

Studies in Neurobiology and Aging at the United States National Institutes of Health-Sponsored Regional Primate Research Centers

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The seven NIH-sponsored Regional Primate Research Centers conduct a wide variety of studies in the neurosciences and on aging. Monkeys and chimpanzees are investigated to validate the results of research obtained with lower species. In addition, primates are often the only species with the appropriate characteristics for studying a particular health problem or certain behavioral or biological principles. One neurological disorder for which the primate model has proven crucial is Parkinson's disease. The surgical implantation of dopaminergic cells and tissue containing a growth factor has been developed in the primate model, and is now being evaluated clinically in humans with Parkinsonism. In addition to neurological diseases such as Parkinson's, multiple sclerosis, and epilepsy, the visual system is a strong focus of basic and applied research at the Centers. In 1981, two neuroscientists whose basic research on vision with application to pediatric ophthalmology took place in part at the New England Regional Primate Research Center, were honored with the Nobel Prize in Physiology and Medicine. Currently, vision studies at the Yerkes Regional Primate Research Center, for example, focus on myopia, post-surgical treatment of congenital cataracts, adult cataract development and treatment, and laser surgery to correct corneal abnormalities. At the Wisconsin Regional Primate Research Center, the role of diet in visual impairment is evaluated during infancy. Diet is also studied to determine its role in the aging process, and the effects of aging on memory. Further, brain cells and other components of the nervous system in aging are also being investigated at these centers. © 1994 Wiley-Liss, Inc.

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The 1990s have been designated as the Decade of the Brain. Thus, it is particularly appropriate at this International Primatological Society (IPS) Congress, the first in this decade, to highlight the vitality and the contributions of the many

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studies in the neurosciences and aging that are conducted at the seven National Institutes of Health–sponsored Regional Primate Research Centers.

At the Primate Centers, monkeys and occasionally chimpanzees are used to validate the results of research with “lower” species, prior to the application of the findings to the human condition, whether it be a medical disorder, a theory about the mechanisms underlying neurological functioning, mental health, or a variety of cognitive and social behaviors. In the fields of neurobiology and aging, primates are at times the only species with the appropriate characteristics required to solve a particular health problem or understand certain behavioral or biological principles. The very close similarities between the human and primate brain and nervous system account for the crucial role that primates play in the efforts of the Regional Primate Research Centers to develop more effective treatment strategies for neurological disorders and health problems associated with aging. It is important to recognize that in neurobiology and aging, clinical advances rest upon a sound body of knowledge stemming from *basic* research. When clinical applications and benefits occur, they may be applied to primates as well as to humans. Aging and neuroscience studies in primates can contribute to conservation not only by increasing longevity, but also by improving the quality of primate life, while contributing to health-related knowledge for humans. The Regional Primate Research Centers not only generate basic research information for the scientific community, but provide researchers throughout the United States and other nations with direct access to their primate expertise, data bases, and specialized resources and facilities for a wide range of primate species. These resources range from the provision of tissues to outside investigators, to training programs and the establishment of research collaboration. For example, the neurobiology laboratories of the Yerkes Center collaborate with scientists at about a dozen institutions. Each of the seven Regional Primate Research Centers has been involved in research on aging and neurobiology, taking different approaches and attacking different research problems within these fields. The following provides some examples that indicate the scope of neurobiology and aging studies at the Regional Primate Research Centers, although many other studies are also in progress.

In 1985, scientists at the Yerkes Center demonstrated, for the first time in a primate model, the feasibility of using surgical implants of dopamine-producing cells taken from the subjects’ own adrenal cortex, or from primate fetal brains, for the treatment of Parkinson’s disease [Bakay et al., 1985, 1987]. As a first step, a Parkinsonian syndrome was created in primates by the administration of the neurotoxic chemical MPTP, which selectively destroys dopamine-producing cells in the brain [Langston et al., 1984]. Dopamine is a neurotransmitter essential to normal body movement and is deficient in individuals with Parkinson’s disease. This deficiency underlies the rigidity and slowness in walking and other body movements that characterize Parkinsonism. Although drugs such as L-dopa have been developed to replenish the brain’s supply of dopamine, these medications have difficulty in effectively crossing the highly protective blood–brain barrier, and thus have limited efficacy. In addition, these drugs can produce unpleasant and undesirable side effects for the patient, and over time lose their effectiveness [Parkinson’s Disease, 1983].

The Yerkes Center’s 1985 findings with rhesus monkeys, followed by similar results with another monkey species, strengthened the rationale and increased clinicians’ confidence in the value of this new transplant surgery in humans. Many patients who have undergone this cell transplant surgery have experienced modest to substantial improvements in their symptoms [Bakay, 1991]. That the surgeries have not been totally successful is due in part to uncertainty about the best ways

to prepare the cells for implantation and to insure their survival after the surgery. The most effective surgical techniques for this treatment also are unknown. As a consequence, research with the MPTP primate model has continued. Recent studies have improved upon the initial surgical transplant treatment. For example, last year, Yerkes researchers showed increased improvement in both graft survival and motor movements when the implant combined the dopamine-producing cells with small portions of intercostal nerves. These peripheral nerves are located beneath the ribs. While they do not contain dopamine, intercostal nerves have powerful growth factors that help maintain the transplanted dopaminergic cells taken from fetal brain tissue or the adrenal gland [Bakay, 1991; Yerkes studies, 1992]. The co-graft resulted in clinically significant improvement in hand function. This approach with intercostal nerve implant plus dopaminergic cells is now being carried out and evaluated in human patients [Yerkes studies, 1992].

Another potentially more effective surgical technique for the implantation of dopaminergic cells was developed at the Regional Primate Research Center at the University of Washington. The ribbon technique, as it is called, has improved survival of the implanted cells in the primate model [Dubach, 1991]. The animals' motor behavior also improved. In the ribbon technique, the adrenal gland dopaminergic tissue to be transplanted to the brain of the affected monkey is first sliced into tiny slivers, or ribbons, placed into a cannula and inserted into the brain of the Parkinsonian monkey. The Washington Center has also shown the feasibility of using, as a dopamine source, fetal mesencephalic cell aggregates, derived from human tissue and cultured for 15 days before implantation (D. Bowden, personal communication). At both the Yerkes Center and the University of Washington Center, Parkinsonian monkeys were given sensitive behavioral tests to determine how the various treatments affect movement and recovery from the Parkinson's disorder [Dubach et al., 1988; German et al., 1988; Watts et al., 1991; Bowden, personal communication]. The Washington Center also generated quantitative data regarding the distribution of dopamine-producing cells in normal and Parkinsonian rhesus monkeys, showing that in the latter the pattern of cell loss is strikingly similar to that of humans with Parkinson's disease. These findings clearly validate the monkey as a suitable model for human Parkinson's disease research [German et al., 1988]. In addition, the Washington Center demonstrated that Parkinsonian monkeys have oculomotor deficits, such as fixational instability, similar to that which occurs in people with Parkinson's disease [Brooks et al., 1986].

The Wisconsin Regional Primate Research Center has also contributed to research on Parkinson's disease and on the aging process through studies using positron emission tomography (PET) probes of the areas of the brain that produce dopamine in rhesus monkeys. As aging occurs, there is a normal loss of these cells, which Wisconsin scientists are now monitoring longitudinally. They have also established a method of monitoring the effectiveness of treatment approaches for Parkinson's disease by tracking the implanted cells in the MPTP model via PET scanning [PET, 1991; DeJesus et al., 1991, 1992; Holden et al., 1991, 1992].

The visual system is another major focus of the Regional Primate Research Centers. The topics of the visual studies at the primate centers range from myopia [Parker, 1990; McDonald et al., 1990; Iuvone et al., 1990; Raviola & Wiesel, 1978] to cataract surgery [McCarey et al., 1989; Parker, 1990]; laser surgery for the correction of corneal abnormalities [Fantas et al., 1990; Sundarraj et al., 1990; In, 1991]; transplants [Prevention of astigmatism, 1988]; and effects of ultraviolet radiation upon the photoreceptors and neurons of the retina [Effects of UV, 1988]. Some of these studies already have findings that are incorporated into human therapy. A prime example of a clinical application of basic research is provided by

the New England Regional Primate Research Center, where investigators who studied the development and function of the visual system in monkeys were honored with a Nobel Prize in medicine and physiology in 1981. These studies proved clinically relevant because they revealed the importance of visual stimulation to the development in cells in the visual cortex of young primates and, by implication, the human child. By showing that the first 4 years of life are the most critical period for normal visual development in a young child, and that interruption of visual stimulation to the cortex can cause permanent deficits in vision [Wiesel, 1982], the New England Center's studies persuaded ophthalmologists to correct congenital cataracts and similar visual deficits in children earlier in life than had formerly been the practice. Delays resulting in later visual weakness, or amblyopia, and loss of vision can be averted by this early surgery. Research on pre- and early postnatal development of visual structures and pathways in the central nervous system, with the goal of understanding defects of vision and congenital disorders of higher brain functions, continues at the Regional Primate Research Centers [Raviola & Wiesel, 1978; Hendrickson, 1987; Kiorpes et al., 1987; Tigges & Herndon, 1992; Boothe et al., 1988, 1990; Tigges et al., 1990, 1992; Wilson et al., 1991].

At the Yerkes Center, one goal is to define through primate research the underlying neuropathology associated with amblyopia and to apply the results of this basic research to the postoperative treatment of children who have had congenital cataracts surgically removed at early ages. Amblyopia is a developmental clinical disorder that causes poor visual acuity affecting 2–5% of the human population [Gammon et al., 1985; Boothe, 1988, 1990]. A unique team at Yerkes of basic research scientists in neuroanatomy, neurophysiology, and the psychophysics of vision collaborate with experts in contact lens design and with clinical pediatric ophthalmologists at Emory University, Columbia University, and in private practice. This team was the first to employ contact lenses to investigate the mechanisms responsible for normal and abnormal visual development. Opaque contact lenses are used in the same manner that patching is employed with human children, to force the use of the amblyopic or lazy eye. Yerkes scientists and animal care staff reared infant monkeys in these studies under various conditions that simulated treatments that may be used for human babies with unilateral cataracts. Development of visual acuity is tested by preferential looking, a method that is also sometimes used to assess acuity in human infants in clinical settings. Previous studies by investigators at the Yerkes Center and other laboratories have documented that the sequence of visual development in humans and macaque monkeys is similar except that monkeys develop four times faster. Based on these findings, scientists can extrapolate from monkey ages to human ages with more accuracy than would be possible from any nonprimate animal model. Thus, developmental ages for visual development events in children can be related to the monkey studies [Boothe, 1988, 1990].

As part of their studies to determine the complex mechanisms by which the brain controls eye growth, New England Center scientists built upon the research findings of the Washington Center [Young, 1965] to develop the first primate model for myopia, a very common refractive disorder of vision. Their studies showed that the eye elongation that characterizes myopia is caused by an alteration of the visual input. At the IPS Congress, in a symposium titled "Environmental Influences on the Primate Visual System," scientists described studies at Yerkes that complement and extend the New England findings, and demonstrate how myopia in young monkeys may be inhibited during development to produce a more normal eye and vision.

Visual development studies also have been conducted at the Oregon Regional

Primate Research Center, whose scientists provided the first direct evidence that deficiency of taurine, an amino acid present in mother's milk, results in retinal changes that cause visual impairment. They found that taurine-deficient diets also changed the primary visual cortex of rhesus monkeys. Because the retina and brain of the human are less developed at birth than the rhesus monkey, the human infant may be more vulnerable to taurine deficiency than is the infant primate [Neuringer et al., 1987, 1990]. Oregon Center studies on the effects of various dietary components on brain development show that infant monkeys fed commercial purified human infant formulas that are taurine deficient had degenerative changes in the cone outer segments of the retina [Imaki et al., 1987]. As a result of this research, the major manufacturers of baby formulas have begun to supplement their products with taurine. The Oregon Center has also found that Omega-3 fatty acid deficiency affects the retina of the eye and the brain of young rhesus monkeys. These effects could explain the subnormal development in these monkeys' visual acuity as well as their poor behavioral performance on a familiar discrimination learning task. These results have focused attention on the need to reevaluate the lipid composition of *human* infant formulas [Neuringer et al., 1986].

Moving from visual to other neurological disorders, the Wisconsin Center has found that dexamethasone, used widely in humans for the prevention of neonatal respiratory distress syndrome or hyaline membrane disease, damages the cells of the hippocampus and cerebral cortex in the brains of infant rhesus monkeys. The monkeys were exposed to the drug prenatally, just as are human infants. These consequences of damage to the hippocampus and cortex on learning and memory are of serious clinical concern and demand further attention [Uno et al., 1990]. At the Wisconsin Center, diet also is explored in the context of how it affects the process of aging. Rhesus monkeys at the Wisconsin Center as well as at the Caribbean Primate Research Center are involved in a test of the effects of reduced caloric intake, without malnutrition, on a variety of dimensions of aging, such as metabolic rate, ocular function, and immunologic function. The rhesus monkeys on the reduced caloric diet have less body fat, lower weight, as well as lower fasting blood sugar levels and much lower insulin levels, than do controls. These findings suggest improved efficiency of blood glucose regulation in calorie-reduced diets in contrast to the opposite trend that occurs in normal aging controls. Like previous studies with rodents that inspired the primate work, Wisconsin Center research suggests that moderate caloric restriction may slow the rate of aging in primates [Schwartz, 1992; Kemnitz et al., 1992]. Ongoing studies will teach us more about aging in primates, which, like humans but unlike rodents, are long living [Bowden, 1979]. From these studies, the Wisconsin Center scientists hope to learn the biomarkers of aging that can be measured noninvasively, and provide valuable information on physiologic age [Kemnitz et al., 1993].

Obesity is a health problem often associated with aging. Scientists at the Wisconsin Center are attempting to determine its mechanisms and to develop therapies to ameliorate complications associated with this condition. Spontaneously obese animals are studied. The Center, in conjunction with a pharmaceutical firm, has found some promising leads for therapies to influence the decreased insulin resistance that often occurs in obesity with aging and causes such complications as elevated blood sugar and blood pressure [Elson et al., 1992; Spontaneous, 1991]. Scientists at the Wisconsin Center have also examined the effects of administration of dehydroepiandrosterone, or DHEA, in rhesus monkeys. This hormone consistently declines with age. Significant, favorable changes in blood lipid profiles occurred in the aging monkeys whose normal decline of DHEA was reversed by administration of the hormone [Serum, 1992].

It is important to keep in mind the great importance of basic neurological studies without immediate application, such as the Tulane Regional Primate Research Center's studies which elucidated the numbers and types of cells in the primate cerebral cortex and how these change as animals age [Bowden, personal communication; Brizzee et al., 1976]. These findings have helped provide the groundwork for the many aging studies that are being conducted with monkeys at other Primate Research Centers and scientific institutions.

The effects of aging on memory also are under study at several of the Regional Primate Research Centers. The California Primate Research Center recently began neuropsychological and neuroanatomical investigations to determine the effects of aging on memory function. It was found that a certain subpopulation of primates shows significant age-related memory dysfunction, while other equally old monkeys are relatively unimpaired. Identification of the characteristics of animals that are mentally impaired will provide models for a wide range of studies, including the understanding of, and testing of experimental drugs for, Alzheimer's disease and other dementias.

The California Center is defining the neural inputs and outputs of the hippocampus in the monkey brain as a model for understanding the circuitry of human memory function. The hippocampus is essential for the establishment of new memories but is not the only site of memory storage, as we have learned from both clinical and animal studies. Understanding the normal organization of memory systems in primates and eventually humans may enable the development of ways to prevent and rectify memory disorders and facilitate normal memory function [Comparative, 1990].

For several decades, it was believed that aging causes a loss of millions of cells in the brain, and that this cell loss contributed to the memory problems that come with age. Studies of certain areas of the cortex of aged rhesus monkeys at Yerkes, however, reveal no such massive loss. Part of the brain thought to be associated with the cell loss of aging is the dentate gyrus of the hippocampal formation, which is almost certainly involved in laying down long-term memory. In a paper presented at this meeting, however, Yerkes scientists demonstrated that the axon terminals of cells in the dentate gyrus do not change with age; and that this area of the brain does not even have the senile plaques or large vacuoles that are associated with aging in other parts of the brain [Tigges & Herndon, 1992]. Another study at the Yerkes Center focused on cortical Betz cells, certain giant cells in the brains of humans and primates. As aging occurs, these cells do not decrease in number, but they do shrink in size. Precisely how their functioning is affected by aging is not yet defined. In addition, inclusion bodies were identified within these giant cells. Inclusion bodies such as these have been implicated in several chronic degenerative diseases such as Parkinson's and Alzheimer's [Tigges, 1992].

The studies on aging described here have been conducted with rhesus and other monkey species. The Yerkes Center is fortunate to have chimpanzees of advanced age, in their 40s and 50s. When they die from natural causes, we have the opportunity to study age-related changes in the brain. Preliminary results with three chimpanzees, aged 45, 56, and 59 (two of which are the oldest chimpanzees on record), revealed the presence of plaques, amyloid deposits, and Alzheimer's-50-positive neurons [Gearing, 1992]; the same characteristics are reported in normal elderly people as well as in patients with Alzheimer's.

Wisconsin, as well as several other of the Regional Primate Research Centers, has been involved in studies in the complex and new field of psychoneuroimmunology. Wisconsin scientists studied the brains of wild adult vervet monkeys who died spontaneously after undergoing prolonged social stress when moved to an

African research laboratory. When compared to control vervets, the stressed animals showed marked neurodegeneration in the hippocampus of their brains, similar to that which has been found in rodents after prolonged exposure to glucocorticoids or to stress itself. The hippocampus is a principal neural target for glucocorticoids, the adrenal steroids secreted during stress. Glucocorticoid neurotoxicity in the hippocampus may be clinically important, since glucocorticoids are used to control poststroke edema [Uno et al., 1989; Sapolsky, 1987].

Multiple sclerosis (MS) is a most perplexing neurological disorder in which the immune system attacks the patient's own brain, producing patchy demyelination. The cause of MS is unknown. The symptoms of this devastating disorder are often so subtle, variable, and intermittent that diagnosis may be delayed long after brain damage has occurred. These same characteristics make it difficult to monitor effectiveness of treatments [Advanced, 1991]. Two Regional Primate Centers, Tulane [Highlights, 1991] and Washington, are involved in studies of MS. At the Tulane Center, studies have shown that certain coronaviruses can produce demyelinating disease in monkeys similar to MS. Two strains of the virus, one derived from the mouse and another isolated from a human patient with MS, were inoculated into the brains of owl and green monkeys. These studies may help determine whether a viral agent is responsible for MS and how it exerts its effects. The Washington Center is studying the cause of an MS-like disease, by using magnetic resonance imaging and magnetic resonance spectroscopy. Changes in the brain detected by these relatively new imaging techniques most likely reflect breakdown of the blood-brain barrier and the influx of inflammatory cells and fluid into the area of damage [Advanced, 1991].

From Parkinson's disease to MS, from diet to stress, and from vision to motor function, the studies of the Regional Primate Research Centers have opened many, many doors in medicine, science, and health care. Their contributions have been significant and often related to disease entities. In this Decade of the Brain, there is no question that the Regional Primate Research Centers play an increasingly vital role.

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