may have potentially important characteristics as animal models to study human disease and can be maintained only through good conservation in source countries.

Thus, from a practical as well as ethical viewpoint, every effort should be made to maintain naturally occurring primate populations as renewable resources in source countries.

Source Country Breeding Projects

For these reasons, we are cooperating with the Pan American Health Organization (PAHO) to provide assistance to Latin American source countries in the management of their primate resources. The objective of such joint efforts is to develop national programs in countries that have important populations of New World primates to ensure the perpetuation of these natural resources. PAHO-supported programs include surveys of primate populations, management and monitoring of those populations, and establishment of breeding programs for indigenous primates (PAHO, 1975).

In mid-1975, a breeding station was established at Iquitos, Peru. Currently,

the following species are being bred at this station: moustached tamarin (*Saguinus mystax*), red-bellied tamarin (*S. labiatus*), pigmy marmoset (*Cebuella pigmaea*), owl monkey (*Aotus trivirgatus*). In addition to the actual net production, much needed knowledge will be gained about the reproductive behavior of these species, in captivity and in free-ranging colonies located on islands, as well as knowledge about other physiological and pathologic features of these animals.

The PAHO/Iquitos project also is providing funding for studies of primate population distribution and densities in cooperation with Peruvian wildlife authorities. Many of the areas studied have not been fully surveyed before. Several spinoff benefits already have resulted from these studies. Since all wildlife, not just primates, is surveyed, national wildlife authorities and project managers can make recommendations affecting all indigenous wildlife. At the same time, they can determine which areas of the country are in danger from such human activities as hunting, farming, homesteading, and oil and mineral exploration.

Several long-term benefits are expected from the Peruvian project. The station at Iquitos is providing an opportunity to create wildlife management programs as well as exchange programs for national and foreign fellows in primatological research. Further, increased attention paid to the primate population provides the native human population with a greater appreciation of the value of these animals and an enhanced understanding of the need for conservation and reduction of unnecessary natural resource and habitat depletion.

Establishment of breeding and conservation programs in source countries ultimately will benefit both the biomedical research community and the source countries. Progeny from the breeding station in Iquitos, Peru, as well as wild animals trapped for export based on animal population census studies, have already been made available to the biomedical community. In return, the biomedical community under PAHO auspices has provided the source country with technical support, financing, and assurance of the long-term survival of valuable natural resources. Based on the success of these PAHO projects, the World Health Organization is exploring the possibilities of establishing similar programs in Africa and Asia.

Limitations on Primate Use

Nonhuman primates must be used effectively and only when essential. Decreasing availability and increasing costs have caused a reduction in primate use within the last decade. Although economics will continue to affect primate usage, the decision that a primate must be used should be based on sound scientific reasoning. A series of five criteria for evaluating research using nonhuman primates has been developed. These criteria are:

1) that the research can be done best with primates;
2) that the species is the most appropriate;
3) that the minimum number for acceptable results be used;
4) that the primates not be sacrificed except where necessary as part of the investigation;
5) and, if possible, that there be a sharing of tissues.

We are incorporating these criteria into the management procedures of government agencies sponsoring primate research.

The committee has also been concerned with the allocation of primate supplies. In view of the uncertainties of current and future primate species, the time may soon be here when there will be insufficient numbers of one or more species to meet minimum health needs of the U.S. The plan provides an outline to be followed in such a situation. When such difficult choices have to be made, the priorities of distribution will be: 1) to fulfill legal requirements; 2) for use in breeding colonies; and 3) for other research and development purposes.

Since the legal requirements are developed by government agencies as a result of their regulatory authority, the National Primate Plan recommends that any proposed federal guideline, standard, or regulation which either requires primate usage or restricts their availability be submitted to the committee to assess the potential impact on the overall national supply. We are also encouraging users to reexamine their needs for acceptable alternatives as well as encouraging the development of new techniques and procedures that will further reduce their primate requirements. In addition, we are encouraging researchers to make the specifications for animals as rational and precise as possible. Finally, we must consider the ethical responsibilities shared by all of us who provide and use primates as research animals. Humane care issues, while not new, have become amplified in recent years. We must be prepared to deal with these issues which are surrounded by so much emotion.

The biomedical community is searching for alternatives to animal experimentation not only for humane, but also for economic reasons. Unfortunately, alternatives to testing the combined complex physiological systems found in the intact animal are currently quite limited, and to meet present needs can only be considered complementary or supplementary. However, such procedures may help to screen agents requiring testing and thus help to slow down the increasing requirements for animals.

Conclusion

In summary, a number of important steps have been taken to assure adequate primate supplies. The research done with these animals is essential to provide knowledge of benefit to all people in all nations. A balanced program is needed worldwide that includes conservation of wild populations; improvement of wildlife management programs; better means of capture, conditioning, and shipping; increased domestic breeding of animals; and judicious use of these precious resources.

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Scientific Issues and Regulation of Primate Use

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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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