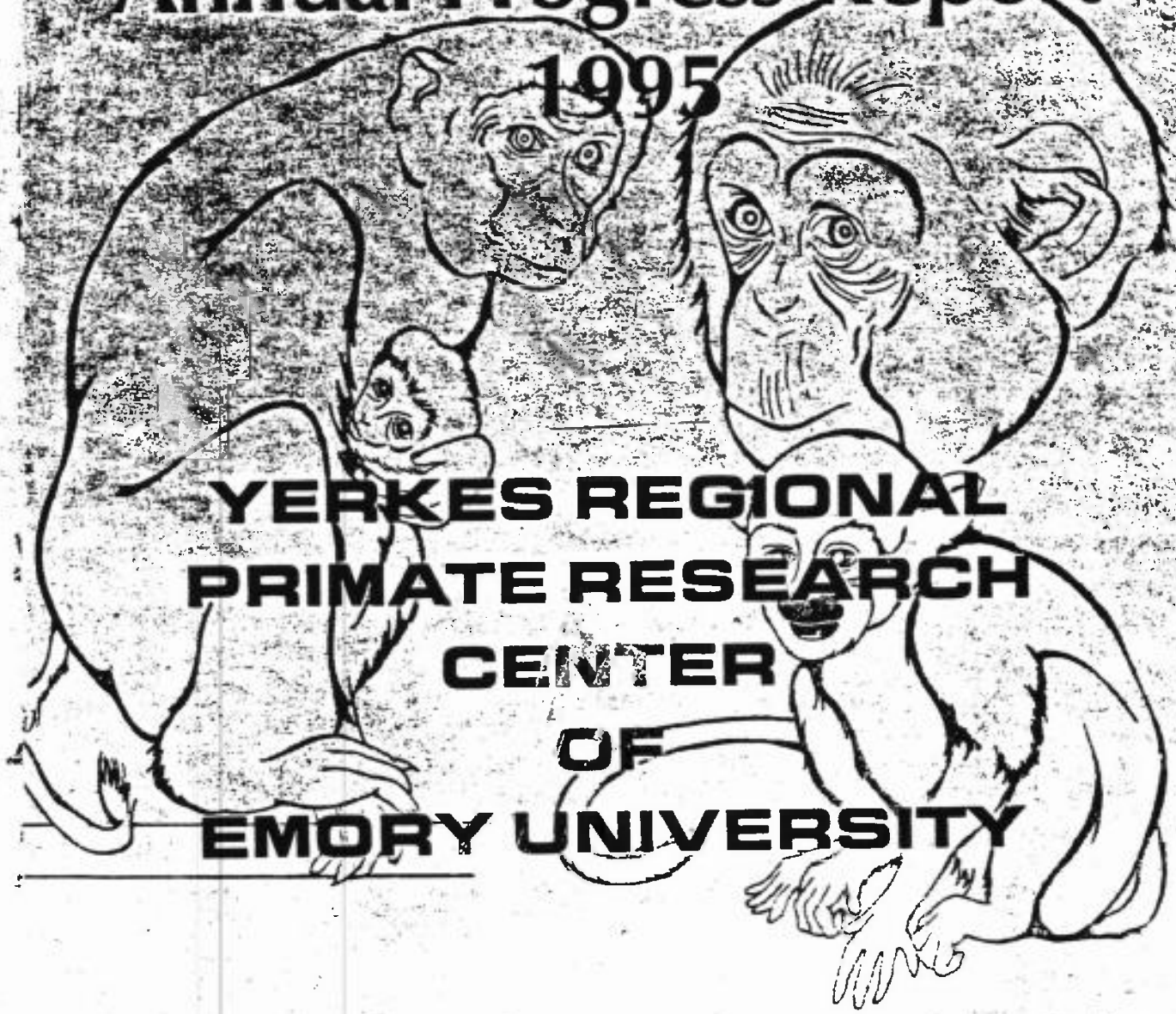
Annual Progress Report 1995



YERKES REGIONAL PRIMATE RESEARCH CENTER OF EMORY UNIVERSITY

January 1, 1995 —December 31, 1995

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR RESEARCH RESOURCES
COMPARATIVE MEDICINE PROGRAM
REGIONAL PRIAMTE RESEARCH CENTERS PROGRAM (rprc)
ANNUAL PROGRESS REPORT

1. PHS GRANT NUMBER: P51RR00165-35

2. NAME OF RECIPIENT INSTITUTION: Yerkes Regional Primate Research Center

3. HEALTH PROFESSIONAL SCHOOL (If applicable): Emory University Woodruff Health Sciences Center

4. REPORTING PERIOD:

   A. FROM (Month, Day, Year): 01/01/95
   B. TO (Month, Day, Year): 12/31/95

5. CENTER DIRECTOR:

   A. NAME: Thomas R. Insel, M.D.

   B. TITLE: Director of Yerkes Regional Primate Research Center, Professor of Psychiatry, and Adjunct Professor of Psychology, Emory University

   C. SIGNATURE: Thomas R Insel

6. DATA SIGNED (Month, Day, Year): April 30, 1996

7. TELEPHONE (Include Area Code): (404) 727-7707

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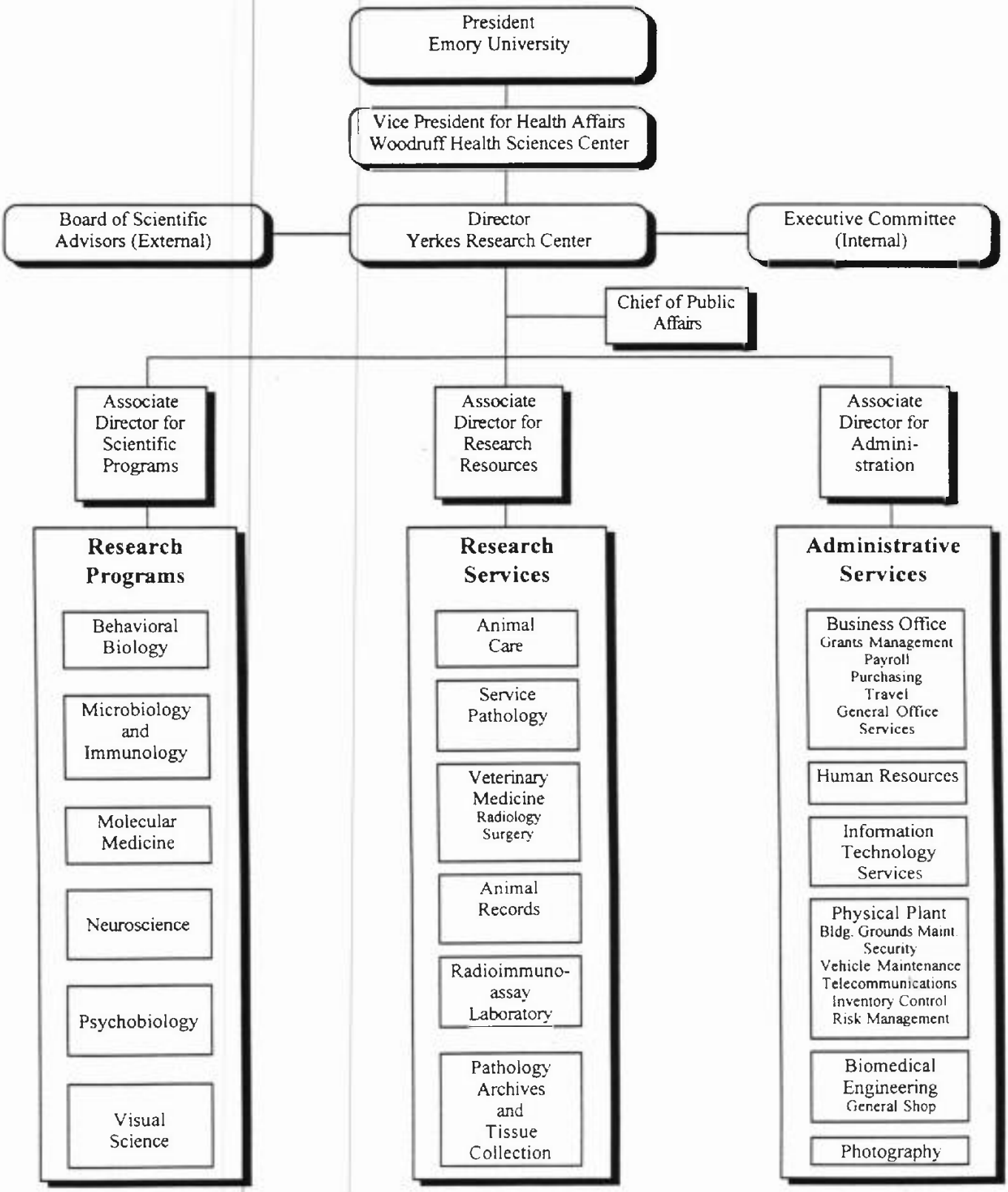
Organizational Chart
Yerkes Regional Primate Research Center
Emory University



FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

EMORY UNIVERSITY

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December 31, 1995

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

Emory University

Atlanta, Georgia

ADMINISTRATION

Yerkes Position	
Director	**T.R. Insel, M.D.**, Research Professor and Acting Chief of Molecular Medicine, Yerkes Center; Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Adjunct Professor of Psychology, Emory University.
Associate Director for Scientific Programs	**T.P. Gordon, M.S.**, Research Professor and Chief of Psychobiology, Yerkes Center; Adjunct Professor of Psychology, Emory University.
Associate Director for Administration	**J.M. Magnotta, B.A.**
Associate Director for Research Resources	**H.M. McClure, D.V.M.**, Research Professor and Acting Chief of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University.
Chief, Public Affairs and Administrative Associate for Special Projects	**C.J. Yarbrough, A.B.J.**

SPECIAL CONSULTANTS TO THE DIRECTOR

Special Consultant in Wildlife Conservation and Paleobiology	**R.E. Leakey**, Managing Director, Richard Leakey and Associates; Adjunct Professor of Anthropology, Emory University.
Special Consultant in Genetics and Molecular Medicine	**D.C. Wallace, Ph.D.**, R. W. Woodruff Professor of Molecular Genetics, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF BEHAVIORAL BIOLOGY
L.D. Byrd, Ph.D., Chief

Core Scientist

L.D. Byrd, Ph.D., Research Professor and Chief of Behavioral Biology, Yerkes Center; Professor of Pharmacology and Adjunct Professor of Psychology, Emory University; Adjunct Professor of Psychology, Georgia Institute of Technology.

Research Scientist

L.L. Howell, Ph.D., Research Scientist of Behavioral Biology, Yerkes Center; Assistant Professor of Pharmacology, Assistant Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine.

Research Associates

W.D. Hopkins, Ph.D., Research Associate of Behavioral Biology, Yerkes Center; Assistant Professor of Psychology, Berry College.

K.F. Schama, Ph.D., Research Associate of Behavioral Biology, Yerkes Center.

Collaborative Scientist

S.G. Holtzman, Ph.D., Collaborative Scientist of Behavioral Biology, Yerkes Center; Professor of Pharmacology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY
H.M. McClure, D.V.M., Acting Chief

Core Scientists

R. Attanasio, D.Sc., Assistant Research Professor of Microbiology and Immunology, Yerkes Center; Assistant Professor of Microbiology and Immunology, Emory University School of Medicine.

H.M. McClure, D.V.M., Associate Director for Research Resources, Research Professor and Acting Chief of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

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Research Associate

F. Scinicariello, M.D., Research Scientist of Microbiology and Immunology, Yerkes Center.

Affiliate Scientists

A.A. Ansari, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Professor of Pathology and Laboratory Medicine and Executive Member, Winship Cancer Center, Emory University School of Medicine.

G.N. Barber, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor, University of Washington Regional Primate Research Center.

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O.J. Finn, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor of Molecular Genetics and Biochemistry and Surgery, University of Pittsburgh School of Medicine.

H.L. Keyserling, M.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pediatrics, Emory University School of Medicine.

C.P. Larsen, M.D., D.Phil., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Surgery, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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Collaborative Scientists

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T.M. Folks, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Chief, Retrovirus Disease Branch of the Division of Viral and Rickettsial Diseases, Centers for Disease Control.

M.N. Golarz, Ph.D., Collaborative Scientist in Microbiology and Immunology, Yerkes Center.

R.M. Grant, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Postdoctoral Fellow, Gladstone Institute of Virology and Immunobiology.

C.D. Hillyer, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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O. Narayan, D.V.M., Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Professor of Microbiology, University of Kansas Medical School.

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R. H. Purcell, M.D., Collaborative Scientist of Microbiology and Immunobiology, Yerkes Center; Head, Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases.

R.F. Schinazi, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor, Department of Pediatrics, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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E.F. Winton, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor of Medicine, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE
T.R. Insel, M.D., Acting Chief

Core Scientists

K.G. Gould, Ph.D., M.R.C.V.S., Research Professor of Molecular Medicine, Yerkes Center; Adjunct Professor of Biology, Emory University.

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Research Scientists

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Associate Scientists

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P.I. Eke, Ph.D., Associate Scientist of Molecular Medicine, Yerkes Center.

Research Associate

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Affiliate Scientists

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D. Graham, M.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Gynecology and Obstetrics Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE (CONTINUED)

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L.A. Hasty, M.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Reproductive Biology Associates, Inc.

N.A. Le, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Reproductive Biology Associates, Inc. Associate Professor of Medicine, Emory University School of Medicine.

J.P. Malmquist, D.M.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Oral and Maxillofacial Surgery, Oregon Health Sciences Center.

D.R. Mann, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Professor of. Physiology, Morehouse School of Medicine

C.P. Markou, Ph.D., Affiliate Scientist of Molecular Medicine, Research Engineer II, School of Mechanical Engineering, Georgia Institute of Technology.

D.E. Martin, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Professor of Respiratory Therapy, Georgia State University.

F.P. Prince, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Biology, Plymouth State College.

K.A. Robinson, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Assistant Professor of Cardiology, Emory University School of Medicine.

E.B. Smithwick, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; BioMedical Research Consultant, Department of Physiology, Emory University School of Medicine.

J.N. Wilcox, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Medicine (Hematology/Oncology), Emory University School of Medicine.

L.G. Young, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Physiology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE (CONTINUED)

Collaborative Scientists

T.F. Dodson, M.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Assistant Professor of Surgery, Emory University School of Medicine.

D.M. Fragaszy, Ph.D. Collaborative Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Psychology, University of Georgia.

B.T. Hinton, Ph.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Assistant Professor of Anatomy and Cell Biology, University of Virginia.

A.B. Lumsden, M.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Assistant Professor of Surgery, Emory University School of Medicine.

L.A. Mueninghoff, D.D.S., Collaborative Scientist of Molecular Medicine, Associate Professor of Restorative Dentistry, University of Alabama.

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N.A. Scott, M.D., Ph.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Assistant Professor of Medicine (Cardiology), Emory University School of Medicine.

R.B. Smith, M.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Professor of Surgery and Head, General Vascular Surgery, Emory University School of Medicine.

M.J. Tucker, Ph.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; Scientific Director, Reproductive Biology Associates.

D.C. Wallace, Ph.D., Collaborative Scientist of Molecular Medicine, Yerkes Center; R.W. Woodruiff Professor of Molecular Genetics, Emory University School of Medicine.

Consultants

S.W.J. Seager, M.A., Consultant in Molecular Medicine, Yerkes Center; Director of Fertility Research Program, National Rehabilitation Hospital, Washington, D.C.

P.N. Srivastava, Ph.D., Consultant in Molecular Medicine, Yerkes Center; Professor of Biochemistry, University of Georgia.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF NEUROSCIENCE
M.J. Kuhar, Ph.D., Chief

Core Scientists

J.G. Herndon, Ph.D., Associate Research Professor of Neuroscience, Yerkes Center; Adjunct Associate Professor of Psychology, Emory University.

T.R. Insel, M.D., Director, Research Professor of Neuroscience and Acting Chief of Molecular Medicine, Yerkes Center; Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine.

M.J. Kuhar, Ph.D., Research Professor and Chief of Neuroscience, Yerkes Center; Professor of Pharmacology, Emory University School of Medicine.

J.W. Tigges, Ph.D., Senior Research Professor of Neuroscience, Yerkes Center; Professor of Anatomy and Cell Biology; Professor of Ophthalmology, Emory University School of Medicine.

Research Associates

R.S. Betarbet, Ph.D., Research Associate of Neuroscience, Yerkes Center.

P.R. Couceyro, Ph.D., Research Associate of Neuroscience, Yerkes Center.

Y.S. Shao, M.D., Ph.D., Research Associate of Neuroscience, Yerkes Center.

J.J. Turner, Ph.D., Research Associate of Neuroscience, Yerkes Center.

Affiliate Scientists

R.A.E. Bakay, M.D., Affiliate Scientist of Neuroscience, Yerkes Center; Professor of Neurological Surgery, Emory University School of Medicine.

A.W. English, Ph.D., Affiliate Scientist of Neuroscience, Yerkes Center; Professor of Anatomy and Cell Biology, Emory University School of Medicine.

M.L. Feldman, Ph.D., Affiliate Scientist of Neuroscience, Yerkes Center; Professor of Anatomy, Boston University.

J.T. Greenamyre, M.D., Ph.D., Affiliate Scientist of Neuroscience, Yerkes Center; Associate Professor of Neurology, Emory University School of Medicine.

J.M. Hoffman, M.D., Affiliate Scientist of Neuroscience, Yerkes Center; Associate Professor of Neurology and Radiology, Associate Director, Center for Positron Emission Tomography, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF NEUROSCIENCE (CONTINUED)

A. Peters, Ph.D., Affiliate Scientist of Neuroscience, Yerkes Center; Waterhouse Professor and Chairman of Anatomy, Boston University.

T. Subramanian, M.D., Affiliate Scientist of Neuroscience, Yerkes Center; Fellow in Neurology, Emory University School of Medicine.

J. Sutin, Ph.D. Affiliate Scientist of Neuroscience, Yerkes Center; Charles Howard Candler Professor and Chair, Anatomy and Cell Biology, Emory University School of Medicine.

R.L. Watts, M.D., Affiliate Scientist of Neuroscience, Yerkes Center; Associate Professor, Department of Neurology, Emory University School of Medicine.

Collaborative Scientists

A.R. Damasio, M.D., Ph.D., Collaborative Scientist of Neuroscience, Yerkes Center; Van Allen Distinguished Professor and Head, Department of Neurology, University of Iowa.

H.B.C. Damasio, M.D., Collaborative Scientist of Neuroscience, Yerkes Center; Professor, Department of Neurology, University of Iowa.

P.R. Kennedy, M.D., Ph.D., Collaborative Scientist of Neuroscience, Yerkes Center; Research Scientist, Bioengineering Center, Georgia Institute of Technology.

S.S. Mirra, M.D., Collaborative Scientist of Neuroscience, Yerkes Center; Professor of Pathology, Emory University School of Medicine.

M.B. Moss, Ph.D., Collaborative Scientist of Neuroscience, Yerkes Center; Associate Professor of Anatomy, Boston University.

P.M. Plotsky, Ph.D. Collaborative Scientist of Neuroscience, Yerkes Center; Professor of Psychiatry and Behavioral Sciences, Emory University School of Medicine.

D.L. Rosene, Ph.D., Collaborative Scientist of Neuroscience, Yerkes Center; Associate Professor of Anatomy, Boston University.

Emeritus

F.A. King, Ph.D., Director Emeritus, Yerkes Center; Professor Emeritus of Neuroscience, Yerkes Center; Professor of Anatomy and Cell Biology, Adjunct Professor of Psychology Emory University.

H. Warner, Consultant in Biomedical Engineering, Division of Neuroscience, Yerkes Center; Professor Emeritus of Psychiatry, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF PSYCHOBIOLOGY
T.P. Gordon, M.S., Chief

Core Scientists

F.B.M. de Waal, Ph.D., Research Professor of Psychobiology, Yerkes Center; Associate Professor of Psychology, Emory University.

T.P. Gordon, M.S., Associate Director for Scientific Programs, Research Professor and Chief of Psychobiology, Yerkes Center; Adjunct Professor of Psychology, Emory University.

H.T. Gouzoules, Ph.D., Associate Research Professor of Psychobiology, Yerkes Center; Associate Professor of Psychology, Emory University.

K. Wallen, Ph.D., Research Professor of Psychobiology, Yerkes Center; Professor of Psychology, Emory University.

M.E. Wilson, Ph.D., Research Professor of Psychobiology and Head, Radioimmuno-assay Laboratory, Yerkes Center; Assistant Professor of Medicine and Associated Professor in Psychology, Emory University.

Associate Scientist

D.A. Gust, Ph.D., Associate Scientist of Psychobiology, Yerkes Center.

Research Associates

F. Aureli, Ph.D., Research Associate of Psychobiology, Yerkes Center.

S.M. Gouzoules, Ph.D., Research Associate of Psychobiology, Yerkes Center; Adjunct Assistant Professor of Anthropology, Emory University.

D. Maestripieri, Ph.D., Research Associate of Psychobiology, Yerkes Center; Postdoctoral Research Associate, Department of Psychology, Emory University; Postdoctoral Research Associate, Department of Physiology, Morehouse School of Medicine.

Affiliate Scientists

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S.T. Boysen, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Assistant Professor of Psychology and Director, Primate Cognition Project, Ohio State University.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF PSYCHOBIOLOGY (CONTINUED)

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T.L. Maple, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Professor of Psychology, Georgia Institute of Technology; Director, Zoo Atlanta.

W.M. Tomasello, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Professor of Psychology and Adjunct Associate Professor of Anthropology, Emory University.

P.L. Whitten, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Assistant Professor of Anthropology, Emory University.

Allied Faculty Member

E.O. Smith, Ph.D., Allied Faculty Member of Psychobiology, Yerkes Center; Associate Professor of Anthropology, Emory University; Affiliate Scientist, Institute for Primate Research and National Museums of Kenya.

Collaborative Scientist

P.G. Judge, Ph.D., Collaborative Scientist of Psychobiology, Yerkes Center; Adjunct Associate Professor of Psychology, Emory University.

Visiting Scientist

E.C. Spada, Ph.D., Visiting Scientist of Psychobiology, Yerkes Center; Research Fellow, Institute of Marine Sciences, University of California at Santa Cruz.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF RESEARCH RESOURCES
H.M. McClure, D.V.M., Associate Director for Research Resources

Animal Resources

Core Scientist

H.M. McClure, D.V.M., Associate Director for Research Resources, Research Professor and Acting Chief of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

Service Pathology

Core Service Faculty

D.C. Anderson, D.V.M., Associate Research Professor of Service Pathology, Yerkes Center

S.A. Klumpp, D.V.M., Veterinary Pathologist of Service Pathology, Yerkes Center.

Primate Enrichment

Research Scientist

K.A. Bard, Ph.D., Research Scientist of Research Resources, Yerkes Center.

Research Associate

K.C. Baker, Ph.D., Research Associate of Research Resources, Yerkes Center.

Veterinary Medicine

Core Service Faculty

J.L. Orkin, D.V.M., Associate Veterinarian, Yerkes Center.

K.S. Paul, D.V.M., Assistant Veterinarian, Yerkes Center.

E.A. Strobert, D.V.M., Associate Veterinarian, Yerkes Center.

R. B. Swenson, D.V.M., Senior Veterinarian, Yerkes Center.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF RESEARCH RESOURCES (CONTINUED)

Consultants

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J.H. Richardson, D.V.M., Consultant in Research Resources, Yerkes Center.

R.E. Weaver, M.D., Ph.D., Consultant in Research Resources, Yerkes Center; Chief, Special Bacteriology Unit, Centers for Disease Control.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF VISUAL SCIENCE
R.G. Boothe, Ph.D., Chief

Core Scientists

R.G. Boothe, Ph.D., Research Professor and Chief of Visual Science, Yerkes Center; Professor of Psychology; Associate Professor of Ophthalmology, Emory University School of Medicine.

M.H. Tigges, Ph.D., Research Professor of Visual Science, Yerkes Center; Associate Professor of Anatomy and Cell Biology; Associate Professor of Ophthalmology, Emory University School of Medicine.

J.R. Wilson, Ph.D., Associate Research Professor of Visual Science, Yerkes Center; Associate Professor of Anatomy and Cell Biology, Emory University School of Medicine.

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Affiliate Scientists

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S.R. Lambert, M.D., Affiliate Scientist of Visual Science, Yerkes Center; Associate Professor and Chief of Pediatric Ophthalmology and Strabismus, Department of Ophthalmology, Emory University School of Medicine.

B.E. McCarey, Ph.D., Affiliate Scientist of Visual Science, Yerkes Center; Professor of Ophthalmology, Emory University School of Medicine.

T.A. Meredith, M.D., Affiliate Scientist of Visual Science, Yerkes Center; Clinical Professor of Ophthalmology, St. Louis University Medical Center.

H.R. Rodman, Ph.D., Affiliate Scientist of Visual Science, Yerkes Center; Assistant Professor of Psychology, Emory University.

P. Sternberg, Jr., M.D., Affiliate Scientist of Visual Science, Yerkes Center; Associate Professor of Ophthalmology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF VISUAL SCIENCE (CONTINUED)

G.O. Waring, M.D., Affiliate Scientist of Visual Science, Yerkes Center; Professor of Ophthalmology, Emory University School of Medicine.

Collaborative Scientists

A.V. Drack, M.D., Collaborative Scientist of Visual Science, Yerkes Center; Assistant Professor of Ophthalmology, Emory University School of Medicine.

P.M. Iuvone, Ph.D., Collaborative Scientist of Visual Science, Yerkes Center; Professor of Pharmacology and Professor of Ophthalmology, Emory University School of Medicine.

W.W. Noyd, M.D., Collaborative Scientist of Visual Science, Yerkes Center; Resident in Psychiatry, Emory University School of Medicine.

R.A. Stone, M.D., Collaborative Scientist of Visual Science, Yerkes Center; Professor of Ophthalmology, University of Pennsylvania.

L.R. Tychsen, M.D., Collaborative Scientist of Visual Science, Yerkes Center; Assistant Professor of Ophthalmology, Pediatrics, Anatomy, and Neurobiology, Washington University School of Medicine.

Visiting Scientists

S.P. Donahue, M.D., Ph.D., Visiting Scientist of Visual Science, Yerkes Center; Fellow, Department of Ophthalmology, University of Iowa Hospitals and Clinics.

R. H. Kardon, M.D., Ph.D., Visiting Scientist of Visual Science, Yerkes Center; Associate Professor, Department of Ophthalmology, University of Iowa Hospitals and Clinics.

J.V. Odom, Ph.D., Visiting Scientist of Visual Science, Yerkes Center; Associate Professor of Ophthalmology, West Virginia University.

Consultant

H.M. Eggers, M.D., Consultant in Visual Science, Yerkes Center; Assistant Professor in Clinical Ophthalmology, Columbia University.

Part I: NARRATIVE DESCRIPTION

A. SUMMARY OF ACCOMPLISHMENTS

1) Strengths and Weaknesses of Current Program

a) Strengths

Close affiliation with host institution: Yerkes' greatest strength derives from its proximity to Emory and its inclusion of some of Emory's most productive investigators. Specifically, programs in cardiology, infectious disease, ophthalmology, and gene therapy are entirely integrated with their corresponding departments in the School of Medicine.

Colony diversity: Yerkes has maintained nine different monkey species as well as all four of the great ape species for comparative research. This is a unique research collection that remains a national resource for investigators interested in hominoid evolution. Yerkes has also played an important role in the conservation of great apes. The Center actively participates in the Species Survival Plan for the orangutan as well as the bonobo.

Field Station: Yerkes has a field site for maintaining breeding colonies in with more naturalistic social compositions than one could achieve with traditional housing. With approximately 350 rhesus monkeys born each year at this site, Yerkes is not only self-sufficient, it is an ideal resource for developmental and reproductive studies.

Research infrastructure: Yerkes has an outstanding cadre of clinical veterinarians experienced with every aspect of husbandry for great apes as well as monkeys. In addition, the Center has a unique service pathology program that provides samples to investigators throughout the country.

b) Weaknesses

Aging facility: Yerkes Main Station was built in 1963. Although several small buildings and trailers have been added since that time for specific projects, the Center does not have the laboratory space or the office space to support the demands of growing research programs.

Aging faculty: Many members of the Core Faculty have been at Yerkes for over 20 years. These investigators are experienced with a range of nonhuman primates and they have enjoyed periods of relatively generous funding. Unfortunately, many of these investigators lack academic appointments and most have not been part of the revolutions in molecular biology, cell biology, and neuroscience that have fundamentally changed research in the past two decades. At a time when nonhuman primate research funding is more difficult to obtain, our Core Faculty must remain competitive than investigators who have worked in other model systems. And we lack diversity: too few young investigators, too few women and too few minority scientists.

Great ape colony: While the Yerkes great ape colony is a unique resource, it is also an expensive endeavor. Yerkes has moved many of its great apes to zoological parks, but roughly 200 chimpanzees remain. These animals grow to 90 Kg, live for 50 years, and require extensive animal care in captivity. In the absence of funding for this colony, more and more of the Center's resources may go into supporting the chimpanzee program. The Center is committed to reducing the size of this colony by contraception and long-term loans, but there is diminishing demand for these animals at other facilities.

2) Changes in Professional Personnel

Dr. Joseph T. Bielitzki resigned his position as Associate Director for Animal Resources to accept an administrative position within the Health Science Center, Emory University

Dr. Harold McClure replaced Dr. Bielitzki as Associate Director for Research Resources. Dr. McClure was replaced as Associate Director for Scientific Programs by Thomas P. Gordon.

3) Major Problems Encountered or Anticipated

During recent years, while the organizational structure and scientific programs at Yerkes remained relatively constant, the world of research funding and the nature of research itself changed dramatically. NIH Base Grant funding has remained flat (actually decreased in real dollars) during this period, investigator-initiated projects have become considerably more difficult to fund, and the use of non-human primates has become more heavily regulated and more expensive. With constraints on funding, Yerkes has had to learn to "do more with less." Indeed, the Base Grant which once

supported animals resources, core scientists, and research technicians is no longer sufficient for salaries of the animal care and clinical veterinary staff. Balancing this dismal change in fiscal support has been the increasing need for non-human primate studies in biomedical research. Now, more than ever, non-human primate models are critical for virology, neuroscience, and molecular medicine, as well as behavioral research. The challenge is to realize this potential when funding is so limited.

In addition to the dismal funding picture, Yerkes faces the challenge of a somewhat cloistered faculty, anxious in the face of change, and an aging physical plant. In my first year as Director, we faced a projected deficit of $600,000 as well as a directive to remove every floor and ceiling in the Center for asbestos abatement. Fortunately, my predecessor had left me a very competent and dedicated administrative team. Working together with the Yerkes Budget Committee, we began the painful process of reducing expenses by restricting or eliminating Base Grant salary support for faculty, down-sizing the administration, freezing new hires, and terminating various services which were duplicated at the host institution, including the Center library. We reformulated the concept of core scientist to require an academic affiliation, at least 60% salary support from non-Base grant sources, and regular evaluation.

But the biggest challenge is in the development of the scientific programs. To that end we have set a clear vision: the Center must strive for scientific excellence if it is to survive. Accordingly, with the help of a newly-formed Scientific Advisory Board (Yerkes' first in 16 years), every scientific program was reviewed in detail. As a result, virtually every division was challenged to become more competitive, not only in the limited domain of primatology but in the larger field of biomedical and biobehavioral research. In some cases this has meant eliminating Center support for research programs; in others, we have merged resources from separate divisions. In every case, we have sculpted divisions to be leaner and more focused. These changes are described in Section 7 below.

4) Major Equipment Items Purchased

Base Grant*

Quantity	Description	Cost
1	Multi-tasking Speedvac System	5,848.00
** 1	Spectronic Genesys 2 115V, 60 Hz	5,920.00
1	32 MB 17" Color-SX-Desktop Pkg.	6,528.00
** 1	Personal Densitometer	16,200.00
1	Airflow Supreme 4' General Purpose Fume Hood with Base Cabinet	6,650.00
1	Airflow Supreme 4' Isotope Hood with Base Cabinet	12,394.00
*1	Chevrolet G10 Cargo Van	18,724.00
*11	Stainless Steel Two Tier Primate Unit with Removable Dividers, Fixed Perch and Auto Waterer	5,362.00
* 6	Stainless Steel Deluxe Primate Caging	5,161.00
* 1	MTP Model 2110 Cage, Rack, and Utensil Washer	60,305.00
1	Primate Caging Unit with Stainless Steel Mobile Angular Rack	5,600.00
1	23 Cubic Foot Upright 86 Degree Centigrade Freezer	6,399.00

* Purchased with Improvement and Modernization Funds
** Purchased with AIDS Funds

Other Grants

1	Cryogenic Freezer with Racking System	6,250.00
1	Experimental Workbench Package with Hardware and Software	7,926.00

5) Improvements and Additions to Facilities

Installation of Relocatable Primate Enclosures	$543,850.00
Installation of Stonhard Flooring System in	13,882.00
Renovation of Room	9,458.00
Installation of Chemical Berms, One at Each of the Three Cage Washer Areas Located	11,283.00
Renovation of Room 241 to Convert to Conference Room at Main Station	15,000.00
Installation of 7.5 Ton Heating and A/C System for Modular Lab Unit at Field Station	17,680.00
Installation of Modular Lab Unit for RIA Facility Located at Field Station	58,454.00

6) Yerkes Speaker Series

Dr. Yoland Smith, Assistant Professor, Department of Anatomy, Faculty of Medicine, Laval University, Quebec, Canada: The Subthalamic Nucleus: A Key Structure in the Functional Organization of the Basal Ganglia in Primates, (12/5/95).

Dr. Linda Porrino, Assistant Professor, Physiology and Pharmacology, Bowman-Gray School of Medicine: The Neurological Consequences of Chronic Cocaine Self-Administration in Primates, (10/26/95)

Dr. Mike Tomasello, Emory Department of Psychology: Chimpanzee Communication and Social Learning, (10/18/95).

Dr. Kate Baker, Yerkes Primate Center: Foraging Instead of Barfing: Normalizing Behavior by Naturalizing Captive Environment, (8/8/95).

Dr. Leonard Howell, Yerkes Primate Center: Pharmacological Modulation of Cocaine's Behavioral Effects, (7/19/96)

Dr. John Glowa, Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health: Development of a Drug Abuse Treatment Model: Issues and Promises, (7/12/95).

Dr. Karl Pribram, James and Anna King Professor and Imminent Scholar at Radford University: Field Concepts in Brain Sciences: Data, (7/11/95).

Dr. Irwin Bernstein, Department of Psychology, University of Georgia: Impressions on Status of India's Primates, (6/9/95).

Dr. Christine M. Johnson, Departments of Anthropology and Cognitive Science, University of California at San Diego: Gaze-Mediated Social Interaction in Pygmy Chimpanzees, (6/9/95).

Dr. Nancy L. Haigwood, Senior Principal Scientists, Department of Immunodeficiency and Immunosuppression Bristol-Myers Squibb Pharmaceutical Research Institute and Affiliate Associate Professor, Department of Microbiology, University of Washington, Seattle, WA: Passive Immune Globulin Delays Disease in the SIV/Macaque Model: A Potential Role for Antibody in AIDS Therapies, (6/8/95).

Dr. Margaret Altemus, Laboratory of Clinical Science, NIMH: Suppression of Stress Responses and Anxiety during Lactation, (6/2/95).

Dr. Andre Nahmias, Professor of Pediatrics and Director Division of Infectious Diseases and Immunology, Department of Pediatrics, Emory School of Medicine and Collaborative Scientist in Division of Immunobiology at Yerkes Center: Thymic Transplantation for AIDS in Monkeys and Children, (6/1/95).

Dr. Dario Maestripieri, Yerkes Research Associate in Psychobiology: Behavioral Studies of Mother-Infant Relationships in Macaques, (5/24/95).

Dr. Alfonso Troisi, Department of Psychiatry, University of Rome: The Relevance of Ethology to Primate and Human Psychopharmacology, (5/15/95).

Dr. Krish Sathian, Department of Neurology, Emory University: Tactile Perception of Texture: Psychophysical and Neurophysiological Studies, (5/5/95).

Dr. Scott Boden, Emory Assistant Professor of Orthopedics and Yerkes Affiliate Scientist in Molecular Medicine: Bone Formation in Spine Using Growth Factors, (5/9/95).

Dr. Filippo Aureli, Yerkes Primate Center, Research Associate in Psychobiology: Tension Reduction and Conflict Resolution in Chimpanzees and Macaques, (4/12/95).

Dr. Krishna K. Murthy, Dept. of Virology and Immunology, SW Foundation for Biomedical Research: AIDS Research: From Man to Chimpanzees and Baboons, (4/14/95).

Dr. William Hopkins, Yerkes Primate Center, Research Associate in Behavioral Biology, Assistant Professor of Psychology at Berry College and Adjunct Assistant Professor Psychology at Emory: Chimpanzees in a Video Arcade: Recent Findings on Cognition and the Brain, (3/9/95).

Dr. Adele Diamond, Professor of Psychology, University of PA: Neural Correlates of Cognitive Activity: Comparisons of Monkeys and Human Children: (2/24/95).

Dr. Jim Herndon, Associate Research Prof. and Dr. Johannes Tigges, Senior Research Professor: Aging of Behavior and Brain in Rhesus Monkeys, (2/22/95).

Dr. Dorothy Cheney, Department of Psychology, University of Pennsylvania: Distinguishing Between Function and Intention in the Calls of Monkeys: (2/3/95).

Deborah Blum, Sacramento Bee newspaper and Pulitzer Price recipient: The Monkey Wars (1/27/95).

Dr. Marla Luskin, Associate Professor in Anatomy and Cell Biology at Emory University: Regulated Proliferation and Migration of Postnatally Generated Forebrain Neurons: (1/12/95).

Dr. Tom Insel, Yerkes Center Director: The Brain and Attachment Behavior, (1/10/95).

7) Administrative and Operational Changes

The Yerkes Regional Primate Research Center is a unit of the Robert W. Woodruff Health Sciences Center of Emory University. The Principal Investigator of this grant, Dr. Charles R. Hatcher, Jr., is the Vice President for Health Affairs and Director of the Robert W. Woodruff Health Science Center. Dr. Hatcher has announced his retirement as of July 1, 1996 when Dr. Michael Johns will arrive as the new Vice President for Health Affairs and new Principal Investigator on the Yerkes Base Grant.

The daily operations of the Center are the responsibility of the Yerkes Director and the Associate Directors for Scientific Programs, Research Resources and Administration. Reporting to the Associate Director for Scientific Programs are the chiefs of the six research divisions. The Associate Director for Research Resources is responsible for veterinary services as well as laboratory pathology, surgery, radioimmunoassay and other support services for research and animal care; and the Associate Director for Administration is responsible for the business office, human resources, and other administrative support units. Also reporting to the Yerkes Director is the Chief of Public Affairs, charged with internal and external communications.

In 1995, the research divisions of the Center were revamped in recognition of changes in the scientific objectives and scientific faculty, as follows:

The previous Division of Immunobiology and Pathobiology has been reconstituted as the Division of Microbiology and Immunobiology, with Service and Research Pathology moving to the Division of Research Resources, headed by Dr. Harold McClure. As recommended in external reviews of Yerkes, the Center is actively recruiting a senior virologist or immunologist to lead the new division (as a replacement for Dr. McClure), with the expectation that this position may be filled within the next fiscal year. In addition, over the next 1-2 years we expect to recruit two additional junior investigators to give the Center a critical mass in AIDS research. Recruitment in this new division will be coordinated with the Emory Department of Microbiology and

Immunology and with the Vaccine Initiative of the Georgia Research Alliance.

The Division of Neurobiology and Vision has been divided to become the Division of Visual Science and the new Division of Neuroscience. Visual Science will be headed by Dr. Ron Boothe, the Chief of the former Neurobiology and Vision, and Neuroscience will be headed by Dr. Michael Kuhar. Dr. Hillary Rodman, currently at Princeton University, has joined the Division of Visual Science as an affiliate scientist (non-core) with an important new program in developmental neurophysiology.

For the Division of Neuroscience, we have recruited Dr. Michael Kuhar, a leading molecular neuropharmacologist in the area of drug abuse, to augment the behavioral pharmacology studies that have been a mainstay at the Center for the past two decades. Dr. Kuhar will occupy an endowed chair in the University, and serve as a Professor of Pharmacology in the School of Medicine. In addition, Dr. Yoland Smith, a well-known primate neuronatomist, will join the faculty in September 1996 and will work closely with the behavioral neurophysiologists (Drs. Wilson and Rodman in the Division of Visual Science), with the imaging program (PET, MRI, and fMRI) at Emory, and with new collaborative scientists from Univ. of Iowa (Drs. Antonio and Hanna Damasio).

A new Division of Molecular Medicine, headed by Dr. Tom Insel on an acting basis, has been established combining elements of the present Division of Reproductive Biology, which no longer has division status, and relevant collaborative programs including cardiovascular medicine, dental research and orthopedic research. The Center will recruit an established scientist in the area of gene therapy to head the division and to establish a major program of research in collaboration with Dr. Doug Wallace, Chair of Emory University Department of Molecular Genetics and head of the Gene Therapy Unit at Emory University Hospital.

The Division of Psychobiology, headed by Thomas Gordon, will retain its current core faculty and add one new member in the area of behavioral pharmacology. Dr. James Winslow has accepted this appointment and will join the faculty in July, 1996.

8) Narrative Progress Report for Non-Research Units

A) Research Resources

Recent reorganization of service units at the Yerkes Center has combined the previous Division of Animal Resources and Veterinary Medicine with Diagnostic Pathology and the Radioimmunoassay Laboratory into a Division of Research Resources. This new division therefore encompasses all Center research resources and services and includes the following units: (1) Office of the Associate Director and Chief, Division of Research Resources, (2) Veterinary Medicine, (3) Service Pathology, (4) Animal Care, Main Station 5) Animal Care, Field Station, (6) Animal Records, (7) Primate Enrichment and (8) Radioimmunoassay Laboratory.

1) Office of Associate Director for Research Resources

The office of the Associate Director for Research Resources provides centralized administration and coordination of the Center's animal care and use program, other resources and support services. This entails continued (1) monitoring of our animal care and use program and facilities to insure compliance with all regulations and requirements of USDA, NIH, AAALAC and other regulatory agencies, (2) provision of clinical veterinary medical care to the animal colony, (3) provision of a diagnostic pathology service to the Center in support of the clinical care of the animal colony as well as in support of ongoing research projects, (4) development of our primate enrichment program to remain in compliance with USDA regulations, (5) maintenance and development of our animal records/computerization program to facilitate storage and retrieval of data for colony management purposes as well as provision of specific information to investigators to assist in ongoing research, (6) provision of animal care and colony management, as required, to insure the availability of the resources and services needed to support Center research activities, (7) provision of veterinary, pathology and animal care support, as needed, to investigators in support of their ongoing research, and (8) collection and distribution of nonhuman primate biological specimens (blood, tissues, etc.) to non-Yerkes investigators. Our overall goal is to provide the resources, services and support structure needed to enhance and facilitate research at the Center.

over last year; 807 of these were monkeys and 83 occurred in apes.

The preventive medicine program for the colony is aimed at interdicting the entry of infectious diseases to the colony by quarantining animals arriving from other sources and by periodic surveillance of established colony animals. The surveillance program includes annual physical examinations, tuberculin skin tests, hematology, clinical chemistries and selected chest radiographs for great apes; tuberculin tests on all individually-housed monkeys at the every 4 months and annually for animals that are group-housed in .

All primates received from outside the Center are quarantined prior to entry into the colony. The quarantine protocol varies depending on the species, source and intended use of the animals, but typically extends for 90 days for old world monkeys, 60 days for new world monkeys and 180 days for apes. Tuberculin tests are given intrapalpebrally every two weeks for monkeys and monthly for apes throughout quarantine. Exit radiographs are often included as well. All new apes are immunized against polio, Streptococcus pneumoniae and Hemophilus influenzae. All colony apes receive the polyvalent type A and B influenza vaccine each year, as recommended for humans by the CDC. Animals housed are immunized with tetanus toxoid. During 1995, 165 new primates were processed through quarantine. This represents a 70% increase over last year.

All personnel working at the Center are tuberculin tested semi-annually if they have animal contact, and annually if they do not have regular animal contact. Positive reactors receive annual chest radiographs that are evaluated by a radiologist at Emory University Hospital. These are coordinated by the Veterinary Section's registered nurse. She also maintains the Center's work-injury log and triages job-related injuries for referral to the occupational health physician on campus.

The Veterinary Section provided support in the form of collection of biological samples, surgery, anesthesia, and diagnostic imaging for 41 core and affiliate scientists on 58 separate projects. This represents an increase of 86.4% and

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Chronic Cocaine Exposure During Gestation

AXIS I: 1a, 2, 15, 21, 23, 24

AXIS II: 36, 50b, 60, 63h, 71, 87

PRC UNIT: Behavioral Biology

INVES1: Byrd, Larry D.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES3: Howell, Leonard L.
DEGREE3: Ph.D.
DEPT3: Behavioral Biology
STAFF3: O

INVES4: Schama, Kevin F.
DEGREE4: Ph.D.
DEPT4: Behavioral Biology
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 38

HOST INSTITUTION: N/A

ABSTRACT: The objectives of this project are to investigate, in a nonhuman primate model, the effects of prenatal cocaine exposure in order to understand better the risks associated with cocaine use during pregnancy. Clinical reports have indicated that an increasing number of pregnant women test positive for cocaine when admitted to the hospital during labor, and that these women and their newborns are at increased risk for a number of abnormalities. The direct effects of cocaine on pregnancy outcome are difficult to ascertain in humans, however, because of a number of confounding factors. Therefore, cocaine's effects on maternal, fetal and neonatal behavior and development are poorly understood. This project is studying in rhesus monkeys the consequences of cocaine administration during gestation in order to characterize effects on the pregnant female, the developing fetus and the resulting offspring in a controlled laboratory environment where the direct contribution of cocaine can be determined. Cocaine was infused via chronically-implanted osmotic minipumps, and drug levels in maternal serum and amniotic fluid were monitored. In control monkeys, saline was substituted for cocaine solution. Sixty pregnancies produced 52 offspring. During the past year, the subjects were tested on cognitive tasks of increasing difficulty in order to assess learning and memory. The respiratory capabilities of the subjects were also assessed, along with the onset of puberty and preliminary studies of brain functioning using magnetic resonance imaging. The monkeys will be studied and assessed during the next 12 months in order to complete testing, and will also be tested for their sensitivity to cocaine when it is self-administered.

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TITLE: Laterality and Cognition in Nonhuman Primates

AXIS I: 1a, 21

AXIS II: 36, 41

PRC UNIT: Behavioral Biology

INVES1: Hopkins, William D.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

SPECIES1: Pan troglodytes
NUM1: 9

SPECIES2: Cebus apella
NUM2: 22

HOST INSTITUTION: N/A

ABSTRACT: During the past year, tests were conducted to determine behavioral and immunological correlates of handedness in nonhuman primates. In one study, left-handed chimpanzees exhibited higher lymphocyte counts compared to right-handed chimpanzees over the course of a three-year assessment of immune response. In a second study, left-handed chimpanzees demonstrated greater avoidance behavior when presented with novel objects compared to right-handed subjects. Finally, a study was conducted on laterality and haptic discrimination in capuchin monkeys. A significant proportion of the subjects exhibited a preference to use their left hand when performing a haptic discrimination task compared to a simple reaching task. Several experiments were also conducted to examine the role of stimulus factors on the expression of cognitive asymmetries in chimpanzees. First, discrimination of compound visual stimuli on the basis of their global configuration or focal elements was examined in eight humans, six chimpanzees and seven monkeys. Overall, the humans performed significantly better than the chimpanzees, and the chimpanzees performed significantly better than the monkeys. For all three species, however, there was an effect for global precedence in the processing of compound stimuli. Thus, performance was significantly better on trials in which stimuli differed on the basis of global configuration compared to focal elements. Preliminary analyses on the chimpanzee data also suggest that discrimination on the basis on the local elements was performed better by the right hemisphere. In a series of experiments, six chimpanzees were tested for lateralization of function in categorical discrimination. A significant left-hemisphere advantage was found for both types of discrimination, but lateralization was much greater for the between-class discrimination. The results suggest that the biological basis of language may be present in nonhuman primates.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY
H.M. McClure, D.V.M., Acting Chief

Core Scientists

R. Attanasio, D.Sc., Assistant Research Professor of Microbiology and Immunology, Yerkes Center; Assistant Professor of Microbiology and Immunology, Emory University School of Medicine.

H.M. McClure, D.V.M., Associate Director for Research Resources, Research Professor and Acting Chief of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

F.J. Novembre, Ph.D., Assistant Research Professor of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

Research Associate

F. Scinicariello, M.D., Research Scientist of Microbiology and Immunology, Yerkes Center.

Affiliate Scientists

A.A. Ansari, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Professor of Pathology and Laboratory Medicine and Executive Member, Winship Cancer Center, Emory University School of Medicine.

G.N. Barber, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor, University of Washington Regional Primate Research Center.

W.E. Collins, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Research Biologist, Division of Parasitic Diseases, Centers for Disease Control.

R.M. Donahoe, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor of Psychiatry, Emory University; Director of Psychoimmunology, Georgia Mental Health Institute.

O.J. Finn, Ph.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor of Molecular Genetics and Biochemistry and Surgery, University of Pittsburgh School of Medicine.

H.L. Keyserling, M.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pediatrics, Emory University School of Medicine.

C.P. Larsen, M.D., D.Phil., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Surgery, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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H.F. Seigler, M.D., Affiliate Scientist of Microbiology and Immunology, Yerkes Center; Professor of Surgery, Duke University.

Collaborative Scientists

R.W. Compans, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Professor and Chair of Microbiology and Immunology, Emory University School of Medicine.

M.L. Eberhard, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center, Chief, Parasitology Activity, Division of Parasitic Diseases, Centers for Disease Control.

M.B. Feinberg, M.D., Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Medicine and Microbiology and Immunology, University of California at San Francisco.

W.H. Fleming, M.D., Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Medicine and Medical Director, Flow Cytometry, Emory Bone Marrow Transplantation Program, Emory University School of Medicine.

T.M. Folks, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Chief, Retrovirus Disease Branch of the Division of Viral and Rickettsial Diseases, Centers for Disease Control.

M.N. Golarz, Ph.D., Collaborative Scientist in Microbiology and Immunology, Yerkes Center.

R.M. Grant, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Postdoctoral Fellow, Gladstone Institute of Virology and Immunobiology.

C.D. Hillyer, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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R. Hong, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Professor of Pediatrics, University of Vermont.

P.R. Johnson, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Henry G. Cramblett Chair in Medicine, Wexner Institute for Pediatric Research, Columbus, Ohio.

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Y. Matsuoka, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Senior Research Associate in Microbiology and Immunology, Emory University School of Medicine.

J.R. Mead, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Research Scientist, Veterans Administration Medical Center.

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G.V. Milton, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Research Scientist, Dialysis Clinic, Inc.

A.J. Nahmias, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Professor of Pediatrics and Director, Division of Infectious Diseases and Immunology, Department of Pediatrics, Emory University School of Medicine.

O. Narayan, D.V.M., Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Professor of Microbiology, University of Kansas Medical School.

C.W. Oettinger, M.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Medical Director, Dialysis Clinic, Atlanta, Georgia.

R. H. Purcell, M.D., Collaborative Scientist of Microbiology and Immunobiology, Yerkes Center; Head, Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases.

R.F. Schinazi, Ph.D., Collaborative Scientist of Microbiology and Immunology, Yerkes Center; Associate Professor, Department of Pediatrics, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY (CONTINUED)

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P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

Title: Role of Virus Specific T Cell Immunity in Primate AIDS

Axis I: 1a, 1d, 2, 7b, 17, 19

Axis II 31, 64, 66

PRC Unit: Microbiology and Immunology

INVES1: Ansari, AA
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
Staff 1: 0

INVES2: Villinger, F
DEGREE2: D.V.M. Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: 0

SPECIES 1: Macaca mulatta
NUM1: 6

SPECIES2: Cercocebus atys
NUM2: 3

NON-HOST INSTITUTION: NA

ABSTRACT: The primary objective of this research is to characterize the temporal changes (if any) in the cytokine profile of lymph node cells of rhesus macaques experimentally infected with SIVmac251. Several studies have previously shown a high degree of correlation between a shift from a prototype TH1 cytokine profile (based on the coordinated expression of sets of distinct but overlapping cytokines synthesized by lymphoid cells) with progression from infection to disease in both human HIV-1 infection and experimental SIV infection. Our purpose has been and continues to be to systematically characterize such changes (if any). Our laboratory has cloned and sequenced nonhuman primate IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-8. IL-10, IL-12α, IL-12β, IL-13, IL-14, IL-15, IL-16, TNF-α, TNF-β, IFN-α, IFN-γ, etc.. In addition, our laboratory has prepared recombinant rhesus macaque IL-2, IL-4, IL-12, IL-15 and IFN-γ. We have also established a semi-quantitative RT-PCR assay to quantitate each cytokine in mRNA. A set of 6 rhesus macaques have been immunized with influenza, tetanus toxoid, KLH and subsequently infected with SIVmac251. Ex vivo PBMC samples and antigen specific PBMC cultures have been collected at varying intervals prior to and post SIV infection. These samples are currently being analyzed for cytokine profile at the mRNA and protein levels.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Regulation of B Cell Immune Responses

AXIS I: 1a, 7b, 19

AXIS II: 31, 64, 66, 91

PRC UNIT: Microbiology and Immunology

INVES1: Attanasio, Roberta
DEGREEI: D. Sc.
DEPT1: Microbiology and Immunology
STAFF1: C

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 25

SPECIES2: Mus musculus
NUM2: 15

NON-HOST INST: NA

ABSTRACT: The objective of this study is to better understand the general mechanisms that lead to the regulation of specific B cell and antibody responses involved either in protective mechanisms against infectious diseases or in deleterious events that may lead to the breakdown of the immune system. To accomplish this objective, we are evaluating 1) the antibody responses generated following viral infection in macaques or experimental injection of selected antigens in mice and 2) the natural autoantibody patterns present in mice and macaques as well as the normal background recognition of non-organ specific autoantigens in macaques. HIV infection in humans and SIV infection in macaques are classical examples in which immune responses specific for the corresponding pathogen are accompanied by B cell dysfunctions and production of autoantibodies. Therefore, we are examining these dysfunctions in SIV-infected rhesus monkeys. Results from this study should help in understanding whether or not such dysfunctions are involved in the pathogenesis of AIDS and in designing strategies for their control. Antibody responses can be regulated, quantitatively and qualitatively, using different immunization methods. For this reason, we are evaluating the influence that DNA immunization exerts on the development of antibodies specific for the CD4 molecule, a major HIV and SIV cellular receptor. Our results show that, in mice, DNA immunization leads to recognition of more conformational epitopes and involvement of different subsets of T helper cells as compared to immunization with soluble CD4. These studies will provide useful information on how to manipulate the antibody production in order to induce protective immunity and avoid deleterious responses.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Induction of Plasmodium Infections to Support Malaria Vaccine Studies

AXIS I: 1a, 3, 4, 7c, 17

AXIS II: 64, 66

PRC UNIT: Microbiology and Immunology

INVES1: Collins, William E.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES 1: Pan troglodytes
NUM1: 9

NON-HOST INST: Centers for Disease Control and Prevention (WEC)

ABSTRACT: Short-term malarial infections were induced in chimpanzees to obtain blood-stage parasites for (1) preparation of genomic libraries, (2) extraction of m-RNA for genetic engineering studies, (3) antigen for serologic tests, (4) infection of mosquitoes through membrane feeding to produce sporozoites for (a) genetic engineering studies, (b) production of monoclonal antibodies, and (c) to infect Aotus and Saimiri monkeys and to test the efficacy of experimental vaccines, and (5) production of immune sera.

The following malarial parasites and animals were inoculated during the past year: Plasmodium ovale---animals CO-529 and CO-547; Plasmodium vivax---animals CO-547, CO-382, CO-529, CO-516, and CO-510. Three of the infections were induced via the bites of infected mosquitoes to circumvent the possibility of viral transmission. These studies will continue in support of the development of vaccines for human malarias.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Mucosal and Systemic Immunity to HTLV and STLV

AXIS I: 1a, 7a

AXIS II: 66, 77, 91

PRC UNIT: Microbiology and Immunology

INVES1: Compans, Richard W.
DEGREEI: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

INVES3: Novembre, Francis J.
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: A STLV-1 related isolate from a baboon is used for vaccine studies. The gene fragment encoding the envelope glycoprotein was cloned into an eukaryotic expression vector (pcDNA1-Amp, Invitrogen). Before using it as a DNA vaccine, we wished to characterize the gene structure and expression. Using Sequence version 2 (USB), the envelope gene was sequenced and its relatedness with known HTLV-1 and STLV-1 isolates was compared. Interestingly, the sequence of the envelope gene of this isolate under study was found to exhibit a high level of sequence identity (97% and 98% respectively at the nucleotide and the amino acid level) to HTLV-1. On the other hand, it was less closely related to STLV-1 (88% at the nt. level and 93% at the amino acid level). Based on the unique sequence of the envelope gene, we have therefore concluded that we have obtained a novel baboon T-cell leukemia virus.

The expression, glycosylation, proteolytic processing, cellular localization and cell surface delivery of the expressed glycoprotein were analyzed using a recombinant vaccinia-based transient expression system. These analyses reveal the functional properties of the envelope as well as the prospects of using the plasmid DNA encoding the env gene in subsequent DNA immunization studies. The envelope precursor was synthesized as a 62-66 kd protein, which is presumably cleaved in to gp46, the extracellular component and gp21, which provides the anchoring function. Although the antiserum analyzed in these assays was not able to immunoprecipitate the

cleavage products, envelope products can be detected on the surfaces of transfected cells as well as on the CEMss cell line established from the infected baboon. In addition, the envelope gene as well as a fragment which should code for a soluble form of the envelope protein are being cloned into several other expression vectors, and their efficiency in protein expression and generation of an immune response are under evaluation.

Infections of macaques with the 1621 virus isolate also have been conducted. For these studies we inoculated three macaques intravenously and three intravaginally with 10^7 infected cells. This was not enough to induce an infection, but did induce an immune response. Repeated infections using greater amounts of cells did not result in infection in these same animals, presumably because of the immune response from the initial challenge. Inoculations of new animals using the 1621 virus, as well as using two additional STLV-1 isolates recently obtained from the AIDS Reagent Respiratory are underway.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Determinants of HIV/SIV Mucosal Transmission

AXIS I: 1a, 7a

AXIS II: 66, 77, 91

PRC UNIT: Microbiology and Immunology

INVES1: Compans, Richard W.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 6

NON-HOST INST: NA

ABSTRACT: Recombinant vaccinia viruses expressing full length or truncated gag or env genes of SIVmac239 are used to investigate the requirements for assembly of SIV proteins. Assembly of virus-like particles (VLPs) was found to be 3 to 5 fold higher with full length env than with the truncated forms, or than VLPs containing only Gag proteins, in primary monkey cells or various human cell lines. When cells expressing Env proteins in the absence of Gag were examined by immunoelectron microscopy, clusters of Env protein and membrane vesicles containing Env proteins were observed at cell surfaces. A low level of vesicles was released from cells expressing full length Env, but about a 10-fold higher level was released in cells expressing a truncated form of Env [Env733(t)] in which the cytoplasmic domain is only 17 amino acids in length. Another truncated protein, Env718(t), with a short cytoplasmic tail of 3 aa was also incorporated into VLPs at a 10-fold higher level than the full length Env protein, and was more efficiently released in vesicles. The mature SU and TM proteins were predominantly incorporated into VLPs with full length Env, but both cleaved and uncleaved precursor proteins were present in VLPs with truncated Env as well as in Env and Env(t) vesicles. A more prominent layer of spikes was seen by electron microscopy in VLPs with truncated Env than in VLPs containing full length Env. These results indicate that truncated Env proteins have the ability to self-associate on the cell surface and are assembled into a more closely packed array than full length Env, which could explain the preferential incorporation of Env proteins with short cytoplasmic tails into virions.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Host-Virus Relationships in Pathogenic and Nonpathogenic SIV Infections

AXIS I: 1a, 7b

AXIS II: 31, 64, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: Feinberg, Mark
DEGREEI: M.D., Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Grant, Robert M.
DEGREE2: M.D., M.P.H. M.S.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Johnson, R. Paul
DEGREE3: M.D.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: Staprans, Silvija
DEGREE4: Ph.D.
DEPT4: Microbiology and Immunology
STAFF4: O

INVES5: Allan, Jonathan
DEGREE5: Ph.D.
DEPT5: Microbiology and Immunology
STAFF5: 0

INVES6: McClure, Harold M.
DEGREE6: D.V.M.
DEPT6: Microbiology and Immunology
STAFF6: C

SPECIES1: Cercocebus atys
NUM1: 12

SPECIES2: Ceropithecus aethiops
NUM2: 12

NON-HOST INST: Gladstone Institute of Virology and Immunology (MBF, RMG, SIS), New England Regional Primate Research Center (RPJ), and Southwest Foundation for Biomedical Research (JA)

ABSTRACT: To investigate the basis for asymptomatic SIV infection in naturally-infected sooty mangabey monkeys and African green monkeys, quantitative-competitive PCR (QC-PCR) (to measure viral load) assays were developed for SIVsmm and SIVagm and the SIVsmm-related virus SIVmac that induces AIDS in rhesus macaques. Interestingly, naturally infected, healthy sooty mangabeys display levels of active SIV replication that equal, and in some cases exceed, those seen in macaques suffering from advanced SIV-induced immunodeficiency. Similarly, SIV-infected African green monkeys demonstrate chronically high levels of plasma viremia. SIV-infected sooty mangabeys have no demonstrable CTL activity against virus expressing cells, and a low titer and antigenically restricted humoral antiviral immune response. The antiviral CTL response of African green monkeys has not been studied, but a similar humoral immune response is seen in infected animals. That SIV replication proceeds at high levels without CD4 depletion and the finding of histologically normal lymphoid tissues in infected animals indicates that the interaction of virus with sooty mangabey host cells is not cytopathic. Results from tissue culture studies support this conclusion, and ongoing studies are focused on elucidating the basis for this lack of cytopathicity.

The evolution of SIVsmm and SIVagm in their natural hosts may have selected for a non-cytophatic course of virus infection of host cells, and a limited or absent antiviral immune response. In species that are not natural hosts for T cell-tropic lentiviruses, and where the virus infection has direct cytopathic consequences, including rhesus macaques and humans, the character of the antiviral immune response may determine the rate of disease progression seen following virus infection, and if incompletely effective, may potentially contribute to immune system compromise.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Dendritic Cell-Based Cancer Vaccines

AXIS I: 1a, 2, 19

AXIS II: 64, 76b, 91

PRC UNIT: Microbiology and Immunology

INVES1: Finn, Olivera J.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES 1: Pan troglodytes
NUM1: 4

NON-HOST INST: University of Pittsburgh

ABSTRACT: Aberrant glycosylation of the mucin molecule (MUC-1) expressed on epithelial tumors leads to the exposure of novel tumor-associated core protein epitopes which are recognized by tumor specific antibodies and cytotoxic T cells (CTL). Consequently, MUC-1 mucin could be considered a possible target for tumor immunotherapy. A candidate anti-mucin cellular vaccine employing autologous dendritic cells instead of tumor cells for the presentation of tumor associated mucin epitopes was tested in chimpanzees because they express the same molecule with the same sequence and tissue distribution. In preparation for the in vivo studies we obtained blood samples from various animals at the time they were undergoing routine physical examinations. We developed a culture system to grow chimpanzee dendritic cells in vitro. This system was then tested in vivo. Dendritic cells were grown for six days in vitro and then loaded with a mucin synthetic peptide or a control antigen ovalbumin. Autologous antigen loaded dendritic cells were then injected IV, and animals boosted once with antigen in conventional adjuvant TIterMax. Three weeks later blood and lymph nodes were collected and examined for the development of mucin-specific or ovalbumin-specific immune response. We found that dendritic cells were effective at inducing OVA-specific immunity, but not much better than the conventional adjuvant. We saw no immunity generated to the mucin peptide with either regimen, confirming our observations in vitro that this peptide sequence does not contain helper epitopes. We are initiating further studies with whole mucin proteins as well as trafficking of dendritic cells after injection.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Breast Tumor Specific Immunity: Vaccine Design

AXIS I: 1a, 2, 19

AXIS II: 64, 76b, 91

PRC UNIT: Microbiology and Immunology

INVES1: Finn, Olivera J.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES 1: Pan troglodytes
NUM1: 2

NON-HOST INST: University of Pittsburgh

ABSTRACT: Aberrant glycosylation of the mucin molecule (MUC-1) expressed on epithelial tumors leads to the exposure of novel tumor-associated core protein epitopes which are recognized by tumor specific antibodies and cytotoxic T cells (CTL). Consequently, MUC-1 mucin could be considered a possible target for tumor immunotherapy. A candidate anti-mucin cellular vaccine employing autologous B cells instead of tumor cells for the presentation of tumor associated mucin epitopes was tested in chimpanzees because they express the same molecule with the same sequence and tissue distribution. EBV-immortalized B lymphoblastoid cell lines (B-LCL) were derived from two chimpanzees, transfected with the MUC1 cDNA and treated with an inhibitor of glycosylation in order to expose the relevant tumor associated epitopes. One cell line was also transduced with a retroviral vector containing IL-2 cDNA and produced low levels of IL-2. Cellular and humoral anti-mucin immune responses were evaluated before vaccination and after each boost by limiting dilution analysis and ELISA assays. Delayed type hypersensitivity (DTH) reaction was measured after the last boost. While no mucin specific antibody or T cells were present prior to vaccination, already after the first injection we found measurable CTL frequency in the peripheral blood and an even higher mucin specific CTL frequency in the lymph nodes draining the vaccination site. The intensity of the response differed between the two animals. Mucin specific DTH was also observed. The vaccine did not elicit antibody responses in either animal. MUC-1 is a self-antigen in the chimpanzee and the anti-mucin immune response can be considered an autoimmune response. Yet, long term observation of the two animals yielded no signs of adverse effects of this immunization.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Human Infection with SIV: Role of *Nef* and its Implications for Live Viral Attenuation

AXIS I: 1a, 7b

AXIS II: 31, 64, 66

PRC UNIT: Microbiology and Immunology

INVES1: Folks, Thomas M.
DEGREEI: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Heneine, W.
DEGREE2: Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Murphy-Corb, M.
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Microbiology and Immunology
STAFF4: C

SPECIES1: Macaca mulatta
NUM1: 6

NON-HOST INST: Centers for Disease Control and Prevention (TMF, WH) and Tulane Regional Primate Research Center (MMC).

ABSTRACT: SIV_{HU} was isolated from an individual who seroconverted to HIV-2/SIV while working with SIV. The individual remains asymptomatic six years after seroconversion, with evidence of extremely low proviral loads, and low, yet stable antibody titers. Sequence analysis of LTR, *vpr*, *env* and *nef* regions of SIV_{HU} show it closest (96-98% homology) to SIV_{B670}, a sooty mangabey strain with which the individual has primarily worked. Sequences of LTR, *vpr*, and *env* revealed no abnormalities of obvious functional significance. In contrast, the *nef* sequence showed a 4 base deletion, a downstream premature stop codon, and a predicted truncation at amino acid 175. *Nef* sequence of SIV_{B670} predicted a full-length protein. Experimental infection of three macaques with SIV_{HU} and three other macaques with SIV_{B670}, resulted in seroconversion in all six animals. All three SIV_{B670} animals died of AIDS-related illnesses at 8.5 and 18 months post inoculation. In contrast, all three SIV_{HU}-infected

monkeys remain healthy at 24 months post inoculation, show evidence of lower viral loads and antibody titers when compared with the SIV_{B670}-animals, and maintain *nef* truncation. These results provide additional evidence for the role of intact *nef* in the pathogenicity of SIV in macaques, and extend our knowledge on the role of *nef* in SIV attenuation in humans.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Hyperimmune Activation and Progression to AIDS in Rhesus Macaques

AXIS I: 1a, 7b

AXIS II: 31, 64, 66

PRC UNIT: Microbiology and Immunology

INVES1: Folks, Thomas M.
DEGREEI: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Villinger, Francois
DEGREE2: D.V.M., Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Anderson, Daniel C.
DEGREE3: D.V.M.
DEPT3: Research Resources
STAFF3: C

INVES4: Ansari, Ahmed A.
DEGREE4: Ph.D.
DEPT4: Microbiology and Immunology
STAFF4: O

INVES5: McClure, Harold M.
DEGREE5: D.V.M.
DEPT5: Microbiology and Immunology
STAFF5: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: Centers for Disease Control and Prevention (TMF)

ABSTRACT: To better understand the contribution of chronic immune activation in progression of lentiviral-induced disease, we infected a total of 9 rhesus macaques with SIVmac251 and followed them for disease onset. At the time of virus infection and at monthly intervals thereafter, groups of 3 animals each were then given either placebo (group I), allogeneic cells (group II), or an alternate schedule of allogeneic cells, KLH, and tetanus toxoid (group III). A fourth group of 3 macaques (group IV, control) was given multiple antigens, similar to the procedures used for group III, but the macaques were not infected. All animals which were hyperactivated and infected with SIV (group III) died within 7 months (2 animals died in 4 months), while only one animal died in group I and II by 7 months. None of the animals in group IV died. The animals in

group III which died by 4 months as well as those in group I and II never seroconverted and had high p24 antigenemia. Studies of immune activation showed that animals in group IV responded with increasing antibody titers to the soluble antigens (Tet Toxoid and KLH) while group II animals initially responded but lost specific antibody titers prior to death. All 5 animals which died of rapid death showed high levels of soluble TNFR-II in their sera.

The data presented here suggest that hyperactivation of SIV-infected rhesus macaques can speed progression of disease. Such information may be useful in understanding the role of immune activation and the contribution of cytokines to the development of AIDS.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Virus-Host Interactions Governing SIV Pathogenesis in vivo

AXIS I: 1a, 7b, 17

AXIS II: 31, 64, 66

PRC UNIT: Microbiology and Immunology

INVES1: Grant, Robert M.
DEGREEI: M.D., MPH, MS
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Feinberg, Mark B.
DEGREE2: Ph.D. , M.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Staprans, Silvja I.
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: Johnson, R. Paul
DEGREE4: MD
DEPT4: Microbiology and Immunology
STAFF4: O

INVES5: McClure, Harold M.
DEGREE5: D.V.M.
DEPT5: Microbiology and Immunology
STAFF5: C

SPECIES1: Cercocebus atys
NUM1: 15

SPECIES2: Macaca mulatta
NUM2: 1

NON-HOST INST: Gladstone Institute of Virology and Immunology (RMG, MBF, SIS) and New England Regional Primate Research Center (RPJ).

ABSTRACT: This study is designed to identify virus-host interactions that correlate with the absence of SIV pathogenesis in sooty mangabeys compared with rhesus macaques that develop simian AIDS after experimental infection. During this reporting period, 14 of 14 naturally infected sooty mangabeys were found to have a high level of plasma viremia using a SIVsmm specific QC-PCR assay developed in this laboratory. Viremia could not be detected in two seronegative mangabeys using assay conditions

capable of detecting as few as 640 SIV RNA copies/ml. There was no evidence for SIV-specific CTL activity in 3 mangabeys with high level viremia using conditions that readily detect anti-SIV CTL activity in rhesus macaques (ie: prestimulation with autologous B cell lines expressing SIV antigens after infection with recombinant vaccinia). These findings suggest that greater immune control of viral replication does not explain the lack of SIV pathogenesis in mangabeys. Analysis of SIVsmm *env* diversity using RNA based heteroduplex mobility assays and direct sequence comparisons indicated that SIV populations in mangabeys are highly diverse. Mangabeys with higher levels of viremia had more diverse virus populations suggesting that random genetic drift, or weak humoral immune selection of structurally unconstrained viral epitopes, were the primary determinants of SIV env diversification in mangabeys. Development of methods for experimental infection of sooty mangabeys were initiated late in the reporting period. One sooty mangabey and one rhesus macaque were intravenously challenged with a common stock of SIVmac239/open nef. Viral replication was attentuated in the mangabey even at early time points (eg:day 2 post-infection) suggesting decreased viral tropism for the mangabey host. Lymphocyte immunophenotyping indicated a surge in CD8 cell activation in the macaque, but not in the mangabey, suggesting that virus-induced cell proliferation may have enhanced viral load in the macaque. Anti-SIV CTL responses were evident in both animals. The strong CTL response in the experimentally infected mangabey differs from the absent or low level CTL activity in naturally infected mangabeys and suggests that the conditions of SIV challenge may affect the induction of cell mediated immune tolerance in mangabeys. Methods of experimental infection will be developed in the coming year to determine the timing and duration of CTL responses after experimental challenge with stocks of SIV derived directly from mangabeys.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Effect of Hematopoietic Cytokines on a Rhesus Monkey Model of AIDS

AXIS I: 1a, 7b, 17

AXIS II: 31, 64, 66

PRC UNIT: Microbiology and Immunology

INVES1: Hillyer, C.D.
DEGREEI: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Ansari, A.A.
DEGREE2: Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Villinger, F.
DEGREE3: D.V.M.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: Novembre, F.
DEGREE4: Ph.D.
DEPT4: Microbiology and Immunology
STAFF4: C

INVES5: Winton, E.F.
DEGREE5: M.D.
DEPT5: Microbiology and Immunology
STAFF5: O

SPECIES1: Macaca mulatta
NUM1: 27

NON-HOST INST: NA

ABSTRACT: Anemia, granulocytopenia, and thrombocytopenia are common in HIV infection though their pathogenesis is not well understood. Bone marrow hypoproliferation (ineffective hematopoiesis) is likely to be a main contributor to the etiology of these hematologic aberrations, and may be due to stem cell infection, or stromal cell infection with loss of a satisfactory microenvironment to support bone marrow growth. This growth is a complex process requiring primary and secondary colony stimulating factors, nutrients, and cell:cell contact. In addition, toxic, inhibitory, and immune factors must not be present if optimal hematopoiesis is expected. In studies of SIV infected rhesus macaques, we have described peripheral blood cytopenias, stage-related CFU-GM and BFU-E hypoproliferation, absence of infection

in CD34+ progenitors, partial restoration of CFU growth with high doses of IL-3 and GM-CSF, and the presence of an inhibitor of rhesus bone marrow secreted by HIV infected H9 cells. These data show the similarity of SIV infected monkeys to HIV infected humans, suggest that ineffective hematopoiesis, with cytokinetic and possibly inhibitory abnormalities, is a factor and support the use of this model for studying the effects of cytokine administration. Herein, we propose a comprehensive study of the hematologic and virologic consequences of exogenous cytokine administration in rhesus macaques experimentally infected with SIV. This model is advantageous as it 1) allows testing of animals (without concomitant antiviral therapy), 2) allows investigators to know the time of infection, 3) has a well-defined disease progression and 4) is supported by preliminary data which suggest that the hematologic consequences of SIV infection are very similar to those of HIV. Specifically, we will study the effects of exogenously administered cytokines on hematopoietic compartment expansion, sites of cellular infection, and viral replication and burden following cytokine administration. We will utilize compartment specific cytokines, tested in monkeys infected with a lymphocyte or a monocyte predominate SIV strain. It is expected that, through these aims, the positive effects of cytokines in SIV infected macaques can be demonstrated, any untoward effects of cytokines on viral replication can be elucidated, and a model can be characterized for future cytokine, bone marrow transportation, and gene therapy experiments.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Investigation of Polyvalent Pneumococcal Conjugate Vaccines in Infant Rhesus Monkeys to Prevent Nasopharyngeal Colonization

AXIS I: 1a, 2, 7a

AXIS II: 64, 66, 91

PRC UNIT: Microbiology and Immunology

INVES1: Keyserling, Harry L.
DEGREEI: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 16

NON-HOST INST: NA

ABSTRACT: This study had three main objectives: (1) To develop and evaluate a rhesus monkey (*Macaca mulatta*) model for nasopharyngeal colonization of Streptococcus pneumoniae. (2) To evaluate various vaccine candidates for human use in infant monkeys to test the hypothesis that a successful parenteral immunization prevents or decreases pneumococcal nasopharyngeal carriage. (3) To correlate the humoral immune responses to pneumococcal vaccine with the mucosal (salivary) responses. During this reporting period, sixteen infant rhesus monkeys (4 groups of 4) were immunized IM at 2, 4, and 6 mo of age with a heptavalent pneumococcal conjugate vaccine (Lederle-Praxis) with adjuvants (either alum alone, alum+MPL, or alum+QS-21); the control group was not immunized. IgG serum antibodies to serogroups 4, 6B, 9V, 14, 18C, 19F, and 23F were measured (pre, post 2, 4, and 7 mo) by ELISA (μg/ml). The vaccine was immunogenic (Table 1) with each of the three adjuvants; alum alone gave the lowest antibody concentrations for all serotypes, alum+MPL gave the highest for serotypes 6B, 9V, and 14, and alum+QS-21 gave the highest for serotypes 4, 18C, 19F, and 23F.

Table 1. IgG (GM) for serotypes measured by ELISA (1 mo post dose 3)

	Serogroups						
Group	4	6B	9V	14	18C	19F	23F
Control	0.16	0.31	0.14	0.30	0.05	0.45	0.12
Alum alone	13.9	28.7	21.8	14.7	11.2	53.6	17.5
Alum+MPL	27.1	89.2	57.5	43.2	19.0	71.8	28.3
Alum+QS-21	31.0	64.0	44.8	25.4	31.9	112.3	50.6

Opsonophagocytic titers (Table 2) were measured using HL-60 cells.

Table 2. Opsonophagocytic titers (GM) for serotypes 14 and 18C

	Serotype 14				Serotype 18C			
Group	pre	post1	post2	post3	pre	post1	post2	post3
Control	4	4	4	4	4	4	4	4
Alum alone	4	7	19	76	4	16	32	128
Alum+MPL	4	13	45	181	4	19	19	90
Alum+QS-21	4	11	19	76	4	32	128	724

In general, antibody levels were higher with alum+MPL or alum+QS-21 than with alum alone.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: An Evaluation of Microspheres Containing Monoclonal Antibodies to TNF*a* and IL–1*B*: Safety and Efficacy in Lethal Gram Negative Peritonitis

AXIS I: 1a, 2, 7a

AXIS II: 50b, 64, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: McClure, Harold M.
DEGREEI: D.V.M.
DEPT1: Microbiology and Immunology
STAFF1: C

INVES2: Oettinger, Carl
DEGREE2: M.D.
DEPT2: Microbiology and Immunology
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INVES3: Milton, Grace
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: D'Souza, Martin
DEGREE4: Ph.D.
DEPT4: Microbiology and Immunology
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 20

NON-HOST INST: Dialysis Clinic, Inc. (CO, GM) and Mercer University (MD)

ABSTRACT: Sepsis due to gram negative and gram positive bacteria is a significant clinical problem despite the advent of antibiotics. Even with effective antibiotic treatment, septic shock continues to be responsible for approximately 400,000 deaths per year in the United States alone. Hallmark complications of septic shock include cardiovascular collapse, increased vascular permeability, pulmonary dysfunction, fever, and alterations in lipoprotein lipase activity characterized by a wasting syndrome. The exact molecular events leading to the progression of sepsis are not clearly understood. However, recent studies have observed that the host response to the invading pathogen contributes to the pathogenesis of sepsis. The cytokines tumor necrosis factor alpha (TNF*a*) and interleukin-1 beta (1L-1*B*) have been implicated as principle immune modulators released from activated macrophages during experimental endotoxin shock. To date, the two primary models used in the majority of sepsis studies are either rats/mice or monkeys. The use of monoclonal antibodies (MoAb)

against TNF*a*, given within minutes of an intravenous septic challenge, have been shown to be beneficial in reducing mortality of septic shock in nonhuman primates. However, there is no experimental data in nonhuman primates with septic shock using an infection model such as peritonitis, and clinical trials with monoclonal antibodies in humans with septic shock have been less effective than suggested by studies in the IV animal model. These studies, therefore, were initiated to establish a model of lethal, gram negative sepsis in the rhesus monkey by intraperitoneal inoculation of E. coli. Once established, this model will be used to evaluate the effect of various treatment regimens on blood levels of various cytokines (specifically TNF*a* and IL-1*B*), and on their ability to prevent death. The initial treatment to be evaluated will be the use of intravenous microencapsulated monoclonal antibodies to TNF*a* and IL-1*B*. Since the microcapsules will be targeted to monocytes/macrophages, a major source of the cytokines, it is believed that microencapsulation of the monoclonal antibodies will result in a much more effective treatment. Specific aims of these initial studies include: (1) an assessment of the safety and toxicity of microcapsules administered intravenously; (2) a determination of the minimal effective *in vivo* dose of microencapsulated cytokine MoAb necessary to sufficiently blunt *in vitro* endotoxin stimulated cytokine release; (3) an assessment of the ability of microencapsulated cytokine MoAb to blunt *in vivo* cytokine production; and (4) a determination of the effectiveness of intravenous microencapsulated cytokine MoAb in preventing death following an intraperitoneal E. coli challenge in the rhesus monkey model.

TITLE: Thymic Transplants for Immune Reconstitution in SIV

AXIS 1: 1a, 4, 7b, 9, 12b

AXIS II: 31, 50b, 63c, 64, 66

PCR UNIT: Microbiology and Immunology

INVES1: Nahmias, André J.
DEGREE1: M.D.
DEPT1: Microbiology and Immunology
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INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

INVES3: Novembre, Francis J.
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: C

INVES4: Hong, Richard
DEGREE4: M.D.
DEPT4: Microbiology and Immunology
STAFF4: 0

SPECIES1: Macaca mulatta
NUM1: 8

NON-HOST INST: University of Vermont (RH)

ABSTRACT: This study's main objective was to develop information on allogeneic and xenogeneic thymic transplantation in SIV immunosuppressed rhesus macaques. This included comparisons between: 1) placing the thymic transplant in the omentum or muscle, with or without adding the recipient's own stem cells (CD34 purified) in culture pre-transplant; 2) treating some of the transplanted animals with zidovudine or PMPA; 3) using anti-thymocyte globulin as the only immunosuppressive drug around the time of transplant; 4) detecting engraftment by biopsy or by MRI; 5) determining immune responses by newly developed flow cytometric and other methods. So far, engraftment has been obtained for 2 to 4 months when: a) anti-viral therapy was used; b) the omentum was the site of transplant; c) allogeneic or human thymic xenograft was employed. Most supportive of the potential benefit of the transplant was the autopsy findings in a severely immunosuppressed monkey in which the mediastinal thymus was markedly lymphopenic, while the omental thymic transplant was populated by lymphocytes (identified as being of monkey origin). No evidence of graft-versus-host

disease or host-versus-graft rejection was demonstrated. MRI was capable of identifying thymic transplant *in vivo*. No definite evidence of immune reconstitution was obtained, although several new approaches for evaluating the immune response have been developed for future studies. This model has already provided important information on the correlative attempts using thymic transplantation for immune reconstitution of children and adults with advanced AIDS.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Derivation of Pathogenic SIV-HIV Chimeric Virus that causes Progressive Loss of CD4+ T Cells and AIDS in Pig-tailed Macaques

AXIS I: 1a, 7b

AXIS II: 31, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: Narayan, Opendra
DEGREE1: D.V.M., Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Joag, Sanjey V.
DEGREE2: Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Foresman, Larry
DEGREE3: D.V.M.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Microbiology and Immunology
STAFF4: C

SPECIES1: Macaca nemestrina
NUM1: 10

NON-HOST INST: University of Kansas (ON, SVJ, LF)

ABSTRACT: Since HIV-1 does not consistently cause disease in nonhuman species, there is no animal model system to evaluate the efficacy of strategies aimed at preventing or ameliorating disease caused by this virus. Since the virus envelope is thought to play a major role in pathogenesis, chimeric simian-human immunodeficiency viruses (SHIV) consisting of the core of SIVmac and the envelope of HIV-1 have been constructed, but have not proven to be pathogenic. We have recently developed a SHIV that is pathogenic in pig-tailed macaques. This is the first model in which primates inoculated with a lentivirus bearing the HIV-1 envelope developed loss of CD4+ T cells and AIDS. SHIV was passaged serially in cohorts of 2 macaques each, using bone marrow to bone marrow transfers at 5, 5, and 16 weeks, respectively. The virus became more virulent with each passage. Virus replication was controlled effectively by CD8+ T cells in animals in passages 1 and 2, but not in animals in passages 3 and 4. Virus resurgence, similar to that seen in HIV-1 infected people, developed in the latter animals and was evident as high virus burden in T cells in blood

and lymphoid tissues, plasma viremia and infection in the CNS. Three of four animals in the last two passages developed CD4+ T cell loss. In one animal, the CD4+ T cell count decreased from 2,000 to 35 cells per ml in 26 weeks with development of AIDS. Two other animals have also developed a second phase of increasing virus burdens, similar to that seen in the fatal case. All animals developed neutralizing antibodies to the virus. Sequence analysis of the *env* gene of the pathogenic virus has shown the basis sequence pattern of the gp120 of HIV-1 HXB2, but with multiple mutations, including some in the V3 loop. The availability of a pathogenic SHIV will be an asset to the development and testing of anti-HIV-1 drugs and vaccines.

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TITLE: Determinants of Pathogenesis in SIVsmmPBj Infection

AXIS I: 1a, 1d, 7b

AXIS II: 31, 39, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: Novembre, Francis J.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: C

INVES2: Lewis, Mark G.
DEGREE2: Ph.D.
DEPT2: Microbiology and Immunology
STAFF2: O

INVES3: Dewhurst, S.
DEGREE3: Ph.D.
DEPT3: Microbiology and Immunology
STAFF3: O

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Microbiology and Immunology
STAFF4: C

SPECIES1: Macaca nemestrina
NUM1: 5

NON-HOST INST: Henry M. Jackson Foundation, Rockville, MD (MGL); and University of Rochester Medical Center (SD).

ABSTRACT: Unlike typical simian immunodeficiency virus infection of macaques, which induces an AIDS-like syndrome, SIVsmmPBj infection in pig-tailed macaques induces an acutely lethal disease. Our group has been involved in elucidating the genetic and biologic mechanisms involved in the induction of this unusual disease. Previous work has shown that multiple viral determinants contribute to the pathogenesis of disease. To further investigate the genetic elements that may contribute to acute disease, we have constructed a molecular clone of SIVsmmPBj which lacks a functional nef gene. Analysis of this virus in vitro shows that it does not appear to have the same biologic activity as typical SIVsmmPBj, i.e. no replication in unstimulated cells, and no induction of PBMC proliferation. When inoculated into pig-tailed macaques, this virus (termed SIVsmmPBjΔnef) did not induce any acute disease. Since the time of infection, animals have remained healthy, with no signs of disease. Recently, we have started to examine the biologic characteristics of disease. Two of

the unique features of this disease are the acute lymphopenia, which appears by day 3 post infection, and the lymphoid hyperplasia observed in the intestinal tract. Investigations into this phenomenon have shown that the lymphopenia is most likely due to the induction of gut-specific integrins on cells infected with SIVsmmPBj, thus redirecting the cells to the intestinal area. Another characteristic of this virus is the acute pathology which develops in the gut. Others have shown that there is an increase in the levels of IL-6 and TNFα after SIVsmmPBj infection. In conjunction with this we have started to examined what role apoptosis plays in pathogenesis. High levels of apoptotic cells are present in intestinal tissue obtained from SIVsmmPBj-infected animals. Cells undergoing apoptosis appear to be uninfected, thus confirming reports of others investigating typical HIV and SIV infection.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Differential Pathogenesis of a Neurotropic SIV

AXIS I: 1a, 1d, 7b

AXIS II: 31, 39, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: Novembre, Francis J.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: C

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES1: Macaca nemestrina
NUM1: 6

SPECIES2: Macaca mulatta
NUM2: 6

NON-HOST INST: NA

ABSTRACT: Despite almost 13 years of research on HIV and its role as the etiologic agent of AIDS, the mechanisms of pathogenesis remain mostly unknown. Specific *in vitro* effects have been identified that may contribute to the overall course of disease development. These include: direct cell killing by HIV (syncytia formation); the induction of apoptosis; and the development of autoimmune responses; among others. While all of these effects have been observed *in vitro* and *in vivo*, the only mechanism consistently identified *in vivo* has been apoptosis. Because the exact time of infection can only be estimated in HIV-infected patients, a majority of the studies involving pathogenesis have been conducted during middle or late stage disease, at the least, following seroconversion. While much research has shown that a number of changes, including viral tropism changes, occur late, the early stages of infection may be as (or more) important in pathogenesis. The initial stages of infection involve viral amplification and seeding of lymphoid tissues, and can possibly dictate later effects, i.e. rapid or slow progression to disease. The SIV/macaque model represents the best system currently available to study AIDS pathogenesis, due to the striking genetic and biologic similarities. This model provides an excellent mechanism to investigate early pathogenesis of lentiviral infection. A recently characterized SIV isolate from a sooty mangabey (SIVsmmFGb) displays varied pathogenesis in pig-tailed and rhesus macaques. In pig-tailed macaques, this virus rapidly induces AIDS, whereas in rhesus macaques, disease progresses at a typically slower rate. The progression in pig-tailed macaques is associated with a high plasma viral load (as measured by p27 assay) and

an insufficient immune response (no anti-SIV antibody detected in most cases). In contrast, the rhesus macaques show a lower viral load, and make high levels of anti-SIV antibody. The pig-tailed macaques all succumbed to AIDS by 9 months post infection. In all cases, SIV-encephalitis was detected, illustrating the neurotropism of this virus. The differences in pathogenesis of this virus between rhesus and pig-tailed macaques should provide an excellent system for investigating determinants of AIDS pathogenesis.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: The Effect of CTLA-4-Ig on Renal Allograft Survival in Primates

AXIS I: 1a, 2, 19, 27

AXIS II: 50b, 64, 86, 88

PRC UNIT: Microbiology and Immunology

INVES1: Pearson, Thomas C.
DEGREE1: M.D., D. Phil.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: Larsen, Christian P.
DEGREE2: M.D., D. Phil.
DEPT2: Microbiology and Immunology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 10

NON-HOST INST: NA

ABSTRACT: The aim of this study was to test the hypothesis that CTLA4-Ig will prolong survival of renal allografts in a nonhuman primate model. CTLA4-Ig has been shown to modify the allograft rejection response to produce prolonged graft survival and/or induce specific unresponsiveness in rodent models. Adult rhesus macaques (11.8 - 13.5 kg) were utilized for these studies. Ten animals received an allogenic renal transplant, a left nephrectomy and simultaneous right contralateral ureter ligation. The paired transplants were performed simultaneously by exchange of kidneys between recipient individuals. One recipient in each pair was treated with CTLA4-Ig and the other served as a control and was treated with human albumin. Renal allografts in the control treatment group promptly failed (4-8 days) and histologic analysis suggested both a cellular and humoral immune mediated mechanism. CTLA4-Ig treatment in one of four recipients was associated with marked prolongation of allograft survival. One CTLA4-Ig treated recipient died secondary to necrosis of the distal transplant ureter and was not included in the analysis. In summary, the results of this pilot study suggest that CTLA-4Ig has the ability to prolong primate renal allograft survival. Further studies are required to determine the significance of this initial observation.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: STTR: Dilazep and Analogs for Treatment of AIDS

AXIS I: 1a, 17

AXIS II: 31, 50, 74c

PRC UNIT: Microbiology and Immunology

INVES1: Sommadossi, Jean-Pierre
DEGREE1: Pharm. D., Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES 1: Macaca mulatta
NUM1: 3

NON-HOST INST: University of Alabama at Birmingham (JPS)

ABSTRACT: The objective of this research is to evaluate the toxicity and/or immunosuppressive effects of novel drug combinations with assessment of transport and metabolic disposition. In particular, effects of selected modulating agents on anti-HIV drugs will be studied in an attempt to prevent or alleviate bone marrow toxicity associated with chronic treatment with certain anti-HIV nucleoside analogs. Pharmacokinetics of anti-HIV drugs and modulation will be studied. Efficacy of selected drug combinations (anti-HIV and modulating agent) will eventually be assessed in SIV-infected rhesus monkeys.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Circulating Antigen Assay Development for Schistosomiasis in Rhesus Monkeys

AXIS I: 1a, 7c

AXIS II: 64, 66, 77

PRC UNIT: Microbiology and Immunology

INVES1: Tsang, Victor C.W.
DEGREE1: Ph.D.
DEPT1: Microbiology and Immunology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES 1: Macaca mulatta
NUM1: 5

NON-HOST INST: Centers for Disease Control and Prevention (VCWT)

ABSTRACT: This study is directed toward the development of field-applicable antigen detecting assays. Rhesus monkeys, experimentally infected with Schistosoma mansoni, will be used to provide a controlled source of infection-related materials such as urine, feces and blood. Such material will be used to identify schistosome-specific antigens. Once identified, these antigens will be used to develop specific diagnostic tests.

To date, five rhesus macaques have been infected with 300 S. mansoni cercaria. Samples of blood, urine and feces were collected bimonthly from the infected animals for 60 weeks, and the animals were treated with Droncit. Samples have continued to be collected following treatment. Both immunological and biological analyses of the collected samples are currently in progress.

In addition to studies with experimentally infected rhesus macaques, three related studies in humans have been initiated during the past year. One study, designed to determine the transmission potential and risk for acquiring schistosomiasis in Lake Malawi, involved a cross-sectional survey of residents and visitors to Malawi. Evidence of current or past schistosome infection was found in one third of the study population. It was subsequently determined that recreational water contact at popular resorts on Lake Malawi was the most likely source of infection. In a second study, an island-wide serosurvey for schistosomiasis in Puerto Rico was initiated. Objectives are to determine the seroprevalence rate, status of transmission on the island and to evaluate the feasibility of controlling or eliminating this disease from Puerto Rico. Preliminary data indicate that schistosomiasis has been transmitted in a focal fashion during the

past 20 years. Lastly, a longitudinal study is underway in which travelers recreationally exposed to schistosomiasis will be monitored, both before and after treatment. Efforts will be made to differentiate between treatment success and failure by following the immunological changes.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: The Effects of flt3 Ligand on Amplification and Mobilization of Primitive Immuno-Hematopoietic Cells in Rhesus Macaques

AXIS I: Ia, Id, 2, 17

AXIS II: 50a, 76b, 88

PRC UNIT: Microbiology and Immunology

INVES1: Winton, Elliott F.
DEGREE1: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: High-dose, marrow lethal chemotherapy (± radiation therapy) with stem cell support is an established, potentially curative treatment modality for patients with a variety of malignancies. The major toxicity of such aggressive treatment is pancytopenia with a resultant increase in susceptibility to infections, and necessitating platelet and red cell transfusions. Recombinant human G-CSF and GM-CSF have been shown to be clinically useful in shortening the period of neutropenia following chemotherapy, with or without stem cell rescue. The optimal means to enhance regeneration of thrombocytes as well as various immunocytes has yet to be defined, although rhIL-6, rhIL-11, and rhIL-3 and the GM-CSF/IL-3 fusion protein, PIXY 321, all have been demonstrated to have enhancing effects on thrombopoietic regeneration following marrow injury.

The number of primitive immuno-hematopoietic regenerating cells in the cell preparation used for grafting after severe marrow damaging chemotherapy directly influences cytokine effectiveness during marrow regeneration. Therefore, reliable methods to enhance the content of regenerating cells in the cell preparation infused following marrow lethal chemo/irradiation therapy are essential. Ideal for this purpose should be the in vivo administration of a cytokine (or cytokines) that stimulates amplification of the cells with the highest proliferative and differentiative capacity (e.g. stem cells or their immediate progeny) prior to collection of the cells to be used for post-treatment hematopoietic rescue.

Flk2/flt3 is a receptor tyrosine kinase identified on brain, placental, testicular and primitive murine hematopoietic cells . The murine flt3 ligand has been recently cloned and has been shown to stimulate proliferation of primitive hematopoietic cells. Flt-3 ligand also functions as an enhancing factor to other early acting cytokines such as Steel factor, IL-6 and IL-3. Therefore, flt-3 ligand, administered in vivo as a single agent or in combination, may be useful for enriching the marrow or blood content of early regenerating cells. The human homologue of murine flt3 ligand has recently been

cloned (rh-flt3 ligand). In the proposed experiments, we administered rh-flt3 to rhesus macaques and assessed blood and marrow for changes in the content of primitive immuno-hematopoietic cells. This cytokine proved highly effective in amplifying marrow clonogenic myeloid cells and CD34+ cells, and mobilizing these cells to the peripheral circulation.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Effects of c-mpl Ligand on the Hematopoietic System, and on Hematopoietic Regeneration Using a Non-Human Primate Model of Stem Cell Damaging Chemotherapy

AXIS I: Ia, Id, 2, 17

AXIS II: 50a, 76b, 88

PRC UNIT: Microbiology and Immunology

INVES1: Winton, Elliott F.
DEGREE1: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 40

NON-HOST INST: NA

ABSTRACT: Cancer chemotherapy is effective in curing or controlling many types of malignancies. A major side effect of most effective chemotherapy regimens has been marrow damage that results in low blood counts, leaving the patient more susceptible to infectious and hemorrhagic complications. Recombinant blood cell growth factors such as G-CSF or GM-CSF have been successful in accelerating the regrowth of white cells after chemotherapy, thereby reducing infections. The optimal way to stimulate post-chemotherapy recovery of platelet production has remained elusive. Recently, a new human blood cell growth factor, termed c-mpl ligand or thrombopoietin (TPO), has been cloned and appears to be the long sought cytokine that primarily regulates platelet production. The proposed studies will be among the first to employ recombinant human (rh) TPO in a large animal model.

In a preliminary dose finding experiment, we administered rhTPO to normal monkeys by daily subcutaneous injection in doses varying over a 100 fold range, and monitored changes in peripheral blood counts. From these studies we observed a ten fold increase in circulating platelets after 14 days of rhTPO administration, and an optimal effective dose was determined. In a second set of studies, we administered rhTPO by daily injection for 10 days to normal rhesus macaques, and serially sampled blood and marrow to determine the longitudinal effects of rhTPO on multiple parameters of blood cell production. An analysis of these findings is currently underway.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Synthokine Effects on the Hematopoietic System, and on Immuno-hematopoietic Regeneration Using a Non-Human Primate Model of Stem Cell Damaging Chemotherapy

AXIS I: Ia, Id, 2, 17

AXIS II: 50a, 76b, 88

PRC UNIT: Microbiology and Immunology

INVES1: Winton, Eiliott F.
DEGREE1: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 14

NON-HOST INST: NA

ABSTRACT: High-dose chemotherapy and marrow lethal chemotherapy with marrow or peripheral blood stem cell support are established, potentially curative treatment modalities for patients with a variety of malignancies. The major toxicity of such aggressive treatment is marrow damage with low blood counts, with a resultant increase in susceptibility to infections, and necessitating platelet and red cell transfusions. Recombinant human G-CSF and GM-CSF have been shown to be clinically useful in shortening the period of neutropenia following chemotherapy. The optimal means to enhance multilineage marrow and immunocyte regeneration has yet to be defined. In addition, little is known about the potential for cytokines to protect stem cells from the cumulative damaging effects of prolonged chemotherapy courses. IL-3 has been demonstrated to have enhancing effects on multiple lineages following marrow injury, but side effects related to histamine release associated with higher dosages of the cytokine have been a problem.

Recently, mutated versions of natural human cytokines were synthesized in efforts to reduce unwanted side-effects, and improve hematopoietic stimulation. One such synthetic cytokine is a recombinant, mutant human IL-3 (Synthokine) which has been selected for clinical development based on its decreased potency in stimulating basophil function and histamine release, and increased potency in stimulating colony formation by cultured hematopoietic cells. In addition, Synthokine has recently been shown to accelerate marrow regeneration following sublethal radiation in a non-human primate model.

Our studies were designed to use Synthokine in 2 types of experiments employing our recently developed non-human primate model of sublethal marrow injury employing hepsulfam. In one type of experiment, animals were treated with Synthokine by subcutaneous injection over 10 days prior to receiving hepsulfam chemotherapy. We quantified the extent of multilineage hematopoietic expansion that occurs in marrow

and blood during Synthokine administration, and determined whether hyperexpansion prior to chemotherapy lessened hepsulfam-induced marrow damage. In a second type of experiment, we administered Synthokine to animals following hepsulfam induced marrow damage. Post-chemotherapy marrow and blood count regeneration in the Synthokine treated animals were compared to results obtained in previous control experiments using no post-chemotherapy cytokine. The results of these studies indicated that the Synthokine markedly expands progenitor cells and CD34+ cells in the marrow and that this expansion did not afford protection from the pancytopenia resulting from subsequent hepsulfam administration. Furthermore, Synthokine administered after hepsulfam induced marrow injury does not result in accelerated marrow recovery. Synthokine's clinical value may be in expanding primitive hematopoietic cells prior to collection for transfusion.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Development of Nonhuman Primate Models of Intravenous Busulfan Induced Reversible Marrow Injury, and Irreversible Marrow Injury Requiring Hematopoietic Stem Cell Rescue

AXIS I: Ia, Id, 2, 17

AXIS II: 50a, 76b, 88

PRC UNIT: Microbiology and Immunology

INVES1: Winton, Elliott F.
DEGREE1: M.D.
DEPT1: Microbiology and Immunology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 28

NON-HOST INST: NA

ABSTRACT: High-dose chemotherapy and marrow-lethal chemotherapy with marrow or peripheral blood stem cell support are effective, potentially curative treatment modalities for patients with a variety of malignancies. The principal short term adverse effect of such aggressive treatment is severe pancytopenia with consequent immediate susceptibility to infection and bleeding, often requiring antibiotics and platelet transfusion support. A long term adverse effect of such therapies is the development of "stem cell exhaustion" characterized by the development of chronic pancytopenias and extreme sensitivity of the hematopoietic system to the suppressive effects of further conventional dose chemotherapy. Animal models of high-dose chemotherapy that produce reversible marrow injury, and that produce marrow-lethal chemotherapy requiring hematopoietic stem cell rescue will be essential in developing new strategies to lessen these short-term and long-term adverse effects. These new strategies, for example, will involve the use of recently cloned recombinant hematopoietic growth factors to accelerate post-chemotherapy marrow regeneration, and to facilitate the collection of marrow regenerating cells for use in stem cell rescue. In addition, the marrow lethal model requiring stem cell rescue will be an essential tool in investigations of stem cell purification techniques and use of genetically altered stem cells for gene therapy.

Previously we have developed a chemotherapy induced marrow injury model employing hepsulfam. This drug will probably not remain available, however intravenous busulfan has just recently been developed and was used in phase I human clinical trials in 1995. Oral busulfan is the major drug in many high dose chemotherapy protocols requiring cell rescue. Intravenous busulfan will probably eventually replace the oral form of the drug in these protocols.

In 1995 we conducted dose escalation studies using intravenous busulfan, and have established a marrow damaging dose from which the hematopoietic system can

regenerate from surviving endogenous stem cells, and a marrow lethal dose that requires post-chemotherapy stem cell rescue. Using this latter dose, we have performed autologous stem cell rescue in several animals. This new intravenous busulfan autologous stem cell model will be valuable for studies to determine the effect on hematopoietic regeneration of various cytokines administered during the post-transplant period.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE
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Core Scientists

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FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE (CONTINUED)

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J.N. Wilcox, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Medicine (Hematology/Oncology), Emory University School of Medicine.

L.G. Young, Ph.D., Affiliate Scientist of Molecular Medicine, Yerkes Center; Associate Professor of Physiology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF MOLECULAR MEDICINE (CONTINUED)

Collaborative Scientists

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P.N. Srivastava, Ph.D., Consultant in Molecular Medicine, Yerkes Center; Professor of Biochemistry, University of Georgia.

P51RR00165-35 1/1/95 -12/31/95 Yerkes Regional Primate Research Center

TITLE: ENHANCEMENT OF LUMBAR FUSION WITH RHBMP-2/COLLAGEN OR BONE PROTEIN (BP)

AXIS I: 1a, 1d, 2, 26

AXIS II: 46, 48, 88, 89

PRC UNIT: Molecular Medicine

INVES1: Boden, Scott D.
DEGREE1: M.D.
DEPT1: Orthopaedic Surgery
STAFF1: O

INVES2: Gould, Kenneth G.
DEGREE2: Ph.D.
DEPT2: Molecular Medicine
STAFF2: C

SPECIES1: Rhesus macaque
NUM1: 36

ABSTRACT: Lumbar spinal fusion is commonly performed in humans but the failure rate of bone union is reported to range from 5-36%. Recently, both osteoinductive growth factors synthesized by recombinant DNA technology and bovine derived bone protein (BP) have been shown to induce bone formation in heterotopic sites. Recombinant human Brain Morphogenetic Protein (rhBMP-2) and BP have both been effective in generating spine fusions in a rabbit model. To determine the appropriate dose of these growth factors for human use and to determine the speed of healing, a non-human primate model has been chosen. Higher doses than expected were required to make bone in the primate, but both treatments were successful. Studies in the upcoming year will focus on the precise doses and explore alternative carrier materials that will better bind the growth factors. These studies are critical to providing the information needed for the next step which is human clinical trials. This treatment, if successful, will significantly impact on the care of spine patients and prevent multiple surgeries in the 5-35% of patients who do not heal their spine fusion on the first attempt.

TITLE: Artificial Breeding of Chimpanzees: Pathologies disrupting female fertility.

AXIS I: 1a, 15, 18, 21, 23

AXIS II: 36, 65, 71, 72, 93

PRC UNIT: Molecular Medicine

INVEST1: Dahl, J.F.
DEGREE1: Ph.D
DEPT1: Molecular Medicine
STAFF1: O

INVEST2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Molecular Medicine
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 60

ABSTRACT: The principal objectives of this work with female chimpanzees (Pan) were to: [A] Non-invasively monitor circulating estrogens and progesterone using an external marker (the Perineal Sex Swelling, PSS) to **either** enable synchronization of Artificial Insemination (AI) procedures **or** identify abnormal conditions that reduce fertility, cause puerperal pathologies, or indicate luteal phase and pre-menstrual pathologies; [B] Test hypotheses about the way that nipple stimulation behavior (NSB) disrupts the progress of the ovarian cycle, implantation, and the establishment of pregnancy; [C] Evaluate the role of stress as either a part of the auto-NSB phenomena or as an independent contribution to infertility. Hyperprolactinemia in adult female Pan caused by NSB is found to prolong the duration of post-partum amenorrhea. It has also been documented at this laboratory that NSB in many mothers continues after ovarian cycles have resumed but that the cycles have an aberrant and non-fertile pattern of ovarian activity. It is hypothesized that the au-NSB causes a disruptive mechanism that prevents conception and implantation probably through the action of prolactin and/or oxytocin. Stress associated with AI or au-NSB may be a confounding or associated disruptive influence. Efforts to understand these mechanisms continued with foci on irregular ovarian cyclicity, measurements of circulating prolactin, urinary cortisol, and behavior.

During this reporting period; [1] Daily scores of the PSS were made on an average of 60 females yielding a total of 22,000 data points (total data set now about 125,000 data points); [2] An additional **250** hours of behavioral data on both allo- and auto-NSB (al-NSB and au-NSB) were collected from **8** subjects (total data set now 1,150 hours on 28 subjects). Moreover, for 150 tests on five subjects (two without and three with infants) all self-directed behaviors (SDBs) were quantitatively assessed (in addition to au-NSB and al-NSB) so that variation in NSB could be contrasted with all other SDBs in the way

that they varied with environmental conditions (subject inside or outside, disturbance), physiological state (amenorrhea and lactation, swelling phases of the ovarian cycle and associated estrogen and progesterone fluctuations, circulating PRL), parity, number of months post-partum or age of the infant and weaning, and activity level. SDBs were found to vary with parity, with location, and with activity level but did not vary significantly with phases of the cycle as did au-NSB. SDBs were significantly reduced after resumption of ovarian cyclicity, however, whereas measures of al-NSB increased approximately 3-5 fold when mothers (with infants) resumed ovarian cycles. These data suggest that au-NSB by mothers without infants during luteal phases more closely resemble al-NSB **during weaning when ovarian activity resumes than they do al-NSB during lactational amenorrhea**.

Study foci during 1996 will include the analyses of stockpiled-blood and urine samples for prolactin and cortisol, further analyses of swelling data and evaluations of abnormality, and more behavioral observations to increase the numbers of subjects in a number of categories: Mothers with young infants, with weaning infants, with weaned juveniles; subjects without infants with or without au-NSB. A new method will be applied for indexing urinary "free" cortisol (uF). This method was developed in this laboratory through knowledge that free cortisol is not actively transported across the kidney. Application of this method allows recognition of baseline uF (reflecting inactivation of **the** HPA), high uF (reflecting major HPA activity), and uF increased over baseline suggesting **chronic low** HPA activity. In general, this work continues to accumulate evidence for the important role of the chimpanzee female as a model for understanding stress related pathologies in the woman.

P51RR00165-35 1/1/95 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Reproductive Biology and Conservation of Belizean Monkeys

AXIS I: 1a, 23, 25a, 25b, 25c, 28 (conservation)

AXIS II: 36, 40, 54b, 65

PRC UNIT: Molecular Medicine

INVEST1: Dahl, J.F.
DEGREE1: Ph.D.
DEPT1: Molecular Medicine

SPECIES1: Alouatta pigra
NUM1: 2500

SPECIES2: Ateles vellerosus
NUM2: 250

ABSTRACT: The objectives were to identify populations of two New World monkey species, and obtain preliminary data for long-term studies of reproduction and ecology. The specialized genitalia of spider monkeys and howler monkeys (genera Ateles and Alouatta: Ceboidea) closely resemble those of apes (Hominoidea); Ateles resembles a monogamous gibbon (Hylobates H. concolor) and Alouatta is most similar to the polygamous chimpanzees (Pan). Evolutionary hypotheses concerning the functional relationships among **mating strategy** and reproductive anatomy, physiology, and social behavior, which have been developed in comparative investigations of the apes, can be further tested in these ceboid species. Furthermore, field studies enable hypotheses to be evaluated in the context of the species' natural daily activity patterns, their ecology, their population dynamics, and their foraging strategies. Aspects of natural and sexual selection, as well as species specificity, can be investigated.

This work has proceeded in collaboration with a number of conservation efforts in Belize including those of the Belize Center for Environmental Studies, and of the Golden Stream Initiative. The latter initiative is aimed at preserving one of the last areas of intact, lowland forest in northern Central America. Apart from well established ethical considerations, this conservation effort is required as long term study necessitates stability for some of the study populations which are under increasing threat from human activity. A central effort was focused on delineating and establishing a large regulated biological corridor of over 3500 km^2 that would, in conjunction with the establishment of a Private Reserve, include five of the six study sites. Conservation is a mission and an obligation of the Yerkes Primate Center, and the effort in Belize is one of the ways in which this obligation can be met.

Field work in 1995 in Belize, Central America, was completed for six local populations of monkeys: [1 and 2] Alouatta at high and low populations densities at low elevation sites [>100 m.] (similar forest structures and environmental conditions); [3 and 4] Alouatta at low population densities at medium (200 - 400 m) and high (550 - 750 m)

elevations (different forest structure and distinctive energetic requirements); [5 and 6] Ateles at similar population densities at medium and high elevations.

The distinctions found in the density of Alouatta populations were striking with some existing at densities as high as about 80-100 individuals/km^2, and others at densities a tenth of this or less. These populations provide a naturally occurring experimental devise to test hypotheses about mate acquisition, mate choice, social behavior and regulatory mechanisms, and the flexibility of mating strategy to accommodate the demands imposed by inter-individual and inter-troop spacing and constraints on food resources. The medium elevation site where Ateles vellerosus was found is extraordinarily accessible given the rarity of the species and its restriction to isolated remnants of mature forest. The species is vulnerable to extinction consequent to insularization, its low reproductive rate, and its low genetic diversity; a Yellow Fever epidemic 30-40 years ago nearly extinguished A.v. yucatanensis in Belize and caused a low effective population size. A program was initiated to protect the species most critical habitats in conjunction with the research effort.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Implant, Prosthetic and Periodontal Studies in Monkeys

AXIS I: 1a, 2, 3, 6, 7, 22

AXIS II: 48, 52, 63, 77, 86

PRC UNIT: Molecular Medicine

INVES1: Fritz, Michael E.
DEGREE1: D.D.S., M.S., Ph.D.
DEPT1: Molecular Medicine
STAFF1: 0

INVES2: Braswell, Laura D.
DEGREE2: D.D.S.
DEPT2: Molecular Medicine
STAFF2: 0

INVES3: Eke, Paul I.
DEGREE3: Ph.D.
DEPT3: Molecular Medicine
STAFF3: 0

INVES4: Jeffcoat, Marjorie
DEGREE4: D.D.S.
DEPT4: Molecular Medicine
STAFF4: 0

SPECIES1: Macaca Mulatta
NUM1: 36

NON-HOST INST: University of Alabama, Birmingham (JEL)

ABSTRACT: The present research involves:

1. Data regarding regeneration of bone from *En Bloc* defects using membrane technology.
2. The possibility of comparing implants and surrounding tissues in newly regenerated bone and non-regenerated bone.
3. The possibility of examining whether newly created bone remodels to lamellar bone with and without stress.
4. The possibility of examining cytokines, growth factors, and strength factors in newly created bone.

36 monkeys have been purchased from NIDR funds in an earlier grant cycle and years of data have been generated in this group of animals. These data can be readily compared with data in newly regenerated bone. Specific Aims of the original study were: (1) to design and perform material analysis of root-form and plate-form implants;

(2) to establish a primate model system to study dental implants; (3) to establish a surgical protocol where plate-form implants are placed atraumatically; (4) to determine the effect of implant design and implant loading on implant survival over time; (5) to ascertain if periodic scaling procedures can prevent peri-implant disease in the primate model over a prolonged period of time; and (6) to create peri-implant disease around loaded implants and measure the effects. Aims 1-5 have been or are now being achieved. Aim 6 is presently under investigation.
Specific Aims for the competing renewal are: (1) to further develop and characterize a model for residual bone resorption in the rhesus monkey; (2) to characterize the rate of mineralization of regenerated new bone in the monkey model; (3) to determine the kinetics and magnitude of growth factor expression in regenerated new bone as compared to fresh extraction sites; (4) to determine if the expression of growth factors is decreased and cytokine release enhanced under exposed membranes; (5) to determine the rate of bone loss around root-form titanium implants placed in the regenerated bone and compare this with prior studies in the same animals; (6) to determine the effect of implant loading on implants in regenerated bone; and (7) to determine if the trabecular micro-structure in regenerated bone is the same morphologically as that produced in fresh extraction sites.

The data thus far recorded have immediate application for implant placement and prosthetic reconstruction. To have the capacity to regenerate a large quantum of resorbed bone in the oral cavity and to understand the kinetics of this has immediate and profound health implications for both dentistry and cancer therapy.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Maturation and Fertilization *In Vitro* of Nonhuman Primate Oocytes

AXIS I: 1a, 23, 15

AXIS II: 60, 77, 93

PRC UNIT: Molecular Medicine

INVES1: Gould, Kenneth G.
DEGREE1: Ph.D. DVM
DEPT1: Molecular Medicine
STAFF1: C

INVES2: Younis, Abdelmonim I.
DEGREE2: Ph.D. DVM
DEPT2: Molecular Medicine
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 5

SPECIES2: Macaca mulatta
NUM2: 8

SPECIES3: Macaca fasicularis
NUM3: 4

NON-HOST INSTITUTION: N/A

ABSTRACT: Experiments were conducted to compare the ovarian stimulatory responses and the numbers and quality of oocytes/IVF embryos following multiple injections of five chimpanzees with FSH and LH. Each of five chimpanzees was subjected to three cycles of gonadotropin treatments. Chimpanzees receiving lower doses of hFSH and hLH had higher estrogen level, significantly higher numbers of large follicles and of oocytes recovered. There was no difference in the number of embryos produced by IVF. These results suggest that some instances of low response to gonadotropin stimulation can be corrected by reducing, not increasing, the dose of gonadotropin used.

Meiotic status and embryonic development after IVF were used to assess 2 follicular superstimulation protocols in 12 monkeys (8 rhesus and 4 cynomolgus). Cumulus-enclosed oocytes (CEO) were recovered from superstimulated ovaries after multiple hFSH and hLH injections or a single SC injection of eCG (PMSG, Sigma; 1000 IU) and hLH (30 IU) followed by ovariectomy (N = 6). Although fewer mature oocytes were obtained using single injection of eCG and hCG combined, high quality MII oocytes were produced that were capable of forming embryos comparable to the commonly used multiple injections of FSH/LH.

P51RR00165-35 1/1/1995-12/31/1995 Yerkes Regional Primate Research Center

TITLE: Endometrial Protein Expression as Associated with Embryo Implantation Rate.

AXIS I: 1a, 15, 23

AXIS II: 60, 74h, 93

PRC UNIT: Molecular Medicine

INVES1: Gould, Kenneth G.
DEGREE1: Ph.D. DVM
DEPT1: Molecular Medicine
STAFF1: C

INVES2: Dahl, Jeremy F.
DEGREE2: Ph.D.
DEPT2: Molecular Medicine
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 12

NON-HOST INSTITUTION: N/A

ABSTRACT: While the endocrine and physiological parameters of the human menstrual cycle are well documented, precise details of the 'fertile' (as identified by established pregnancy) as opposed to the 'nonfertile' cycle, are not well defined. In addition, there is a recognized incidence of 'idiopathic infertility' which exists even when male factors have been eliminated. Such "normal" though "infertile" cycles also appear to occur in female common chimpanzees (Pan troglodytes), and have been identified by detailed monitoring of estrogen and progesterone fluctuations. It is hypothesized that the infertility is due to altered protein expression by the endometrium at time of implantation; this alteration appears to follow on from a distinctive pattern of estrogen secretion during the follicular phase. A matched series of serum samples and endometrial biopsies were collected from the two types of cycle using a sensitive external marker of follicular activity (the Perineal Swelling pattern) to distinguish the two types of cycle and schedule the sampling. Serum samples were obtained between six and nine days after menses either before or after a critical change in the marker; this change has been demonstrated to occur immediately prior to a doubling of estrogen concentrations. Endometrial biopsies were collected during the luteal phase five days after the peri-ovulatory peak in luteinizing hormone (LH) and three or four days after a distinctive and associated alteration in the external marker. These biopsies are being processed to identify the relative expression of various integrins (attachment proteins), particularly $\alpha V\beta 3$, which has been shown to vary in expression during the luteal phase. Histological sections are subject to quantitative fluorescence microscopy. After quantitation of the protein expression, we will verify the predicted fertility status of the cycle by use of artificial insemination, a technique which can now achieve greater than 80% pregnancy after a single insemination.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Improved Storage of Semen at Low Temperature

AXIS I: 1a, 23,

AXIS II: 92 (conservation)

PRC UNIT: Molecular Medicine

INVES1: Gould, Kenneth G.
DEGREE1: Ph.D. DVM
DEPT1: Molecular Medicine
STAFF1: C

INVES2: Younis, Abdelmoneim I.
DEGREE2: Ph.D. DVM
DEPT2: Molecular Medicine
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 8

NON-HOST INSTITUTION: N/A

ABSTRACT: In order to develop improved methods for semen preservation which do not require sophisticated technology and which will permit collection of semen samples from the wild if needed, we are presently assessing the effects of Antifreeze Protein (AFP) and Insulin- Transferrin-Selenium (ITS) on chimpanzee (Pan troglodytes) spermatozoa during an abbreviated freeze-thaw process. The AFP or ITS are added to the diluent of the semen sample at concentrations of 0, 1, 10 and 100 mg/ ml. The semen from each animal was processed independently prior to exposure to the AFP or ITS. The fresh semen samples were collected by artificial vagina, analyzed for sperm count, viability, and motility using computer assisted motion analysis (CAMA). CAMA was performed on these samples to determine the post-thaw motility characteristics. Semen was frozen at wet ice temperature (approx 0 deg C.) for up to 96 hours. The motility of sperm in the fresh semen sample of the AFP experimental group was 66.0 %. The addition of AFP in varied concentrations of 1,10, and 100 mg/ml resulted in a decline in the motility but a constancy in all four motility parameters. The 100 mg/ml treatment gave a 96% post-thaw sperm motility which was similar to that of the fresh sample. The other two concentrations resulted in a dramatic decline with approximately a 10% recovery of sperm motility. The motility of sperm in the fresh semen sample of the ITS experimental group was 88.5%. Cryopreservation accompanied with addition of ITS in concentrations of 1, 10, and 100 mg/ml resulted in a decline in motility as well as a decline in three of the four motility parameters. The Curvilinear Velocity, Linearity, and Straight Line Velocity declined from the original pre-freeze value but remained constant among the different concentrations of ITS. The Lateral Head Movement remained close to the pre-freeze value. A concentration of 100 mg/ml ITS gave no recovery of sperm motility. Best results were obtained after addition of 100 mg/ml AFP

TITLE: Vascular Lesion Formation in Baboon Models

AXIS I: 1a, 2, 9, 13, 17

AXIS II: 48, 50b, 52, 63i, 77, 86

PCR UNIT: Molecular Medicine

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Molecular Medicine
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Molecular Medicine
STAFF2: O

INVES4: Kelly, Andrew B.
DEGREE4: D.V.M.
DEPT4: Molecular Medicine
STAFF4: C

SPECIES1: Papio cynocephalus
NUM1: 12

ABSTRACT: These studies are designed to evaluate mechanisms and strategies for the prevention of vascular lesion formation induced by arterial injury. Restenosis that develops after interventional procedures for symptomatic atherosclerotic disease (e.g. balloon catheter angioplasty) frequently compromises the benefits of treatment. The present experiments were designed to test the role of the platelet-derived growth factor (PDGF) in the restenotic process. PDGF was originally identified as a releasable component of platelet granules, but has now been identified in other vascular cells including macrophages and endothelial cells and is thought to play a key role in orchestrating the vascular response to injury. This hypothesis was tested by by infusion of a monoclonal antibody (2A1E2) against the platelet-derived growth factor β-receptor (PDGF-R). This antibody recognizes only human and baboon PDGF-R. Therefore, baboons were evaluated following single daily bolus injections of the antibody, which produced plasma levels ranging between 150 and 100 nM (peak-to-trough levels). Although the antibody was only administered for the first 7 days after balloon catheter injury of the superficial femoral artery (similar in size to human coronary arteries) the extent of arterial wall thickening at 30 days was strikingly reduced by 40-45%. This study demonstrates that: 1) the PDGF pathway is important for arterial injury repair in primates; 2) early short-term blockade of this pathway may produce a late anti-restenotic benefit after discontinuance of therapy; and 3) the monoclonal antibody 2A1E2 may be an attractive therapeutic agent for anti-arteriosclerotic applications in man.

TITLE: Vascular Lesion Formation in Baboon Models

AXIS I: 1a, 2, 9, 13, 17

AXIS II: 48, 50b, 52, 63i, 77, 86

PCR UNIT: Molecular Medicine

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Molecular Medicine
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Molecular Medicine
STAFF2: O

INVES4: Kelly, Andrew B.
DEGREE4: D.V.M.
DEPT4: Molecular Medicine
STAFF4: C

SPECIES1: Papio cynocephalus
NUM1: 12

ABSTRACT: These studies are designed to evaluate mechanisms and strategies for the prevention of vascular lesion formation induced by arterial injury. Restenosis that develops after interventional procedures for symptomatic atherosclerotic disease (e.g. balloon catheter angioplasty) frequently compromises the benefits of treatment. The present experiments were designed to test the role of the platelet-derived growth factor (PDGF) in the restenotic process. PDGF was originally identified as a releasable component of platelet granules, but has now been identified in other vascular cells including macrophages and endothelial cells and is thought to play a key role in orchestrating the vascular response to injury. This hypothesis was tested by by infusion of a monoclonal antibody (2A1E2) against the platelet-derived growth factor β-receptor (PDGF-R). This antibody recognizes only human and baboon PDGF-R. Therefore, baboons were evaluated following single daily bolus injections of the antibody, which produced plasma levels ranging between 150 and 100 nM (peak-to-trough levels). Although the antibody was only administered for the first 7 days after balloon catheter injury of the superficial femoral artery (similar in size to human coronary arteries) the extent of arterial wall thickening at 30 days was strikingly reduced by 40-45%. This study demonstrates that: 1) the PDGF pathway is important for arterial injury repair in primates; 2) early short-term blockade of this pathway may produce a late anti-restenotic benefit after discontinuance of therapy; and 3) the monoclonal antibody 2A1E2 may be an attractive therapeutic agent for anti-arteriosclerotic applications in man.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Endarterectomy: Prevention of Thrombosis and Restenosis

AXIS I: 1a, 2, 3, 9, 13, 17

AXIS II: 48, 50b, 63f, 86

PRC UNIT: Molecular Medicine

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Molecular Medicine
STAFF1: 0

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Molecular Medicine
STAFF2: 0

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Molecular Medicine
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Molecular Medicine
STAFF4: 0

SPECIES1: Papio cynocephalus
NUM1: 11

ABSTRACT: The effects of regulating endothelial cell (EC) plasminogen activator production on thrombus accumulation in vivo are incompletely understood. By over expressing plasminogen activators in ECs via gene transfer the hypothesis was tested that increased levels of plasminogen activators inhibit the accumulation of thrombus in vivo. Cultured baboon ECs transduced with human for wild-type tissue plasminogen activator (tPA) or for glycosylphosphatidylinositol-anchored urokinase plasminogen activator (a-uPA) were seeded onto collagen-coated segments of vascular graft (collagen segments) and exposed overnight to flow using an in vitro perfusion circuit. The antigenic levels of tPA and uPA each increased 10-fold in the media perfusing the corresponding transduced ECs, compared with untransduced ECs (p 0.05 in both cases). In baboons the antithrombotic effects of tPA- or a-uPA-transduced ECs were measured as ^{111}In-platelet deposition and ^{125}I-fibrin accumulation on collagen segments bearing sparsely attached ECs (transduced vs untransduced) interposed in exteriorized arterio-venous (AV) femoral shunts. Platelet-rich thrombus formed on the collagen segments with fibrin-rich thrombus propagated distally. The presence of tPA- or a-uPA-transduced ECs on collagen segments at a density of 25,000 ECs/cm^2 decreased ^{111}In-platelet deposition and ^{125}I-fibrin accumulation on collagen surfaces,

compared with untransduced ECs present at equivalent density. The systemic levels of fibrinopeptide A (FPA), thrombin-antithrombin complex (TAT), D-dimer, and both local and systemic levels of tPA and uPA were not increased by transduced ECs, compared with untransduced ECs. The focal antithrombotic effects of transduced ECs appear to be due to local enhancement of thrombolysis. ECs transduced with recombinant tPA and a-uPA enhance local antithrombotic activity in vivo. This strategy of attaching transduced ECs overexpressing plasminogen activators may be therapeutically useful by preventing thrombo-occlusive failure of implanted cardiovascular devices or mechanically denuded vessels.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Megakaryocyte Growth and Development Factor (MGDF) in Baboons

AXIS I: 1a, 2, 3, 9, 13, 17

AXIS II: 48, 50b, 63f, 86

PRC UNIT: Molecular Medicine

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Molecular Medicine
STAFF1: 0

INVES2: Kelly, Andrew B.
DEGREE2: D.V.M.
DEPT2: Molecular Medicine
STAFF2: 3

SPECIES1: Papio cynocephalus
NUM1: 32

SPECIES2: Rhesus
NUM2: 28

ABSTRACT: The primary physiologic regulator of platelet production, Mpl ligand, has recently been cloned and characterized. To define the regulatory role of Mpl ligand on platelet production and function we measured the effects of a recombinant truncated human Mpl ligand, megakaryocyte growth and development factor (rHu-MGDF) on megakaryocytopoiesis, platelet function and thrombogenesis in non-human primates. rHu-MGDF was administered to ten baboons for 28 days while performing pharmacokinteics and repeated measurements of: 1) platelet count, volume, turnover and function ex vivo and in vitro; 2) marrow megakaryocyte number, volume, and ploidy; and 3) platelet deposition and fibrin accumulation on segments of vascular graft and endarterectomized aorta in vivo. Our results demonstrate that rHu-MGDF has the potential for achieving platelet hemostatic protection with minimal thrombo-occlusive risk.

In related studies, we investigated the dose-response effects of pegylated rHu-MGDF (PEG-rHuMGDF) on platelet production and function. PEG-rHuMGDF is in a truncated polypeptide Mpl-ligand derivitized with poly-(ethylene glyco). In baboons, we demonstrated that PEG-rHuMGDF increases platelet production in a linear log-dose-dependent manner by stimulating megakaryocyte endoreduplication and new megakaryocyte formation from marrow hematopoietic progenitors. These findings suggest that appropriate dosing of PEG-rHuMGDF therapy during periods of chemotherapy-induced marrow suppression may maintain hemostatic concentrations of peripheral platelets without increasing the risk of thrombosis.

Finally, in a rhesus monkey model of hepsulfam marrow suppression, both thrombocytopenia and neutropenia were abolished by initiating PEG-rHuMGDF therapy on day one and subsequently adding recombinant human granulocyte colony stimulating factor (rHu-GCSF) after one week for the remaining period of therapy. This study demonstrates the importance of optimizing the dose and schedule of cytokine combinations after severe myelosuppressive chemotherapy.

TITLE: Initiating Events in Vascular Lesion Formation

AXIS I: 1a, 2, 3, 9, 13, 17

AXIS II: 48, 50b, 63f, 86

PRC UNIT: Molecular Medicine

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Molecular Medicine
STAFF1: 0

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Molecular Medicine
STAFF2: 0

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Molecular Medicine
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 12

ABSTRACT: The relative antithrombotic and antihemostatic effects of an orally active synthetic inhibitor of FXa, (2S)-2-[4-[[(3S)-1-acetimidoyl-3-pyrrolidinyl]oxy]phenyl]-3-(7-amidino-2-naphthyl) propionic acid hydrochloride pentahydrate (APAP), has been evaluated in baboons using a two-component thrombogenic device inducing the concurrent formation of both arterial-type platelet-rich (on segments of vascular graft) and venous-type fibrin-rich thrombus (in expanded chambers exhibiting disturbed flow) when interposed in chronic exteriorized arteriovenous (AV) femoral shunts flowing at 40 mL/min. Thrombus formation was compared for oral vs parenteral APAP by measuring ^{111}In-platelet deposition, ^{125}I-fibrin accumulation, thrombotic obstruction of flow, and circulating levels of blood biochemical markers of thrombosis. Both oral and infused APAP reduced platelet deposition in a dose-dependent manner for venous-type fibrin-rich thrombus. However, neither platelet deposition nor fibrin accumulation were reduced significantly for platelet-rich arterial-type thrombus formation on segments of vascular graft ($p>0.1$ in all cases). Oral and infused APAP prolonged the APTT, and prevented thrombus-dependent elevations in plasma fibrinopeptide A (FPA), thrombin-antithrombin III complex (TAT), beta-thromboglobulin (ßTG), and platelet factor 4 (PF4) levels. Additionally, APAP produced dose-dependent inhibition of activated factor X bound to thrombus on segments of vascular graft interposed in exteriorized AV shunts for 15 min. Bleeding time measurements were not prolonged by APAP at any of the doses administered ($p>0.5$). We conclude that oral APAP inhibits the formation of venous-type fibrin-rich thrombus by inactivating bound and soluble FXa without impairing platelet hemostasis. In related studies, we have demonstrated that

intravenous injections of inactivated factor VIIa, a competitive inhibitor of tissue-factor-dependent activation of coagulation factor X, reduced vascular lesion and vascular thrombosis during carotid endarterectomy or femoral artery balloon catheter angioplasty.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Mitrochrondrial Gene Therapy

AXIS I: 1a, 6, 9, 20

AXIS II: 39, 58, 81

PRC UNIT: Neuroscience

INVES1: Wallace, Douglas
DEGREE1: Ph.D.
DEPT1: Molecular Medicine
STAFF1: O

INVES2: Yang, L.
DEGREE2: M.D., Ph.D.
DEPT2: Molecular Medicine
STAFF2: O

SPECIES1: Rhesus monkeys
NUM1: 2

NON-HOST INSTITUTION: N/A

ABSTRACT: This study will use the rhesus monkey to develop gene therapy approaches for diseases involving mitochondrial DNA (mtDNA). The target diseases are Chronic Progressive External Ophthalmoplegia (CPEO) and the Kearn's Sayre Syndrome, both diseases of extraocular muscles and both due to single gene mutations in mtDNA. Clinical studies of these syndromes are underway at the Gene Therapy Suite of the Emory Clinical Research Center (CRC). At Yerkes, myoblast cultures from rhesus monkey extraocular muscles have been established for optimizing cybrid transfer. Following transfection with beta galactosidase-neomycin retroviral vectors, the positive myoblasts will be injected to repopulate the extraocular muscle. Recombinant cells can be detected by beta-galactosidase staining. This model system has the advantage of providing a small muscle where sufficient transfected cells can be reintroduced to alter function. When the optimal conditions for transfection and reimplantation are defined in the monkey, the same approach will be attempted in the patients studied in the CRC.

P51RR00165-35 1/1/1995-12/31/1995 Yerkes Regional Primate Research Center

TITLE: Epididymal Physiology of the Chimpanzee

AXIS I: 1a, 9, 23

AXIS II: 60, 71, 74h, 77

PRC UNIT: Molecular Medicine

INVES1: Young, L.G.
DEGREE1: Ph.D.
DEPT1: Physiology
STAFF1: 0

INVES2: Gould, K.G.
DEGREE2: Ph.D. DVM.
DEPT2: Molecular Medicine
STAFF2: C

INVES3: Froelich, O.
DEGREE3: Ph.D
DEPT3: Physiology
STAFF3: 0

SPECIES1: Pan troglodytes
NUM1: 5

NON-HOST INSTITUTION: N/A

ABSTRACT: As part of ongoing studies directed to identification of potential male contraceptives and to greater understanding of basic reproductive physiology of the chimpanzee, we have used tissues obtained from reproductively normal chimpanzees at time of necropsy and have conducted PCR and Northern Blot analyses to identify messages for five epididymis specific proteins (EPI-1- EPI-5) thought to have a potential function in induction and maintenance of sperm fertilizing capacity. We have subcloned and sequenced PCR fragments for EPI-1 - EPI-3 and demonstrated that they have the expected sequences. We have used subcloned fragments for EPI-1 and EPI-2 as probes for Northern analysis. Using Northern analysis message for EPI-1 was detected in chimpanzee epididymis and not testis, kidney or uterus. EPI-2 was also detected in epididymis but not testis, kidney or uterus. Using subdivided epididymis, it appears that EPI-1 and EPI-2 are synthesized in the posterior portion of the caput epididymis. Using antibodies generated in the rabbit, EPI-1 has been shown to have an effect on fertilization as demonstrated by reduction in the success of the Sperm Penetration Assay (SPA) using hamster oocytes when antibody to EPI-1 is present. The precise function of this protein in fertilization is currently under study. These studies will provide information applicable to maintenance of the captive chimpanzee population and results will be directly applicable to the human.

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FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

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H. Warner, Consultant in Biomedical Engineering, Division of Neuroscience, Yerkes Center; Professor Emeritus of Psychiatry, Emory University School of Medicine.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Oxytocin and Vasopressin Studies in the Non-Human Primate Brain

AXIS I: 1a, 6, 21

AXIS II: 36, 71, 72, 93

PRC UNIT: Neuroscience

INVES1: Insel, Thomas R.
DEGREE1: M.D.
DEPT1: Neuroscience
STAFF1: C

SPECIES1: Rhesus monkeys
NUM1: 6

NON-HOST INSTITUTION: N/A

ABSTRACT: This study has three objectives: (1) mapping oxytocin and vasopressin receptors in the rhesus monkey brain, (2) investigating the release of oxytocin and vasopressin in the monkey brain, and (3) describing the behavioral and cognitive effects of oxytocin and vasopressin. Oxytocin and vasopressin are neuropeptides that have been previously implicated in complex social behaviors in rodents. These studies will extend much of this earlier work to non-human primates preparatory to investigating oxytocin and vasopressin in selective neuropsychiatric disorders such as schizophrenia and autism. In the first year of this study, we have mapped oxytocin and vasopressin receptors in four rhesus monkey brains using receptor autoradiography and we have cloned and sequenced receptors for both neuropeptides. The distribution of vasopressin receptors is markedly different than previously reported from maps of rodent brains. The binding of a putative selective oxytocin receptor ligand appears to overlap the vasopressin receptor pattern and studies using RT-PCR followed by Southern blotting have demonstrated that much of this binding is indeed for the V1a receptor rather than the oxytocin receptor. In the coming year we plan to pursue these neuroanatomic studies further to determine if the rhesus monkey brain contains an oxytocin receptor. In addition, we plan to initiate in vivo microdialysis studies to measure oxytocin and vasopressin release from limbic sites. Finally, we hope to begin administering both peptides to both adult and infant monkeys to determine functional roles for these hormones in the macaque brain.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: The Structural Evolution of the Primate Brain

AXIS I: 1a, 9, 21

AXIS II: 34, 36, 41, 63c

PRC UNIT: Neuroscience

INVES1: Insel, Thomas R.
DEGREE1: M.D.
DEPT1: Neuroscience
STAFF1: C

SPECIES1: Saimiri sciureus
NUM1: 6

SPECIES2: Cebus apella
NUM2: 6

SPECIES3: Macaca mulatta
NUM3: 6

SPECIES4: Hylobates lar
NUM4: 6

SPECIES5: Pan paniscus
NUM5: 6

SPECIES6: Pan troglodytes
NUM6: 6

SPECIES7: Pongo pygmaeus
NUM7: 6

SPECIES8: Gorilla gorilla
NUM8: 6

NON-HOST INSTITUTION: University of Iowa

ABSTRACT: The goal of this project is to establish a database for comparative neuroanatomy of primates using high resolution magnetic resonance imaging (MRI). The following species will be studied: New World (Saimiri sciureus, Cebus apella), Old World (Macaca mulatta), Lesser Apes (Hylobates lar), and Great Apes (Pan paniscus, Pan troglodytes, Pongo pygmaeus, Gorilla gorilla). Three males and three females of each species will be compared. In the first year, at least one of each species (except G. gorilla) have been studied with a high resolution echoplanar scanning protocol that permits 3-dimensional reconstruction and segmentation analysis for measuring volumes. Comparisons across species are just beginning.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF PSYCHOBIOLOGY
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H.T. Gouzoules, Ph.D., Associate Research Professor of Psychobiology, Yerkes Center; Associate Professor of Psychology, Emory University.

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M.E. Wilson, Ph.D., Research Professor of Psychobiology and Head, Radioimmuno-assay Laboratory, Yerkes Center; Assistant Professor of Medicine and Associated Professor in Psychology, Emory University.

Associate Scientist

D.A. Gust, Ph.D., Associate Scientist of Psychobiology, Yerkes Center.

Research Associates

F. Aureli, Ph.D., Research Associate of Psychobiology, Yerkes Center.

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D. Maestripieri, Ph.D., Research Associate of Psychobiology, Yerkes Center; Postdoctoral Research Associate, Department of Psychology, Emory University; Postdoctoral Research Associate, Department of Physiology, Morehouse School of Medicine.

Affiliate Scientists

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S.T. Boysen, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Assistant Professor of Psychology and Director, Primate Cognition Project, Ohio State University.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF PSYCHOBIOLOGY (CONTINUED)

D.L. Forthman, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Coordinator of Scientific Programs in Conservation and Research Department, Zoo Atlanta; Adjunct Professor, Georgia Institute of Technology.

T.L. Maple, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Professor of Psychology, Georgia Institute of Technology; Director, Zoo Atlanta.

W.M. Tomasello, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Professor of Psychology and Adjunct Associate Professor of Anthropology, Emory University.

P.L. Whitten, Ph.D., Affiliate Scientist of Psychobiology, Yerkes Center; Assistant Professor of Anthropology, Emory University.

Allied Faculty Member

E.O. Smith, Ph.D., Allied Faculty Member of Psychobiology, Yerkes Center; Associate Professor of Anthropology, Emory University; Affiliate Scientist, Institute for Primate Research and National Museums of Kenya.

Collaborative Scientist

P.G. Judge, Ph.D., Collaborative Scientist of Psychobiology, Yerkes Center; Adjunct Associate Professor of Psychology, Emory University.

Visiting Scientist

E.C. Spada, Ph.D., Visiting Scientist of Psychobiology, Yerkes Center; Research Fellow, Institute of Marine Sciences, University of California at Santa Cruz.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE Managed Breeding, Genetic Characterization and B-virus Testing in Support of Animal Model Project

AXIS1: 1a,17,23

AXIS2: 31,36,58

PRC UNIT: Psychobiology

INVES1: Gordon, T.P.
DEGREE1: M.S.
DEPT1: Psychobiology
STAFF1: C

INVES2: Gust, D.A.
DEGREE2: Ph.D.
DEPT1: Psychobiology
STAFF1: O

INVES3: McClure, H.M.
DEGREE3: D.V.M.
DEPT1: Microbiology and Immunology
STAFF1: C

SPECIES1: Cercocebus atys
NUM1: 150

SPECIES2: Macaca mulatta
NUM2: 150

SPECIES3: Macaca nemestrina
NUM3: 150

ABSTRACT: The objective of this project is to maintain breeding populations of three species of nonhuman primates which contribute to the Center's AIDS Animal Model Project and to manage these populations to promote optimal breeding. The specific goal is to provide for long term colony maintenance and to produce sufficient progeny to meet the Center's requirements related to AIDS research from this dedicated breeding effort. In support of this effort, programs are in place to provide for behavioral management, serum banking, genetic analysis and B-virus screening. Breeding productivity was excellent in all three species during this project period. DNA profile have been conducted on the pigtail and mangabey populations in order to provide genetic characterization of the colony, to assign paternity to recent offspring and to determine the relative relatedness within and between two populations with quite different histories. Screening for herpes B-virus continued with fifty additional juvenile rhesus monkeys identified as negative and recruited into the program. The oldest identified negative population (born in 1992) has been formed as a B-virus negative breeding group and is expected to product progeny in 1996.

P51RR00165-35 1/1/95 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Ontogeny and function of primate vocal signatures

AXIS I: 1a

AXIS II: 36, 40

PRC UNIT: Psychobiology

INVEST1: Gouzoules, Harold T.
DEGREE1: Ph.D.
DEPT1: Psychobiology
STAFF1: O

INVEST2: Gouzoules, Sarah M.
DEGREE2: Ph.D.
DEPT2: Psychobiology
STAFF2: 0

SPECIES1: Macaca nemestrina
NUM1: 41

SPECIES2: Macaca mulatta
NUM2: 101

ABSTRACT: The overall goal of our research program is to understand the function and ontogeny of nonhuman primate vocal communication in complex social contexts. The long-term aim of this work is to explore cognitive dimensions of primate behavior that may ultimately provide insights into the evolutionary origins of human language. A recent focus has been the evolution of skeptical responding in primates. Signalers who misinform sufficiently often may become devalued as sources of information; however, "skepticism" and any comparisons involved in testing reliability entail a cost that involves delays and energy expenditures. Skepticism may be less costly though, if, as a rule, animals are not equally skeptical of the signals of *all* conspecifics. Animals with the ability to recognize individual conspecifics and recall past encounters with them may have the capacity to restrict skepticism to those subsets of animals most likely to benefit from deception. Tape-recorded alarm calls of high- and low-ranking rhesus monkeys were played to their groups in a feeding context once daily. Response was greater to the calls of high-ranking monkeys, adult response patterns were different from those of juveniles and, for adults especially, decline in responsiveness was punctuated by partial resurgences of response. These differences may be the consequence of the adults' more extensive history of interaction with group members that, though generally reliable, vary with respect to the potential benefits of deceptive signaling.

P51RR00165-35 1/195 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Between and Within Species Differences in Aggression and the CSF Serotonin Metabolite in Sooty Mangabeys and Rhesus Macaques

AXIS I: 1a, 15
AXIS II: 36
PRC UNIT: Psychobiology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Psychobiology
STAFF1: 0

SPECIES1: Cercocebus torquatus atys
NUM1: 10

SPECIES 2: Macaca mulatta
NUM2: 10

ABSTRACT: Over the last decade new research has offered the strong possibility that some aggressive behavior may be modulated by brain neurotransmittors. Recent research using human subjects has demonstrated a relationship between psychopathological syndromes, including excessive aggressive and impulsive tendencies and low 5-HIAA levels. The purpose of this study is to assess the relationship between serotonin metabolite (5-hydroxyindoleacetic acid, 5-HIAA) concentrations in cerebrospinal fluid (CSF) and behavior in two species which exhibit aggression at similar rates but distinctly different degrees of severity. Subjects from each group were studied from September-November 1995 and will be studied from March-May 1996 to include the rhesus monkey's breeding season and nonbreeding season. From September-November 1995 behavioral data was collected on each of the groups concurrently and a CFS sample was collected at the mid point of the three month sample period. The hypothesis to be tested is that sooty mangabeys exhibit less serious aggression than rhesus macques and that increased serious aggression will be reflected in lower concentrations of 5-HIAA. It is also anticipated that within-group variability will exist and will be related to such other positive behaviors as grooming and reconciliation.

TITLE: Paternity in Sooty Mangabeys

AXIS I: 1a, 15
AXIS II: 36
PRC UNIT: Psychobiology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Psychobiology
STAFF1: 0

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Psychobiology
STAFF2: 0

INVES3: McClure, Harold M.
DEGREE: D.V.M.
DEPT2: Microbiology and Immunology
STAFF2: C

SPECIES1: Cercocebus torquatus atys
NUM1: 78

ABSTRACT: Paternity was determined for 78 sooty mangabeys (Cercocebus torquatus atys), born from 1986 to 1993, using a DNA profile analysis. This analysis was based on two independent assays of the genome of each individual using multilocus DNA probes. The mangabeys were descendants of 28 individuals acquired in 1968 and were members of either a large breeding group (n=98) or a smaller group (n=18). The small group was studied only to assess the relationship between dominance rank and reproductive success. A significant correlation was found between dominance rank and reproductive success in both the large and small groups, although the effect was more pronounced in the smaller group. There was also a significant correlation between mounts and the number of surviving offspring each male sired in one birth year. The same male did not always sire the offspring of a given female from year to year. Behavioral data focusing on male-offspring interactions found that offspring (n=15) did not preferentially affiliate with their sire and that males affiliated with infants too infrequently for analysis. Additionally, there was some evidence for incest avoidance. Thus, this study of a large sooty mangabey colony demonstrates that: 1) dominance rank is a predictor of reproductive success; 2) there is no preferential attraction for one's own offspring by males or one's own sire by offspring; 3) the same male generally does not sire the offspring of a given female year to year and 4) incest avoidance may be operating.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Social Influences on Mother-Infant Relationships in Three Species of Macaques

AXIS I: 1a

AXIS II: 36, 71

PRC UNIT: Psychobiology

INVES1: Maestripieri, Dario
DEGREE1: Ph.D.
DEPT1: Psychobiology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 22

SPECIES2: Macaca nemestrina
NUM2: 30

SPECIES3: Macaca arctoides
NUM3: 12

ABSTRACT: This project has investigated several aspects of maternal behavior and infant development in rhesus, pigtail, and stumptail macaques including: the development of maternal responsiveness during pregnancy, social influences on normal and abnormal maternal behavior, mother-infant communication and maternal encouragement of infant independence, and social and hormonal influences on infant development. The dataset for this project includes over 1000 hours of focal observation of mothers and infants living in large captive social groups. This project has produced the first quantitative evidence that female interest in infants increases during pregnancy and that macaque mothers encourage their infants to walk independently and to follow. The findings of this research project have improved our understanding of some general principles underlying the mother-infant relationship in primates and the influence exerted by social and physiological variables on parenting and infant development.

P51RR00165-35 1/1/95 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Gestural Communication in Chimpanzees

AXIS 1: 1a

AXIS II: 36

PRC UNIT: Psychobiology

INVEST1: Tomasello, Mike
DEGREE1: Ph.D.
DEPT1: Psychology
STAFF1: O

SPECIES1: Chimpanzees
NUM1: 20

ABSTRACT: Studies are being conducted with apes in two behavioral domains: (1) gestural communication, and (2) cooperative interactions. In the domain of gestural communication, the gestural signals of a complex social group of chimpanzees at the was documented. This is the same group that has been documented on three previous occasions (1983, 1987, 1991) and so the longitudinal data base was significantly enhanced. In addition, the recent establishment of a new chimpanzee group at Yerkes allowed a very important point of comparison. Also, in an experimental study one individual was removed from the group, taught a novel gesture, returned to the group, and the group observed for signal acquisition. Using longitudinal comparisons across the four time points, comparison between two different groups, and experimental data, the focus is on the specific learning processes involved. In the domain of cooperation, some socially-housed chimpanzee dyads were presented with a task in which cooperation was required. The basic idea was to observe how they coordinate their behavior in these situations and how they communicate about the task. Determining precisely how chimpanzees transfer information socially in these two behavioral domains is important because it will help to elucidate the nature of the proximate mechanisms by means of which this species takes advantage of the knowledge of conspecifics.

P51RR0016-35 11/1995-12/31/1995 Yerkes Regional Primate Research Center

TITLE: Behavioral Development: Prenatal hormonal Influences

AXIS I: 1a,15,23

AXIS II: 36

PRC UNIT: Psychobiology

INVES1: Kim Wallen
DEGREE1: Ph.D.
DEPT1: Psychobiology
STAFF1: C

INVES2: David R. Mann
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF1: adjunct

INVES2: Benjamin Jones
DEGREE2: B.A.
DEPT2: Psychobiology
STAFF2: Lead Research Specialist

SPECIES1: Macaca mulatta
Num1: 48

ABSTRACT: In order to study the effects of altering the prenatal hormonal environment on behavioral development in males and females we produced time-mated pregnancies in a two large social group of 75 rhesus monkeys each. Five times weekly 90 min of behavioral observations were collected where all sexual interactions between any male and the groups' females was recorded using computerized event-sequential methodology. Twenty to 24 days after the last day of mating pregnancy was verified using ultrasonic visualization.

This technique produced 41 verified pregnancies. 12 pregnancies received 30mg/kg of the anti-androgen flutamide (FL) dissolved in DMSO IM twice daily from gestational days 40-70, five pregnancies received FL from gestational days 110-140. 12 pregnant females received weekly IM injections of 20mg of testosterone enanthate (TE) dissolved in oil, and six pregnant females received TE treatment from gestational days 110-140. An additional six females received twice-daily control vehicle injections. The injection schedule had only just begun at the end of the reporting period thus the outcome awaits the current birth season. It is anticipated that fetal females exposed to TE during days 40-70 of gestation will be extensively anatomically virilized, but show little modification of sexually dimorphic behavior. Late TE-treated females, in contrast will show little physical virilization, but are likely to show extensive behavioral masculinization. Fetal males exposed to FL early in pregnancy should not be anatomically masculinized, but will be masculinized behaviorally. Late FL treatment should have the opposite effects on anatomy and behavior in fetal males.

P51RR00165-35 1/1/95 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Growth hormone regulation of puberty and fertility.

AXIS I: 1a, 2, 15, 23, 26

AXIS II: 60, 71

PRC UNIT: Psychobiology

INVES 1: Wilson, Mark E.
DEGREE 1: PhD
DEPT 1: Psychobiology
STAFF 1: C

SPECIES 1: Macaca mulatta
NUMBER 1: 34

ABSTRACT: Growth hormone (GH) and its primary effector, insulin-like growth factor-I (IGF-I), govern the tempo and degree of adolescent growth. In addition to anabolic effects, the GH axis may regulate the hypothalamic - pituitary - ovarian unit (HPO) during puberty and affect ovarian physiology in adults. It is not clear whether the GH axis is obligatory for the normal progression of puberty and adult fertility and, if so, whether these effects are mediated through changes in H-P regulation of luteinizing hormone releasing hormone and LH and/or ovarian sensitivity. Studies were initiated this year, using female rhesus monkeys, that will not only clarify the neuroendocrine regulation of the GH axis in adolescents and adults but will also determine whether the effects of GH and IGF-I on reproduction are limited to the puberty and how these may alter the HPO function, regulating LH secretion. Age-dependent changes in pulsatile GH secretion are being assessed in intact (n = 12) and ovariectomized (OVX; n= 12) adolescent females and OVX adult females (n = 10) treated with varying doses of estradiol (E_2) to determine if the regulation of pulsatile GH by E_2 is differentially affected by age. In addition, one half of the animals in each group are being treated with IGF-I (100 µg/kg/day, SC) to determine if IGF-I differentially regulates pulsatile GH under specific E_2 treatment conditions and E_2 negative feedback of LH in adult and adolescent females. The response in GH secretion is being assessed at specific ages following administration of GH releasing hormone (hGHRH-40). In addition, the response in GH and LH secretion under varying treatment conditions is being assessed following treatment with the excitatory amino acid, NMDA. Basal serum samples are also being collected twice weekly and are being assayed for IGF-I, IGFBP-3, GHBP, E2, LH, and progesterone (gonadally intact groups only). The results of these studies will significantly advance our understanding of how GH synthesis and secretion is regulated in adolescent and adult females. Since GH is an important metabolic and anabolic hormone, a more clear understanding of how GH is released from adolescence through adulthood may provide insights into treatment methods for abnormalities in the GH axis. In addition, these data will also determine the importance of GH and IGF-I in controlling reproduction in females and whether the positive effects of these growth factors on fertility act at the level of the brain or the gonad. This information may assist in the clinical treatment of infertility.

P51RR00165-35 1/1/95 - 12/31/95 Yerkes Regional Primate Research Center

TITLE: Action of growth hormone antagonists in primates

AXIS I: 1a, 2, 9, 15

AXIS II: 50b, 74e

PRC UNIT: Psychobiology

INVES 1: Wilson, Mark E.
DEGREE 1: PhD
DEPT 1: Psychobiology
STAFF 1: C

SPECIES 1: Macaca mulatta
NUMBER 1: 45

ABSTRACT: Four studies were conducted on adolescent male rhesus monkeys (*Macaca mulatta*) to determine the effects of acute administration of growth hormone (GH) antagonists (As) on a number of physiological parameters including serum concentrations of insulin-like growth factor-I (IGF-I), IGF binding protein 3 (IGFBP-3), and the antigenicity of the GHAs. Based on studies in mice, a dose of 1.0 mg/kg of the GHA B-2036-PEG was hypothesized to be maximally effective. Study I determine the time course of changes in IGF-I and IGFBP-3 following placebo administration or treatment with 1.0 mg/kg B2036-PEG given either SC or IV. The decline in these growth factors was evident within 8 hours of treatment with levels reaching nadir concentrations by day 4 and remaining suppressed through day 7 before increasing to baseline values by day 14. Study II investigated how varying doses (0, 0.03, 0.10, 0.30, and 1.0 mg/kg) of B2036-PEG and G120K-PEG affected IGF-I and IGFBP-3. Results indicated that only the 0.3 and 1.0 mg/kg dose of B2036-PEG effectively lowered serum IGF-I by day 3 from treatment (-40 % and -80% of baseline, respectively). However, serum IGF-I had returned to baseline values by day 7 following the 0.3 mg/kg dose but remained suppressed by the maximum dose of B2036-PEG. The third study investigated the effects of varying doses (0, 0.1, 0.3, and 1.0 mg/kg) of B2036-PEG administered at 7 day intervals for 7 weeks. Samples were obtained at 7 day intervals also just prior to the next treatment. Under this sampling regimen, only the maximum dose lowered serum IGF-I. An analysis of serum GH concentrations indicated that there was an inverse relationship between serum GH and the degree to which serum IGF-I was suppressed by B2036-PEG. In contrast, this maximum dose of B2036-PEG had no effect on fasting concentrations of other metabolic and clinical parameters. Antigenicity of each GHA (G120K, G120K-PEG, B2024, B2024-PEG, B2036, B2036-PEG) was assessed by administering the 1.0 mg daily for 14 days. The antigenicity data were not made available for this report. However, the treatment with this concentration of B2036-PEG, which equaled a dose of ~0.2 mg/kg, effectively suppressed serum IGF-I and IGFBP-3 up to 7 days after the treatment. None of the other GHAs had an effect on these growth factors. These data indicate that a dose of 1.0 mg/kg of B2036-PEG administered weekly can suppress IGF-I and its primary binding protein for up to 7 days following treatment and that such treatment has no observed side effects in other metabolic parameters. Additional studies are needed to determine if a smaller dose administered more frequently can maintain the suppression of the GH axis.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF RESEARCH RESOURCES
H.M. McClure, D.V.M., Associate Director for Research Resources

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Core Scientist

H.M. McClure, D.V.M., Associate Director for Research Resources, Research Professor and Acting Chief of Microbiology and Immunology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

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Core Service Faculty

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S.A. Klumpp, D.V.M., Veterinary Pathologist of Service Pathology, Yerkes Center.

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R. B. Swenson, D.V.M., Senior Veterinarian, Yerkes Center.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF RESEARCH RESOURCES (CONTINUED)

Consultants

G.R. Healy, Ph.D., Consultant in Research Resources, Yerkes Center.

V. Nassar, M.D., Consultant in Research Resources, Yerkes Center; Director, Surgical Pathology, Veterans Administration Hospital; Associate Professor of Pathology, Emory University School of Medicine

J.H. Richardson, D.V.M., Consultant in Research Resources, Yerkes Center.

R.E. Weaver, M.D., Ph.D., Consultant in Research Resources, Yerkes Center; Chief, Special Bacteriology Unit, Centers for Disease Control.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Chimpanzees in Single Cages and Small Social Groups: Effects on Behavior and Well-being

AXIS I: 1a

AXIS II: 36

PRC UNIT: Research Resources

INVES1: Baker, Kate C.
DEGREE1 Ph.D.
DEPT1: Research Resources
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 36

NON-HOST INST: NA

ABSTRACT: Documenting the influence of housing condition on the well-being of captive primates is critical for guiding management decisions and facility design. This study contributes to our understanding of the behavioral consequences of two types of indoor housing common to biomedical research on chimpanzees: housing in single cages and in small social groups of two to three individuals. Multiple measures of behavioral well-being were assessed from 132 hours of focal animal sampling of 23 singly caged and 13 socially housed chimpanzees. Analysis of variance revealed no sex differences in the behavioral categories analyzed. However, housing in single cages resulted in significantly lower inactivity scores and higher scores for the categories of environmental manipulation, locomotion, aggression to the observer, and tension-related behaviors. Singly caged subjects were significantly more reactive to others' displays than socially housed individuals. Abnormal behavior, affiliative observer-directed behavior, self-grooming, and temper tantrum scores were not significantly affected by housing condition. Housing tenure of three to nine years in the current study permitted a comparison of long-term effects of housing condition with previously published short-term effects; long- and short-term effects differed for several behavioral categories. Pair- and trio-housed individuals showed similar levels of well-being. Findings of this study may be useful for guiding enrichment regimens for chimpanzees housed in the conditions investigated here, and for determining the level of social complexity that will produce consistently positive effects on various measures of well-being.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: The Neighbor Effect in Captive Chimpanzees: Other Groups Influence Intragroup Agonistic Behavior and Anxiety

AXIS I: 1a

AXIS II: 36

PRC UNIT: Research Resources

INVES1: Baker, Kate C.
DEGREE1 Ph.D.
DEPT1: Research Resources
STAFF1: 0

INVES2: Aureli, Filippo
DEGREE2 Ph.D.
DEPT2: Psychobiology
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 81

NON-HOST INST: NA

ABSTRACT: The influence of calls and displays produced by neighboring groups ('external noise') on the behavior of 81 adult and juvenile chimpanzees (Pan troglodytes) was assessed from 219 hours of behavioral data. Higher rates of hooting, bluff displays, and agonistic behavior were found when levels of external noise were high. Incidents of external noise were directly responsible for such an increase: intragroup agonism was significantly more common after neighboring individuals vocalized or displayed than before. This effect is congruous with behavioral patterns observed in the wild, and is therefore considered an expression of species-typical behavior as opposed to an artifact of captivity. External noise is likely to produce uncertainty among members of social groups because of the increased risk of being the target of agonistic behavior. It is therefore a useful tool for examining the relationship between anxiety and behaviors that have been previously reported as displacement activities in other primates (scratching, self-grooming, and yawning). Single-caged chimpanzees, for whom external noise carries no risk of aggression by group members, showed no increase in self-directed behavior when external noise level was high. Socially-housed chimpanzees, however, showed a correspondence between levels of rough scratching and external noise. Incidents of external noise produced an immediate effect on levels of rough scratching, as well as gentle scratching and yawning. However, the effect on rough scratching persisted longer after neighboring individuals vocalized or displayed. No association was found between self-grooming and the stressful situation investigated here. This study suggests that rough scratching is the most reliable and sensitive indicator of anxiety in chimpanzees, and that gentle scratching and yawning can be considered displacement activities in this species.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Regurgitation and Reingestion in Captive Chimpanzees

AXIS I: 1a

AXIS II: 36

PRC UNIT: Research Resources

INVES1: Baker, Kate C.
DEGREE1 Ph.D.
DEPT1: Research Resources
STAFF1: 0

INVES2: Easley, Stephen P.
DEGREE2 Ph.D.
DEPT2: Research Resources
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 13

NON-HOST INST: New Mexico State University, Alamogordo, NM (SPE)

ABSTRACT: The abnormal behavioral pattern of regurgitation and reingestion (R/R) is poorly understood in chimpanzees (Pan troglodytes). This study assesses R/R in thirteen indoor-housed chimpanzees living in pairs and trios. Focal animal sampling data were used to calculate scores for R/R, two other classes of abnormal behavior (abnormal behaviors with oral components and those without oral components), and affiliative social behavior. R/R was observed in 85% of study subjects, an elevated proportion in comparison to a previously published survey of captive chimpanzee populations. Contexts and temporal patterns of R/R suggest that detection of this behavior may in many cases require observations outside of daily management routines. Social disturbances did not elicit this behavior. Statistical tests showed no relationship between individual differences in R/R rates and rates of other abnormal behavior classes, time engaged in affiliative behaviors, number of cagemates, or housing history; nor were sex differences detected. Meal composition was not found to effect the time devoted to R/R. Statistical tests did show a strong positive relationship between rates of R/R and elapsed time since feeding. These results suggest that increasing meal frequency or providing consistently available edible material may prove more broadly effective than altering meal composition. Temporal distributions of R/R differed from those of abnormal behaviors, suggesting that factors such as boredom, hunger, or other sources of stress may differentially affect the expression of various classes of abnormal behavior.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Neurobehavioral Responsivity of Chimpanzees

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Research Resources

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Research Resources
STAFF1: O

SPECIES1: Pan troglodytes
NUM1: 51

NON-HOST INST: NA

ABSTRACT: This project has multiple aims: to describe development in chimpanzees in comparison to humans; to compare development in chimpanzees raised under different rearing conditions; to better understand developmental processes through the cross-species comparison of rates of development across systems (e.g., perceptual, motor, emotional, and cognitive). Humans and chimpanzees differ in developmental rates within the cognitive and motoric systems. They do not appear to differ in developmental rates within visual system. We are still investigating comparative development within the social, and emotional systems. With regard to parenting, it appears that certain developmental experiences are crucial. Due to a lack of experience in handling infants, there are some adult female chimpanzees without adequate maternal behaviors to raise their infants. To insure infant survival, these infants are raised in the Great Ape Nursery (GAN). The GAN has utilized two types of rearing in the last 10 years, Standard Care (ST) and Responsive Care (RC). ST was designed to maximize species-typical development primarily through conspecific peer interactions. RC was designed to more closely approximate species-typical rearing by training adult human caregivers to interact with infants using chimpanzee species-typical behaviors based on competent chimpanzee mothers. Normative data have been collected on infants raised under these two nursery settings and compared with data collected from mother-reared infants. Analyses indicate that the neurobehavioral integrity of infants, 2 to 30 days of age, differs somewhat: RC are more alert but ST are more capable of self-regulating. RC infants were more like mother-reared infants, exhibiting a less well developed ability to self-quiet and regulate their state compared with ST. Meaningful differences were found in emotional expressiveness from 3 to 12 months of age. Chimpanzees given RC were significantly more positive in their emotional responsiveness on standardized tests of cognitive and manipulative performance compared with chimpanzees given ST. Rearing environment can alter the temperament of chimpanzees. The comparison of development across species with consideration of the differences in coordination between systems can broaden our understanding of necessary and sufficient conditions which may underlie development. For example, chimpanzees compared with humans infants are more advanced in

motoric ability but similar in the development of attachment and wariness of strangers. Thus, locomotor ability can not be the necessary condition for the development of wariness of strangers: these events co-occur in human infants but there is substantial lag in chimpanzee infants. Cross-species comparisons, developmentally focused, are invaluable to disentangle those processes that are confounded in human development.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Animal Training with Positive Reinforcement

AXIS I: 1a

AXIS II: 36

PRC UNIT: Research Resources

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Research Resources
STAFF1: O

SPECIES1: Pan troglodytes
NUM1: 9

NON-HOST INST: NA

ABSTRACT: Operant conditioning techniques have been used with chimpanzees at the Yerkes Center over the past 30 years, however, training has been sporadic, often limited, and rarely documented with regard to results. This project was a structured effort to use positive reinforcement to behaviorally manage a small number of chimpanzees as a pilot project for implementation of positive reinforcement as the primary management technique throughout the Yerkes Center. Four young adults (2 males and 2 females) and five young juveniles (4 females and 1 male) were subjects for this study. A data collection system was designed to assess behavioral well-being: contra-indications of well-being were abnormal/stereotyped behavior and distress; indications of well-being were species-typical social and self-directed behaviors. In addition, the quality of human interactions with the chimpanzees were recorded. Results of the baseline observations will be used to compare behavioral well-being before and after training. Additional observations were made on two chimpanzees on the day of their annual veterinary survey in order to assess the benefits and costs of this labor intensive procedure before and after training. Training was begun for compliance with regular caregiving activities (moving inside, moving outside, moving to the next cage, sitting, and climbing up on the cage fence) with the use of positive reinforcements upon compliance with verbal and hand-signal commands. For the juveniles an assortment of tasks involving the showing of body parts was added to the training regime. Desensitization to the transport box was accomplished for all. In addition, 3 adults and all the juveniles entered the box on command at least once to receive positive reinforcement. This program is in progress.

P51RR00165-35 1/1/95-12/31/95 Yerkes Regional Primate Research Center

TITLE: Chimpanzee Breeding and Research Program

AXIS I: 1a, 23

AXIS II: 36, 92-Resource production

PRC UNIT: Research Resources

INVES1: Insel, Thomas R.
DEGREE1: M.D.
DEPT1: Neuroscience
STAFF1: C

INVES2: Swenson, R. Brent
DEGREE2: D.V.M.
DEPT2: Research Resources
STAFF2: C

INVES3: Gould, Kenneth G.
DEGREE3: D.V.M., Ph.D.
DEPT3: Molecular Medicine
STAFF3: C

INVES4: Bard, Kim A.
DEGREE4: Ph.D.
DEPT4: Research Resources
STAFF4: O

SPECIES1: Pan troglodytes
NUM1: 75

NON-HOST INSTITUTION: N/A

ABSTRACT: The goal of this project is to maintain a self-sustaining colony of chimpanzees for behavioral and biomedical research. In the past year the rate of reproduction within this colony was intentionally curtailed due to limited space and limited funding for investigator-initiated chimpanzee research. Two groups of animals (total of 15) were placed on loan to zoological parks. Through contraception, no additional animals were added to the breeding cohort. Although there were no additions to the nursery in this year, the cohort of animals previously raised in the nursery with our responsive care program were evaluated for social skills as young adolescents. Building on changes in the previous year, the focus of attention has continued to shift from production of chimpanzees to optimizing the housing, the training, and the use of the current colony. A chimpanzee management committee has been formed to optimize progress in each of these areas.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF VISUAL SCIENCE
R.G. Boothe, Ph.D., Chief

Core Scientists

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M.H. Tigges, Ph.D., Research Professor of Visual Science, Yerkes Center; Associate Professor of Anatomy and Cell Biology; Associate Professor of Ophthalmology, Emory University School of Medicine.

J.R. Wilson, Ph.D., Associate Research Professor of Visual Science, Yerkes Center; Associate Professor of Anatomy and Cell Biology, Emory University School of Medicine.

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A. Fernandes, M.D., Research Associate of Visual Science, Yerkes Center; Associate, Department of Ophthalmology, Emory University.

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T.A. Meredith, M.D., Affiliate Scientist of Visual Science, Yerkes Center; Clinical Professor of Ophthalmology, St. Louis University Medical Center.

H.R. Rodman, Ph.D., Affiliate Scientist of Visual Science, Yerkes Center; Assistant Professor of Psychology, Emory University.

P. Sternberg, Jr., M.D., Affiliate Scientist of Visual Science, Yerkes Center; Associate Professor of Ophthalmology, Emory University School of Medicine.

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

DIVISION OF VISUAL SCIENCE (CONTINUED)

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L.R. Tychsen, M.D., Collaborative Scientist of Visual Science, Yerkes Center; Assistant Professor of Ophthalmology, Pediatrics, Anatomy, and Neurobiology, Washington University School of Medicine.

Visiting Scientists

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R. H. Kardon, M.D., Ph.D., Visiting Scientist of Visual Science, Yerkes Center; Associate Professor, Department of Ophthalmology, University of Iowa Hospitals and Clinics.

J.V. Odom, Ph.D., Visiting Scientist of Visual Science, Yerkes Center; Associate Professor of Ophthalmology, West Virginia University.

Consultant

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P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Treatments for Aphakic Amblyopia

AXISI: 1a, 21, 25b
AXISII: 36, 44, 60

PRC UNIT: Visual Science

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Visual Science
STAFF1: C

INVES2: Wilson, James R.
DEGREE2: Ph.D.
DEPT2: Visual Science
STAFF2: C

INVES3: Tigges, Margarete
DEGREE3: Ph.D.
DEPT3: Visual Science
STAFF3: C

INVES4: Fernandes, Alcides
DEGREE4: M.D.
DEPT4: Visual Science
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 8

NON-HOST INST: NA

ABSTRACT: The amblyopia that develops in children after the removal of a cataract is particularly difficult to treat and often leads to blindness. The objectives of this project are to understand the neural bases for this and related disorders and, ultimately, to design treatments for amblyopia that are based on sound scientific knowledge. The primary probe used is a neurological defect in motion processing that is linked to loss of binocular function following neonatal deprivation. During the past year, a combination of behavioral, electrophysiological, and neuroanatomical, and physiological optics methods were used to assess these deficits. Findings have demonstrated that motion processing deficits are present even following treatment conditions that give rise to near normal acuity and contrast sensitivity. Thus, treatments for children need to be evaluated in terms of their effects on motion processing as well as on spatial vision. These findings have been presented in abstract form at major scientific meetings, including the Society for Neuroscience and the Association for Research in Vision and Ophthalmology, and have also been published in peer-reviewed journals. Our findings in monkeys can be extrapolated to human infants with aphakic amblyopia, because of

the close similarities between this condition as it occurs naturally in humans and experimentally in our monkeys.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Acuity in Monkeys with Neonatal Intraocular Lens Implantation

AXIS I: 1a, 21, 25b
AXIS II: 36, 44, 60

PRC UNIT: Visual Science

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Visual Science
STAFF1: C

INVES2: Lambert, Scott R.
DEGREE2: M.D.
DEPT2: Visual Science
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 6

NON-HOST INST: NA

ABSTRACT: The overall goal of this project was to evaluate the effectiveness of intraocular lens implants in preserving visual function when used as a treatment of infantile cataracts in humans. The emphases in the past year have been on comparing monofocal and multifocal lenses, and on comparing rehabilitation treatments that involve patching versus no patching. Specifically, four treatment groups are being compared (multi-lens, patched; multi-lens, no-patch; mono-lens, patched; and mono-lens, no-patch). It was found that patching leads to a significant improvement compared to no-patching, but multifocal and monofocal lenses do not lead to significant differences. For all groups, even when grating acuity in the pseudophakic eyes matured to normal adult levels, assessments of optotype acuity revealed amblyopic deficits and contrast sensitivity was also found to be impaired at middle and low spatial frequencies. Thus, tests of grating acuity are not sufficient to conclude that the treatments lead to a good outcome. These results have been presented at major scientific meetings, including the Association for Research in Vision and Ophthalmology; and have been published in peer-reviewed journals, including Investigative Ophthalmology & Visual Science. These results can be extrapolated to human children with intraocular lens implants, because of the close similarities between the eyes and visual systems of humans and monkeys.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Peptidergic Innervation of the Primate Meibomian Gland

AXIS I: 1a, 21, 25b

AXIS II: 60, 62

PRC UNIT: Visual Science

INVES1: Chung, Christine W.
DEGREE1: M.D.
DEPT1:
STAFF1: O

INVES2: Tigges, Margarete
DEGREE2: Ph.D.
DEPT2: Visual Science
STAFF2: C

INVES3: Stone, Richard A.
DEGREE3: M.D.
DEPT3: Visual Science
STAFF3: O

SPECIES1: Macaca mulatta
NUM1: 7

NON-HOST INST: Scheie Eye Institute, University of Pennsylvania School of Medicine (CC, RAS)

ABSTRACT: Meibomian glands are sebaceous glands in the eyelids. They secrete a mixture of lipids and other components that form the outer layer of the tear film. This layer functions to decrease tear evaporation and surface tension of the tear film. The clinical importance of these secretions is evident from gland dysfunctions that can cause dry eye symptoms, keratoconjunctivitis, and cataract lens intolerance. Thus, a better understanding of the mechanisms that control meibomian gland secretion could be of importance in preventing some of these incapacitating and painful eye disorders. Meibomian glands receive significant innervations in rats, but information on primates is limited. To characterize the innervation of monkey meibomian glands, we were able to collect eyelids from monkeys that became available from other experiments. To localize and characterize nerves in meibomian glands, we used immunohistochemical staining for neuropeptides and neuronal enzymes, including NSE, TH, NPY, VIP, CGRP and SP. Antibodies to NSE, NPY and VIP revealed abundant nerve fibers closely opposed to the basement membrane of acini. Nerve fibers containing TH, CGRP, and SP were more sparse. Thus, primate meibomian glands are richly innervated by nerve fibers largely of parasympathetic origin and by a relatively smaller contribution from sympathetic and sensory sources. Based on the diversity of neurotransmitter-neuromodulator substances, meibomian gland secretion must be controlled by diverse mechanism. This project was partly supported by EY09737. Number of monkeys: 7, they are the same used in eye growth experiments.

P51RR00165-35 1/1/1995 - 12/31/1995 Yerkes Regional Primate Research Center

TITLE: Anatomy and Physiology of Neurons in the Primate's Lateral Geniculate Nucleus

AXIS I: 1a, 21, 25b

AXIS II: 92, Neuroscience

PRC UNIT: Visual Science

INVES1: Wilson, James R.
DEGREE1: Ph.D.
DEPT1: Visual Science
STAFF1: C

INVES2: Forestner, Donna M.
DEGREE2: B.A.
DEPT2: Visual Science
STAFF2: O

SPECIES1: Saimiri sciureus
NUM1: 5

SPECIES2: Macaca mulatta
NUM2: 5

NON-HOST INST: NA

ABSTRACT: This lab continues to study the primate's dorsal lateral geniculate nucleus to understand its structure and function. The dorsal lateral geniculate nucleus (dLGN) is the thalamic region responsible for transmitting retina signals to cortex. Brainstem pathways to this nucleus have been described in several species and are believed to control the retinocortical pathway depending on the state of the animal (awake, asleep, drowsy, etc.). The purpose of the studies was to (1) determine all of the subcortical sources of afferents to the dLGN in a higher primate, the macaque monkey, whose visual system is similar to that of humans, and (2) compare neurons in normal and monocularly deprived monkeys for differences in synaptic inputs. It was concluded that (1) there are seven subcortical regions that send afferents to the dLGNs of macaque monkeys; (2) the synaptic densities onto deprived neurons are higher at all dendritic distances compared to those onto normal neurons. Furthermore, HRP-filled deprived neurons received an average of 25 synapses onto their somata compared with only an average of 7 somal synapses on the HRP-filled normal neurons. Most of the increase in the number of synapses onto the deprived neurons was from GABAergic type profiles. This abnormality of the deprived neurons of the LGN could be the underlying cause of their lesser responses compared with normal or nondeprived LGN neurons. It could also be the initial stage that causes blindness in monocularly lid-sutured primates.

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: XXX OTHER:

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Attanasio, R.	FED	NCRR	RR/OD10755	$50,000	100
Boothe, R.	FED	NIH/NEI	EY-05975	$234,030	100
Byrd, L.	FED	NIDA	DA-01161	$332,162	100
Byrd, L.	FED	NIDA	DA-06264	$331,153	100
DeWaal, F.	FED	NIMH	MH-49475	$85,456	100
DeWaal, F.	FED	NCRR	RR-09797	$170,767	100
Gould, K.	FED	NIH	RR093587	$302,025	100
Gould, K.	FED	NIH	RR-03587-S1	$77,900	100
Gould, K.	FED	NCRR	RR-05944	$169,140	100
Gould, K.	FED	NIH	HD-16423	$100,522	100
Hemdon, J.	FED	NIH	AG-12610	$50,000	100
Insel, T./Swenson, B.	FED	NIH/NCRR	RR03591	$866,263	100
McClure, H.	FED	NIH/NCRR	RR-06753	$89,811	100
McClure, H.	FED	NIH/STTR	Anda Phar.	$23,370	100
McClure, H.	FED	NIH	SW Found.	$114,708	100
McClure, H.	FED	CDC	100-95-0019	$116,323	100
Novembre, F.	FED	NIH	CA-67364	$155,656	100
Tigges, J.	FED	NIH	AG-00001	$193,168	100
Tigges, M.	FED	NIH/NEI	EY09737	$193,934	100

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: XXX OTHER:

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Wallen, K.	FED	NIH/NIMH	MH50268	$188,820	100
Wilson, M.	FED	NIH-NICHD	HD-16305	$162,596	100
TOTAL PHS SUPPORT			This page:	$4,007,804	
			Grand (Cumulative) Total:	$4,007,804	

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Ansari, A.	FED	NIH	R01-27057	$183,079	25
Bakay, R.	FED	NIH/INDS	NS-24340	$227,192	100
Bard, K.	FED	NIH/NCRR	RR06158	$217,561	100
Bard, K.	FED	NIH/NCRR	RR06158 Msupp	$17,052	100
Bradley, D.	FED	NIH	EY06492	$28,600	100
Compans, R.	FED	NIH	CA-62934	$58,210	100
Compans, R.	FED	NIH	AI-38501	$205,047	100
Dodson, T.	FED	NIH/NIDR	DE-10762	$37,724	100
Fleming, W.	FED	NIH/NHLBI	HL52965	$207,725	55
Fritz, M.	FED	NIH/NIDR	DE-08917	$642,010	100
Hanson, S.	FED	NIH/NHLBI	HL-31469	$329,578	50
Hanson, S.	FED	NIH	HL-48667	$110,091	50
Harker, L.	FED	NIH/NHLBI	HL41691	$333,407	20
Harker, L.	FED	NIH	HL-48667	$104,295	50
Harwerth, R.	FED	NIH	EY01139	$21,782	100
Hopkins, W.	FED	NIH/NINDS	NS-20574	$102,415	100
Howell, L.	FED	NIH/NIDA	DA-05346	$133,441	100

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Lambert, S.	FED	NIH/NEI	EY-08544	$213,201	100
Mann, D.	FED	NIH/NICHD	HD-26423	$131,499	31
Moss, M.	FED	NIH	AG-00001	$69,993	55
Peters, A.	FED	NIH	NS07152	$165,229	5
Peters, A.	FED	NIH	NS07016	$131,668	35
Peters, A.	FED	NIH	AG-00001	$107,575	25
Schinazi, R.	FED	NIH	AI-25899	$78,365	15
Sommadossi, J.	FED	NIH	HL42125	$244,877	1
Wilcox, J.	FED	NIH/NHLBI	HL-47838	$381,406	60

TOTAL PHS SUPPORT This page: $4,483,022
Grand (Cumulative) Total: $8,490,826

INVESTIGATORS WITH SUPPORT OTHER THAN PUBLIC HEALTH SERVICE

CORE: XXX OTHER:

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Attanasio, R.					
Boothe, R.					
Byrd, L.					
DeWaal, F.	FED	NSF	IBN-9321195	$74,990	100
Gouzoules, H.	FED	NSF	IBN-9209844	$44,800	100
Insel, T.					
McClure, H.					
McClure, H.					
McClure, H.					
Novembre, F.					
Wilson, J.					
Wilson, M.					

TOTAL PHS SUPPORT	This page:	$ 732,259
	Grand (Cumulative) Total:	$9,223,085

INVESTIGATORS WITH SUPPORT OTHER THAN PUBLIC HEALTH SERVICE

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Boden, S.					
Boden, S.					
Boden, S.					
Chronos, N.					
Chronos, N.					
Dodson, T.					
Fernandes, A.					
Fleming, W.					
Fleming, W.					
Forthman, D.					
Fritz, M.					
Fritz, M.					
Gust, D.					
Hanson, S.					
Hanson, S.					
Hanson, S.					
Harker, L.					

INVESTIGATORS WITH SUPPORT OTHER THAN PUBLIC HEALTH SERVICE

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT CONTRACT	TOTAL FUNDS	%RPRC USED
Harker, L.					
Harker, L.					
Harker, L.					
Iuvone, P.					
Malizia, A.					
Nahamias, A.					
Pearson, T.					
Pearson, T.					
Tomasello, M.	FED	NSF	IBN-9507418	$70,638	100
Tomasello, M.	FED	NSF	IBN-9507419-supp	$6,000	100
Tychsen, L.					
Tsang, V.					
Winton, E.					
Winton, E.					
Winton, E.					
TOTAL PHS SUPPORT			This page:	$ 2,789,693	
			Grand (Cumulative) Total:	$12,012,778	

PART II, SECTION C BOOKS/PAPERS/ABSTRACTS P51RR00165-35

CORE: XXX OTHER:

Number Published: Books: 0 Papers: 16 Abstracts: 6

Number In Press: Books: 1 Papers: 21 Abstracts: 1

*Boothe, R.G., Lambert, S.R., Louden, T., White, J., Ladinsky, E. and Gilzenrat, M.: Part-time occulsion improves visual function following implantation of an intraocular lens in one eye of a neonatal monkey. Invest. Ophthalmol. Vis. Sci. Suppl. 36: 44, 1995 (Abstract).

*deWaal, F.B.M.: Sex as an alternative to aggression in the bonobo. In: Sexual Nature, Sexual Culture. P. Abramson and S. Pinkerton (eds). The University of Chicago Press, Chicago, 1995.

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*Gouzoules, H.: Review of Female Choices: Sexual Behavior of Female Primates, M.F. Small, Cornell University Press, 1993, Int. J. Prim. 16:333-335, 1995.

*Gouzoules, H., Gouzoules, S. and Ashley, J.L.: Representational signaling in nonhuman primate vocal communication. In: Current Topics in Primate Vocal Communication, E. Zimmermann, J.D. Newman and U. Jurgens, eds., Plenum Publishing, New York, pp. 235-252, 1995.

*Gouzoules, H. and Gouzoules, S.: Recruitment screams of pigtail monkeys (Macaca nemestrina): ontogenetic perspectives, Behaviour 132:431-450, 1995.

Insel, T.R., Preston, S. and Winslow, J.T.: Mating in the monogamous male: Behavioral consequences. Physio. and Behav. 54(4): 615-627, 1995.

Insel, T.R. and Hulihan, T.J.: A gender-specific mechanism for pair bonding: Oxytocin and partner preference formation in monogamous voles. Behav. Neurosci. 109(4): 782-789, 1995.

*Nadler, R.D.: Proximate and ultimate influences on the regulation of mating in the great apea. Amer. J. Primatol. 37:93-102, 1995.

*Nadler, R.D., Galdikas, B.M.F., Sheeran, L.K. and Rosen, N. (eds.): The Neglected Ape. New York, Plenum Publishing Corp, 1995.

*Nadler, R.D.: Sexual Behavior of Orangutans (*Pongo* pygmaeus): Basic and Applied Implications. In: R. D. Nadler, B.M.F. Galdikas, L.K. Sheeran, and N. Rosen (eds), The Neglected Ape. Ne York, Plenum Publishing Corp., 223-237, 1995.

*Center Support Acknowledged

*Nadler, R.D.: The social nexus of immature wild mountain gorillas (*Gorilla gorilla gorilla*). In: Abstracts of the International Symposium, Primate Ontogeny, Konarovice, Czech Republic, 1995 (Abstract).

*Novembre, F.J., Saucier, M.M., Klumpp, S.A., Anderson, D.C. and McClure, H.M.: A neurotropic SIV derived from a sooty m angabey demonstrates varied pathogenesis for pig-tailed and rhesus macaques. In: 13th Annual Symposium on Nonhuman Primate Models for AIDS, November 5-8, 1995, Monterey, CA, p142 (Abstract).

*Novembre, F.J., Gummuluru, S., Gelbard, H.A., Seshi, B., McClure, H.M. and Dewhurst, S.: Immune activation and the pathogenesis of SIVsmmPBj14. In: 13th Annual Symposium on Nonhuman Primate Models for AIDS, November 5-8, 1995, Monterey, CA, p168 (Abstract #88).

*Novembre, F.J., Saucier, M.M., Anderson, D.C., Klumpp, S.A., Swenson, R.B., Brodie, A.R. and McClure, H.M.: Development of AIDS in a chimpanzee infected with HIV-1. In: 13th Annual Symposium on Nonhuman Primate Models for AIDS, November 5-8, 1995, Monterey, CA, p168 (Abstract #160).

*Tigges, J., Herndon, J.G. and Rosene, D.L.: Mild age-related changes in the dentate gyrus of adult rhesus monkeys. Acta Anat. 153:39-48, 1995.

*Tigges, M., Tigges, J., Rees, H.D., Rye, D.B and Levey, A.I.: Visual deprivation does not alter muscarinic receptor protein distribution in area 17 of rhesus monkeys. Soc. Neurosci. Abstr. 21:1654, 1995 (Abstract).

*Wilson, M.E. and Taner, J.M.: Somatostatin analog treatment slows growth and the tempo of reproductive maturation in female rhesus monkeys. J. Clin. Endocrinol. Metab. 79:495-501, 1995.

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*Wilson, J.R., and Forestner, D.M.: Synaptic inputs to single neurons in the LGN of normal and monocularly deprived squirrel monkeys. J. Comp. Neurol. 362: 468-488, 1995.

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IN PRESS:

*Boothe, R.G.: Visual development following treatment of a unilateral infantile cataract. In Infant Vision, F. Vital-Durand, J. Atkinson and O.J. Braddick, eds., Oxford University, (In press).

*Boothe, R.G. and Brown, R.J.: What happens to binocularity in primates strabismus?, Eye (In press).

*Boothe, R.G., Louden, T. and Lambert, S.R.: Acuity and contrast sensitivity in monkeys following neonatal intraocular lens implantations with and without part-time occulsion of the fellow eye. Invest. Ophthalmol. Vis. Sci. (In press).

deWaal, F.B.M.: BONOBO: Natural History of a Forgotten Ape. University of California Press, Berkeley (In press).

*deWaal, F.B.M.: Macaque social culture: Development and perpetuation of affiliative networks. J. Comp. Psychol. (In press).

*deWaal, F.B.M.: The biological basis of peaceful coexistence: A review of reconciliation research on monkeys and apes. In: A National History of Peace, T. Gregor (ed.) Vanderbilt Univ. Press, Nashville, TN, 1995 (In press).

*deWaal, F.B.M.: Conflict as negotiation. In: Great Ape Societies. W.C. McGrew, L. Marchant and T. Nishida (eds.). Cambridge University Press, Cambridge, pp. 159-172 (In press).

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*deWaal, F.B.M. and Aureli, F.: Conflict resolution and distress alleviation in monkeys and apes. New York Academy of Sciences, (In press).

*deWaal, F.B.M. and Aureli, F.: Consolation, reconciliation, and a possible cognitive difference between macaque and chimpanzee. In: Reaching into Thought: The Minds of the Great Apes. A. E. Russon, K.A. Bard and S. T. Parker (eds.). Cambridge University Press (In press).

*Gouzoules, H.: The transcendent step. [Review of the Information Continuum: Evolution of Social Information Transfer in Monkeys, Apes and Hominids, B. J. King, School of American Research Press, 1941], Amer. J. Prim. (In press).

*Gouzoules, H., Gouzoules, S. and Miller, K.: Skeptical responding in rhesus monkeys (Macaca mulatta). Int. J. Prim. (In press).

Insel, T.R. and Wang, Z.: Parental Behavior in Voles. In Advances for the Study of Behavior. P. Slater, J. Rosenblatt, M. Milinski, and C. Snowdon, eds., Academic Press, San Diego, California (In press).

Insel, T. R., Winslow, J. T., Wang, A., Young, L. and Hulihan, T.J.: Oxytocin and the molecular basis of monogamy. In: Oxytocin: Cellular and Molecular Approaches in Medicine and Research. R. Ivell, and J. Russell (eds.), Plenum Press, New York, New York (In press).

*Center Support Acknowledged

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*McClure, H.M. and Novembre, F.J.: Simian immunodeficiency virus variants: threat of new lentiviruses. Am J. Med. Sci. (in press).

*Nadler, R.D.: The social nexus of immature wild mountain gorillas (*Gorilla gorilla gorilla*). Anthropologie (Bmo), (In press).

*Nadler, R.D. and Dukelow, W.R.: The first symposium on the history of primatology, Primate Report, (In press).

*Nadler, R.D.: Robert M. Yerkes and the early studies of primate sexual behavior. Primate Report, (In press).

*Tigges, M., Sugrue, M.F., Mallorga, P., Stone, R.A., Laties, A.M., Fernandes, A. And Iuvone, P.M.: Effects of atropine (ART) and pirenzepine (PIR) on ocular growth and muscarinic cholinergic receptors in young rhesus monkeys. Invest Ophthalmol. Vis. Sci. Suppl. 37: Abstract (In press).

*Wilson, J.R., Cowey, A. and Somogyi, P.: GABA Immunopositive axons in the optic nerve and opti tract of macaque monkeys. Vision Res. (In press).

CORE: OTHER: XXX

Number Published:	Books:	0	Papers:	90	Abstracts:	47
Number in Press:	Books:	2	Papers:	55	Abstracts:	9

*Abou-Elella, A.A., Camarillo, T., Allen, M.B., Barclay, S., Pierce, J.A., Holland, H.K., Wingard, J.R., Bray, R.A., Rodey, G.E. and Hillyer, C.D.: Low incidence of red blood cell and HLA antibody formation by bone marrow transplant patients. Transfusion 35: 931-35, 1995.

*Aiyer, A., Brown, R.J., Stevens, L. and Boothe, R. G.: Visually evoked potential (VEP) assessments of visual function in a monkey model of treatments for human unilateral infantile cataracts. Soc. Neuorsci. Abstr. 21:2024, 1995 (Abstract).

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*Augustine, J.R., Mascani, F. and Tigges, J.: Immunocytological staining of calbindin in the insular lobe of the rhesus monkey: A light microscopic study. Soc. Neurosci. 21:411, 1995 (Abstract).

*Baker, K.: Differences in behavior between chimpanzees housed long-term in individual cages and small groups. Am. J. Primatol. 36:108, 1995 (Abstract).

*Bard, K.A.: Parenting in primates. In: Handbook of Parenting: Vol II Ecology and Biology of Parenting, Edited by M. Bornstein, pp27-58, Hillsdale, N.J.: Lawrence Erlbaum, 1995.

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*Bard, K.A., Street, E.A., McCrary, C. and Boothe, R.G.: Development of visual acuity in infant chimpanzees. Infant Behav. Dev. 18:225-232, 1995.

Boden, S.D., Schimandle, J.H. and Hutton, W.C.: The 1995 Volvo Award in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 20:2633-2644, 1995.

*Bradley, D.V., Aiyer, A., Brown, R.J., Patel, M. and Boothe, R.G.: Evaluation of a monkey model for unilateral infantile cataract that used myopic focus of the fellow eye to force usage of the aphakic eye. Invest. Ophthalmol. Vis. Sci. Suppl. 36:45, 1995 (Abstract).

Branch, T.P., Mosunjac, M., Lackey, D.A., Goldberg, D., Zubovic-Morusa, M. and Hillyer, C.D.: The type-C synovial cell: immunohistochemical identification. Proc. Orthopaedic Res. Soc. Orlando, FL, 1995.

*Bradley, D.V., Tigges, M. and Boothe, R.G.: Development of ocular dominance columns and its relationship to visual function in rhesus monkeys raised with binocular, unequal, visual deprivation. Soc. Neurosci. Abstr. 21:393, 1995 (Abstract).

*Brown, R.J., Wilson, J.R., Boothe, R.G., and Norcia, A.M.: Spatio-temporal properties of directional motion asymmetry assessed in VEPS of infant monkeys. Invest. Ophthalmol. Vis. Sci. Suppl. 36:910, 1995 (Abstract).

Byrne, R. and Tomasello, M.: Do rats ape? Animal Behavior, 50:1417-20, 1995.

Bucur, S.Z., Strobert, E.A., Hillyer, C.D., Orkin, J.A., McClure, H.M., McKeam, J.P. and Winton, E.F.: Synthokine effect on the hematopoietic system and the effect of synthokine priming on subsequent hepsulfam induced marrow injury using a non-human primate model. Blood 86(suppl 1):688a, 1995.

*Call, J. and Tomasello, M.: The use of social information in the problem-solving of orangutans and human children. Journal of Comparative Psychology 109:308-310, 1995.

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*Castles, D.L., Aureli, F. and deWaal, F.B.M.: Reconciliation, relationships, and social networks of pigtail macaques. Abstract Book of the XXIV International Ethological Conference, p34, 1995.

*Carpenter, M., Tomasello, M. and Savage-Rumbaugh, S: Joint attention and imitative learning in children, chimpanzees, and enculturated chimpanzees. Social Development 4:218-237, 1995.

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*Devine, S.M., Geller, R.B., Dix, S.P., Connaghan, D.G., Fleming, W.H., Heffner, L.T., Hillyer, C.D., Holland, H.K., Waller, E.K., Winton, E.F., Wingard, J.R.: Tacrolimus (FK506) combined with methotrexate is effective in preventing acute graft versus host disease following allongeneic bone marrow transplantation. Blood 86(supp. 1):395a, 1995.

*Devine, S.M. Dix, S.P, Geller, R.B., Holland, H.K., Colbaugh, J., Connaghan, D.G., Fleming, W.H., Hillyer, C.D., Mullins, R., Waller, E.K., Winton, E.F. and Wingard, J.R.: Phase I trial of busulfan, cyclophosphamide, and diaziquone (AZQ) following autologous or allogeneic bone marrow transplantation. Blood 86 (suppl 1):211a, 1995.

*Dix, S.P., Bucur, S.Z., Mullins, R.E. McCulloch, W., Thomas, G.R., Hillyer, C.D., McClure, H.M., Strobert, E.A., Orkin, J.L., Winton, E.F.: Pharmacokinetic study of intravenous busulfan in non-human primates receiving once-daily infusions. Blood 86 (suppl 1):225a, 1995.

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PUBLICATIONS SUPPORTED BY RECEIPT OF SPECIMENS: XXX

Number Published:	Books: 1	Papers: 11	Abstracts: 09
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