Primates

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Nonhuman primates demonstrate marked similarities to humans in almost all aspects of their anatomy, endocrinology, and physiology. These similarities underlie the value of these animals for appropriate studies in neurobiology, immunology, pathology, reproductive biology, teratology, neonatology, endocrinology, cardiology, and psychology. Investigations with nonhuman primates has made, and continues to make, significant contributions to biomedical and behavioral research. This review provides an overview of basic and applied studies for which primates are appropriate subjects and a summary of the advantages and problems of using nonhuman primates in research.

OUR GENETIC RELATIONSHIP TO APES AND MONKEYS, THE consequence of our relatively recent common evolutionary ancestry, underlies the similar structural organizational development, and functioning of humans and primates. The term primates actually includes humans, although for purposes of simplicity and distinction we will not refer to them as primates in this review. There are almost 200 primate species which include the great apes (chimpanzees, gorillas, and orangutans), lesser apes (gibbons and siamangs), Old World monkeys, New World monkeys, and prosimians. Ninety-eight percent of human DNA can be found in the genes of chimpanzees, the most widely used of the great apes. The New World monkeys of tropical America and Old World monkeys of Africa and Asia share 85% and 92% of their DNA, respectively, with humans (*1*). However, while the numerical differences in nucleic acids may be small, differences in genes and gene control mechanisms are the bases for the obvious phenotypic distinctions between humans and primates (*2*).

These similarities in the biological mechanisms of humans and primates underlie the value of these animals for research in a broad range of disciplines. Monkeys and, to a lesser extent, chimpanzees often serve as the final test system for the safety and efficacy of treatments, preventive agents and vaccines developed in studies with other laboratory animals. In many basic and applied studies, primates are the only appropriate animal model when other species are not susceptible to the disease under study, or when primates possess the biological or behavioral characteristics needed to investigate the scientific question most effectively.

The most commonly used primates in research are the Old World species from Africa and Asia, which have been studied for many years and adapt to and reproduce well in captivity. The rhesus monkey, followed by the long-tailed macaque and the baboon are the most frequently used Old World species, while the squirrel monkey is the most popular New World monkey from the American tropics in research (*3*). Approximately 30 primate species are currently used in biomedical and behavioral research.

Because of their aforementioned similarities to humans and demonstrated value to medical and scientific research, primates often are an investigator's first choice as an animal model. However, of the approximately 20 million laboratory animals studied annually by U.S. scientists, only about 60,000 or 3.5% are primates, and most of these are used in multiple research programs of a noninvasive nature. Approximately 90% of laboratory animals in the United Stattes are rodents (*4*). Several factors explain the relatively limited use of primates in research. These include cost, restricted supply, and (perhaps the most important factor) appropriateness. Primates are clearly not appropriate or necessary for all studies. Because of their relatively limited numbers, primates should be used judiciously. While federal regulations require that Institutional Animal Care and Use Committees insure humane treatments of research animals, many research institutions also evaluate proposals for scientific value as well, particularly in the case of primates, because they are an exceptionally valuable resource. Table 1 lists several of the questions considered for each proposal placed before the Yerkes Regional Primate Research Center's Committee in the interest of the humane and parsimonious use of primates as well as science of high quality.

For example, scientists have developed techniques to reduce levels of sex steroid hormones without having to remove the ovaries or testes. A mini-pump is implanted subcutaneously to provide continuous release of a gonadotropin-releasing hormone agonist which decreases the sex steroids to near immature values. At the conclusion of the study when the pump is removed, sex steroids are secreted normally. This approach both avoided major surgery and retained reproductive capacity (*5*).

The limited supply of some primates can severely restrict or preclude their use in research. In the 1970s, the governments of India and Bangladesh placed an embargo on the export of rhesus monkeys which is still in effect. It can be argued that from a wildlife conservation viewpoint the embargo was a fortunate occurrence, although the cost of these monkeys has greatly increased as a consequence of having to breed them in this country. However, captive-born animals are typically healthier than their wild-born counterparts, which are often infected with parasites and other infectious agents. The embargo also prompted use of other primate species as research models and led to the development of captive

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breeding programs for more than 30 primate species in this country (*6*).

Successful breeding programs insure that primates used in terminal experiments, or which die as a result of natural causes, are replaced. It should be understood that most primates in research are not involved in terminal experiments, nor in studies that compromise their use in subsequent investigations (*6*) or affect their breeding. Recently the National Institutes of Health (NIH) initiated a program to establish a stable supply of chimpanzees for essential biomedical and behavioral research without depleting the captive population of these animals. The program also will perpetuate the chimpanzee population through the birth and maintenance of physically healthy and behaviorally normal animals for future generations. While chimpanzees are among the laboratory animals of least number (the research population in the U.S. totals 1200), they are essential to the development and final safety and efficacy testing of certain vaccines (*7*), the investigation of diseases which only they share with humans, as well as to behavioral studies such as those on cognition and language development that have already provided benefits for handicapped human children (*8*). In the following sections, the opportunities, and in some cases limitations, for primate research are highlighted. This article is not intended to be a comprehensive review of the many kinds of studies in which primates are used, or the accomplishments of research. Our intention is to convey an understanding of the range of biological, behavioral, and medical disciplines in which primates play an important or essential role.

Neuroscience, Neuropsychology, and Neurological Disorders

In the neurosciences and neuropsychology, primates are often the most appropriate subjects for research in the identification of mechanisms underlying human sensory and motor capacities, perception, learning, memory, reasoning, cognition, and cerebral dominance (*9*). Primates have played a major role in increasing our knowledge of the structure, organization, chemistry, and physiology of the human brain (*10*). The complexity of the primate brain and its similarity to that of humans makes primates excellent subjects for the study of motivational states such as hunger, thirst, sexual behavior, and emotion (*11*).

Certain primates are regarded as prime animal models for research on human vision because the morphology and responses of the eyes and central nervous visual pathways closely resemble those of the human (*12*). For example, the center of the retina, the macula, of both humans and primates has several morphologic features that allow a high degree of visual acuity, color discrimination, and complex central neural processing (*13*). Primates are the only species other than humans known to have true Schlemn's canals, highly developed trabecular meshworks, and scleral spurs. In both humans and primates there is a sophisticated functional relationship between the ciliary muscles and the eye's outflow mechanisms. These similarities make the primate an ideal model for research on trauma, ocular defense mechanisms, and the relationship between visual accommodation and aging (*12*).

The understanding and treatment of children's visual disorders benefit from basic and applied research with young primates. Recent behavioral and anatomical studies (*14*) suggest major similarities of visual development in humans and primates, with rough parity at birth. The rate of visual development occurs about four times faster in Old World monkeys than in humans which makes them a convenient model. Studies in monkeys designed to understand human visual development have been strengthened by new techniques and methods, such as near retinoscopy and photorefraction; by modern variants of behavioral methods, such as preferential looking and operant techniques (*15*); and by extended wear contact lenses which can be worn by monkeys in vision studies (*16*).

Despite its many visual similarities to humans, the primate is not the only animal model for eye research. Because there is not a great deal of diversity among mammals in the basic biochemistry or gross morphological organization of tissue, the rabbit has been regarded as possessing the basic structure of the human visual system (*12*). However, it is virtually impossible to conduct experimental procedures on the rabbit eye without inducing an ocular irritative response that includes blood-aqueous barrier breakdown, pupillary miosis, increased intraocular pressure, and anterior uveal hyperemia (*12*). These major differences between rabbit and human eye are not a question in primates, and hence monkeys are more suitable subjects for research on aqueous humor dynamics and related conditions, such as glaucoma.

Primates provide significant advantages over rodents and other lower laboratory animals in studying other aspects of the nervous system as well. The organization of the primate central nervous system, especially the forebrain, is much more complex than in rodents and other laboratory species. This advanced development underlies the expression of higher order motor behaviors and their fine control, such as distal limb and digit movement, in primates. The large, convoluted cerebral cortex, with great areas devoted to associational activities, is almost certainly responsible for the primate's ability to learn highly complex cognitive tasks (*17*) beyond the capacity of species other than humans.

Because the primate brain shares with humans a high degree of plasticity, their cognitive and social behaviors are heavily dependent on learning and the environment, as is the human behavioral repertoire. Hence in studies of the relationship of neural plasticity and the emergence of behaviors dependent upon social learning primates are often the subjects of choice. Primates are suitable

Table 1. Criteria for evaluation of primate research proposals at the Yerkes Regional Primate Research Center of Emory University.

1. Are primates necessary for the proposed study, or can the work be as well conducted with another species or an alternative, nonanimal method?
2. Is the particular primate species selected appropriate biologically or behaviorally for the proposed investigation?
3. Is the study likely to contribute significantly to scientific knowledge or to human or animal health?
4. Is the investigator scientifically and technically qualified to conduct the study?
5. Will the study be conducted in a humane fashion, with proper consideration for the welfare of the animal, and in compliance with existing regulations?
6. If invasive procedures or others likely to produce pain or discomfort are proposed, are they essential to the study?
7. In proposals involving potentially painful procedures or surgery, has provision been made for elimination or minimization of pain or discomfort including proper anesthesia, analgesia, and round-the-clock post-operative care and surveillance?
8. If the research is replication of previous or other ongoing studies, is it justified and needed?
9. Is the number of animals to be used and the research design adequate to produce clearly interpretable results, but not excessive?
10. Will the study limit reproductive capacity in a way that will be injurious to breeding in the particular primate colony or to the species itself?

models for studying the mechanisms underlying various neurological disorders, such as epilepsy (*18*), and for the development and testing of treatments. They have been used extensively in investigations of the genesis and spread of the epileptic seizure and the nature of its focus. In certain species of baboons there is a significant incidence of naturally occurring epilepsy. In these baboons seizures appear to have a genetic basis, since geographical distribution is a major determinant of incidence.

Much of the new knowledge about Parkinsonism and the resurgence of interest in research on this disorder are due to the use of the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated primate as a model. The chronic administration of MPTP in monkeys produces the major neuropathologic features of Parkinson's disease. These features include the bilateral lesions of the substantial nigra and loss of striatal dopamine as well as motor abnormalities that are the hallmark of Parkinson's disease in humans (*19*). The MPTP primate model of Parkinsonism provides scientists with a system for studying the behavioral anomalies, the specific biochemical characteristics, and the pathological manifestations that occur in humans with the disorder. The primate Parkinson-like syndrome also provides a model for designing and testing therapeutic strategies including pharmacological agents and neural grafts (*20*).

In 1985, scientists reported that surgical implants of dopamine-producing fetal monkey brain cells survived and established cellular connections with preexisting tissue in the brains of rhesus monkeys with MPTP-induced Parkinson's-like disorder. Other behavioral and biochemical changes were noted. Within a year several other scientific teams announced replication of the results in several different primate species, strengthening the possibility that this treatment approach may prove safe and effective in patients with Parkinson's disease (*19*). Clinical studies soon were undertaken to evaluate adrenal medullary grafts to treat Parkinson's disease. However, without previous primate studies on adrenal tissue as a guide, the clinical studies have struggled to determine efficacy. Adrenal tissue implants are now being studied in primates (*21*).

The MPTP primate model also is an excellent example of the value of conducting research with primates. The rodent, the initial model for MPTP research, appears to be refractory to the neurotoxic effects of MPTP. If scientists had not proceeded to the monkey, research on Parkinson's disease would have been severely hampered. In addition, at the same time that the toxic effects of MPTP were being recognized in primates, MPTP was being studied as a potential antihypertensive drug (*22*). Thus potential human tragedies were averted by use of the primate as a model system.

Research on Alzheimer's disease does not have the advantage of a primate model that replicates the disorder as well as the MPTP-primate model of Parkinson's disease. Aged rhesus monkeys—those older than 23 years of age—have cognitive and memory deficits and develop senile plaques with neurites derived from cholinergic and other transmitter systems. These aged macaques, while they do not have Alzheimer's disease, nonetheless provide a system for studying the relations between age-associated cognitive deficits and pathological changes that occur in certain transmitter systems of primates and humans (*20*). Alzheimer's disease is primarily a disease of cortical derangement and cognitive impairment. The well-developed cerebral cortex of primates makes these animals extremely valuable for research on Alzheimer's disease. One of the neuropathological changes that has received intensive evaluation by scientists is the cholinergic deficit in the neocortex and the forebrain limbic system. Alzheimer's patients lose 75 to 85% of their neurons in the nucleus basalis of Meynert (nbM). The memory impairments of monkeys in which lesions have been made in the nbM and medial septum are similar to the memory impairments of humans with Alzheimer's disease. The same type of lesion in the rat, which does not have a well-defined nbM, does not produce the type of neuropathologic or behavioral impairments seen in primates (*17*).

There are other damaged areas in the brains of patients with Alzheimer's disease and an alteration in a number of neurotransmitters (*23*). It is unlikely that a single lesion can reproduce the spectrum of neuropathological changes. A better model of Alzheimer's disease may be produced by lesions in the nbM and locus ceruleus (*17*) in the lower brainstem.

Aging

In 1981, Dr. Edward Brandt, then Assistant Secretary for Health, said at a meeting marking the 20th anniversary of the NIH regional primate research centers: "As we begin to delve more deeply into the health problems of aging humans, we will be turning more frequently to nonhuman primates for clues" (*24*). Like humans, primates have life-spans of multiple decades. Captive rhesus monkeys can live into the fourth decade. Monkeys older than 20 years are the equivalent of humans 60 to 70 years old (*13*). Chimpanzees can survive well into their sixth decade.

As they grow older, humans and primates experience many of the same age-related changes in anatomy, physiology, mental function, and behavior (*25*). Monkeys, like humans but unlike rodents, undergo a significant reduction in total brain weight between early and late adulthood. As macaque monkeys age, their brain weight reduces at a rate equal to or greater than the brain weight changes that occur in humans as they age. The losses in brain weight in monkeys and humans occurs in the forebrain, brainstem, and cerebellum, and at the same rate (*13*).

Rhesus monkeys are often used in studies of the aging visual system, because these monkeys have an ocular aging process that is similar to humans, in both the time course of development of presbyopia and in the frequency of the occurrence of senile cataracts and glaucoma (*12*). In aging humans and rhesus monkeys, reductions occur in visual acuity as measured by amplitude of electroretinographic and evoked potential responses to light stimuli. The vitreous body of the aging rhesus eye, like the human eye, undergoes gradual multifocal liquefaction which may increase risk of retinal detachment. Lens opacification also occurs in aging rhesus and humans. The degenerative changes of the maculae of macques older than 20 years of age are similar to the loss of pigmentation and vascular lesions of senile macular degeneration of humans. However, it must be noted that there are some differences in the way that aging changes the visual systems of primates and humans. From the research viewpoint, one of the most notable is that intraocular pressure does not increase with aging in primates as it does in humans (*13*).

As they age, primates also have lower levels of certain neurotransmitters. In the cerebral cortex the capillary walls become thinner with age, suggesting changes in the blood-brain barrier. In aging primates, the coronary vessels thicken, a common antecedent of atherosclerosis in humans that is often related to the behavioral deficits observed in both aged humans and primates (see below) (*26*).

Indeed, the similarities of the learning and memory deficits that accompany aging in primates and humans make these animals excellent models for studying intellectual and social aspects of aging (*27*), correlating the cognitive/memory changes to neurochemical and neuropathological processes (*22*), and devising and attempting experimental interventions and treatments (*27*). Primates, as they grow older, have deficits in memory for recent, but not immediate, events, an increased sensitivity to interfering stimuli, and decreased behavioral flexibility (*27*). Other memory changes that occur in

these animals as they age include slowed reversal learning, increased stereotyping of spontaneous behavior, increased reaction time, changes in sensory processing, and reduced long-term memory. Additional research is required for an understanding of these changes and possible ways of prevention and treatment in humans (*13, 27*).

The use of primates in research on aging is limited somewhat by the availability of macaques and other monkeys that can be characterized as living to an "old age." However, several of the NIH regional primate research centers, which have been documenting and studying the physical and behavioral changes that accompany aging in primates, have colonies which include rhesus monkeys over 20 years old. One center has a group of chimpanzees 45 to 55 years of age. This represents a considerable achievement, because in the wild these apes rarely live more than 35 years.

Reproduction

Primates provide scientists with the closest models of all aspects of reproduction. Similarities exist in the prenatal development of sexual phenotype, in the endocrine control of the reproductive cycle, and in complications of reproductive processes during mature life and during aging. Investigation of the endocrine mechanisms in macaques that underlie the determination of the sexual phenotype have shown the role of prenatal hormone exposure (*28*). Such experiments would be ethically unacceptable in the human, but have great significance with regard to the development of reproductive competence in children, with direct relation to the psychological problems associated with misdiagnosis of neonatal sex. Similarly, investigations using primates are shedding light on the role played by the elevated levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) detected in the early months of life. Reversible elimination of these elevated levels by administration of agonists of gonadotropin-releasing hormone (*29*) show that the perinatal elevations of steroid hormones may influence subsequent normal sexual development, at least in the male (*30*).

Primates pass through puberty during development, as do humans. The endocrine control of this change is still unclear, but components of the change (known as adrenarche), reflected in alteration of secretions by the adrenal cortex, are susceptible to study only in certain nonhuman primates, including the chimpanzee and possibly the baboon (*31*). Such investigations have been directed to determination of the possible existence of a novel pituitary hormone specifically associated with the maturation process. The endocrine control of spermatogenesis in the male and ovarian function in the female is similar to that of the human in those primate species which exhibit a menstrual, as opposed to an estrous, cycle. The hypothalamo-hypophyseal control of the menstrual cycle in primates and humans is quite different from that of the estrous cycle in other animal species (*32*). Using monoclonal antibodies against components of the sperm surface, and sophisticated analyses of sperm surface composition as the sperm traverses the epididymis, investigators are for the first time gaining an understanding of changes at the molecular level associated with the acquisition of fertilizing capacity by primate spermatozoa. This understanding will help in development of specific methods for control of male fertility at the cellular level (*33*).

Information on the pituitary control of the menstrual cycle, including the understanding that it is dependent upon intermittent hormonal stimuli, and that similarly intermittent stimuli exist in the male, has been derived from study of the primate (*34*). Understanding of this control mechanism has opened the way for identification of abnormalities in the pulsatile secretion of reproductive hormones in the human female which have been implicated in precocious and delayed puberty, anovulation, and inadequate luteal phase. The last two clinical problems have a direct bearing on individual fertility. Macaques have been used for comparison of potential hormonal treatments for endometriosis (*35*). The similarities between human and primate females extend beyond endocrine control and into the behavior patterns resulting from the presence of hormones associated with reproduction. These similarities, plus the difference in social influences and patterns between human and primate females, make it practical and valuable to investigate the effects on behavior of continuous alteration of normal circulating hormone levels, as occurs when women are exposed to contraceptive hormones (*36*).

The anatomical similarities between the species, together with the physiologically similar response to endocrine stimuli, frequently make the primate suitable for the evaluation and development of novel methods for fertility control as well as for investigations of pregnancy. Evaluation of, for example, Gossypol as a male contraceptive was conducted with primate males. Those studies permitted the determination of a site of action for the compound and provided evidence of potential side effects. Hormonal methods for male contraception are also being tested in primates. Analogs of gonadotropin-releasing hormone effectively block pituitary hormone support for spermatogenesis, resulting in reversible sterility. Use of primate models has also shown the presence of undesirable effects of certain of these analogs on secondary sexual characteristics, and further experiments are being undertaken in an effort to identify a mixture of hormones that will avoid the problems (*37*). The anatomical, physiological, and endocrinological similarity of human and primate females makes the latter suitable for evaluation of novel contraceptive modalities that cannot be tested initially in the human because of the possibility of unacceptable pregnancy rates during the test period. Such methods include nonhormonal modification of cervical secretions to prevent sperm penetration (*38*).

An early breakthrough in the area of the immunology of pregnancy resulted from the use of primates—the identification of the Rh (Rhesus) factor. Today, species as diverse as the marmoset and baboon are being used to study the immunology of implantation and pregnancy, with the goal of developing contraceptive vaccines and determining the mechanism of early pregnancy loss associated with immunological deficits (*39*). The application of techniques for gamete recovery and in vitro fertilization, very similar to those used in the human, make it feasible to investigate the teratogenic effect of drugs used in the ovulatory and early pregnancy period as well as to evaluate further any risks associated with the process of in vitro maturation and fertilization of gametes. The value of primates in testing for teratogenicity was tragically illustrated by the demonstration of adverse effects of thalidomide on the human fetus in the 1950s and early 1960s. While thalidomide did not reveal its teratogenicity in rodents, its potential for causing fetal abnormalities was readily demonstrated by testing in primates (*40*).

Research in this area is not a one-way street in which animal research is beneficial solely to humans. For example, methods for monitoring fetal development with amniocentesis and ultrasound are important in the management of the captive primate colony. Techniques for collection of gametes developed for domestic species have been modified to permit collection and storage of sperm and ova from the primate. These techniques will have an important role to play in the conservation and management of endangered primate species, such as the gorilla, pygmy chimpanzee (bonobo), and golden lion tamarin (*41*).

As in the human, nonhuman primates exhibit considerable longevity. The chimpanzee and rhesus macaque, in particular, may be suitable models for study of the menopause and its associated clinical and physiological changes such as osteoporesis. The underlying

mechanism for the endocrine changes that occur at the time of menopause in the human are not known, but similar alterations occur over a more prolonged period in the chimpanzee, thus permitting a more detailed longitudinal analysis of the changes as they occur (*42, 43*). Such studies complement those conducted in the clinical setting, and extend the evaluation of treatment methods into areas not ethically possible with humans.

Behavior

The primate order is composed of species which, while diverse with respect to some elements of social organization, ecology, and behavioral function, share a marked gregariousness, a large brain, and a relatively long period of development. As a consequence of these shared features, primate species exhibit prolonged dependence on others after birth. In addition, they display highly complex behavior which is modified by learning and by social, environmental, and experiential factors. Primates, therefore, provide excellent models for the study of behavioral phenomena ranging from basic social structure and function to analysis of cognitive capacity, including learning and communication. Of particular importance, primate studies provide the opportunity to examine the development, expression, and biological etiology of complex behaviors in a system that is not modified by cultural influences. While each species has its own behavioral proclivities, based on the interaction of biology and experience (*2*), primates in general develop socially and relate to each other and their environments in ways that are more similar to humans than to other animals (*44*).

Behavioral investigations of monkeys and apes have been conducted in a variety of settings including the natural habitat, captive social environments such as zoological parks, and the laboratory. Each study environment offers advantages and disadvantages which make it well suited for addressing certain research issues but not others. For example, studies in the field, which have expanded greatly in the past two decades, have focused on a wide range of species and provided a wealth of information on the basic structure of social systems, behavioral patterns, and the interplay between behavior and ecology (*45*). The disadvantages of field studies include the inability to control variables, the need to monitor complex environments, and, increasingly, the destruction of natural habitats (*44*). On the other hand, the typical laboratory environment, in which animals are housed either singly or in small groups, offers great control of extraneous variables and allows the investigation to focus on a particular behavior in a minimal social context. In such a setting the animal is far removed from the natural environment, and isolated from many variables that normally exert an influence. While the range of relevant research issues is consequently narrowed, the laboratory environment is highly suited for focus on a particular behavior, such as cognition, or to measuring or manipulating biological variables to examine their behavioral influences. An intermediate environment may be found in the captive social setting, such as the large colony which has been maintained on a Puerto Rican island for several decades and permits systematic study of a variety of behaviors in a population of established genetic identity and history (*46*). In addition, socially housed animals living in outdoor corrals may be trained to routine capture and handling, permitting the assessment of the influence of biological variables on behavior in a social context; this kind of setting combines some of the advantages of the field and the laboratory (*47*).

Studies of primates have focused on a wide variety of behavioral phenomena with emphasis on such areas as social organization, mother-infant interactions, aggression, growth and development, puberty, communication, learning, and memory (*48*). Some topics that address questions of fundamental theoretical interest have been extensively studied in multiple contexts. For example, reproductive behavior has been examined from such diverse viewpoints as mating strategies and sexual competition to the role of hormones in the regulation of sexual and reproductive behavior (*48*).

Because of the similarities in humans and primate endocrinology, primates provide scientists with an ideal system for detailing the role of hormones in behavior. Scientists interested in reproduction not only must select a primate species appropriate to the research question, but also a research environment suitable for the study, because the sexual interactions of some primates vary with the conditions under which the animals are studied (*49*). Rhesus macaques, for example, are seasonal breeders when exposed to an outdoor environment, but reproduce year-round when living indoors (*48*).

Another area of behavioral research is communication. Monkeys can transmit information through their vocalizations (*50*), and apes are able to learn and communicate with American Sign Language (*51*), plastic chips that represent English words (*52*), and a computer-operated keyboard of word-symbols that represent objects, actions, events, and people (*53*). In addition to defining the requisites for language acquisition in the human species, language studies with apes have enabled scientists to develop and evaluate language systems for handicapped humans (*8*).

Also directly applicable to understanding human behavioral problems are studies on the effects of infant separation from mothers, mother surrogates, and peers. The separation studies were based on observations of the protest-despair-detachment sequence of reactions by human children separated from their parents (*54*). Signs of distress in young monkeys separated from their mothers are, along with accompanying physiologic changes, very similar to the symptoms that occur in depressed humans (*55*). Numerous biological alterations occur in activity, sleep, heart rate, temperature, endocrine function, immune function, and monomine systems (*56*). Separation studies with primates allow investigators to distinguish betwen the neurobiological mechanisms that mediate and the social factors that modulate the separation response (*57*) and apply the findings to treatment of human situations.

It has been theorized that separation or object loss underlies the development of depression in humans, although not all studies concur. Object loss or separation seems to lead to the development of a grief reaction but not to severe depression except in otherwise vulnerable individuals. Research to define the vulnerability in humans has been limited, and indeed, this is an area in which animal studies may define the conditions which, in humans, lead to depressive-type responses (*58*). Prospective studies with primates in which environmental, social, and individual physiologic factors are systematically manipulated will be instructive. Studies also can focus on individual predisposition (possibly genetically determined), which may interact synergistically with the other variables to cause a particular type of behavior and/or physiological response.

Recent research has strengthened the theory that genetic-environmental interactions are worthy of additional study (*59*) in both primates and humans. Recent studies of human toddlers and preschool children have revealed the existence of developmentally stable individual differences in personality or behavioral characteristics. Some of the children consistently showed fearfulness, anxiety, and cautious withdrawal in response to novelty or challenge, and also had individual differences in psychophysiological and adrenocorticoid reactivity that seem to closely parallel the results with monkeys (*59, 60*). A related and newly emergent area of research, psychoneuroimmunology, combines several disciplines to focus on the psychological events (including environmental, social, and behavioral stress) that can alter immune responses and consequently

susceptibility to disease. Psychologists, neuroscientists, immunologists, and endocrinologists are utilizing the many similarities in behavioral and immunologic function of primates and humans to address questions relating to psychosocial influences on immune competence (*61*).

Atherosclerosis

Until the 1960s, the laboratory animals primarily used in cardiovascular research included rabbits, chickens, dogs, rats, and swine. Today, however, primates are also used extensively for research on human atherosclerosis. One reason for this is that the plaques that develop in monkeys and humans are virtually identical in microscopic and biochemical appearance (*62*). These similarities provide scientists with several unique opportunities in atherosclerosis research. In some primate species, dietary manipulation can produce hyperlipidemia which resembles that seen in humans; the males of some primate species have a greater susceptibility to clinical disease, a phenomenon that occurs in some human populations (*63*). Primates are appropriate for studies to identify the mechanisms of atherosclerotic destruction at cellular and molecular levels (*64*); to determine the course and progress of atherosclerotic disease; and to define the relative influence of such risk factors as hypertension, diabetes, tobacco, alcohol, gender, fats and other nutrients, obesity, and heredity (*65*). Primates are also ideal models for studying the extent to which psychological and social phenomena influence the development of atherosclerotic lesions (*66*).

Old World monkeys are preferred to New World monkeys for studies of atherosclerosis. However, significant species differences exist among Old World monkeys that influence the selection of a primate model for atherosclerosis research. For example, stumptail macaques tend to exhibit obesity with increasing age, a characteristic that limits their use. Baboons have a high prevalence of naturally occurring arterial lesions, but are not prone to developing diet-induced atherosclerosis (*63*). In cynomolgus and rhesus monkeys, atherosclerosis also occurs naturally (*67*), but in the rhesus, lesions develop to a lesser degree (*63*). Among the New World primates only the squirrel monkey, which is susceptible to both spontaneous and diet-induced atherosclerosis, is frequently used in atherosclerosis research. In addition, genetic strains exist that are either hyper- or hyporesponsive to dietary cholesterol (*63*).

Stumptails fed atherogenic diets have a high prevalence of hypertension and high-fat diets generate coronary artery atherosclerosis in both male and female stumptail macaques. In contrast, rhesus and cynomolgus macaques more closely mirror the human species in that males are more prone to develop diet-induced disease than are females (*67*).

Rhesus monkeys also can undergo diet-induced regression of atherosclerosis to a much greater extent than do cynomolgus monkeys (*67*). Various therapies against atherosclerosis are being developed and tested in primates. Indeed, the effectiveness of calcium-blocking drugs in modifying the atherosclerotic process was demonstrated in monkeys after positive studies with rabbits (*68*). Research on high blood pressure can be conducted with monkeys, because the natural hormones that control blood pressure in humans and primates are identical. Monkeys also are models for research on the genetic transmission of high blood pressure (*69*).

Infectious Diseases and Vaccine Development

During the past 25 years, primates have been extensively studied as models for a variety of naturally occurring and experimentally induced bacterial, viral, parasitic, and fungal infections that cause disease in humans (*7, 70, 71*). In many instances, primates are the only animal species in which these diseases occur spontaneously or can be experimentally induced (*70*).

The understanding and control of infectious diseases such as poliomyelitis, yellow fever, measles, and rubella depended on research with primates (*7*). Unusual infectious agents such as the etiologic agent of kuru, a slow virus, have been identified through primate research (*72*). Scientists did not have an animal model for hepatitis B until it was discovered that the chimpanzee could be infected with the virus. Subsequently chimpanzees and marmosets were used in the development of a vaccine against this disease (*73*).

For some infectious diseases, species other than primates are more suitable research models. The primates are truly important in infectious disease studies that are unique to primates and humans, or in which the immunological responses under consideration closely resemble those seen in humans.

Probably no better example of the need for animal models for the intervention of human disease can be found than in the current epidemic of the acquired immunodeficiency syndrome (AIDS). Animal models are needed to test antiviral therapy and to aid in vaccine development. Currently, only chimpanzees can be infected with strains of the human immunodeficiency virus (HIV) and approximately 90 chimpanzees have been infected to date. Of these, none has yet developed an AIDS-like disease. This is not surprising since only a small number of chimpanzees have been infected for more than 4 years and the incubation period for AIDS may extend up to 10 years in humans. It is beyond the scope of this article to provide an exhaustive review due to the extremely large amount of work and the rapid pace of new developments in this area. Recent reviews of animal models of retroviral infections and acquired immunodeficiency diseases have included various animal and nonhuman primate infections (*74, 75*).

Of considerable interest are the occurrence of simian immunodeficiency viruses (SIV), which are closely related morphologically and antigenically to HIV and other lentiviruses. The original SIV viruses (initially termed STLV-III) were isolated from captive rhesus macaques. Preliminary studies revealed that the isolates induced an immunosuppressive disease in juvenile rhesus monkeys in a relatively short time, with many characteristics similar to those of AIDS in humans (*75*). Since that time, similar STLV-III–like viruses were isolated from African Green monkeys and sooty mangabey monkeys. The viruses appear to cause little or no pathogenicity in their natural hosts: however, the sooty mangabey isolate has been shown to induce immunosuppressive disease in macaques (*76*). Monkeys infected with SIV provide models for development and testing of drugs and vaccines and for studies of the influences of various suspected cofactors in the pathogenesis of AIDS. Even though the SIV studies in monkeys cannot at this time replace safety and efficacy testing in chimpanzees, they will greatly complement studies for which sufficient numbers of chimpanzees are not available, and permit rapid screening of vaccines, antiviral agents, and immunomodulators.

Cancer

Primates are susceptible to many oncogenic viruses: type C viruses are related to cancers in owl monkeys and gibbons (*77*), and foamy agents (a subgroup of the leukoviruses) appear to be responsible for lymphomas in rhesus macaques (*78*). A variety of herpes viruses are oncogenic in cotton top marmosets, owl monkeys, and other primates (*79*). Further studies in primates may help to establish the viral etiology of certain tumors. Primates are rarely

used in studies of chemical carcinogenesis, because of the cost and limited supply of primates, the time period needed to complete life studies (*80*), and the primates' extended latency period of tumor development (which can be as long as 10 to 12 years). Although it mirrors the human situation, the long latency period restricts the use of primates for rapid testing of chemicals (*81*). While primates cannot replace rodents for screening chemical carcinogens, the animals can be used to screen chemicals for which data from studies of rodents are ambiguous and conflicting, or chemicals to which large numbers of humans are exposed (*80*).

Primates have been used in the development and testing of monoclonal antibodies against certain forms of cancer, primarily those that arise from solid tumors. Because of the immunological similarities between humans and primates, particularly chimpanzees, monoclonal antibodies derived from primate material should be highly specific when used in laboratory diagnostic assays. For example, human melanoma and leukemia-associated antigens have been defined by antisera from primates (*82*). The immunological similarities should increase the safety of monoclonal antibodies when used in human treatment.

Because of their immunological and physiological similarities to humans, primates are used in evaluating certain cancer treatments, such as the effectiveness of recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) on hematopoietic reconstruction after autologous bone marrow transplantation (*83*).

Limitations and Constraints in the Use of Primates

Systematic scientific study of primates is constrained by a number of factors including progressive destruction of the natural habitat of many species, the high cost of producing and housing monkeys and apes, problems attendant to the large size and aggressive disposition of some primates, the potential for disease transmission between humans and primates, and the objection of anti–animal research organizations which target dogs, cats, and primates in particular.

Expense is a major limitation in the conduct of primate research. For example, a rhesus monkey costs from $600 to $2000 to purchase, and several hundred dollars annually to maintain. Consequently, studies requiring large numbers of primates are rarely feasible. In addition to cost factors, the supply of many species of primates is limited. Indeed, most of the commonly used monkeys and apes are obtained from domestic breeding programs. Nonetheless, the low reproduction rates (as compared to rodents, for example) and long developmental period limit supply and elevate costs. Space for housing and care of the animals is also a consideration, with substantial space and expensive materials required.

The size and natural aggressiveness of some primate species pose potential problems for researchers that require special precautions in the handling, management, and care of primates and in training personnel. In particular, investigators must employ procedures designed to eliminate stress in the animal and protect personnel and animals from injury and disease. For example, herpes B, a neurotropic virus, occurs naturally in macaque monkeys; all macaques should be presumed to carry the virus, which may cause fatal infections in humans and certain other primate species (*84*). Similarly, the Marburg virus was first discovered because it produced a fatal hemorrhagic fever in laboratory workers and personnel who were in contact with infected African Green monkeys (*85*). While there is presently no evidence that the SIVs can be transmitted to or cause illness in humans, research and animal care personnel must be especially cautious about handling primates known to be infected with or likely to harbor SIV. The incidence of tuberculosis in captive primate colonies has decreased in recent years because few primates are imported from the wild and because surveillance programs have been instituted in both animal colonies and research personnel. Surveillance eliminates infected animals and decreases the spread of disease in domestic colonies (*86*).

Another impediment to primate research is the animal rights movement, which holds the view that research with animals, particularly primates, is unnecessary, inhumane, and unethical. The campaign against primate research is actually based on the scientists' rationale for studying primates: the biological and behavioral similarities of primates to humans. As an example, antiresearch groups in 1983 singled out the NIH regional primate research centers as a target, and opposition to primate research has remained as a major focus of the animal rights agenda. One consequence of this activity has been new legislation, including a directive to the Department of Agriculture to develop standards for physical environments that promote the "psychological well-being" of laboratory primates. The U.S. Department of Agriculture's interpretation of that stipulation has been slow to be articulated chiefly because neither the regulators nor the scientists who study primates can define a concept as vague as "psychological well-being." Ideally, the interpretation will ultimately be based on scientific studies, some of which are under way, and on factors that influence the development and expression of normal behavior in laboratory primates. Such studies, by qualified scientists, are needed before primate research laboratories are required by federal regulation to build costly new facilities and adopt new labor-intensive husbandry routines (*87*) that may turn out to be irrelevant to the "psychological well-being" of primates. This illustrates how well intentioned legislation based on emotional rather than empirical arguments can negatively impact scientific inquiry, with as yet, unmeasured consequences for behavioral and biomedical research directed toward the improvement of both human and animal health.

REFERENCES AND NOTES

1. C. G. Sibley and J. E. Ahlquist, *J. Mol. Evol.* **26**, 99 (1987).
2. D. M. Rumbaugh, in *G. Stanley Hall Lecture Series*, A. M. Rogers and C. J. Scheirer, Eds. (American Psychological Association, Washington, DC, 1985), vol. 5, pp. 7–53.
3. T. Ruch, in *Biology and Pathology of Monkeys; Studies of Human Diseases in Experiments on Monkeys, Proceedings of the International Symposium in Sukhumi, 17 to 22 October 1966* (Tbilisi, Moscow, 1966), p. 104; R. A. Mittermeier and A. F. Coimbra-Filho, in *Reproduction in New World Primates*, J. P. Hearn, Ed. (MTP, Lancaster, U.K., 1982), pp. 3–37; W. I. Gay, in *Primates, the Road to Self-Sustaining Populations*, K. Benirschke, Ed. (Springer-Verlag, New York, 1986), pp. 513–520.
4. U.S. Congress, Office of Technology Assessment, *Alternatives to Animal Research Testing and Education* (Government Printing Office, Washington, DC, 1986).
5. D. R. Mann, D. C. Collins, M. M. Smith, M. J. Kessler, K. G. Gould, *J. Clin. Endocrinol. Metab.* **63**, 1277 (1986).
6. W. R. Dukelow, in *Nonhuman Primate Models for Human Diseases*, W. R. Dukelow, Ed. (CRC, Boca Raton, FL, 1983), preface; D. O. Johnsen and L. A. Whitehair, in *Primates, the Road to Self-Sustaining Populations*, K. Benirschke, Ed. (Springer-Verlag, New York, 1986), pp. 499–511.
7. F. A. King and C. J. Yarbrough, *Physiologist* **28**, 75, (1985).
8. M. A. Romski, R. A. White, C. E. Millen, D. M. Rumbaugh, *Psychol. Rec.* **34**, 39, (1984).
9. F. A. King, testimony presented before the Committee on the Use of Laboratory Animals in Biomedical and Behavior Research of the Commission on Life Sciences and Institute of Medicine, 11 February 1986, Washington, DC; J. H. R. Maunsell and W. T. Newsome, *Annu. Rev. Neurosci.* **10**, 363 (1987); J. Moran and R. Desimone, *Science* **229**, 782 (1985); H. Spitzer, R. Desimone, J. Moran, *ibid.* **240**, 338 (1988).
10. F. A. King, in *Using Psychological Science, Making the Public Case*, F. Farely and C. Null, Eds. (Federation of Behavioral, Psychological, and Cognitive Sciences, Washington, DC, 1987), pp 5–12.
11. E. Satinoff and P. Teitelbaum, in *Handbook of Behavioral Neurobiology: Motivation*, F. A. King, Ed. (Plenum, New York, 1983), p. 6.
12. L. Z. Bito, *Exp. Eye Res.* **39**, 807 (1984).
13. D. M. Bowden and D. D. Williams, *Adv. Vet. Sci. Comp. Med.* **28**, 305 (1984).
14. T. N. Wiesel, *Nature* **299**, 583 (1982).
15. R. G. Boothe, V. Dobson, D. Y. Teller, *Annu. Rev. Neurosci.* **8**, 495 (1985).
16. J. A. Gammon, R. G. Boothe, C. V. Chandler, M. Tigges, J. R. Wilson, *Invest. Ophthalmol. Vis. Sci.* **26**, 1636 (1985); R. G. Boothe, L. Kiorpes, M. R. Carlson, *J.*

Pediatr. Ophthalmol. Strabismus **22**, 206 (1985).
17. J. H. Kordower and D. M. Gash, *Integr. Psychiatry* **4**, 64 (1986).
18. E. D. Louis, P. D. Williamson, T. D. Darcey, *Yale J. Biol. Med.* **60**, 255 (1987).
19. R. S. Burns *et al., Proc. Natl. Acad. Sci. U.S.A.* **80**, 4546 (1983); R. A. E. Bakay, D. L. Barrow, M. S., Fiandaca, A. Schiff, D. C. Collins, *Ann. N.Y. Acad. Sci.* **495**, 623 (1987); R. A. E. Bakay, D. Barrow, A. Schiff, M. Fiandaca, *Congr. Neurol. Surg. Sci. Program* **35**, 210 (1985); D. E. Redmond, Jr., *et al., Lancet* **i**, 1125 (1986).
20. L. C. Cork, C. A. Kitt, R. G. Struble, J. W. Griffin, D. L. Price, *Prog. Clin. Biol. Res.* **229**, 241 (1987).
21. R. Lewin, *Science* **240**, 390 (1988).
22. J. W. Langston, *Integr. Psychiatry* **78**, 64 (1986).
23. J. Hardy *et al., Neurochem. Int.* 7, 545 (1985).
24. E. N. Brandt, Jr., speech for the 20th anniversary of the regional primate research centers program, 19 November 1981, Atlanta, GA.
25. J. M. Ordy, in *Neurobiology of Aging*, J. M. Ordy, Ed. (Plenum, New York, 1975), vol. 16, pp. 575–594.
26. D. Bowden, Ed., *Aging in Nonhuman Primates* (Van Nostrand Reinhold, New York, 1979).
27. R. T. Bartus, R. L. Dean, B. Beer, *Psychopharmacol. Bull.* **19**, 168 (1983); L. D. Byrd *et al., Primate Rep.* **14**, 132 (1986).
28. R. W. Goy and J. A. Resko, *Recent Prog. Horm. Res.* **28**, 707 (1972).
29. Gonadotropin-releasing hormone agonists are molecules modified from the basic decapeptide gonadotropin-releasing hormone, which is a hypothalamic hormone responsible for stimulation of release of follicle-stimulating hormone and luteinizing hormone from the anterior pituitary gland.
30. D. R. Mann *et al., J. Clin. Endrocrinol.* **59**, 207 (1984); D. R. Mann, K. Wallen, D. C. Collins, K. G. Gould, unpublished data.
31. G. B. Cutler *et al., Endocrinology* **103**, 2112 (1978).
32. D. L. Healy and G. D. Hodgen, *Excerpta Med. Int. Congr. Ser.* **658**, 117 (1985); R. Johnson, *Res. Resour. Rep.* **4** (no. 6), (1986).
33. L. G. Young, B. T. Hinton, K. G. Gould, *Biol. Reprod.* **32**, 399 (1985).
34. E. Knobil, *Recent Prog. Horm. Res.* **30**, 1 (1974).
35. D. R. Mann, D. C. Collins, M. M. Smith, M. J. Kessler, K. G. Gould, *J. Clin. Endocrinol. Metab.* **63**, 1277 (1986).
36. R. D. Nadler, J. F. Dahl, D. C. Collins, K. G. Gould, M. E. Wilson, in *Proceedings of the National Center for Research in Reproduction Conference on Comparative Reproduction in Mammals and Man* (National Museums of Kenya, Nairobi, in press).
37. F. B. Akhtar, G. R. Marshall, E. Nieschlag, *Int. J. Androl.* **6**, 461 (1983); D. R. Mann, M. M. Smith, K. G. Gould, D. C. Collins, *Fertil. Steril.* **43**, 115 (1985).
38. K. G. Gould and A. H. Ansari, *Am. J. Obstet. Gynecol.* **145**, 92 (1983).
39. J. P. Hearn, *J. Reprod. Fertil.* **76**, 809 (1986); G. D. Hodgen, in *Animal Models for Research on Contraception and Fertility,* N. J. H. Alexander, Ed. (Harper and Row, New York, 1985), pp. 425–436.
40. C. S. Delahunt and L. J. Lassen, *Science* **146**, 1300 (1964); A. G. Hendrickx, L. R. Axelrod, L. D. Claborn, *Nature* **201**, 958 (1966); G. G. Hendrickx and M. A. Cukierski, *Prog. Clin. Biol. Res.* **235**, 73 (1987).
41. K. G. Gould and D. E. Martin, in *Primates, the Road to Self-Sustaining Populations*, K. Benirschke, Ed. (Springer-Verlag, New York, 1986), pp. 425–443.
42. W. V. Holt, *ibid.,* pp. 413–424.
43. K. G. Gould, M. Flint, C. E. Graham, *Maturitas* **3**, 157 (1981).
44. D. L. Cheney, R. M. Seyfarth, B. B. Smuts, R. W. Wrangham, in *Primate Societies*, B. B. Smuts *et al.*, Eds. (Univ. of Chicago Press, Chicago, 1987), pp. 491–497.
45. J. van-Lawick Goodall in *Animal Behavior Monographs*, J. M. Cullen and C. G. Beers, Eds. (Baillier, Tindall and Cassell, London, 1968), vol. 1, part 3, pp. 161–311; S. A. Altmann, *Social Communication Among Primates* (Univ. of Chicago Press, Chicago, 1967); I. Devore, Ed., *Primate Behavior* (Rinehart and Winston, Boulder, CO, 1965).
46. R. G. Rawlins and M. J. Kessler, Eds., *The Cayo Santiago Macaques: History, Behavior and Biology* (State University of New York, Albany, 1986).
47. M. L. Walker, T. P. Gordon, M. E. Wilson, *J. Med. Primatol.* **11**, 291 (1982).
48. R. D. Nadler, J. G. Herndon, J. Wallis, in *Comparative Primate Biology*, vol. 2A, *Behavior, Conservation and Ecology*, G. Mitchell and J. Irwin, Eds. (Liss, New York, 1986), pp. 363–407; M. E. Wilson, *Endocrinology*, **119**, 666 (1986); I. S. Bernstein, *Behav. Brain Sci.* **4**, 419 (1981); I. S. Bernstein and T. P. Gordon, *Am. Sci.* **63**, 304 (1974); T. P. Gordon, *Am. Zool.* **21**, 185 (1981); K. Wallen and L. A. Winston, *Physiol. Behav.* **32**, 629 (1984); I. S. Bernstein and L. E. Williams, in *Comparative Primate Biology*, vol. 2A, *Behavior, Conservation and Ecology*, G. Mitchell and J. Irwin, Eds. (Liss, New York, 1986), pp. 195–213; H. D. Steklis and M. J. Raleigh, *Neurobiology of Social Communication in Primates* (Academic Press, New York, 1980); R. A. Hinde and M. J. A. Simpson, *Ciba Found. Symp. 33* (Elsevier/North-Holland, New York, 1975), pp. 39–67.
49. K. Wallen, *Science* **217**, 375 (1982).
50. R. M. Seyfarth, D. L. Cheney, P. Marler, *ibid.* **210**, 801 (1980).
51. R. A. Gardner and B. T. Gardner, *ibid.* **165**, 664 (1969).
52. D. Premack, *Intelligence in Ape Language*, in *Ape and Man* (Erlbaum, Hillsdale, NJ, 1976).
53. E. S. Savage-Rumbaugh, in *Conditioned Response to Symbol*, H. S. Terrace, Ed. (Columbia Univ. Press, New York, 1986), p. 433; D. M. Rumbaugh, T. V. Gill, von E. C. Glaserfeld, *Science* **182**, 731 (1973); E. S. Savage-Rumbaugh, D. Rumbaugh, S. T. Smith, J. Lawson, *ibid.* **210**, 922 (1980).
54. J. Bowlby, *Psychoanal. Study Child* **15**, 9 (1960); J. Bowlby, *Int. J. Psycho-Anal.* **41**, 8 (1960).
55. L. A. Rosenblum and G. S. Paully, *Psychiatr. Clin. N. Am.* **10**, 437 (1987).
56. N. H. Kalin and M. Carnes, *Neuro-Psychopharmacol. Biol. Psychiatry* **8**, 459 (1984).
57. M. Reite and R. A. Short, *Arch. Gen. Psychiatry*, **35**, 1247 (1978); ———, I. C. Kaufman, A. J. Stynes, J. D. Pauley, *Biol. Psychiatry* **13**, 91 (1978); M. R. Gunnar, C. A. Gonzalez, B. L. Goodlin, S. Levine, *Psychoneuroendocrinology* **6**, 65 (1981); M. L. Laudenslayer, M. Reite, R. J. Harbeck, *Behav. Neural Biol.* **36**, 408 (1982).
58. W. T. McKinney, E. C. Moran, G. W. Kraemer, in *Frontiers of Clinical Neuroscience*, R. M. Post and J. C. Ballenger, Eds. (Williams and Wilkins, Baltimore, MD 1984), pp. 393–406.
59. S. J. Suomi, in *Anxiety-Like Disorders in Young Nonhuman Primates, Anxiety Disorders of Children*, R. Gittelman, Ed. (Guilford, New York, 1986), pp. 1–23.
60. J. Kagan, in *Measuring Emotions in Infants and Children*, C. E. Izard, Ed. (Cambridge Univ. Press, New York, 1982), pp. 38–66.
61. R. Ader, *Psychoneuroimmunology* (Academic Press, New York, 1981).
62. T. B. Clarkson, in *The Use of Nonhuman Primates in Cardiovascular Diseases*, S. S. Kalter, Ed. (Univ. of Texas Press, Austin, 1980), p. 452; T. B. Clarkson *et al., Ann. N.Y. Acad. Sci.* **162**, 103 (1969); C. B. Taylor, G. E. Cox, P. Manolo-Estrella, J. Southworth, *Arch. Pathol.* **74**, 16 (1962); C. B. Taylor, P. Manalo-Estrella, G. E. Cox, *ibid.* **76**, 239 (1963); C. B. Taylor *et al., ibid.*, p. 404.
63. M. P. Jokinen, T. B. Clarkson, R. W. Prichard, *Exp. Mol. Pathol.* **42**, 1 (1985).
64. R. Ross, *J. Am. Geriatr. Soc.* **31**, 213, 1983).
65. R. W. Wissler, in *The Use of Nonhuman Primates in Cardiovascular Diseases*, S. S. Kalter, Ed. (Univ. of Texas Press, Austin, 1980), pp. 15–32.
66. T. B. Clarkson, K. W. Weingard, J. R. Kaplan, M. R. Adams, *Circulation* **76** (Suppl I), 120 (1987).
67. T. B. Clarkson, M. S. Anthony, R. W. Prichard in *The Comparative Pathology of Nonhuman Primate Atherosclerosis, Regression of Atherosclerotic Lesions*, M. R. Malinow and V. H. Blatow, Eds. (Plenum, New York, 1984), pp. 61–78.
68. W. W. Parmley, S. Blumlein, R. Sievers, *Am. J. Cardiol.* **55**, 165B (1985).
69. W. R. Hendee, J. M. Loeb, M. R. Schwarz, S. J. Smith, *Use of Animals in Biomedical Research, the Challenge and Responsibility*, AMA White Paper (American Medical Association, Chicago, IL, 1988).
70. H. M. McClure, *Vet. Sci. Comp. Med.* **28**, 267 (1984).
71. K. F. Soike, S. R. S. Rangan, P. J. Gerone, *ibid.*, p. 151.
72. D. C. Gajdusek, C. J. Gibbs, Jr., M. Alpers, *Nature* **209**, 794 (1966).
73. W. I. Gay, in *Primates, the Road to Self-Sustaining Populations*, K. Benirschke, Ed. (Springer-Verlag, New York, 1986), pp. 513–520.
74. N. W. King, *Vet. Pathol.* **23**, 345 (1986).
75. R. C. Desrosiers and N. L. Letvin, *Rev. Infect. Dis.* **9**, 438 (1987).
76. J. M. Ward, *Am. J. Pathol.* **127**, 199 (1987); H. M. McClure *et al., Proceedings of the Third International Conference on AIDS*, June 1987, Washington, DC, p. 212.
77. H. Rabin, in *Recent Advances in Primatology*, D. J. Chivers and E. H. R. Ford, Eds. (Academic Press, New York, 1978), vol. 4, pp. 101–115.
78. J. L. VandeBerg, *Genetics of Nonhuman Primates in Relation to Viral Diseases in Viral and Immunological Diseases in Nonhuman Primates* (Liss, New York, 1983), pp. 39–66.
79. M. D. Daniel, N. W. King, R. D. Hunt, in *Nonhuman Primate Models for Human Diseases*, W. R. Dukelow, Ed. (CRC Press, Boca Raton, FL, 1983), pp. 55–56; R. D. Hunt, in *Recent Advances in Primatology*, D. J. Chivers and E. H. R. Ford, Eds. (Academic Press, New York, 1978), vol. 4, pp. 117–124.
80. R. H. Adamson and S. M. Sieber, *Basic Life Sci.* **24**, 129 (1983).
81. B. A. Lapin, *J. Med. Primatol.* **11**, 327 (1982).
82. J. R. Held, in *Viral and Immunological Diseases in Nonhuman Primates*, S. S. Kalter, Ed. (Liss, New York, 1983), pp. 3–16; H. F. Siegler, R. S. Metzgar, T. Mohoakumar, G. M. Stuhlmiller, *Fed. Proc.* **34**, 1642 (1983).
83. A. W. Nienhais *et al., J. Clin. Invest.* **80**, 573 (1987).
84. A. Hellman, M. N. Oxman, R. Pollack, Eds., *Biohazards in Biological Research* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1973).
85. R. Siegert and W. Slenczka, in *Laboratory Diagnosis and Pathogenesis in Marburg Virus Disease*, G. A. Martini and R. Siegert, Eds. (Springer-Verlag, Berlin, 1971), pp. 155–160.
86. H. M. McClure *et al.*, in *Primates, the Road to Self-Sustaining Populations*, K. Benirschke, Ed. (Springer-Verlag, New York, 1986), pp. 531–556.
87. D. M. Bowden, *Neurosci. Newslett.* **19** (no. 2), 1 (1988).
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