NONHUMAN PRIMATES IN BIOMEDICAL RESEARCH

Biology and Management

EDITORS:
B. Taylor Bennett, Christian R. Abee, Roy Henrickson

American College of Laboratory Animal Medicine Series

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Preface

Nonhuman Primates in Biomedical Research represents the first definitive reference source for those who work with and care for nonhuman primates in biomedical research. Prior to the development of this work, available information was contained in a variety of journals, species-specific reference books, and in the minds of a limited number of experienced primatologists and veterinarians specializing in the care of nonhuman primates. This lack of a central information source was compounded by the fact that very few laboratory animal veterinarians had training and/or experience in managing and caring for these very unique and valuable animals. To meet this need, the Board of Directors of the American College of Laboratory Animal Medicine voted to add these books on nonhuman primates to the college's collection of published texts.

This volume provides basic information on the biology and management of the commonly used primate species in a format that can be used by veterinarians or nonveterinarians with the day-to-day responsibility for the care and use of these animals. Thus it serves as a general reference for those who care for and use nonhuman primates in biomedical research.

Since the maintenance of large populations of primates for biomedical research is limited to relatively few institutions, those with the prerequisite experience to author the various chapters were somewhat limited. Additionally, the number of animals available for study was very small compared to the number of other commonly used laboratory animals. The size of study populations is reflected in the small number of available publications on a subject or condition. This lack of published information presented a formidable challenge in producing this addition to the ACLAM series and served to emphasize the need for consolidating the information in a single reference source. To meet this challenge, it was necessary to seek authors whose areas of expertise covered a broad range of topics and whose careers had focused on the care and study of primates. Hence, this volume represents the work of a variety of scientists drawn from within our college, from the ranks of primate clinicians, and from the field of primatology. The authors relied heavily on their experience and extrapolation from the human and veterinary medical literature. We extend our sincere appreciation to this diverse group without whom this work would not have been possible.

While the authors are the heart and soul of a volume such as this, the reviewers are the conscience. They serve to provide an overview and to focus our attention which may have been obscured by familiarity with a task.

As for all volumes of the ACLAM series, the editors and authors have served without compensation, and have donated all publication royalties to the American College of Laboratory Animal Medicine to continue the work for which it was founded in 1957: to encourage education, training, and research in laboratory animal medicine and to recognize veterinary medical specialists in the field by certification and other means. We wish to express our appreciation to the officers and members of the college for their support and assistance during the evolution of this project.

We would like to acknowledge an author whose death during this project cost our community a respected and valued colleague, Dr. Benjamin Blood. His knowledge of the field and historical perspective will be missed.

B. Taylor Bennett
Christian R. Abee
Roy Henrickson

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Contents

CHAPTER 1

History

Dennis O. Johnsen

I. HUMAN AND NONHUMAN PRIMATES TO 1960

A. Roots of Modern Primatology

Nonhuman primates probably first became valuable to man as pets, but they are also the oldest recorded animal subjects for scientific research (Hill, 1977). Nonhuman primate pet trading is known to have occurred in Egypt as long as 5000 years ago (Morris and Morris, 1966); their use for medical purposes came somewhat later, although still in respectably ancient times. Galen (130–200 AD) did anatomical studies on animals including monkeys (Cohen and Loew, 1984), and Vesalius (1514–1564) used barbary apes (*Macaca sylvanus*) in his studies of circulatory anatomy (Kavanaugh, 1984; Morris and Morris, 1966; Loeb *et al.*, 1989). Ruch (1941) has documented that monkeys and apes were studied from ancient times through the middle ages by Hanno, Aristotle, Pliny the Elder, Pliny the Younger, Petrus, Candidus, and others (Morris and Morris, 1966; Loeb *et al.*, 1989).

Darwin's research on evolution, and particularly his notes on the behavior of the gorilla, established his credentials as one of

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the first observational primatologists (Darwin, 1871). Also late in the 19th century, the British physician David Ferrier conducted comparative neuroanatomy studies of apes and monkeys (Morris and Morris, 1966). During this same time period, Pasteur discovered that rabies virus passaged through monkeys lost its virulence for dogs (Pasteur *et al.*, 1884a,b). Some 20 years later, the poliovirus was isolated by inoculating spinal cord material collected from fatal human cases intraperitoneally into monkeys (Landsteiner and Popper, 1908, 1909).

The primatological knowledge that was generated came largely from relatively few behavioral and biomedical investigators working independently. With the institutionalization of nonhuman primate research, a profound change became possible.

B. First Primate Centers

1. Soviet Institute of Experimental Pathology and Therapy

According to Held and Gay (1983) and Lapin (1983), the first Commissar of Health in the USSR was persuaded by Mechnikov, a pioneer of modern Soviet experimental primatology, to establish a primate breeding station in 1923. Located in Sukhumi on the subtropical shores of the Black Sea in the then Soviet State of Georgia, the station was intended to be a quarantine, breeding, and holding center for nonhuman primates and support a network of 50 medical and biomedical research institutions. It began operations in 1927 when it received the first shipment of hamadryas baboons (*Papio hamadryas*) and chimpanzees (*Pan troglodytes*) from Africa. At first, captive breeding was unsuccessful. However, there was improvement as experience in maintaining and breeding nonhuman primates was gained. Charting a course that has been followed elsewhere, activities of the Sukhumi station's service gradually expanded to encompass initiatives in independent research. In 1957, now under the auspices of the Academy of Medical Sciences of the USSR, the station became the Institute of Experimental Pathology and Therapy (IEPT) in recognition of its status as a full-fledged research institution. By 1990, IEPT had production colonies of over 7000 animals consisting primarily of baboon and macaque species, a staff of about 1000 people, and research programs focusing on oncology, physiology, biochemistry, infectious diseases, and the biology of nonhuman primates (B. A. Lapin, personal communication, 1990). The institute also served as a principal source of nonhuman primates for the Virology Institute in Moscow and the Russian space program and served as an international resource as well with productive research links to medical scientists in the United States and elsewhere.

The secession of Georgia from the Soviet Union and the disturbances associated with the declaration of independence of Abkhazia seriously disrupted operations in Sukhumi. These problems forced completion in 1992 of a move of less than 100 miles to a satellite site in Russia near the city of Adler (D. M. Bowden, personal communication, 1993). Despite this adversity, the institute, now the Institute of Medical Primatology of the Russian Academy of Medical Sciences, remains one of the largest nonhuman primate research centers in the world.

2. Robert Yerkes and the Primate Laboratory of the Yale Institute of Psychobiology

Robert Yerkes, an accomplished comparative psychologist, had a vision of what the future held for nonhuman primate research and how to realize those dreams (Yerkes, 1916). Yerkes established the Primate Laboratory of the Yale Institute of Psychobiology at Orange Park, Florida, in 1930 (Bourne, 1971; Maple, 1979). His plan was to establish and develop "an institute of comparative psychobiology in which the resources of the various natural sciences should be used effectively for the solution of varied problems of life" (Yerkes, 1932). As early as 1919, he proposed the idea of establishing a nonhuman primate research institute for the systematic study of the "fundamental instincts" and "social relations" of nonhuman primates. Yerkes was a contemporary of other notable early investigators of the time such as Kohler and Kohts who were interested in nonhuman primate research (Maple, 1979). Interest in Kohts' perceptual and sensory work with chimpanzees in the Soviet Union may have contributed to the initiative for establishment of the Sukhumi station (Yerkes, 1943).

Yerkes established his Orange Park station in 1930 with funds from Yale University and the Rockefeller and Carnegie Foundations. He received an initial gift of 13 chimpanzees from a breeding facility belonging to Rosalia Abreu in Cuba (Maple, 1979). The colony was expanded during the next several years with 16 additional chimpanzees from Africa, a gift from the Pasteur Institute. Laboratory studies were multicategorical, encompassing neurophysiology, anatomy, pathology, nutrition, growth, and development (Bourne, 1971). The station set an early, if not the first, organizational precedent for a comprehensive nonhuman primate research center.

In 1965, the laboratories in Orange Park were moved to Atlanta, Georgia, and the animals were reestablished in the new Yerkes Regional Primate Research Center of Emory University.

3. Cayo Santiago Colony

Clarence Ray Carpenter, a student of Yerkes and an accomplished field primatologist (Maple, 1979), has as one of his most enduring accomplishments the establishment of the Cayo Santiago Colony of rhesus monkeys. Rawlins and Kessler (1986) and Kessler (1989) have provided extensive accounts of the history of the Cayo Santiago Colony. Much of the historical information cited next is derived from those accounts.

Carpenter formulated plans in the early 1930s for establishing a population of both gibbons and rhesus macaques on an island in the American tropics. The possibility of conducting both behavioral and biomedical research on an island colony

was basic to those plans. He interested a number of people, including the staff of Harvard's Museum of Comparative Zoology, the faculty of Columbia University's College of Physicians and Surgeons, and the Columbia University/University of Puerto Rico's School of Tropical Medicine (later to become a component of the University of Puerto Rico School of Medicine), in the planning effort. He selected Cayo Santiago, a 15.2-ha (approximately 38 acres) island 1 mile off Puerto Rico's eastern coastal town of Humacao, as the site for the colony.

With the help of a $60,000 grant from a private foundation, Carpenter set off for Indochina and India in 1938. He fared well in collecting rhesus monkeys but not gibbons. Survival of the 47-day voyage from Calcutta as deck cargo was a testimonial to the enduring qualities of the rhesus monkeys and the care that they received. By early 1939, 409 rhesus monkeys, 14 gibbons, and 3 pig-tailed macaques were released on Cayo Santiago. Eventually only the rhesus monkeys remained.

Maintenance of the island and breeding were not without problems. Local fruits and vegetables did not provide an adequate diet and malnutrition was overcome only by feeding fox chow, the early precursor to monkey chow. Wells were dug, but the water was brackish. Cisterns and a system for collecting rainwater had to be constructed. A number of monkeys were lost through fighting or simply through being crowded out in the establishment of a stable social structure. Some escaped by swimming the channel to the mainland. Various diseases also took their toll and there were few opportunities to limit spread. However, persistent efforts did finally result in eliminating tuberculosis.

Another problem was the lack of dependable financial support for the project. In 1944, the University of Puerto Rico assumed full responsibility for support of the colony. Operations languished until 1948 when efforts to attract badly needed outside support were successful. At that time, the National Institutes of Health (NIH) awarded the first of a number of federal awards to the University of Puerto Rico to help support Cayo Santiago. Eventually, the island operation was incorporated as a component of the University's Caribbean Primate Research Center.

Cayo Santiago has been a valuable resource through the years for both the production of monkeys and for biomedical and behavioral research. The experiences with Cayo Santiago have also shown that outside support, primarily federal government support, is essential for the long-term maintenance of nonhuman primate resources.

C. Virological Research and Nonhuman Primates

Technically, the modern use of nonhuman primates in biomedical research had its origins in Pasteur's work with rabies and the studies of others with smallpox and vaccinia in the late 1800s. Kalter and Heberling (1971) and Gerone (1974) have provided comprehensive reviews of virological research in nonhuman primates, including work on yellow fever and a variety of encephalitis viruses through the 1930s.

The Nobel prizewinning achievement of Landsteiner and Popper in isolating poliovirus in Vienna (1908, 1909) provided the real beginning of serious and widespread use of nonhuman primates in biomedical research, using rhesus monkeys, baboons, and chimpanzees in their work. The unique susceptibility of nonhuman primates to a relatively new and frightening disease threat clearly established their special importance in research.

The intense efforts to develop a vaccine against polio that followed was unprecedented. It spanned the next 45 years, was international in scope, and involved a host of major investigators. However, it was a complex process that experienced serious setbacks. There were some promising early findings based on nonhuman primate studies using inactivated, or partially inactivated, vaccines. However, those findings led to disastrous results when cases of paralytic polio occurred following vaccinations in human clinical trials (Horstmann, 1985).

Nevertheless, nonhuman primates played an important role in helping to put polio research back on track. In 1931, throat washings from patients were inoculated into monkeys and resulted in infection (Paul and Trask, 1932). Later work showed that poliomyelitis was an enteric and not an olfactory infection. The discovery by Enders and co-workers (1949) that poliovirus could be grown in human tissue culture was a major scientific advance which brought them the Nobel Prize for Medicine in 1954. It also provided a means to reduce the need for nonhuman primates. However, like the promise computers initially offered for reduction of paperwork, any reduction in the use of nonhuman primates was soon masked by a vastly expanded and accelerated research effort which required even more animals.

Salk's report of a formalin-inactivated polio vaccine grown in monkey kidney cell culture paved the way for extensive and successful field trials (Salk *et al.*, 1953). Unfortunately, this dramatic achievement was clouded by uncertainty when improperly inactivated vaccine caused a number of cases of polio in 1955 (Horstmann, 1985).

At about the same time, Sabin was working on the development of a polio vaccine from another direction. Depending greatly on the use of monkeys and chimpanzees, he searched for attenuated strains of naturally occurring poliovirus. His painstaking work reportedly used 9000 monkeys and 150 chimpanzees (Sabin, 1985). The result was the development of an oral polio vaccine that remains in widest use today.

While relatively modest in the early years, the use of monkeys increased dramatically following Salk's discovery of an effective vaccine. The high point of this usage was in 1957 and 1958 when about 200,000 monkeys were imported annually into the United States (Lecornu and Rowan, 1979). According to Lecornu and Rowan, the greatest single use of the more than 1.2 million rhesus monkeys that were imported into the United States during the 20 years that followed Salk's discovery was for producing and testing polio vaccine.

The legacy of the 1955 polio vaccine incident continues even today. The more rigorous testing program that was adopted after the incident accounts for 20–25% of all nonhuman primates used in research and testing (Marten, 1981). However, the number of animals required for testing polio vaccine has declined dramatically. Polio ushered in an era of sponsored research that was necessary for the development of domestic nonhuman primate resources. It also firmly established nonhuman primates in the public eye as research animals rather than curiosities.

D. Other Contributions

1. Work of Harry Harlow

Harry Harlow started his studies on the learning abilities of monkeys in 1930 at the University of Wisconsin. After conducting comparative studies of learning capabilities of cebus and rhesus monkeys at the local Vilas Park Zoo, he developed a modest laboratory on the university campus. During a career spanning nearly 50 years, Harlow expanded these resources into a large and interdisciplinary research complex that included the Wisconsin Regional Primate Research Center (Davenport, 1979). This research enterprise eventually had a staff of over 200 people and a nonhuman primate colony numbering in excess of 1000 monkeys.

Harlow shed light on the nature and limits of rhesus monkey intelligence. Studies in the infant monkey nursery focused on the results of enriched versus impoverished social rearing conditions, development of measures of learning ability, and surrogate-mother testing to demonstrate the importance of infant–maternal tactile sensations relative to biological drives such as hunger. His work opened new areas of study including nonhuman primate emotions such as love, parent–child relationships, peer interaction, play, heterosexual behavior, and psychological impairments that result from social deprivation and separation (Suomi and Leroy, 1982).

Attempts have been made to discredit Harlow's work as cruel and trivial. On the contrary, Harlow's research provided insight into nonhuman primate well-being, captive breeding, rearing, and maintenance. This important work continues to have a major influence on both nonhuman primate and human behavioral research.

2. Breeding and Reproductive Physiology

Surprisingly little information on the subject of nonhuman primate reproductive physiology and breeding prior to the 1960s exists. The first chimpanzee, or any ape for that matter, was not born in captivity until 1915 (Montane, 1915). As late as 1938, Carl Hartman, a prominent reproductive physiologist, predicted that rhesus monkeys would not breed in the American tropics (Rawlins and Kessler, 1986).

Gertrude van Wagenen, a faculty member in the Department of Obstetrics and Gynecology at Yale University School of Medicine, may have been the first to establish a captive rhesus monkey laboratory breeding colony (van Wagenen, 1972; D. M. Horstmann, personal communication, 1989). Over a career spanning 45 years, she collected detailed information from birth to death on all of the 1261 monkeys that lived in the colony. The colony produced 600 live births through 15 generations. Her many publications provided an abundance of basic information on rhesus reproduction and rearing. This work represents one of the first major efforts to focus on characterizing this facet of rhesus monkey biology. Studies of monkey biology, as an end in itself, did not come until later.

3. Herpesvirus B and Other Biohazards

Until relatively recently, people did not appreciate that there was much to fear from nonhuman primates except physical injury. Tuberculosis was recognized fairly early as a relatively common disease in humans. However, it was more devastating to nonhuman primates than it was to man. It was not until 1934 that serious concerns arose about other biohazards in nonhuman primates. In that year, a fatal human case of encephalitis caused by the herpesvirus B occured following a monkey bite (Sabin and Wright, 1934).

Since 1934, there have been more than 20 fatal cases of human infections with herpesvirus B (Palmer, 1987). There have been few survivors among these cases, although the use of acyclovir now appears to hold infection in abeyance. Hull (1973) reported earlier that there had been at least 83 cases of human diseases caused by simian viruses, including 23 deaths. In addition to herpesvirus B, hepatitis virus (Hillis, 1961) and Marburg virus (Kissling *et al.*, 1968) represent two of the more important diseases. Concern about these diseases and the precautions that laboratory personnel must take when working with the nonhuman primates placed these animals in a very special class among laboratory animals.

II. ESTABLISHMENT OF PRIMATE CENTERS: CROSSING THE THRESHOLD

A. Initial Activity

The extended process that led to the establishment of the NIH Regional Primate Research Centers Program (RPRCP) has been well documented (Anonymous, 1968). It dates back to 1947 and 1949 when NIH unsuccessfully tried to establish a procurement program to make an adequate supply of chimpanzees available to researchers in the United States.

In the period from 1955 to 1957, a number of groups and individuals advising NIH and the National Academy of Sciences–National Research Council noted the need for developing additional nonhuman primate research facilities. Not much happened until the director of the NIH National Heart Institute

(NHI), and eventually the director of NIH, became interested in the problem.

B. Developing the Concept

In 1956, Karl F. Meyer, initially trained as a veterinarian and known to the world of science for his research in microbiology and directorship of the University of California at San Francisco's Hooper Institute, visited the Sukhumi station in the USSR. On his return, he urged the NIH Director, James Shannon, to develop a nonhuman primate research colony in the United States. In the same year, NHI Director James Watt also visited Sukhumi because of the work in experimental hypertension being done there using nonhuman primates.

Watt's report led the advisory council of the NHI in 1957 to recommend the development of a nonhuman primate colony associated with a university to serve as a site for a long-term multidisciplinary approach to research on cardiovascular problems. Shannon had differing views about the wisdom of establishing a single station with a focus limited to long-term cardiovascular research.

In late 1958, the NHI concluded that a nonhuman primate station was both feasible and desirable. With increased interest in this idea within Congress, NHI began to plan for a station. Conspicuous in this planning effort were George Burch, a noted cardiovascular researcher from Tulane University, and Willard "Hal" Eyestone. Eyestone was the responsible NHI staff officer who would eventually become first director of the new regional nonhuman primate research centers program.

Congress received the planning report on NIH's plans for a nonhuman primate program in mid-1959. This plan reflected a transition in thinking about a single station, as conceived by NHI, to a number of smaller nonhuman primate research centers. These centers were still to focus on cardiovascular research, but their roles were expected to expand to include "other disease categories and other disciplines, until ultimately the functions of the stations or centers is the full and complete investigation of the primate" (Anonymous, 1968).

The NIH planners felt that the focus of the centers should be on research, not just serving as a source of monkeys, and that support should be provided by NIH for a long period of time. Fifty to 100 years was originally suggested. Other ideas also became cornerstones of the new program. Research was to be conducted on nonhuman primates in conjunction with other basic and clinical studies. Investigations were to be carried out on the usefulness of various species of nonhuman primates in research. A national reservoir of information on nonhuman primates and for nonhuman primate research was to be provided. There were to be facilities for visiting scientists and research training. Extensive local participation with appropriate universities or research institutions and the need for seeking outside funding to augment the core budget were also identified as basic concepts.

C. Launching the New Program

Congress appropriated the first funding for the program, $2 million, in 1959. There were to be several centers. These centers were to be geographically distributed, be part of a university environment, and support biomedical and health research broadly instead of being limited to a particular area such as cardiovascular research.

Following announcement of the new program in January, 1960, NHI received 11 applications. Seven applications were approved by the study section which reviewed the applications. NHI awarded the first grant to establish the Oregon Regional Primate Research Center at Beaverton, Oregon.

With a congressional appropriation of $7 million for the following year (FY 1961), NHI awarded grants to establish the Washington Regional Primate Research Center (RPRC) at the University of Washington in Seattle; the Wisconsin RPRC at the University of Wisconsin in Madison; the Yerkes RPRC in Atlanta in association with Emory University; the Delta RPRC in association with Tulane University at Covington, Louisiana (now the Tulane RPRC); and the New England RPRC in association with Harvard University at Southboro, Massachusetts.

Still preoccupied with the perceived need for a national "station," the advisory council of the NHI continued to urge the establishment of a conditioning center for nonhuman primates. Its function was to be the development of techniques for procuring, conditioning, and maintaining various nonhuman primates for study. In 1962, NHI awarded a grant to establish such a center at the University of California, Davis. The center, initially designated as the "National Center for Primate Biology," later became the California RPRC. This change was made after it became apparent that it was much more important and realistic to have the California center function as a RPRC rather than serving the specialized role originally envisaged.

By the time the initial establishment of the seven centers was complete in 1968, the 8 years of cumulative federal funding provided by NIH totaled about $52 million, including funds for the purchase of land sites, construction of the centers' facilities, other start-up costs, and a rapidly expanding research program. Administration of the Regional Primate Research Centers Program was formally transferred in 1962 to NIH's Division of Research Facilities and Resources. This division later became the NIH Division of Research Resources (DRR) and, in 1990, the National Center for Research Resources (NCRR).

D. Regional Primate Research Centers Program Today

By the end of 1991, the seven RPRCs had 199 core staff scientists, 835 collaborators and affiliates, 34 visiting scientists, and a total of about 17,000 nonhuman primates representing 32 different species; their breeding colonies produced about 2400 live births annually (L. H. Whitehair, personal communication, 1991). The program has been very successful. The seven cen-