NURSERY REARING OF NONHUMAN PRIMATES IN THE 21st CENTURY

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PREFACE: OUR HISTORICAL NOTE

It was 1970 when Gerry Ruppenthal and Jim Sackett moved from the University of Wisconsin in Madison to the University of Washington in Seattle. In Wisconsin, Gerry had been working for Harry and Margaret Harlow for over a decade and supervised many of their classic studies of the 1960s. Jim was an associate professor in the psychology department and was in his seventh year of primate research in what is now the Harlow Primate Laboratory. Collectively, we were experienced in studying infant, juvenile, and adult rhesus macaques that had been reared under a variety of captive conditions. Many of these monkeys had been reared in the Harlow Primate Laboratory nursery.

We were brought to Seattle by the Regional Primate Research Center (PC) and the Child Development and Mental Retardation Center (CDMRC), now called the Center on Human Development and Disability (CHDD). Gerry was a research scientist with both NIH-funded centers, while Jim was a professor in the psychology department, a PC core staff member, and PI of a CDMRC 3-year new program grant. Harry Harlow generously allowed us to take a great deal of equipment from Wisconsin—cages, rearing units, developmental testing apparatus, and recording devices. If he had paid more attention, we probably would not have gotten away with as much "loot," but the University of Wisconsin and NIH approved it all. With some additional local start-up funds and a really large amount of space, we started a primate nursery and organized a developmental rearing room and some testing rooms. Our equipment and methods were essentially identical to those used for over 15 years in the Wisconsin laboratory.

Our initial goal was to replicate the effects of isolation and peer rearing found in rhesus macaques in the classic Harlow work. We wanted to do this to learn why male rhesus macaques were affected so much more than females by asocial rearing. Because the PC breeding colony consisted of pigtailed macaques (*Macaca nemestrina*), we needed to demonstrate that they responded like rhesus macaques with the same sex and rearing differences before going on to mechanistic studies of possible causes. Not only did we fail to find sex differences following asocial rearing of pigtails, we also failed to find the same devastating effects of isolation rearing on postrearing social and exploratory behavior. This convinced us that gene–environment interactions were to be expected in assessing acute and chronic effects of rearing conditions on behavior, and probably also on physiology. This theme, in one guise or another, will be found through much of this book.

Our nursery is situated adjacent to the University Hospital, just below the human neonatal intensive care unit, and word soon got out that it was possible to study monkey pregnancy, neonates, and infants in a primate nursery located almost next to one's own office and laboratory. This led to requests to use our facilities by a number of medical researchers, especially a group of neonatologists who were studying lung function in premature newborns. With their help, our nursery came to include a primate neonatal intensive care unit. Also, rather than euthanizing newborns that were premature or low birth weight, ill, had life-threatening birth defects, or whose mothers were ill, wounded, or dead, the PC breeding colony managers began sending such at-risk neonates and young infants to our nursery, initiating an "Infant-Save" program that continues to this day.

By 1971 it was obvious that our nursery was a valuable resource for scientists who were interested in prenatal, perinatal, and infancy studies. As both the PC and CDMRC 5-year core grants were being written for renewal in 1972, we convinced the directors of both centers to include a proposal to support a nursery facility, the Infant Primate Research Laboratory (IPRL). In what appears to be a unique relationship among NIH-supported university centers, our proposal was funded by both core grant requests and we have shared this funding ever since.

From our point of view, the IPRL has had two main purposes. The first has been to use primate models to study important human medical

and behavioral problems. This has been the major reason for continued grant success in the CDMRC arm of our endeavors. Equally important, we have spent much of our PC-based resources studying primate medicine and husbandry issues related to breeding, pregnancy and fetal development, hand-rearing methods, and methods of assessing growth, physiology, and behavioral development. Our NIH-supported efforts and those of many other researchers and veterinarians led to the then state-of-the-art publication, *Nursery Care of Nonhuman Primates*, edited by Gerry Ruppenthal and Dorothy Reese, published by Plenum in 1979.

Although much of that book is still relevant today, methods of nursery care, methods of testing, and types of experimental and husbandry problems have changed markedly since 1979. This has resulted in new challenges involving nursery rearing of monkeys with many types of naturally occurring and experimentally induced medical and developmental conditions. New challenges have arisen through changes in attitudes toward animal testing and resulting changes in standards of animal care involving concerns for both the physical and psychological well-being of captive primates. One goal of this book is to describe how these challenges have been met over the past 25 years. The other goal is to show how changes in rearing methods have altered for the better the developmental outcomes of nursery rearing, at least in some species and some facilities. We hope that our story, begun in the 1979 book and continued in the current one, will produce a more realistic view of nursery rearing and its effects than that claimed by opponents of nursery rearing on the basis of antiquated methods now used by only a few facilities or individuals.

This book originated in a workshop of the same name, *Nursery Rearing of Nonhuman Primates in the 21st Century*, held in 2002 at the Oklahoma City meeting of the American Society of Primatologists. All of the workshop presenters are represented, in addition to a number of authors recruited to present important topics not covered in the workshop. We are grateful to all our contributors. We had hoped to include either a section or a CD of basic growth and health data for nursery-compared with mother-reared primates that would serve as normative comparison data for current and future research. Unfortunately, we were able to collect such data on only a few species, although they are ones that are frequently nursery reared in current work. Data on health sta-

tistics are included in the final section as an example of basic data that can, and probably should, be collected and disseminated for all laboratory and zoo nursery-reared primate species.

Over the decades our work has involved a large number of students, scientists, health workers, technical personnel, and administrators. They are too numerous to list here, but we must thank our earliest University of Washington students, Dick Holm, Sharon Ramey (nee Landesman), and Jon Lewis, who helped us start the IPRL in both concept and fact. Carol Fahrenbruch, Sherry Savage, Colleen Walker-Gelatt, and Gary Bartram provided invaluable effort in developing and implementing our rearing and developmental testing methods. Without the support of our Primate Center directors, especially Orville Smith, and our CDMRC directors, especially Irvin Emanuel and Michael Guralnick, we would have had quite different careers. We are also grateful to the NIH for its continued support from the National Center for Research Resources, grant RR00166, and NICHHD Mental Retardation Branch, grant HD02274.

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Seattle and Pittsburgh, 2004

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INTRODUCTION

As described in the preface, this book originated in a workshop focused on changes in nursery-rearing practices over the past 35 years and the state of the art in the early 21st century. In designing the workshop, we identified four areas of change: (1) new or modified goals of nursery rearing, (2) new concepts concerning these goals, (3) new methods for attaining these goals, and (4) new data concerning the effects of nursery or hand rearing on the health and biobehavioral and social development of infant and juvenile primates.

1. GOALS

There are two primary goals of contemporary nursery rearing. The first involves saving at-risk newborns and young infants that cannot be reared by their mothers. This goal serves the purposes of conservation of endangered species, display in zoos, production of future breeders, and preservation of natural models of human health or behavior problems. Examples of the latter include low-birth-weight or premature neonates and neonates with genetic defects such as trisomic chromosome conditions. The second goal involves nursery rearing and its variations as specific experimental procedures in research studies. Examples of new research goals include the need for biological containment of neonates and infants in viral and other disease research, the production of specific pathogen-free (SPF) colonies by removal of neonates from the mother, and the production of phenotypes for genome manipulation, assisted reproduction technology, and molecular biology studies.

2. CONCEPTS

A major change in concepts concerning nursery rearing is that nursery-reared primates no longer are simply warehoused for future assignment to research projects. Instead, modern methods are aimed at providing psychologically rich environments to foster reasonably normative behavioral and physiological development as compared with some standard such as rearing with mothers in captive environments. The underlying concept is that normal animals make better research subjects. In the extreme view, only normal animals provide valid subjects in most primate research projects, whether these are behavioral or biological in nature. A variant of this view is that some degree of normal development is necessary for producing successful breeders and healthy colony members. A major problem, however, is how to define "normal." Many of the chapters in this book are relevant to this definitional issue.

On the other hand, research over the past 50 years in developmental sciences, ranging from molecular biology to developmental psychology, shows that genes and environment work together to produce a variety of "normal" phenotypes at all levels of study (e.g., Gottlieb, 1998). With respect to the development of nonhuman primates following variations in rearing conditions, gene–environment interactions appear to be the norm rather than the exception. An important example of this interaction in nonhuman primates is seen in work by Suomi and his colleagues at the Laboratory of Comparative Ethology of the National Institute of Child Health and Human Development.

Rhesus macaques have a variation in the serotonin transporter gene regulatory region (5-HTTLPR), with some individuals having a long allele and some having a short allele. Humans have a similar polymorphism in this same region, which appears to be associated with phenotypic variation in levels of anxiety, depression, affective disorders, and aggression. In one study, Bennet *et al.* (2002) compared concentrations of serotonin in the cerebrospinal fluid of monkeys that were reared with their mothers versus monkeys that were reared in a nursery and then housed with agemates. Among nursery-peer monkeys, those with the short allele had a marked reduction in serotonin compared with monkeys that had the long allele. Similarly. in a study of social play and aggres-

sion (Barr *et al.*, 2003), nursery-peer monkeys with the long allele displayed more play and less aggression than those with the short allele, whereas mother-reared infants showed no allele-related differences in behavior. Thus, the effects of genotype on both neurochemistry and behavior depended on how the monkeys were reared.

We were not surprised by these results. In two studies we addressed the question of species differences in the effects of social-isolation rearing (Sackett *et al.*, 1976, 1981). Three species of macaque—rhesus (*Macaca mulatta*), pigtailed (*M. nemestrina*), and longtailed (*M. fascicularus*)—were reared in identical environments with no social or sensory contact with other monkeys for 6–7 months from birth. During the rearing period the rhesus macaques developed a typical isolation syndrome: they displayed no play or exploration behaviors and spent most of their time in self-directed and repetitive behaviors. Longtailed macaques displayed more moderate levels of the isolation syndrome, while pigtailed macaques showed much lower levels of isolate behavior and a relatively high level of play. During postrearing social behavior tests, rhesus macaques continued to show mostly isolate syndrome behaviors, with no play or socially initiated activity. Pigtailed macaques had greatly reduced isolate syndrome behavior, and engaged in some positive social behavior and the same high levels of environmental exploration as controls reared with mothers and peer experience. Longtailed macaques also had a great deal of isolate behavior, but engaged in as much positive social behavior as did control animals reared with mothers and peers. Thus, when reared in an identical impoverished environment, genetically different primate species were differentially affected in degree of both deviant and species-typical behaviors. Furthermore, the results showed that the classic "isolation rearing syndrome" of abnormal personal behavior, neophobia, and lack of social behavior was valid only for the rhesus macaque species.

The lesson of studies such as these is that we should expect to see variations in the effects of nursery rearing both within and between species. This variation does not necessarily mean that we have produced abnormal monkeys. Rather, depending on genotype, each species and individual responds to environmental variation with behaviors that are adaptive in that environment. Motherless rearing in a nursery imposes a major

challenge on this adaptability during and after the rearing experience. Chapters in this book suggest that some primate species, especially prosimians, may be difficult to rear under motherless conditions, whereas other species appear to thrive when reared under modern husbandry and social conditions (e.g., Sackett *et al.*, 2002). We believe that there are nursery-rearing conditions that can produce adaptable juveniles and adults, capable of reproducing their species, for all normal genotypes of all primate species. Although this ideal has not been accomplished for all species to date, we hope the data presented in this book and the questions these data raise for future research will help us learn how to attain this goal.

3. METHODS

Research over the past 35 years has led to the development of new nursery-rearing methods. So far, these methods have been specific for particular primate species and institutions that rear primates in captivity. In addition, the psychological well-being movement and the Institutional Animal Care Committee (IACC) have introduced new dimensions into the methods for rearing primates in captivity. These dimensions involve both the physical environment and social–behavioral considerations. In this context, rules and regulations regarding rearing methods may bring bureaucracy into conflict with the conditions that actually foster development for meeting the goals of research, breeding and husbandry, conservation, or public display. IACC and related regulations specify factors ranging from cage sizes to protective gear for primate researchers and caregivers. This has greatly increased the costs of nursery rearing and of doing research with nonhuman primates in general. It has also greatly reduced both the quantity and quality of contact between humans and their monkey charges. On the other hand, these influences have greatly increased the quality and quantity of peer social contact and nonsocial environmental enrichment afforded nursery-reared individuals. A number of methods to cope with these influences are illustrated in chapters in this book, but many issues still remain to be solved by future research and technological innovation.

4. DATA

Newer data of particular importance concern variations in physiological and growth systems that differentially affect nursery-reared compared with mother-reared primates. Examples of such data are maturational, immunological, neurochemical, and hormonal effects that impact all aspects of development. Such information is critical for identifying appropriate research subjects in biobehavioral experiments, as well as for understanding deviations from normative developmental patterns. These new data are also of importance for understanding nongenetic intergenerational phenomena that affect the health and behavior of future offspring. Of course, new data identifying conditions that produce healthy and adaptive nursery-reared individuals are equally important. Chapters throughout the first four sections of this book present such data.

5. CHAPTER ORGANIZATION

The chapters in this book represent as wide a range of genera—great apes, macques and baboons, squirrel and marmoset monkeys, and prosimians—as we could identify for which developmental data on nursery-reared animals have been collected systematically under describable conditions. The book is organized in five sections. Section 1 presents a brief history of nursery rearing and some practical and theoretical issues bearing on contemporary nursery-rearing practices. Sections 2 and 3 present methods and outcomes of nursery rearing in prosimian and simian species. Section 4 deals with general veterinary issues, the rearing of high-risk infants, and some contemporary rearing and research methods important for current and future studies of primate development. The fifth section presents some difficult-to-find health data for representative species commonly reared in nursery environments.

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