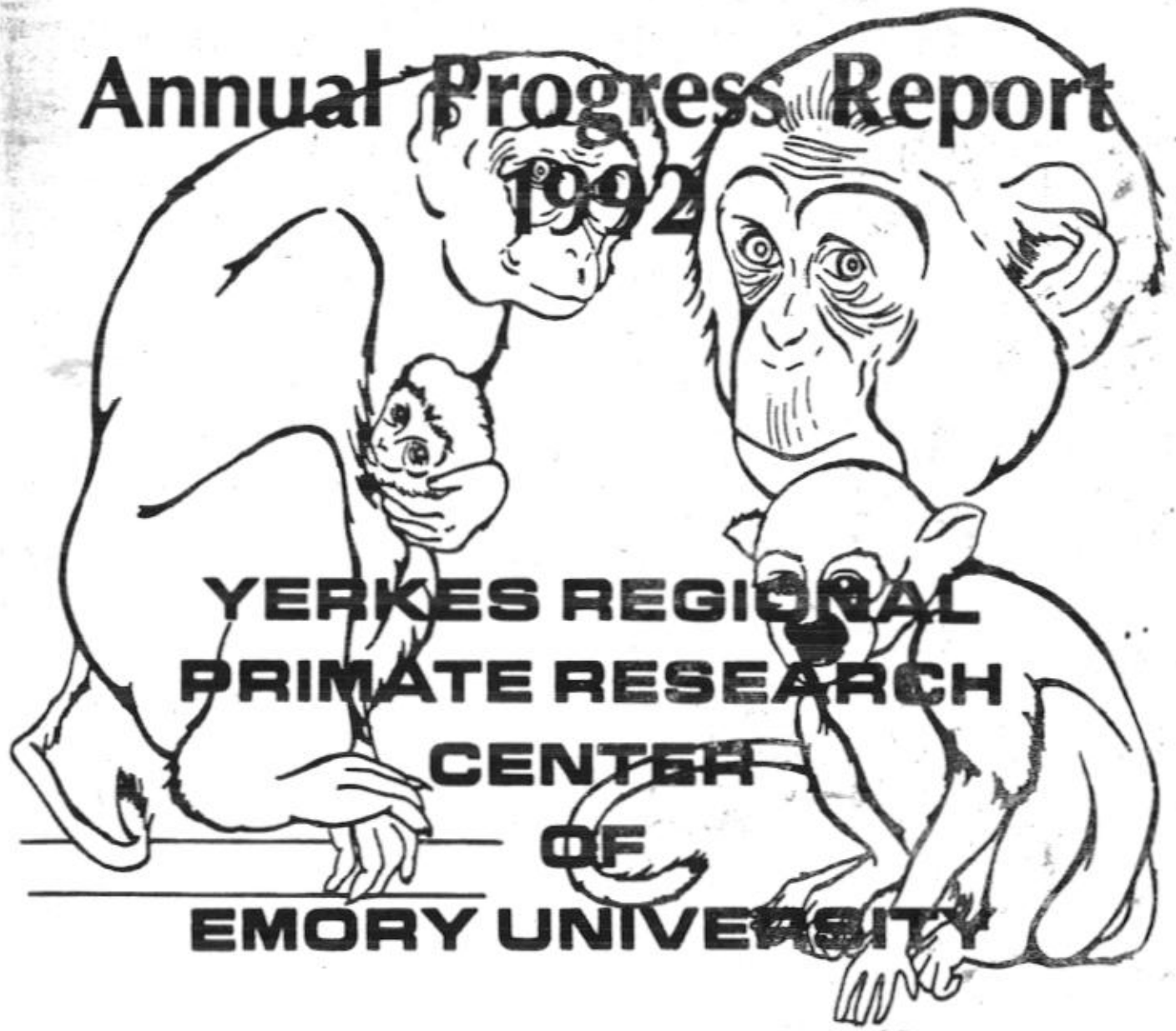
Annual Progress Report 1992



YERKES REGIONAL PRIMATE RESEARCH CENTER OF EMORY UNIVERSITY

Charles R. Hatcher, Jr., M.D.
Principal Investigator
5 P51 RR00165-33

32nd Budget Year
January 1, 1992 - December 31, 1992

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

NATIONAL CENTER FOR RESEARCH RESOURCES
COMPARATIVE MEDICINE PROGRAM
REGIONAL PRIMATE RESEARCH CENTERS PROGRAM (RPRC)
ANNUAL PROGRESS REPORT

1. PHS GRANT NUMBER: P51RR00165-32

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

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

4. REPORTING PERIOD:

   A. FROM (Month, Day, Year): 01-01-92

   B. TO (Month, Day, Year): 12-31-92

5. CENTER DIRECTOR:

   A. NAME: Frederick A. King, Ph.D.

   B. TITLE: Director and Professor, Yerkes Regional Primate Research Center; Professor, Department of Anatomy; Adjunct Professor, Department of Psychology; Associate Dean, Emory University School of Medicine

   C. SIGNATURE: Frederick A. King

6. DATE SIGNED (Month, Day, Year): April 6, 1993

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

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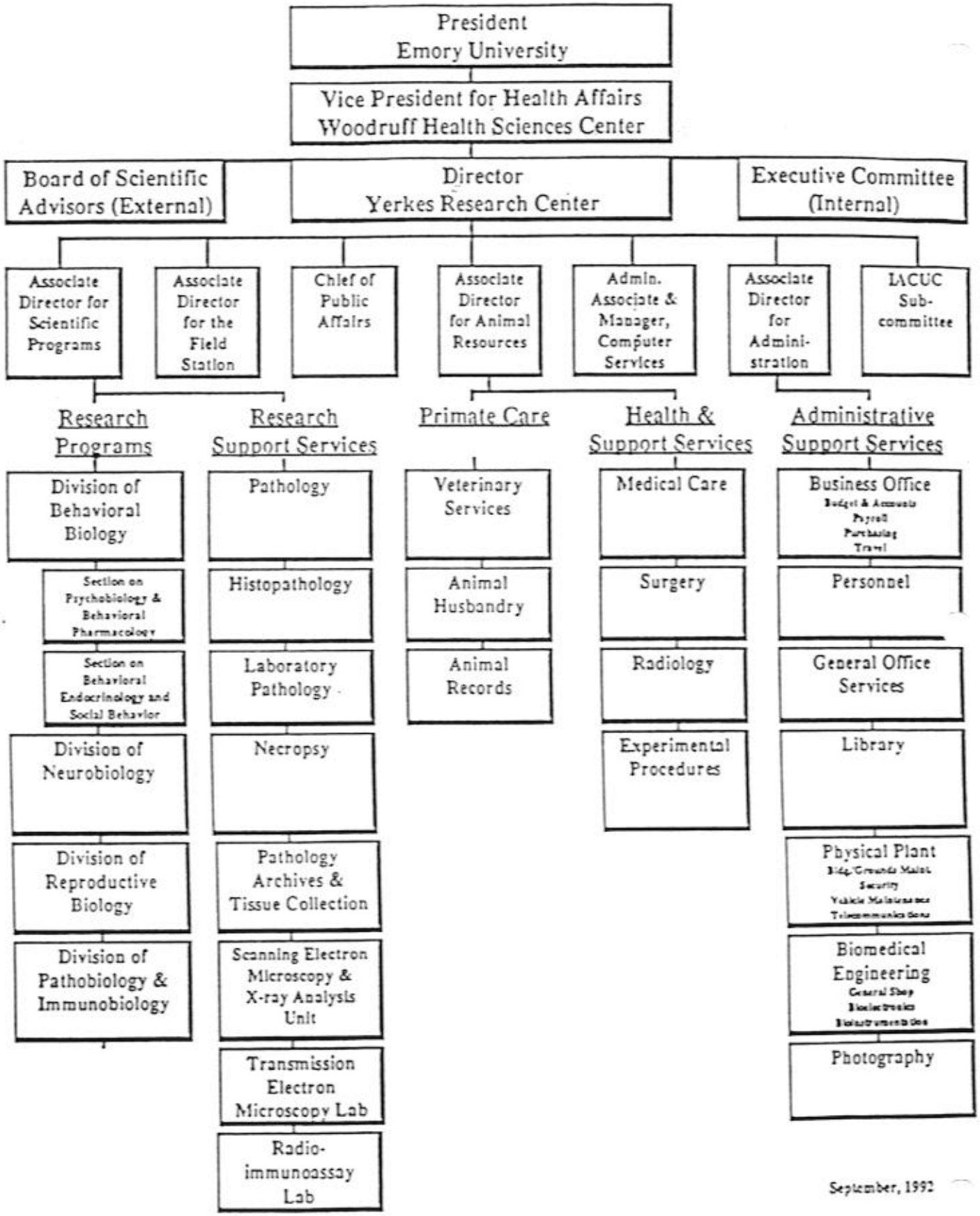
Organizational Chart

Yerkes Regional Primate Research Center

Emory University



September, 1992

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

EMORY UNIVERSITY

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December 31, 1992

FACULTY OF THE YERKES REGIONAL PRIMATE RESEARCH CENTER

Emory University

Atlanta, Georgia, U.S.A.

ADMINISTRATION

Yerkes Position	
Director	F.A. King, Ph.D., Research Professor, Division of Neurobiology, Yerkes Center; Professor of Anatomy and Cell Biology; Adjunct Professor of Psychology; Associate Dean of Medicine, Emory University.
Associate Director for Scientific Programs	H.M. McClure, D.V.M., Research Professor and Chief of Pathobiology and Immunobiology, Yerkes Center; Assistant Professor of Pathology, Emory University.
Associate Director for Administration	J.M. Magnotta, B.A.
Associate Director for the Field Station	T.P. Gordon, M.S., Associate Research Professor of Behavioral Biology, Yerkes Center; Adjunct Professor of Psychology, Emory University.
Administrative Associate and Manager, Computer Services	R.W. Buddington, Ph.D.
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, Director, Kenya Wildlife Service; Adjunct Professor of Anthropology, Emory University.
Special Consultant in African Primatology and Conservation	J.G. Else, M.S., D.V.M., M.P.V.M., Deputy Director for Wildlife Services, Kenya Wildlife Service

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

Section on Psychobiology and Behavioral Pharmacology
L.D. Byrd, Ph.D., Section Head

Core Scientist

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

Associate Scientist

L.L. Howell, Ph.D., Associate Scientist in Behavioral Biology, Yerkes Center.

Research Associate

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

Affiliate Scientists

G.G. Berntson, Ph.D., Affiliate Scientist in Behavioral Biology, Yerkes Center; Professor of Psychology and Pediatrics, Ohio State University.

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

Collaborative Scientist

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

DIVISION OF BEHAVIORAL BIOLOGY (CONTINUED)

Section on Behavioral Endocrinology and Social Behavior
T.P. Gordon, M.S., Section Head

Core Scientists

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

T.P. Gordon, M.S., Associate Director for the Field Station, Associate Research Professor of Behavioral Biology, Yerkes Center; Adjunct Professor of Psychology, Emory University.

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

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

K. Wallen, Ph.D., Associate Research Professor of Behavioral Biology, Yerkes Center; Professor of Psychology, Emory University.

Associate Scientist

D.A. Gust, Ph.D., Associate Scientist in Behavioral Biology, Yerkes Center.

Research Associate(s)

F. Aureli, Ph.D., Research Associate in Behavioral Biology, Yerkes Center.

S.M. Gouzoules, Ph.D., Research Associate in Behavioral Biology, Yerkes Center.

P.G. Judge, Ph.D., Research Associate in Behavioral Biology, Yerkes Center.

D. Maestripieri, Ph.D., Research Associate in Behavioral Biology, Yerkes Center; Research Associate, Department of Psychology, Emory University.

Affiliate Scientists

I.S. Bernstein, Ph.D., Affiliate Scientist in Behavioral Biology, Yerkes Center; Research Professor of Psychology and Zoology, University of Georgia.

C.L. Ehardt, Ph.D., Affiliate Scientist in Behavioral Biology, Yerkes Center; Associate Professor of Anthropology and Linguistics, University of Georgia.

DIVISION OF BEHAVIORAL BIOLOGY (CONTINUED)

D.L. Forthman, Ph.D., Affiliate Scientist in Behavioral Biology, Yerkes Center; Coordinator of Scientific Programs in Conservation and Research Department, Zoo Atlanta.

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

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

Collaborative Scientists

D.M. Fragaszy, Ph.D. Collaborative Scientist in Behavioral Biology, Yerkes Center; Associate Professor of Psychology, University of Georgia.

E. Visalberghi, Ph.D. Collaborative Scientist in Behavioral Biology, Yerkes Center; Senior Research Scientist and Primate Laboratory Unit Chief, Istituto de Psicologia (CNR), Rome, Italy.

Visiting Scientist

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

Section on Language, Cognition, and Neuropsychology
D.M. Rumbaugh, Ph.D., Section Head

Research Associates

D.T. Cerutti, Ph.D., Research Associate in Behavioral Biology, Yerkes Center; Research Associate, Language Research Center, Georgia State University.

W.D. Hopkins, Ph.D., Research Associate in Behavioral Biology, Yerkes Center; Research Associate, Language Research Center, Georgia State University.

R.A. Sevcik, Ph.D., Research Associate in Behavioral Biology, Yerkes Center; Research Associate, Language Research Center, Georgia State University.

S.L. Williams, Ph.D., Research Associate in Behavioral Biology, Yerkes Center; Research Associate, Language Research Center, Georgia State University.

Affiliate Scientist

D.M. Rumbaugh, Ph.D., Affiliate Scientist in Behavioral Biology, Yerkes Center; Regent's Professor of Psychology and Director of Language Research Center, Georgia State University.

Collaborative Scientists

E.W. Menzel, Ph.D., Collaborative Scientist in Behavioral Biology, Yerkes Center; Professor of Psychology, State University of New York at Stony Brook.

D.L. Molfese, Ph.D., Collaborative Scientist in Behavioral Biology, Yerkes Center: Professor of Psychology, Physiology and Behavioral and Social Sciences, Southern Illinois University at Carbondale.

R.D. Morris, Ph.D., Collaborative Scientist in Behavioral Biology, Yerkes Center; Associate Professor of Psychology and Director of Assessment Laboratory, Georgia State University.

M.A. Romski, Ph.D., Collaborative Scientist in Behavioral Biology, Yerkes Center; Associate Professor of Communication, Georgia State University; Speech-Language Pathologist, Center for Developmental Neurobiology and Neuropsychology.

Consultants, Language Formation Studies Program

P.M. Greenfield, Ph.D., Consultant in Language Research, Division of Behavioral Biology, Yerkes Center; Professor of Psychology, University of California at Los Angeles.

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J.L. Pate, Ph.D., Consultant in Language Research, Division of Behavioral Biology, Yerkes Center; Professor of Psychology, Georgia State University.

DIVISION OF NEUROBIOLOGY
J.W. Tigges, Ph.D., Chief

Core Scientists

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

F.A. King, Ph.D., Research Professor of Neurobiology, Yerkes Center; Professor of Anatomy and Cell Biology, Adjunct Professor of Psychology and Associate Dean, Emory University.

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

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

Research Associate

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J.J. Turner, Ph.D., Research Associate in Neurobiology, Yerkes Center.

Affiliate Scientists

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

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

DIVISION OF NEUROBIOLOGY (CONTINUED)

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

D.R. Humphrey, Ph.D., Affiliate Scientist in Neurobiology, Yerkes Center; Associate Dean for Research, Emory University School of Medicine.

J.I. Lim, M.D., Affiliate Scientist in Neurobiology, Yerkes Center; Assistant Professor of Ophthalmology, Emory University School of Medicine.

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

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

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

Collaborative Scientists

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K.L. Boyer, M.D., Collaborative Scientist in Neurobiology, Yerkes Center; Resident in Neurological Surgery, Emory University School of Medicine.

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

J.B. Justice, Ph.D., Collaborative Scientist in Neurobiology, Yerkes Center; Professor of Chemistry, Emory University.

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

S.R. Lambert, M.D., Collaborative Scientist in Neurobiology, Yerkes Center; Assistant Professor and Chief of Pediatric Ophthalmology and Strabismus, Department of Ophthalmology, Emory University School of Medicine.

DIVISION OF NEUROBIOLOGY (CONTINUED)

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M.B. Moss, Ph.D., Collaborative Scientist in Neurobiology, Yerkes Center; Assistant Professor of Anatomy, Boston University.

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

R.A. Stone, M.D., Collaborative Scientist in Neurobiology, Yerkes Center; Associate Member, Professor of Ophthalmology, University of Pennsylvania.

Visiting Scientists

A. Fernandes, M.D., Visiting Scientist in Neurobiology, Yerkes Center; Fellow, Pediatric Ophthalmology, Emory University School of Medicine.

J.T. Mizuno, M.D., Visiting Scientist in Neurobiology, Yerkes Center; Visiting Scientist in Neurological Surgery, Emory University School of Medicine.

S. Mori, M.Ed., Visiting Scientist in Neurobiology, Yerkes Center.

Consultants

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

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

J.P. Wilmeth, M.D., Consultant in Neurobiology, Yerkes Center; Anderson Eye and Ear Associates, Anderson, South Carolina.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY
H.M. McClure, D.V.M., Chief

Core Scientists

D.C. Anderson, D.V.M., Associate Research Professor of Pathobiology and Immunobiology, Yerkes Center.

A.A. Ansari, Ph.D., Research Professor of Pathobiology and Immunobiology, Yerkes Center; Professor of Pathology and Laboratory Medicine and Executive Member, Winship Cancer Center, Emory University School of Medicine.

A.B. Kelly, D.V.M., Associate Research Professor of Pathobiology and Immunobiology and Associate Research Professor, Division of Veterinary Medicine, Yerkes Center.

H.M. McClure, D.V.M., Associate Director for Scientific Programs, Research Professor and Chief of Pathobiology and Immunobiology, Yerkes Center; Assistant Professor of Pathology, Emory University School of Medicine.

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

Research Scientist

M.E. Fritz, D.D.S., Ph.D., Research Scientist in Pathobiology and Immunobiology, Yerkes Center; Charles Howard Candler Professor of Periodontology, Emory University.

Associate Scientists

L.D. Braswell, D.D.S., Associate Scientist in Pathobiology and Immunobiology, Yerkes Center; Assistant Professor, School of Periodontology, Emory University.

P.I. Eke, Ph.D., Associate Scientist in Pathobiology and Immunobiology, Yerkes Center; Postdoctoral Research Associate, Department of Periodontology, Emory University.

S.A. Klumpp, D.V.M., Associate Scientist and Veterinary Pathologist, Division of Pathobiology and Immunobiology, Yerkes Center.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

Research Associates

K. Paul, D.V.M., Research Associate in Pathobiology and Immunobiology and Assistant Veterinarian, Division of Veterinary Medicine, Yerkes Center.

Q. Ren, Ph.D., Research Associate in Pathobiology and Immunobiology, Yerkes Center; Graduate Research Assistant of Electrical Engineering, Ohio State University.

Affiliate Scientists

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

A.G. Gillin, F.R.A.C.P., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Postdoctoral Research Fellow in Renal Medicine, Emory University School of Medicine.

S.R. Hanson, Ph.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Associate Professor of Medicine, Division of Hematology-Oncology, Emory University School of Medicine.

L.A. Harker, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Medicine and Director, Division of Hematology-Oncology, Emory University School of Medicine.

T.R. Hester, Jr., M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Associate Professor of Plastic, Reconstructive and Maxillofacial Surgery, Emory University School of Medicine.

H.L. Keyserling, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Assistant Professor, Department of Pediatrics, Emory University School of Medicine.

A.A. Malizia, Jr., M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Clinical Instructor of Surgery (Urology), Emory University School of Medicine.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

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

C.H. Manning, Ph.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Senior Research Assistant in Pediatrics, Emory University School of Medicine.

B.E. McCarey, Ph.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Ophthalmology, Emory University School of Medicine.

T.A. Meredith, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Ophthalmology, Emory University School of Medicine.

R.S. Metzgar, Ph.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Immunology, Duke University.

J.J. Olson, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Assistant Professor of Surgery, Emory University School of Medicine.

H.F. Seigler, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Surgery, Duke University.

P. Sternberg, Jr., M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Associate Professor of Ophthalmology, Emory University School of Medicine.

G.O. Waring, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Ophthalmology, Emory University School of Medicine.

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

J.R. Woodard, M.D., Affiliate Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Surgery (Urology) and Director of Pediatric Urology, Emory University School of Medicine.

Collaborative Scientists

R.C. Allen, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Fellow, Department of Surgery, Emory University School of Medicine.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

M.W. Bidez, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Assistant Professor and Director, Biomechanics Laboratory, University of Alabama at Birmingham.

G.H. Campbell, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Microbiologist, Centers for Disease Control.

D.B. Caplan, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Pediatrics, Emory University School of Medicine.

R.J. Chiodini, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Assistant Professor of Medicine, Brown University.

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

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

M.N. Golarz, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Professor of Histology and Dean of Women, St. Georges University School of Medicine.

D.L. Harker, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Surgical Intern, Grant United States Air Force Medical Center.

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

V.M. Hirsch, D.V.M., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Assistant Professor of Microbiology, Georgetown University Medical School.

P.R. Johnson, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Assistant Professor of Molecular Virology and Immunology, Department of Microbiology, Georgetown University School of Medicine.

M.C. Knuchel, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Postdoctoral Fellow in Pathology and Laboratory Medicine, Emory University School of Medicine.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

P.J. Lammie, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Biologist, Center for Infectious Diseases, Centers for Disease Control.

A.B. Lumsden, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Fellow in Vascular Surgery, Emory University School of Medicine.

S.W. McLoughlin, B.S.M.E., Collaborative Scientist in Pathobiology and Immunobiology; Graduate Student in Biomedical Engineering, University of Alabama.

J.R. Mead, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Scientist, Veterans Administration Medical Center.

S.S. Mirra, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Associate Professor of Pathology, Emory University School of Medicine.

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

M. Panigel, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology; Visiting Scientist, Department of Pediatrics, Emory University School of Medicine.

C.A. Patterson, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center.

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

J.L. Ribas, D.V.M., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Staff Pathologist/HIV Project Officer, Division of Retrovirology, Walter Reed Army Institute of Research.

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

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

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

M.A. Smith, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Associate of Periodontology, Emory University School of Medicine.

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

J.P. Sommadossi, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Associate Professor and Director, Pharmacology AIDS Program, University of Alabama at Birmingham.

W.D. Suggs, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Vascular Surgery Fellow, Emory University School of Medicine.

K.P. Thompson, M.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Corneal Research Fellow, Department of Ophthalmology, Emory University School of Medicine.

V.C.W. Tsang, Ph.D., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Research Chemist, Division of Parasitic Diseases, Centers for Disease Control.

F. Villinger, D.V.M., Collaborative Scientist in Pathobiology and Immunobiology, Yerkes Center; Distinguished Visiting Fellow of Pathology, Emory University School of Medicine.

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

Visiting Scientist

A.K. Lindahl, M.D., Ph.D., Visiting Scientist in Pathobiology and Immunobiology, Yerkes Center; Postdoctoral Research Fellow, Division of Hematology/Oncology, Emory University School of Medicine.

J.D. Reid, M.D., Visiting Scientist in Pathobiology and Immunobiology, Yerkes Center; Pathologist, Robinson Memorial Hospital, Ravenna, Ohio.

Consultants

G.R. Healy, Ph.D., Consultant in Pathobiology and Immunobiology, Yerkes Center; Chief, General Parasitology Branch, Centers for Disease Control.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY (CONTINUED)

M.A. Isahakia, B.V.M., Ph.D., Consultant in Pathobiology and Immunobiology, Yerkes Center; Director, Institute of Primate Research, Nairobi, Kenya.

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

J.H. Richardson, D.V.M., Consultant in Pathobiology and Immunobiology, Yerkes Center; University Biosafety Officer, Emory University.

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

DIVISION OF REPRODUCTIVE BIOLOGY
K.G. Gould, Ph.D., M.R.C.V.S., Chief

Core Scientists

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

R.D. Nadler, Ph.D., Research Professor of Reproductive Biology, Yerkes Center; Adjunct Associate Professor of Psychology, Emory University.

M.E. Wilson, Ph.D., Associate Research Professor of Reproductive Biology and Head, Radioimmunoassay Laboratory, Yerkes Center; Associate Professor of Medicine and Associate Professor of Psychology, Emory University.

Research Scientist(s)

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K.A. Bard, Ph.D., Research Scientist in Reproductive Biology, Yerkes Center.

Research Associate

J.F. Dahl, Ph.D., Research Associate in Reproductive Biology, Yerkes Center; Adjunct Assistant Professor of Anthropology, Emory University; Adjunct Professor of Anthropology, Georgia State University.

Affiliate Scientists

B.C. Bruot, Ph.D., Affiliate Scientist in Reproductive Biology, Yerkes Center; Associate Professor of Biological Sciences, Kent State University, Kent, Ohio.

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

D.E. Martin, Ph.D., Affiliate Scientist in Reproductive Biology, Yerkes Center; Professor of Respiratory Therapy, Georgia State University.

P.I. Musey, Ph.D., Affiliate Scientist in Reproductive Biology, Yerkes Center; Professor of Biological Sciences, Clark Atlanta University.

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

DIVISION OF REPRODUCTIVE BIOLOGY (CONTINUED)

Collaborative Scientists

D.C. Collins, Ph.D., Collaborative Scientist in Reproductive Biology, Yerkes Center; Vice Chancellor for Research and Graduate Studies, University of Kentucky.

R.A. Hess, Ph.D., Collaborative Scientist in Reproductive Biology, Yerkes Center; Assistant Professor of Morphology and Toxicology, University of Illinois College of Veterinary Medicine.

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

K.A. Platzman, Ph.D., Collaborative Scientist in Reproductive Biology, Yerkes Center; Assistant Professor of Psychiatry, Emory University.

P.N. Srivastava, Ph.D., Collaborative Scientist in Reproductive Biology, Yerkes Center; Professor of Biochemistry, University of Georgia.

S.J. Suomi, Ph.D., Collaborative Scientist in Reproductive Biology, Yerkes Center; Chief, Laboratory of Comparative Ethology, National Institute of Child Health and Human Development, Bethesda, Maryland.

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

Visiting Scientists

K.V. Asatrian, M.S., Visiting Scientist in Reproductive Biology, Yerkes Center; Researcher of Physical Chemistry, Institute of Chemical Physics, Armenian Academy of Sciences.

O.J. Castejon, Ph.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Director of Latin American School of Electron Microscopy, Venezuela.

D.C. Joy, Ph.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Director of EM Facility and Professor of Zoology, University of Tennessee at Knoxville.

G. Pasquinelli, Ph.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Adjunct Professor of Hematology, University of Bologna, Italy.

R. Reichelt, Ph.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Professor of Biophysics at Westfalische Wilhelms-Universitat, Munster, Germany.

DIVISION OF REPRODUCTIVE BIOLOGY (CONTINUED)

K.A. Robinson, Ph.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Assistant Professor, Department of Health, Physical Education, and Recreation, Western Carolina University.

E. Valdivia, M.D., Visiting Scientist in Reproductive Biology, Yerkes Center; Professor of Pathology and Preventive Medicine, University of Wisconsin Medical School.

H. Yue, M.D., Visiting Scientist in Reproductive Biology, Yerkes Center; World Health Organization Fellow.

Consultant

C.E. Graham, Ph.D., Consultant in Reproductive Biology, Yerkes Center; Director of Office of Sponsored Programs, University of Alaska, Fairbanks, Alaska.

DIVISION OF ANIMAL RESOURCES AND VETERINARY MEDICINE

R. Brent Swenson, D.V.M., Chief of Veterinary Medicine and Senior Veterinarian

Core Scientists

A.B. Kelly, D.V.M., Associate Research Professor of Veterinary Medicine and Associate Research Professor of Pathobiology and Immunobiology, Yerkes Center; Assistant Professor of Medicine, Emory University School of Medicine.

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

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

R.B. Swenson, D.V.M., Senior Veterinarian and Chief of Veterinary Medicine, Yerkes Center.

Research Associate

K.S. Paul, D.V.M., Research Associate in Pathobiology and Immunobiology and Assistant Veterinarian, Yerkes Center.

Part I: NARRATIVE DESCRIPTION

A. SUMMARY OF ACCOMPLISHMENTS

1) Strengths and Weaknesses of Current Program

Major strengths of the Yerkes Center during the past year continues to be an active and productive adjunct faculty research program, continued improvements in the physical plant and animal housing facilities and continued productive interactions with scientists at the host institution, especially the School of Medicine.

Our adjunct faculty program which includes scientists at the host institution as well as scientists at institutions throughout the region, nation and internationally, is a major strength of the Yerkes Center that contributes substantially to the scientific productivity of the Center. These activities also make a major contribution towards the Center's commitment and responsibilities to serve as a regional, national and international resource for the conduct of behavioral and biomedical research with nonhuman primates. During 1992, 130 Affiliate, Collaborative and Visiting Scientists participated in the research programs and activities of the Yerkes Center. Sixty of these adjunct faculty were Emory University faculty, the majority of whom were faculty of the School of Medicine. There was also a significant number of faculty members from the College of Arts and Sciences, particularly the Psychology Department, who participated in the adjunct faculty research programs of the Center. Pre-clinical studies using nonhuman primates by members of the School of Medicine has resulted in instances in which therapeutic regimens evaluated in nonhuman primates have moved directly and quickly into the clinic for use in treating serious human disease problems. Salient examples include the use of various combinations of cytokines to modulate immunosuppression or speed-up recovery of the bone marrow following radiation or chemotherapy in cases of leukemia or other neoplastic diseases, and the use of adrenal or fetal brain transplants or co-transplants with nerve cells in the treatment of Parkinson's disease patients.

The Yerkes Center also continues to provide a valuable resource and training ground for undergraduate, graduate and postdoctoral students, primarily from the host institution, but also from other regional, national and international institutions. During 1992, 118 students participated in training programs and research activities of the Yerkes Center. The Yerkes Center continues to contribute substantially to the research activities of the host institution and to regional, national and international investigators through the provision of a variety of biological

specimens from nonhuman primates. This important contribution by the Yerkes Center to investigators throughout the world has increased substantially over the past several years and continues at a high level, with 4,914 specimens (blood, serum, tissues) provided to non-Yerkes investigators during 1992. These specimens were provided to 12 investigators in 8 different departments at the host institution and to 71 investigators at institutions other than Emory University (69 U.S. institutions and 2 foreign institutions).

During 1992, the Yerkes Center continued to improve the physical plant and animal housing facilities, although at a slower rate than we would have liked, due to funding constraints. These continued efforts have made it possible for the Yerkes Center to remain fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). Some of the major accomplishments in this area during 1992 included:

a) installation of polypropylene panels to the walls of a number of animal rooms and to the walls of the Great Ape Wing at the Main Station.

b) expansion of the fire alarm and security systems at the Main Station and Field Station.

c) replacement of a steam autoclave system for sterilization of surgical instruments and supplies, laboratory supplies and biomedical wastes.

d) replacement of the chiller serving the Ophthalmic Research Facility and air handling systems for the Small Primate Wing and one compound indoor housing area at the Field Station.

e) Replacement of the roof of the Small Primate Wing.

A weakness of our current program, as noted during the past several years, is the continued reductions in base grant funding and the difficulties in obtaining funding by individual investigators. This reduced funding has prevented the Center from adequately expanding the number of core faculty and technical positions necessary to provide the support services needed by the core and expanded adjunct faculty research program. Funding constraints have also prevented the replacement or upgrading of major items of equipment needed to meet the increased demands of ongoing research programs and increasing number of animals in the colony. The continued lack of an adequate funding base will have an adverse impact on the maintenance of an adequate infrastructure for long-term support of research programs which use nonhuman primates.

2) Changes in Professional Personnel

There were no changes in professional personnel during 1992.

3) Major Problems Encountered or Anticipated

As previously noted in this report, as well as in previous Annual Progress Reports, the most significant problem encountered by the Center is the continued decrease in base grant funding as a consequence of cuts in the NCRR budget and inflation and the continued difficulties in obtaining research funding by individual investigators. An inadequate funding base makes it difficult for the Center to provide the necessary infrastructure and support services needed to adequately accommodate the research programs of our core and adjunct faculty. This results in delays in the initiation and completion of research projects of importance to human health problems.

Other major continuing problems faced by the Center include the increasing numbers of rules and regulations that restrict and hamper the use of laboratory animals in behavioral and biomedical research, the increasing volumes of paperwork required to comply with these regulations, and the continued harassment by misguided and ill-informed animal rights groups intent on stopping all use of animals for the benefit of humans, including biomedical research as well as their use for food and clothing. These factors all tend to unnecessarily increase the cost of research with laboratory animals, and substantially decrease productivity and impede progress toward finding solutions to human health problems.

4) Major Equipment Items Purchased

Base Grant

Quantity	Description	Cost
* 1	Rotor Package	$ 9,033.00
* 1	Objective	565.00
* 1	20.6 Cu. Ft. Refrigerator	588.00
* 1	Universal Centrifuge	2,075.00
* 1	Flow Cell for FACScan	4,218.00
* 2	Konica Royal 1290 Copier	1,800.00

Base Grant (Cont'd)

Quantity	Description	Cost
* 1	Tissue Prep Flotation Bath	528.00
* 1	Diamond Knife	3,250.00
* 1	Benchtop Autoclave	3,271.00
* 1	Seralyzer III System	3,820.00
* 1	Ultra Low Temperature Up-Right Freezer	4,964.00
* 1	Carbon Coater	4,895.00
* 1	Rotary Vacuum Pump	1,400.00
* 1	Chromatography Refrigerator	1,432.00
* 1	Turbo Evaporator	5,105.00
* 1	Cell-Porator Electroporation System	1,975.00
* 1	Cell-Porator Voltage Booster	925.00
* 2	Gel Dryer	1,990.00
* 1	Benchtop Environmental Shaker	2,864.00
* 1	Gravity Convection Oven	889.00
* 2	Microcentrifuge	2,957.00
* 1	Speed-Vac Concentrator	1,695.00
* 1	200/2.0 Power Supply	715.00
* 1	Retriever II Fraction Collector	1,495.00
* 1	DNA Photographic Transilluminator System	3,720.00
* 1	Eppendorf Centrifuge	1,499.00
* 2	DNA Thermal Cycler	10,000.00

Base Grant (Cont'd)

Quantity	Description	Cost
* 1	Electrophoresis Power Supply	1,051.00
* 1	Welch Director Vacuum Pump	1,138.00
* 1	Automatic Slide Stainer with Fume Hood	9,145.00
* 1	Flaked Ice Maker	1,717.00
* 1	Cryo-Fridge Up-Right Laboratory Freezer	1,140.00
* 1	Microscope Stand	690.00
* 1	Olympus Microscope Model BHT With Sony Video	14,803.00
* 1	DNA Sequencing Unit	926.00
* 1	Jung 2035 Rotary Microtome	8,790.00
* 1	DNA Synthesizer	21,726.00
* 1	Olympus 35mm Automatic Camera System	3,510.00
* 1	Ultra Wash II	4,950.00
* 1	Row Head Ultra Wash II	500.00
* 1	Fujinon Endoscope Package	8,300.00
** 1	Cardiac Monitor	1,090.00
** 1	Cardio-Tracre Single Channel ECG	1,753.00
** 2	Mitsubishi Mighty MIT Vehicles	15,000.00
** 14	3 - Compartment Cages	15,883.00
** 7	Stainless Steel Racks to Include 32 Primate Cages	34,600.00

Base Grant (Cont'd)

Quantity	Description	Cost
1	Multi-Tube Vortexor	854.00
1	31" Deep Fire Proof File	790.00
4	GE MPI II Series Radios	2,142.00
1	Credenza	639.00
1	Hydraulic System	2,703.00
1	Dual Operator Hole Digger	574.00
1	Camcorder	1,350.00
2	Plain Paper FAX Machine	4,482.00
2	Genie Lifts	1,460.00
1	18 Cu. Ft. Refrigerator	824.00
1	Electronic Accounting System	550.00
1	Office Unit with Hutch	699.00
1	Barlock 100 with Power Supply	1,590.00
2	Manual Coase Movement	2,220.00
2	Hydraulic Hanging Joysticks	11,100.00
1	Pipette Puller	2,430.00
1	Micro Grinder	1,736.00
1	Microforge	5,638.00
1	Extension of Fire Alarm	10,350.00

* Purchased with AIDS Supplemental Funds

** Purchased with Improvement and Modernization Supplemental Funds

Base Grant Computer Equipment

Quantity	Description	Cost
* 1	15 Parameter Upgrade for K1000 Cell Counter	3,350.00
* 1	80 MB Hard Disc with V-RAM	1,308.00
* 1	Powerbook 160 Computer	2,209.00
* 1	5 MB RAM, 80 MB Hard Disk	2,745.00
* 1	RGB Monitor	623.00
1	FORA 80386-25DX System	940.00
1	SPARC Staton	4,017.00
1	SIMM Memory Module	871.00
1	Personal Laser Writer NTR	1,444.00
2	MAC LC II 4MB HD-80 with VRAM	2,616.00
1	Port Host Module	1,136.00
1	13" Color Monitor	623.00
1	Apple Laserwriter II	3,013.00
1	Classic II Logic Board Upgrade	728.00
1	Quick 486-33 Basic System	2,100.00
1	2100VA UPS Unit	1,492.00
2	1.6 KVA UPS-Serial Port DAT	1,932.00
2	1.6 KVA UPS Unit	1,818.00

* Purchased with AIDS Supplemental Funds

** Purchased with Improvement and Modernization Supplemental Funds

Other Grants

Quantity	Description	Cost
1	Digital I/O Board	1,150.00
1	7033 Facsimile Machine	3,309.00
1	Quadra 700 Hard Disk 80 CPU	3,864.00
1	Color High Resolution Monitor	524.00
1	Laser PIX 3.1 Software with Hardware Interface Board	1,345.00
1	Video Card Quadra 700	805.00
1	Titan Sonic Scaler	550.00
1	VHS Camcorder with Accessories	1,350.00
2	Panasonic VCR	1,209.00
1	Lanier Dictator	549.00
1	Lanier Transcriber	549.00
5	Touch Information Display Units	4,900.00
1	240MB Seagate IDE Hard Disc	575.00
1	Medifuge Benchtop Centrifuge	805.00
4	Magnavox 386/SX Computer	3,600.00
1	Panasonic Color Camera	729.00
1	Microscope Stage Warmer	1,900.00
12	Quick - 486-33 Basic System	22,197.00
1	Quick - 486-50 Basic System	2,200.00
1	HP II Plus Printer	685.00
3	HP Laserjet III Printer	3,945.00

Other Grants (Cont'd)

Quantity	Description	Cost
1	Vertical Electrophoresis Unit	613.00
1	ELC Diskless Work Station	3,347.00
1	16 MB SIMM Memory Module	871.00
1	Flow Cell HPLC Heat Exchanger	550.00
2	Analog - to Digital Converter	1,996.00
1	Oscillation Saw	1,700.00
1	Command 2 Console	995.00
1	Footswitch	580.00
1	Quadra 700, 4MB RAM, 160MB HD	4,586.00
1	4MB Hard Disk 80 CPU with VRAM	1,308.00
1	Color High Resolution RGB Monitor	623.00
1	19" Monochrome Monitor	729.00
3	316SX Computers with Monitors	2,597.00
1	V-COM 486/33C Computer	1,797.00
1	Nikon SMZ-U Optical Body with 10:1 Zoom Ratio	1,559.00
1	SMA-UFOCUS Mount with "Sure Grip" Coaxial Coarse	609.00
1	SMZ-U Binocular Eyepiece Tube	775.00
1	ED Plan 2.0X Objective	854.00

5) Improvements and Additions to Facilities

Installation of pre-engineered structure to be used for storage at Field Station	$17,881.00
Installation of polypropylene panels in the Great Ape Wing at the Main Station	5,522.00
Expansion of fire alarm and security system at the Main Center	10,350.00

6) Yerkes Speaker Series

Dr. Kenneth Gould, Chief of Reproductive Biology, Yerkes Center, "Primate Conservation and the Tropical Rainforest," Association of Emory Alumni meeting, Emory University, January 18, 1992.

Dr. Ronald Nadler, Research Professor of Reproductive Biology, Yerkes Center, "Effects of Combined Oral Contraceptives on Sexual Behavior of Chimpanzees," Yerkes Speaker Series, February 12, 1992.

Dr. Stephen Glickman, University of California at Berkeley: "Hormones and Behavior in Spotted Hyenas," co-sponsored by Emory Department of Psychology, March 20, 1992.

Dr. Delores Bradley, Brown University, "Visual Short-Term Memory and Its Interactions with Stimulus Dimension," co-sponsored by Emory Department of Ophthalmology, March 27, 1992.

Seventh Annual Neuroscience Spring Symposium, "Excitatory Amino Acids: Simple Molecules, Complex Functions," co-sponsored with Atlanta Chapter of the Society of Neuroscience and the Emory Neuroscience Group, April 25, 1992.

Dr. Jane Ellis, Research Associate in Behavioral Biology at Yerkes Center, "Yerkes Studies on the Effects of Prenatal Exposure to cocaine," Yerkes Lunch-Time Speaker Series, June 11, 1992.

Dr. William Hopkins, Research Associate in Behavioral Biology at Yerkes Center, "Function of the Left and Right Brain in Chimpanzees," Yerkes Lunch-Time Speaker Series, July 8, 1992.

Drs. Peter Biberfeld and Hans Feichtinger, Immunopathology Laboratory, Department of Pathology, Karolinska Institute, Stockholm, Sweden, "Pathobiology and Lymphomagenesis in SIV-Infected Cynomolgus Macaques," August 17, 1992.

Dr. Andrew Kelly, Associate Research Professor of Pathobiology and Immunobiology and of Veterinary Medicine, Yerkes Center, "Bloodclotting in the 1990's," Yerkes Lunch-Time Speaker Series, August 26, 1992.

Dr. Margarete Tigges, Research Professor of Neurobiology at Yerkes and Associate Professor of Anatomy and Cell Biology at Emory University, "Myopia," Yerkes Speaker Series, October 7, 1992.

Dr. Peter Verbeck, graduate student in Emory Psychobiology Program and in Yerkes Division of Behavioral Biology,"Conflict Resolution in Young Children," Yerkes Speaker Series, November 18, 1992.

Dr. Kim Wallen, Associate Research Professor of Behavioral Biology at Yerkes Center and Professor of Psychology at Emory University, "Role of Sexual Hormones in Primate Sexual Differentiation," Yerkes Speaker Series, December 17, 1992.

7) Administrative and Operational Changes

There were no significant administrative or operational changes during 1992. The revised method for processing grant applications and research proposals, as described in the 1991 Progress Report, became operational in early 1992. The internal Yerkes Research Advisory Committee also became functional in 1992.

8) Narrative Progress Report for Non-Research Units

A. Animal Resources: Yerkes Animal Resources includes the Division of Veterinary Medicine, Animal Records and the three Animal Care Units; the Main Station Great Ape and Small Primate Units and the Field Station. Animal Resources personnel are responsible for all aspects of laboratory animal care at the Center. This includes routine husbandry, veterinary care, meeting federal regulations and guidelines, and interfacing with scientists undertaking studies with animals.

An Enrichment Committee was formed to develop a program to meet the Animal Welfare Standards environmental enhancement requirements. The Committee, chaired by Dr. Elizabeth Strobert, Associate Veterinarian, wrote the Yerkes Primate Enrichment Plan and has subsequently overseen the implementation of the plan. Funds were secured for the purchase of various "play items," cage modifications and hiring a primate care technician to manage and evaluate the various strategies. During the past year, a number of single monkey cages have been modified to permit social housing and all caged primates have some type of enrichment device.

The Center continues to place a high priority on the proper training of all personnel working with Center animals and encourages personnel to participate in the AALAS certification courses. To that end, the Center provides funds for training manuals, examination fees, and awards a monetary reward to staff that become certified. Over fifty percent of all primate care staff and veterinary technicians are now AALAS certified and an increasing number of research staff are also participating in the program.

1. Clinical Medicine

The Division of Veterinary Medicine is a service unit that provided health care in 1992 for approximately 2600 great apes and monkeys at the Atlanta, Lawrenceville and Panthersville facilities. The Division was also responsible for providing research support to core and affiliate investigators. The unit consists of 4 veterinarians, a registered nurse and 4 veterinary technicians.

The Division supervises the Center's two operating rooms where all non-terminal surgical operations are performed. In 1992 a total of 317 surgical operations were performed under the supervision of the veterinary unit. Of these, 260 were experimental procedures done by the investigator, 8 were experimental procedures done by the veterinary staff for investigators and 49 were clinical procedures done by the veterinary staff. Anesthesia or surgical assistance was provided by the veterinary staff for 100% of the investigator performed surgery and all post-operative care was provided by the veterinary staff.

The radiology service of the Division was utilized to image 947 animals. Of these, 324 animals were imaged for clinical reasons (illness, injury or obstetrical problems), 343 were done for health surveillance or quarantine and 260 were done for experimental reasons.

During 1992, 992 new cases of illness or injury were treated; 851 of these were in monkeys and 141 were in apes. The preventive medicine program for the colony was administered by the Division of Veterinary Medicine. This program included physical examination, hematology, blood chemistries, tuberculin testing and chest radiography conducted annually on great apes. Tuberculin tests on all individually housed monkeys are done every 4 months and annually on compound housed animals. All primates received from outside the Center are quarantined prior to entry into the colony. New apes were immunized against polio, Streptococcus pneumoniae and Hemophilus influenzae. All apes received polyvalent type A and B influenza virus vaccine. A tetanus immunization program was instituted at the Field Station. All personnel were tuberculin tested semi-annually if they had animal contact and annually if they did not have regular animal contact. Positive reactors received annual chest radiographs which were submitted to a radiologist at Emory for evaluation. Pre-employment reference serum was collected from new

employees and current employees for whom there was not stored serum current within two years. A total of 114 monkeys were quarantined in 1992.

The Division provided support in the form of the collection of biological samples, surgery, anesthesia, radiography and consultation to 21 core and affiliate scientists on 35 separate projects. In addition, biological samples were made available to outside investigators. These are listed elsewhere. Comparable activity is anticipated in 1993.

2. Animal Records

Animals Records is comprised of the Animal Records Registrar and 2 data entry clerks at the Main Station and one data entry coordinator at the Field Station. The unit maintains all colony records on a Sun Systems microcomputer using a custom relational data base. Clinical records, colony statistics, animal assignments, caging records and some research records are maintained for each animal. The unit accumulates per diem costs and sends them to the Business Office for billing. The Animal Records Registrar in conjunction with the Computer Services office and the Division of Veterinary Medicine also provides records searches for investigators when feasible.

3. Primate Care and Housing --- Main Station

a) Great Ape Wing

The majority of the Center's great apes are socially housed at the Main Station on the Great Ape Wing in 59 indoor/outdoor cage units. There are 3 areas in which great apes can be temporarily housed in metabolism cages for research or clinical reasons. A fifth area socially houses chimpanzees involved in long-term acquired immunodeficiency studies. Additionally, the Great Ape Nursery provides specialized attention for those great ape infants who have to be separated from their mothers for clinical reasons or due to maternal rejection.

Currently, there are 189 common chimpanzees, 3 pygmy chimpanzees and 11 orangutans at the Main Station.

During the past year the following significant changes occurred:

1) The remaining 5 gorillas at the Main Station were transferred to Busch Gardens in Tampa on permanent loan.

2) The installation of interior partition doors in the Great ape Wing indoor cage units was begun. This allows easy movement of animals, as well as, increasing versatility of the cage space.

3) Polypropylene panels and mirrored plexiglass were alternately installed on the inside corridor walls of the Great Ape Wing, so that animals could see themselves and their neighbors and at the same time provide a more sanitizable wall surface. Mirrored plexiglass has also been installed in the metabolism cage areas as enrichment for animals housed individually.

4) Funds were obtained and plans begun to enclose 2 outdoor sections of the Great Ape Wing so that animals can have access to the outdoor cages during inclement weather.

5) Continued emphasis has been placed on education and/or training for the Primate Care staff. Fifty five percent of the Great ape Primate Care Technicians are AALAS certified and/or have Bachelors degrees.

b) Small Primate Wing

Currently, there are 1055 monkeys (9 species) housed at the Main Station in 12 separate buildings or enclosures.

During the past year, the following significant changes have occurred:

1) A nationwide recruitment for an Associate Superintendent who will be primarily responsible for the management of the Small Primate Wing areas was conducted. Mr. John Duktig, LATG, will assume his duties in February, 1993.

2) Continued emphasis was placed on upgrading the primate care staff through eduction and training. AALAS courses continue to be given for the staff and, currently, 61 percent of the Small Primate Wing staff is AALAS certified and/or have a Bachelors degree.

3) A consultant was hired to assist in upgrading the

Primate Care Program. To date, the Primate Care Technician job descriptions have been rewritten, daily protocols redefined and implemented, an orientation program for all Center employees created, and expansion of the training programs for new Primate Care Technicians begun.

4) Fourteen cage units with 3 compartments per unit were purchased for the Small Primate Wing nursery animals. The cage units have removable partitions so that animals can be socialized and then separated easily.

5) Funds were obtained for erecting an additional primate enclosure and for renovation of a portion of the Small Primate Wing. Work should be completed by August 1993.

6) Two Primate Care Technicians were added to the staff. One was needed due to the increased number of animals. The second technician assists in the implementation of the Enrichment Program and assesses the effectiveness of various strategies.

4. Primate Care and Housing --- Field Station

The Field Station Animal Care subunit is a service unit that provides care for approximately 1600 great apes and monkeys at the Yerkes Primate Center Field Station located in Lawrenceville. In addition, the unit is responsible for providing support to the Division of Veterinary Medicine and for providing research support to core and affiliate investigators. The unit consists of 1 Superintendent, 1 Associate Superintendent, 1 Administrative Assistant, 13 Primate Care Technicians and 1 Night Security Attendant.

The unit assists the Division of Veterinary Medicine by monitoring the health of the colony, providing support during diagnostic and therapeutic procedures and the administration of the preventive medicine program. The care staff also provides after hours and weekend care for hospitalized animals.

The unit closely coordinates its activities with the research personnel to provide assistance, equipment and support for their work. Primate care technicians are also assigned to research units for the purpose of collecting and processing behavioral data and biological samples.

During 1992, continued emphasis was placed on improving methods of animal care, housing and the performance of the primate care personnel. Accomplishments during the past year are summarized below:

Two Mitsubishi utility vehicles were purchased and are used to haul feed, produce, caging and equipment to animal areas and work sites.

Polypropylene panels were installed in the indoor animal area of the S-2 compound. The panels will provide a bright and easily sanitized surface and eliminate the need for frequent repainting.

Playground equipment was purchased for all the outdoor animal areas. When installed, they will provide the animals with additional climbing structures, thereby enriching their environment.

Three solid walls were installed in the G-2 compound and serve as visual barriers which aid in the control of aggressive interactions. They also are important for the investigator studying the behavior of the animals in that group.

Assembly of a 32' x 64' Relocatable Exterior Primate Enclosure (REPE) with a 71' x 80' outdoor compound and 5 10' x 15' outdoor runs was begun. This caging unit will provide social housing space for up to 40 chimpanzees.

B. Physical Plant

1) Main Station

Significant progress accomplished during 1992 includes:

a) One of the Center's steam autoclaves was replaced. This autoclave is used to sterilize surgical instruments, surgical clothing, laboratory supplies, and certain biomedical waste.

b) Steam lines were reinsulated in the primary mechanical room of the Main Building.

c) The chiller serving the Ophthalmic Research Facility was replaced. The old chiller had developed extensive leaks in the freon gas lines. The replacement chiller provides greater cooling capacity and operates much

more efficiently.

d) The air handler serving five large rooms in the Small Primate Wing was replaced. The new unit will more effectively control room temperatures during extreme heat and cold.

e) Two electrical breaker boxes located in the Metabolism Room of the Great Ape Wing were waterproofed.

f) A concrete pad was put in next to the General Shop. This pad provides appropriate space to store materials and items needing repairs.

g) Fire alarm systems were installed in the following facilities: REPE A, REPE B, IDB, and the Infectious Disease REPE. These and all other fire alarm systems throughout the Center were upgraded to allow immediate notification of alarms to the Emory Police Department.

h) The roof of the Small Primate Wing was replaced.

i) Room 341 of the Main Building was renovated for the Computer Services Department. Renovation included removal of casework, installation of carpeting and painting.

j) Doors to the General Shop were added to the Center's security system. Installed were a magnetic lock, access card reader and contact alarms.

2) Field Station

During 1992 the following items were accomplished:

a) A new HVAC unit was installed in G-4. This heater replaced a unit that did not have the capacity required to maintain the proper temperature.

b) The renovation of the office/chimpanzee observation tower was completed. The facility now serves as a base of operations for chimpanzee behavioral observations.

c) Work was started on a new entrance road. When completed the road will provide a paved access to the facility that is entirely on Emory property.

d) Work on a new telecommunication system for the Field Station was begun. When completed the Field Station

will be fully integrated into the Emory system.

e) A 100' x 25' storage facility was built. It will provide storage space for the Main Center and the Field Station.

C. Service Pathology

Necropsy Service: During 1992, 309 nonhuman primates were submitted for postmortem examination, and 153 biopsies were submitted for histopathologic evaluation. When compared to the preceding year (1991), this represents a decrease of 4% (12 cases) in the number of necropsies; the number of biopsies decreased 7% during the same period.

The postmortem examinations done in 1992 can be categorized as follows:

	Total Number	Percent Total
Deaths Associated with Experimental Procedures	107	34.6
Deaths During Quarantine Period	0	0
Deaths Associated with Clinical Problems	72	23.3
Abortuses/Stillbirths	46	14.9
Neonatal Deaths	48	15.5
Deaths Due to Accidents/Fights/Exposure	36	11.7
Necropsies on Other than Center Animals	0	0

Selected postmortem observations recorded during 1992 are summarized as follows:

	Total Number	Percent Total
Animals with Parasite Infections	59	19.9
Animals with Pneumonia	7	2.3
Animals with Gastritis/Enteritis/Colitis	21	6.8
Animals with Tumors	14	4.5
Animals with Yersiniosis	11	3.6
Animals with Mycobacteriosis	1	0.3
Animals with Shigellosis	7	2.3
Animals with Campylobacteriosis	45	14.6
Animals with Amyloidosis	9	2.9
Animals with Listeriosis	8	2.6

When compared with the preceding year (1991), the above information reflects the following:

1) The number of deaths associated with experimental procedures decreased from 119 to 107 (10% decrease). The percent of necropsies associated with experimental procedures decreased from 37.1% to 34.6%.

2) There was a decrease in 1992 in the number of deaths associated with clinical problems (decrease of 22%---20 animals), when compared to the number of deaths associated with clinical problems in 1991. There was a slight decrease in the number of abortuses and stillbirths and a slight increase in the number of neonatal deaths in 1992 as compared to 1991.

3) Nine cases of amyloidosis were diagnosed in 1992. This represents a decrease from 18 cases of amyloidosis diagnosed in 1991. Amyloidosis continues to be a problem in outdoor housed Field Station animals, with 159 cases diagnosed from 1975 to 1992.

4) An additional 11 cases of yersiniosis were diagnosed at necropsy during 1992. This naturally occurring enteric bacterial infection continues to be a problem in our Field Station colony. Yersinia species have been isolated from 202 necropsy cases since the disease was first diagnosed in 1968. Most of the cases have been due to either Yersinia enterocolitica or Y. pseudotuberculosis infection, although a small number of Y. intermedia, Y. fredericksenii and Y. kristensenii organisms have been isolated. Some of these isolates represent nonpathogenic, environmental strains of Yersinia, as lesions were not detectable in some animals from which Yersinia were isolated.

5) Fourteen animals (4.5% of necropsies) were found to have neoplasms in 1992. Tumors encountered in 1992 included two carcinomas of the ileocolic region in a 17 year old rhesus monkey and a 12 year old rhesus monkey, one adenoma of the kidney in a 24 year old rhesus, two adrenal carcinomas in an 18 year old and a 22 year old rhesus, one carcinoma of the uterine cervix in a 23 year old rhesus, one squamous cell carcinoma of the penis in a 29 year old rhesus, one carcinoma of the cecum in a 16 year old rhesus, one fibroma of the ear in a 26 year old rhesus, one uterine leiomyoma in a 36 year old chimpanzee, one hepatic lymphoma in a 7 year old pigtail macaque, two subcutaneous lipomas in an 18 and a 23 year old rhesus,

and a papilloma of the penis in a baboon. Seven additional tumors were diagnosed from biopsy specimens (5 rhesus monkeys and 2 chimpanzees). These included a carcinoma of the colon, 2 carcinomas of the ileocolic junction, an adenoma of the kidney, a basosquamous carcinoma of the skin, a leiomyoma of the vagina and a lipoma of the subcutis.

6) Eight additional cases of listeriosis were diagnosed in 1992. These included one newborn pigtail monkey, four rhesus abortuses or stillbirths, two pig-tailed macaque abortuses or stillbirths, and one stump-tailed macaque stillbirth.

   This brings the total number of cases of listeriosis seen in our colony to 73, since the disease was first diagnosed in 1982.

Significant lesions observed in the 153 surgical pathology specimens examined in 1992 included amyloidosis, chronic colitis, a herpesvirus infection of the skin of a chimpanzee, three carcinomas of the intestine or colon, an adenoma of the kidney, a basosquamous carcinoma of the skin, a vaginal leiomyoma, a subcutaneous lipoma, herpes B infection in an infant pig-tailed macaque, Crohn's-like disease of the small intestine in a gorilla, chronic synovitis, endometriosis, adenomyosis and intestinal mycobacteriosis.

Histopathology Service: During 1992 the histopathology laboratory processed 566 necropsy cases and/or biopsies. This entailed the production, and subsequent filing of 22,550 paraffin blocks. A total of 15,448 microslides were prepared from these blocks. Following microscopic review, all slides are maintained on file in the light microscopy laboratory.

Clinical Pathology Service: During 1992, the clinical pathology laboratory received 10,674 specimens for evaluation. These determinations can be categorized as follows:

Laboratory Determination	Number of Specimens
Hematology Examinations	2,589
Bone Marrow Examinations	17
Bacterial Cultures	2,510
Fungal Cultures	9
Fecal Parasitology Examinations	482
Serum Chemistries	1,000
Pregnancy Tests	31
Urine Analysis	148

Laboratory Determination (Cont'd)	Number of Specimens
Imprint Smear Preparations	612
Spinal Fluid Examinations	78
Immunologic Examinations	1,184
Specific Gravity	3
Virology and Serology	2,008
Cell Count, Fetal	3

When compared with 1991, this number of laboratory specimens represents an increase of 129 submissions (1.2% increase).

Selected pathogenic microorganisms isolated during the past year include:

Staphylococcus aureus	Streptococcus pneumoniae
Candida albicans	Listeria monocytogenes
Yersinia pseudotuberculosis	Shigella flexneri
Yersinia kristensenii	Yersinia enterocolitica
Yersinia intermedia	Campylobacter coli
Enteropath. E. coli	Campylobacter fetus
Campylobacter jejuni	Campylobacter laridis
Corynebacterium ulcerans	Mycobacterium simiae
Salmonella anatum	Arcobacter butzleri

A total of 276 antibiograms were done on bacterial isolates during the year.

The most frequently encountered parasites continue to be Balantidium coli, Trichomonas species, Blastocystis species and Trichuris species. During 1992, cryptosporidiosis occurred in 2 animals and 4 cases of giardiasis were diagnosed.

Pathology Electron Microscopy Laboratory: During 1992, the pathology electron microscopy laboratory received 139 specimens for processing for ultrastructural evaluation. Specimens received included 5 kidney specimens, 4 mesenteric lymph nodes, 3 sections of Peyer's patch, 2 pancreas, 9 liver specimens, 3 lung, 1 skin lesion, 3 sections of colon, 7 tumor specimens, 74 testicular biopsies, 3 adrenal specimens, 8 cell cultures, 4 CNS specimens, 1 fecal specimen, 2 placental specimens, 8 spleen specimens, 1 specimen of stomach and 1 specimen of uterus.

Specimens Collected for Other Investigators: During 1992, 4,914 specimens were collected and shipped to 83 investigators. A partial listing of specimens provided includes serum, blood, a variety of tissue specimens,

carcasses, eyes, bone, brain, bone marrow, milk, fecal samples, urine samples and cerebrospinal fluid. Specimens provided includes 29,330 ml of whole blood, 1,010 ml of serum, and 125 ml of plasma from 12 nonhuman primate species. These specimens were provided to 12 investigators in 8 different departments at the host institution and to 71 investigators at institutions other than Emory University (69 U.S. institutions and 2 foreign institutions).

D. Radioimmunoassay

The Yerkes Radioimmunoassay (RIA) Laboratory is a fully equipped laboratory providing services of radioimmunoassay, bioassay, spectrophotometric analyses, and fluorometric analyses of biological samples. The Yerkes RIA facility provides this service to Yerkes core faculty and affiliated scientist, scientists from Emory University, and other investigators outside the Emory community. Determinations are provided on a sample charge basis comprised of the cost of technical time, chemical reagents, equipment used, and waste disposal. During calendar year 1992, individuals who utilized the services of the RIA Laboratory are as follows:

Yerkes Core Scientists

Dr. Daniel Anderson, Division of Pathobiology and Immunobiology
Dr. Larry Byrd, Division of Behavioral Biology
Professor Tom Gordon, Division of Behavioral Biology
Dr. Ken Gould, Division of Reproductive Biology
Dr. Jim Herndon, Division of Neurobiology
Dr. Ron Nadler, Division of Reproductive Biology
Dr. Jack Orkin, Division of Behavioral Biology
Dr. Mark E. Wilson, Division of Reproductive Biology

Yerkes Affiliated Scientists

Dr. Kim Bard, Division of Reproductive Biology
Dr. Debbie Gust, Division of Behavioral Biology
Dr. Leonard Howell, Division of Behavioral Biology
Dr. David Martin, Division of Reproductive Biology and Georgia State University
Dr. David Mann, Division of Reproductive Biology and Morehouse School of Medicine

Non-affiliated Scientists

Dr. Mike Adams, Department of Comparative Medicine, Bowman Gray University School of Medicine

Non-affiliated Scientists (Cont'd)

Dr. Thomas Clarkson, Department of Comparative Medicine, Bowman Gray University School of Medicine
Dr. Robin Crouse, Department of Medicine, Bowman Gray University School of Medicine
Dr. Floyd Culler, Department of Pediatrics, Emory University School of Medicine
Dr. Patrick Delafontaine, Department of Medicine, Emory University School of Medicine
Dr. Maria DeGirolamo, Department of Medicine, Emory University School of Medicine
Dr. Robert Donahoe, Department of Psychiatry, Emory University School of Medicine
Dr. Dorothy Fragaszy, Department of Psychology, University of Georgia
Dr. Susan Gebhart, Department of OB/GYN, Emory University School of Medicine
Dr. Kathleen Grant, Department of Comparative Medicine, Bowman Gray University School of Medicine
Dr. Paul Irwin, Department of Urology, Emory University School of Medicine
Dr. Jay Kaplan, Department of Comparative Medicine, Bowman Gray University School of Medicine
Dr. Gordon Leitch, Department of Physiology, Morehouse School of Medicine
Dr. Lillian Meacham, Department of Pediatrics, Emory University School of Medicine
Dr. Larry Phillips, Department of Medicine, Emory University School of Medicine
Dr. Meraida Polak, Department of Neurology, Emory University School of Medicine
Dr. Brian Rogers, Genetech Inc., South San Francisco
Dr. Carol Shively, Department of Comparative Medicine, Bowman Gray University School of Medicine
Dr. Ora Strickland, School of Nursing, Emory University School of Medicine
Dr. Margaret Walker, Department of Psychology, Towson State College
Dr. Dave Weaver, Department of Comparative Medicine, Bowman Gray University School of Medicine

The following is a list of assays currently available in the RIA Laboratory:

Steroid Hormones

androstenedione
cortisol
dihydrotestosterone
levonorgestrel
progesterone
medroxyprogesterone

Steroid Hormones (Cont'd)

estradiol (total and free)
estrone
estrone glucuronide
estrone sulfate
pregnenediol
testosterone (total and free)
ethinylestradiol
estriol
estriol glucuronide
dehydroepiandrosterone sulfate

Other

lactose
creatinine
free fatty acids
melatonin
B-endorphin
glucose (spectrophotometric)
custom iodinations
prostaglandin E_2 alpha

Protein hormones

adrenocorticotropin hormone
luteinizing hormone (LH)
follicle stimulating hormone (FSH)
human chorionic gonadotropin
growth hormone (GH)
prolactin (human, monkey)
insulin-like growth factor-1(IGF-I)
T_3
T_4 (total and free)
total proteins
T_3 (reverse)
osteocalcin
sex steroid binding globulin
somatostatin
insulin (free and total)
C-peptide of insulin
oxytocin
IGF binding protein-3
TSH
glucagon

During the calendar year 1992, the RIA Laboratory performed 31,396 determinations as follows:

Hormone	Number
B-endorphin	0
ACTH	516
androstenedione	330
C-peptide	111
cortisol	2,091
creatinine	262
custom iodinations	6
DHEA-So_4	109
dihydrotestosterone	0
estradiol	6,265
estradiol (free)	0
estriol glucuronide	0
estrone	573

Hormone (Cont'd)	Number
estrone glucuronide	43
ethinyl	342
free fatty acids	44
FSH	187
GH	771
glucagon	155
glucose	184
IGF-1	2,056
IGFBP-3	510
insulin	1,837
insulin (free)	379
levonorgestrel	453
LH	4,231
medroxyprogesterone	341
melatonin	143
osteocalcin	397
oxytocin	0
pregnenediol	0
progesterone	6,108
prolactin	912
prostaglandin E_2 alpha	138
SHBG	136
T_3 (total)	48
T_4 (free)	48
T_4 (total)	377
testosterone (free)	51
testosterone (total)	1,194
TSH	48

E) Information Services

The Information Services Office is the Yerkes Center's primary contact with the public. Staffed by two individuals, Cathy Yarbrough, Chief of Public Affairs, and Diana Lewis, Public Affairs Assistant, the Information Services Office reports to the Director of the Yerkes Center and is responsible for external communications to professional scientific and medical organizations, the media as well as the general public.

Internal communications -- tours of the Yerkes Center for new employees, and a monthly newsletter and a speakers' series -- also are the responsibilities of the Information Services Office whose goal is to improve public and employee understanding of the programs and accomplishments of the Yerkes Center.

The Information Services Office's activities include:

1) creation and implementation of communications strategies to help Yerkes officials anticipate, prepare for and respond to situations that can affect employee and community attitudes about the Center;

2) advising Yerkes Director and the Center's scientists about public relations issues affecting the organization, and the development of appropriate communications in response to these issues;

3) selection of Yerkes research activities to highlight in media contacts and reports (many of which also are prepared by the office) for the National Institutes of Health, Emory and other agencies;

4) initiating international, national and local news media coverage and responding to media requests;

5) planning, writing and editing and producing audiovisual and print materials, on a limited budget, for public education and public relations;

6) conducting tours for scientific, student and community groups;

7) speaking to educational, scientific and civic organizations and writing speeches and developing audiovisual materials for use by the Yerkes Director;

8) organization and management of Yerkes sponsored conferences; and

9) representing Yerkes Director on task forces and committees of the university and other organizations.

The following section highlights the activities of the Information Services Office in the following areas: Media Relations; Employee Relations; Community Relations and Special Projects; and Publications.

Media Relations

The Information Services Office issued news releases to inform the community, via the media, about a variety of Yerkes activities, including the following:

1) results of Yerkes studies on the vocal signals used by social groups of pigtail monkeys, that indicate that the primates' vocalizations contain vocal signatures, or dialects;

2) findings of Yerkes studies with rhesus monkeys that suggest that prenatal exposure to cocaine may not be the cause of the behavioral and developmental problems that can occur in fetuses and children whose mothers took cocaine while pregnant;

3) the Yerkes Center's loan of a rare bonobo chimpanzee to Fort Worth Zoo in Texas;

4) loan of five Yerkes gorillas to Busch Gardens in Tampa, FL, and the opening of the zoological park's Myombe Reserve: The Great Ape Domain;

5) the conduct of extensive cardiology tests by Emory clinicians on a Yerkes gorilla on loan to Zoo Atlanta to determine the cause of the ape's ill health;

6) appointment of a Yerkes scientist to National Families in Action Scientific Advisory Committee

7) election of Yerkes scientist to Executive Committee of the American Association for the Accreditation of Laboratory Animal Care;

8) receipt of Bryan W. Robinson Neurological Foundation award by an Emory graduate student who works at Yerkes;

9) increase in number of female students and minority students at Yerkes;

10) receipt of American Psychological Association award by Yerkes Director;

11) appointment of Yerkes Director to National Task Force on the NIH's Strategic Plan

The Yerkes Information Services Office worked with many news media organizations to assist in the preparation of their stories. Examples include:

1) ABC-TV, Associated Press, Cable News Network, Atlanta WXIA-TV, and Atlanta WSB-TV "Primate Edition" reports on the prenatal effects of exposure to cocaine on the baby and developing child;

2) ABC-TV "Nightline" segment that featured a Yerkes scientist and other researchers on the topic of bonobo chimpanzees and human evolution;
3) Atlanta Journal and Constitution, Florida Catholic Monthly and various other Florida media on the opening of the Myombe Reserve: The Great Ape Domain at Busch Gardens, with five gorillas on loan from Yerkes;
4) U.S. News and World Report story titled, "The Evolution of Aggression";
5) Atlanta WAGA-TV story about development of a contraceptive for men that maintains normal libido while halting sperm production;
6) Various Atlanta news media stories about the death of Yerkes chimpanzee Gamma, the oldest chimpanzee on record;
7) WAGA-TV story about parenting in primate and human societies;
8) American Psychological Society newsletter, for illustrations about primate research;
9) Sacramento Bee Pulitzer Prize award winning series on primate research;
10) Atlanta Journal and Constitution story about Yerkes studies on vocal communications of primates;
11) Emory Voice, student newspaper, and other media for articles about animal rights movement;
12) British Broadcasting Corporation programs for Horizon and Natural History Units' series on primate and human behavior;
13) Seven Days in DeKalb County book
14) Emory Report, Emory Magazine, Emory Medicine, Emory Wheel and other Emory publications on stories of various topics; and
15) City Paper of Washington,D.C., on story about gorillas

Employee Relations

During 1992, the Information Services Office initiated a monthly, one-page bulletin of news and other information about Yerkes for distribution to Yerkes employees. The newsletter's first issue was published in June. In addition, a total of seven informal presentations were given by Yerkes scientists for employees. Two orientation tours of the Center also were organized and conducted. The office also assisted in the production of a video for new Primate Care Technicians. In addition, the Public Affairs Assistant helped to organize a Saturday picnic for Yerkes faculty and staff in association with Zoo Atlanta.

Community Relations and Special Projects

The Information Services Office organized and in many cases hosted tours for 643 individuals who ranged from students to journalists. Groups visiting the Center ranged from minority students who were participating in a summer program at Emory for talented youth interested in pursing degrees in the biological sciences, to attendees in the Association of Emory Alumni conference.

Numerous requests for information about the Yerkes Center and the use of animals in research were handled by telephone and mail by the Information Services Office.

In addition, the Chief of Public Affairs gave presentations at an American Medical Association workshop for Atlanta area physicians and medical students and at the annual meeting of the American Association for Laboratory Animal Science. The office also assisted in the organization and conduct of Evening at Emory sessions cosponsored by the Public Relations Society of America.

The Information Services Office also:

1) Served as Yerkes liaison for Emory University's United Way campaign;
2) participated in Emory University's Communications Committee on EmoryCare, the university's new managed care/insurance program;
3) Wrote description of Yerkes Center for Emory Employee Handbook;
4) Presented proposals for meeting topics and speakers for Emory Board of Visitors' meetings
5) Contributed to new internal university publication on Points of Excellence at the university;
6) Prepared report about Yerkes Center for inclusion in an Emory School of Medicine self-assessment study;
7) Assisted substantially in the preparation of report about Yerkes Center for use in the Emory's reaccreditation by Southern Association of Colleges and Schools;
8) Helped Emory pre-med student group in the organization of an information session for students titled, "Animal Research Awareness, Why You Should Care about and Support Laboratory Studies with Animals";
9) Contributed to Emory Experts Guide;
10) Developed display about Yerkes Center for Zoo Atlanta Conservation Day; and staffed the display that Saturday;
11) Developed table-top display about the Yerkes Center for use at the annual dinner banquet of the DeKalb Chamber of Commerce;

12) Participated in Florida State University video for students, titled, "Science for Life"
13) Compiled Executive Summary of the 1991 Progress Report to National Institutes of Health, for distribution to Emory Board of Trustees and other Emory officials;
14) Assisted Director of the Yerkes Center in the preparation of his various presentations to scientific, educational and community groups. These included his International Primatological Congress speech on, "Neurobiology and Aging Studies at the Regional Primate Research Centers" and the manuscript of the presentation for publication in the American Journal of Primatology. The Yerkes Director's presentation, "The Emergence of Chimpanzees in Research," at the Immuno A.G. Symposium," The Role of Chimpanzees in Research," May 22-24, also involved the Information Services Office.
15) Assisted Yerkes Chief of Reproductive Biology in the preparation of this presentation on "Primate Conservation and the Tropical Rainforests" at the Association of Emory Alumni conference on the environment.
16) Organized the Yerkes Center's extensive slide collection for use by Yerkes Director and other scientists in their presentations and publications. Copies of the slides also are loaned to other researchers and publications.
17) Initiated the in-house production of a video that will provide an historical view of the Yerkes Center through the presentation of segments of films and other audiovisuals that have been made about the Yerkes Center since 1930.

Publications

During 1992, two issues of the Inside Yerkes magazine were produced using low-cost desktop publishing technology and distributed to over 1,500 individuals. The magazines were written, and designed by the Information Services Office.

The Spring 1992 issue reported on developments in the treatment of Parkinson's disease that have resulted from Yerkes studies; the positive results of clinical testing of a male contraceptive that was based in part on Yerkes research; the opening of an American Psychological Association exhibit with a display about Yerkes communication studies; and an National Institute of Drug Abuse-sponsored educational videotape about drug addiction, for showing middle-school students.

The second issue, published in Fall-Winter 1992, included stories about Yerkes research on primate vocal signals; effects of aging on brain cells; chimpanzee self-recognition; learning abilities of rhesus monkeys; the medical treatment of

children with congenital cataracts; the origin of the HumanImmunodeficiency Virus; and the loan of Yerkes gorillas to Busch Gardens.

A brochure about Yerkes, titled, "Yerkes: Dedicated To You" and written and designed by a student intern for distribution to other students, also was published by the Information Services Office. The office also updated the text and design of its fact sheet titled, "Conduct of Research and Animal Care at the Yerkes Primate Research Center".

As previously mentioned, a monthly employee bulletin was initiated in June.

F) Administrative Associate to the Director

The Office of the Administrative Associate is responsible for coordination of computerization at the Yerkes Center, review of selected administrative procedures as designated by the Center Director, management of the Yerkes Center Quality Assurance Unit for non-clinical laboratory studies conducted according to Food and Drug Administration guidelines for good laboratory practice, liaison with selected government and professional agencies, oversight of contracts and agreements with the private sector, and administrative coordination of fund raising activities. In addition the Administrative Associate serves as chairman of the Yerkes Animal Records Committee, chairman of the Yerkes Task Force for Review of Grant Administration, and as chairman of the Yerkes "No-Smoking" Task Force.

Computerization - System Administration and Hardware Support - The following were areas of special emphasis during 1992:

Plans for establishing a high speed data link between the Yerkes Field Station and Main Center were finalized and initiated. Although computer data communication via modem connection with the Field Station has been available for several years, the growing need for a more direct link to the Yerkes computer network is necessary for efficient access to the Main Center animal records database and to allow scientific communication over national and international communication networks. This project has now begun and awaits the installation of a high speed communication circuit by the Emory Telecommunication Division. It is anticipated that the project will be completed within the next few months at which time the Field Station will be an integral part of both the Yerkes and Emory computer network for both voice and data communication.

Support services for computing were increased by one part-time work-study student. While this does not restore manpower to the level prior to last year's budget cuts, it will be possible to provide a modest increase in the level of support to computer users. This will be especially important due to the growing number of computer users and require increased maintenance due to failure of aging components (e.g. the failure of hard drives and similar items). CPU upgrades continue to be necessary for some machines due to the increased demands resulting from more sophisticated software, especially with the advent of graphical user interfaces on the IBM compatible models. Wherever possible mother boards are replaced but in many instances it is more cost effective to utilize IBM clones as total replacements for existing machines. The few personal computers purchased from base grant funds during the last year were 80386 or 80486 CPU based machines. Most new users of PCs during the last year at the Main Center requested access and were connected to the Ethernet network. In addition, incidents of printer and monitor failure continued to increase during the last 12 months as these components became more than three or four years old. Software upgrades, with few exceptions, involved word processing, system development, or operating system software.

Computerization - Software Development: The following were areas of special emphasis during 1992:

The primary focus of attention for scheduled application development during the year was in the Budgets and Accounts System (BAS), as it was the previous year. Enhancements were made in several areas to accommodate changes in Emory accounting, including indirect cost sharing and Yerkes income accounting.

Support activities for the Animal Records System (ARS) continued to be centered around maintenance programming. A number of changes were made to programs based on user requests. A previously free-standing facility that tracks specimen collection was incorporated into ARS.

A major upgrade was made to the program that assists investigators in creating budgets for projected animal per diem charges for grant applications. The new version added several new features, and provided support for the new method of estimating per diem charges, which was significantly revised for FY92-93.

A number of additions and enhancements were made to system utilities and application subsystems to support operations on

a second server computer system.

A technical paper that discussed running multiple Informix applications against a single database in a secure manner under UNIX was presented at the Informix Worldwide User Conference.

In late December, a Senior Programmer/Analyst was hired, increasing the software development staff to a total of two people. Increased programming manpower is critical in maintaining and expanding both the Animal Records and Budget and Accounts databases to accommodate the growing utilization of the data and the many requests for additional functionality.

Review of Selected Administrative Procedures: The Task Force for review of research project administration, chaired by the Administrative Associate to the Director, completed it's review of administrative procedures during 1992 and delivered it's recommendations to the Center Director and the Division Chiefs/Section Heads. The modified procedures were approved and implementation was begun, affecting nearly every department in the Center. The Task Force continues to monitor implementation of the new procedures and to recommend adjustments and extensions as necessary.

Quality Assurance Unit: The Quality Assurance Unit continues to monitor non-clinical laboratory studies conducted according to Food and Drug Administration guidelines for good laboratory practice (GLP). During 1992, the Quality Assurance Unit completed monitoring one GLP study conducted for private industry by Yerkes scientists.

Liaison with Selected Government and Professional Agencies:

Georgia Biomedical Partnership, Inc: The Yerkes Center is involved with the development of biomedical-technology industry in Georgia through its participation in the Georgia Biomedical Partnership. The Partnership, originally the DeKalb Chamber of Commerce Biotechnology Research Council and Clifton Corridor Council, brings together representatives of private industry, academia, political figures, and businessmen from other countries to promote the biotechnology resources of Georgia as a whole and in particular the resources of the Clifton Corridor. The Clifton Corridor encompasses Emory University including the Yerkes Center, the Georgia Institute of Technology, the US. Centers for Disease Control, the national headquarters of the American Cancer Society, and the many surrounding academic and private facilities involved in biotechnology research and development. The aim of the

Council is to stimulate advances in biotechnology research and technological development. During 1992, the Yerkes Center attended the membership meetings of the Council, and hosted tours for individuals and organizations related to the Partnership, including such dignitaries as the French Trade Commissioner and top executives of several biotechnology companies.

American Psychological Society: Since the formation in 1988 of the American Psychological Society (APS), the office of the Administrative Associate to the Director has served as the Yerkes liaison to the Society. Liaison activities include the recruitment of new members, dissemination of membership materials, notification of scientific meetings sponsored by APS, and serving as the designated contact person with the Society.

American Psychological Association: The Yerkes Director serves as an Associate Editor for the American Psychologist, a major journal of the American Psychological Association (APA). The office of the Administrative Associate to the Director assists in the management of manuscripts received for review by the Director.

Contracts and Agreements with Outside Agencies: The Yerkes Center is currently involved in more than 30 agreements and contracts for research sponsored by, or carried out for, private industry, universities, and other outside agencies. The Yerkes Center is also involved in agreements relating to patents. The following is a partial list of organizations with one or more current agreements with the Center.

Boston University
Busch Entertainment Corporation
Georgia Institute of Technology
Genentech
Institute of Primate Research, Kenya
Johns Hopkins University
Morehouse University School of Medicine
Robinson Neurological Foundation
R.W. Johnson Pharmaceutical Research Institute
Sandoz Pharmaceutical Corporation
Smith-Kettlewell Eye Research Institute
Smokeless Tobacco Research Council
Summit Technology Incorporated
University of Alabama
University of Washington
W.L. Gore Associates Incorporated
Zeus Scientific Incorporated

G) Biomedical Engineering Unit

The Biomedical Engineering Unit, including the General Shop, accommodated over 450 job requests in 1992. One hundred eighty of these required emergency response. Included in the more routine tasks were the following:

1) Began installation of interior communicating doors in the Great Ape Wing.

2) Began an extensive program of small primate cage modification in compliance with USDA regulations.

3) Completed gibbon housing unit at Field Station.

4) Assumed responsibility for Field Station security system.

5) Designed and built group caging for socializing young macaques.

H) Library

The Yerkes Research Center Library is an essential resource in the research process. The library serves the information needs of the research staff and administration and provides full library service by acquiring, organizing, and disseminating information for current use, and by preserving relevant materials for future access.

The library contains 2,000 journal volumes and 2,000 books. There are 725 books and 4,500 reprints in special collections. These consist of archival and personal books from the libraries of former directors, and from a reprint collection begun by Robert M. Yerkes. Faculty publications added to the volumes, "Contributions from Yerkes Regional Primate Research Center," now total 3,500. This bound, indexed, reprint collection dates back to 1925.

Circulation figures, 6,000, remained approximately the same as for the previous year. This figure includes inhouse use, as routing journals, checking out books, photocopying requested materials, loaning or dispensing reprints (publications of Yerkes' faculty and collected reprints); borrowing and photocopying at Campus libraries; and borrowing through interlibrary loan from libraries off campus.

The online databases of DIALOG, and DOBIS, the online catalog of Emory's library holdings, were indispensable for reference use, and for literature and bibliographic searches as were the databases RLIN (Research Libraries Information Network) and

PsycINFO which are accessible through Emory. The National Library of Medicine's Grateful Med was added this year as a cost saving literature searching aid.

The library is open around the clock. Additionally, it is utilized for research projects requiring a quiet work space, such as video coding and viewing, and for small group meetings when the conference rooms are unavailable.

I) Business Office

The Business Office provides five main service functions to the Center.

1) Purchasing - includes procurement, accounts receivable, accounts payable, shipping/receiving, express mail and petty cash.

2) Grants Management - includes grants and contracts preparation, grant administration and indirect cost tracking. During 1992 this office administered 70 accounts.

3) Travel - includes travel arrangements and travel voucher processing.

4) Payroll - includes leave accrual, record keeping, time sheet processing and paycheck distribution.

5) General Office Services - includes processing and distributing mail, answering telephone calls, greeting and assisting visitors, maintaining and distributing office supplies and assisting in the operation of the photocopying machines.

J) Photography

The Photography Department provides photographic services to the scientific and administrative staff.

During 1992, 713 requests for photographic services were received and processed. The types of photographic illustrations provided included black and white photographs, color slides and prints of people, animals, caging, lesions, equipment, experimental procedures, electronic circuitry, buildings, surgery, necropsy, gross tissue specimens, and polaroid I.D. cards.

Other accomplishments included:

1) Black and white negative processing and darkroom sessions for printing were done in cooperation with investigators;

2) Slides were made from charts and graphs, radiographs, electron micrographs, book and magazine illustrations, photographs and other slides;

3) Black and white line negatives, prints and slides were produced for publication from charts and graphs;

4) Motion picture and slide projectors were operated for meetings and photographs of meeting sessions and speakers were taken;

5) Computer-generated charts, graphs and slides were prepared using Sigma-Plot, Freelance Plus, and Picture It software;

6) Acted as liaison with color lab for color prints for poster sessions and wall displays;

7) Prints from file negatives were produced to fill requests from publishers of textbooks and magazines; and

8) Photographs, letters and certificates were framed for display.

K) Integrated Scanning Electron Microscopy & Microanalytical Facility

Significant technical advances have taken place this year all of which expanded the correlative microscopic services routinely available in the integrated facility. A P-41 NIH Facilities grant was submitted, approved but not funded. Nevertheless, constructive comments from the NIH site visiting team prompted quick low cost technical development. Digital image acquisition for light microscopy was coupled to enhanced computer processing and instantaneous high resolution printouts. Additionally new specimen preparation techniques were developed for research and service users to provide simultaneous HRSEM and STEM images on the field emission SEM and highlighted the "electron optical" advances.
Trained personnel included one full-time person, one temporary 3 month appointment technician and a high project volume user (Dr. Keith Robinson) who conducted his own conventional SEM operations. This resulted in doubling of revenue over any previous year. In December 1992, a second permanent full-time microscopist agreed to join the facility in early 1993. Also during December, Topcon Technologies Inc. sold Yerkes Center a third DS-130 SEM at a fraction of the cost of a new instrument

and which will be configured for "Wet SEM" (given to us by Topcon in 1991) and X-ray microanalysis operation. Thus two service SEMs and one research SEM will be in place in 1993 and should greatly enhance the user access and productivity.

The Division of Hematology completed a few projects to assess platelet aggregation on gortex vascular grafts and plans were made for extensive studies in 1993. Dr. Fred Menger and a graduate student of the Chemistry Department conducted several studies involving HRSEM and STEM in order to assess their synthesis of long-chained amphiphiles. These studies have been completed.

Dr. Robinson has been very active in vascular studies which include: cell growth on stent material, treatment with the porous balloon catheter, quantitative assessment of leukocyte adhesion to rabbit aortic endothelium in experimental atherosclerosis, evaluation of acute thrombosis and reendothelialization of vascular grafts and carotid stents in swine, and new studies on oxidant stress and therapy in atherosclerosis. These projects will be ongoing in 1993.

B. HIGHLIGHTS

1) Research Completed

a) Comparative Neuropathological Study of Aged Primate Brains

Aged nonhuman primates provide an important model system for investigation of changes associated with aging and Alzheimer's disease in humans. Although there have been many studies of the brains of aged animals of various species, neuropathological studies of the brains of aged nonhuman primates, especially of great apes, have been limited. Investigators in the Division of Neurobiology have recently had the opportunity to conduct such studies on the brains of three aged chimpanzees (a male 45 years old and two females that were 56 and 59 years old), and have compared these findings with observations in 20 to 30 year old rhesus monkeys and with changes noted in aged humans.

Gross examination of the brains of the older chimpanzees and rhesus monkeys revealed discoloration of the globus pallidus and substantia nigra, corresponding to iron deposition and swollen axons, as have been previously described in older macaques. Silver stains and immunohistochemistry revealed amyloid deposition in plaques in the cortex and hippocampus, and in meningeal and cortical blood vessels that was more striking in the older animals of both species. The brains of the aged chimpanzees showed prominent amyloid angiopathy by

light and electron microscopy as well as occasional diffuse plaque-like structures with silver and amyloid stains. In contrast, the cortex of the aged rhesus monkeys showed numerous neuritic plaques with dense bodies and mitochondria in swollen neurites often associated with fibrillar amyloid. Amyloid angiopathy was also seen in some of the aged rhesus macaques. The neuritic plaques in the aged rhesus monkeys showed considerably more amyloid precursor protein immunoreactivity than the diffuse plaque-like structures seen in the aged chimpanzees. Neurofibrillary tangles and/or paired helical filaments, as seen in aged humans, were not observed in either the aged chimpanzees or aged rhesus monkeys.

Although the number of aged chimpanzees and aged rhesus monkeys examined to date is small, these observations suggest that species differences may modulate amyloid deposition and plaque formation. Further analysis to provide a better understanding of these differences may contribute to a better understanding of related changes in human aging and Alzheimer's disease.

b) Social Factors Affect the Stress Response and Immune Parameters in Nonhuman Primates

Psychosocial stress in humans has been related to the occurrence or progression of certain diseases, and a positive social environment has been shown in some cases to ameliorate this effect. A number of studies with nonhuman primates during the past year support this concept. These studies with nonhuman primates have shown that relatively minor social and/or environmental stressors result in elevated cortisol levels and alterations in selected immune parameters.

In a study designed to determine the specific social behaviors which affect the endocrine-defined stress response (i.e., changes in serum cortisol), studies were conducted with an established, long-term group of rhesus monkeys and a recently formed group of unfamiliar rhesus monkeys. When regression techniques were applied, neither group nor dominance rank was a predictor of cortisol levels, although when groups were analyzed separately, rank significantly correlated with cortisol level in the established group, but not in the recently formed group. It was found that reconciliatory behaviors occurred significantly more often following dyadic agonistic episodes in the recently-formed versus the long-term group. These observations demonstrated that cortisol levels are influenced not only by negative interactions (e.g., being bitten), but also by positive interactions (e.g., being groomed). These steroid hormones, acting as immunoregulators,

are known to affect immune function.

In another study, psychosocial stress associated with the transfer of six naive, juvenile rhesus monkeys from their natal social group to peer housing resulted in increased basal cortisol secretion and significant decrements in the absolute numbers of T lymphocyte subsets in the peripheral blood. When compared to controls (six subjects matched for age and social rank left in the social group), the experimental animals showed a significant decrease in the absolute numbers of $CD4^+$ and $CD8^+$ T cells and a significant increase in basal cortisol levels 24 hours following removal to peer housing. Group difference in the absolute numbers of T cells persisted through 11 weeks, whereas cortisol differences lasted only through two weeks. In this study, there was no modulating effect of randomly chosen peer-mates on the stress effect produced by social separation.

In studies with adult female rhesus monkeys in a stable social group, it was found that removal to individual housing resulted in significant increases in cortisol levels and significant decreases in the number of $CD4^+$ and $CD8^+$ T cells. Differences in baseline values were evident at 2 hours and 24 hours, with recovery evident at 4 days following separation. Separation to housing with a companion also produced evidence of stress which, however, was significantly modulated in the majority of subjects. These observations support the concept that social support modulates the physiological response to stress.

2) Research in Progress

a) Effect of GnRH Analogues on Immune System Development in Male Rhesus Monkeys

In these studies, rhesus neonates were treated with GnRH agonist or antagonist for the first four months of life and immunologic parameters evaluated at 4 months, 6 months and 18 months of age or at 7 to 8 years of age. Immunologic parameters evaluated included a determination of lymphocyte subsets by FACScan flow cytometry, mitogen response of lymphocytes and a determination of the immune response to tetanus toxoid.

In animals evaluated at 7 to 8 years of age, the numbers of T-helper cells (CD4) were unchanged, but T-suppressor cells (CD8) were significantly elevated and B cells were decreased. Lymphocytes from these animals showed an increased response to T-cell mitogens (Con-A and PHA), but their response to PWM and SLO was normal. Anti-tetanus antibody production did not

differ between control and experimental animals.

In animals evaluated at 4 to 18 months, CD8 cells and B cell numbers were significantly decreased at 4 months of age, whereas CD4 cell numbers were normal. At 6 months of age, lymphocyte responses to Con-A, PHA and PWM were normal, but the response to SLO was elevated. Anti-tetanus antibody production was normal in treated animals after the initial tetanus toxoid injection, but the response to a booster was increased in the treated animals.

Results of these preliminary studies suggest that early postnatal treatment of male monkeys with GnRH analogues many alter immunologic parameters. However, the significance of these changes and whether the immune system is permanently impaired will require additional studies.

b) Cytokine Effects on Post-Chemotherapy Immunohematopoietic Regeneration Using a Nonhuman Primate Model

High dose chemotherapy, with or without hematopoietic stem cell rescue, has become an important component of treatment strategies for patients with various types of malignancies. Damage to the hematopoietic system with resultant low blood counts is the major, dose-limiting toxicity of high dose chemotherapy. Consequently, these studies were initiated to determine the optimal use of newly available recombinant hematopoietic growth factors to decrease the hematopoietic suppression associated with chemotherapy.

During the past year, a high dose chemotherapy model was developed in the rhesus monkey using hepsulfam. Following hepsulfam treatment, this model develops a predictable severe suppression of circulating platelets, granulocytes and erythrocytes. The hepsulfam is administered by a single intravenous infusion, and the following day cytokines are administered subcutaneously over a period of three weeks. Post-chemotherapy blood counts are obtained three times per week, and bone marrow samples to assay for primitive hematopoietic cells are obtained weekly. The animals are supported with prophylactic antimicrobials, and administered blood or platelet transfusions as needed to treat low platelet or red cell counts.

Following development of the model, the effects of a single cytokine (rhIL-3, rhIL-6, GM-CSF) or combination cytokines (rhIL-3 plus rhIL-6, rhGM-CSF plus rhIL-3) on the severity and duration of the cytopenias have been determined. Treatment with rhIL-6, rhIL-6 plus rhIL-3 or rhGM-CSF plus rhIL-3 has been shown to prevent the severe platelet counts associated

with hepsulfam therapy. The duration and severity of post-hepsulfam granulocytopenia has also been decreased by the same cytokines and combinations. Additional combinations and cytokines will be evaluated during the coming year.

C. INSTITUTIONAL REVIEW COMMITTEES AND ALLOCATION OF RESOURCES

1) Executive Committee

The Yerkes Executive Committee is charged with the overall and general responsibilities in the areas of policy and program planning for the Center. This committee consists of the Center Director (Chair), Associate Director for Scientific Programs, Associate Director for Animal Resources, Associate Director of Field Station, Associate Director for Administration, Division Chiefs, and Coordinator for the Language Research Center. This committee meets monthly.

Composition of the committee is as follows:

Executive Committee

Name	Degree	Academic Titles	Department or Division	Institution
F. King (Chair)	Ph.D.	Center Director	Administration	Yerkes
		Professor	Anatomy and Cell Biology	Emory Univ.
		Professor	Psychology	Emory Univ.
		Associate Dean Medicine	School of	Emory Univ.
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes
H. McClure	D.V.M.	Associate Director for Scientific Programs, Research Professor and Chief, Division of Pathobiology and Immunobiology	Pathobiology and Immunobiology	Yerkes
		Assistant Professor	Pathology	Emory Univ.

Executive Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
L. Byrd	Ph.D.	Research Professor and Chief, Division of Behavioral Biology	Behavioral Biology	Yerkes
		Associate Professor	Pharmacology	Emory Univ.
		Adjunct Professor	Psychology	Emory Univ.
		Adjunct Professor	Psychology	Ga. Tech.
K. Gould	D.V.M. Ph.D.	Research Professor and Chief, Division of Reproductive Biology	Reproductive Biology	Yerkes
		Adjunct Professor	Biology	Emory Univ.
B. Swenson	D.V.M.	Associate Research Professor and Chief of Veterinary Medicine	Animal Resources	Yerkes
J. Tigges	Ph.D.	Research Professor and Chief, Division of Neurobiology	Neurobiology	Yerkes
		Professor	Anatomy and Cell Biology	Emory Univ.
		Professor	Ophthalmology	Emory Univ.
T. Gordon	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
		Adjunct Professor	Psychology	Emory Univ.
D. Rumbaugh	Ph.D.	Affiliate Scientist and Language Research Center Coordinator	Behavioral Biology	Yerkes
		Professor	Psychology	Georgia State Univ.

2) IACUC Primate Subcommittee

This committee was formally established in January, 1990, and was charged with the responsibility for review of research proposals for humane treatment of laboratory animals and other elements mandated by USDA/PHS regulations. This committee is a subcommittee of the University IACUC and has the responsibility for review of all University proposals that involve the use of nonhuman primates. Actions taken by the IACUC Primate Subcommittee are forwarded directly to the University IACUC for final disposition. The composition of this committee is as follows:

IACUC Primate Subcommittee

Name	Degree	Academic Titles	Department or Division	Institution
K. Gould* (Chair)	D.V.M. Ph.D.	Research Professor and Chief, Division of Reproductive Biology	Reproductive Biology	Yerkes
		Adjunct Professor	Biology	Emory Univ.
T. Gordon (Co-Chair)	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
		Adjunct Professor	Psychology	Emory Univ.
R. Boothe	Ph.D.	Research Professor	Neurobiology	Emory Univ.
		Associate Professor	Psychology	Emory Univ.
		Assistant Professor	Ophthalmology	Emory Univ.
J. Magnotta	B.S.	Associate Director for Administration	Administration	Yerkes
F. Novembre,	Ph.D.	Assistant Research Professor	Pathobiology and Immunobiology	Yerkes
E. Strobert	D.V.M.	Associate Veterinarian	Veterinary Medicine	Yerkes
F. King (ex-officio)	Ph.D.	Director and Professor	Administration	Yerkes

3) Yerkes AAALAC Accreditation Committee

This Committee was formally established to analyze the deficiencies and needs of the Center in order to obtain AAALAC accreditation, and to set a timetable and plan for the achievement of the required improvements. Although full AAALAC accreditation has been received, this committee has remained active. The committee meets at least two times per year to review animal housing facilities and animal use to assure that full AAALAC accreditation is maintained. The composition of this Committee is as follows:

Yerkes AAALAC Accreditation Committee

Name	Degree	Academic Titles	Department or Division	Institution
H. McClure (Chair)	D.V.M.	Associate Director for Scientific Programs; Research Professor and Chief, Division of Pathobiology and Immunobiology	Pathobiology and Immunobiology	Yerkes
		Assistant Professor	Pathology	Emory Univ.
B. Swenson	D.V.M.	Associate Research Professor and Chief of Veterinary Medicine	Animal Resources	Yerkes
J. Roberts		Chief Superintendent	Main Station	Yerkes
D. Chikazawa		Superintendent	Field Station	Yerkes
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes
T. Gordon	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
K. Pralinsky	B.A.	Superintendent	Main Station	Yerkes

4) Computer Committee

This committee reviews all base grant computer purchases and coordinates computer use at the Yerkes Main Station and Field Station. The committee is also available as a resource to any investigator who needs information about computers. The composition of this committee is as follows:

Computer Committee

Name	Degree	Academic Titles	Department or Division	Institution
R. Boothe (Chair)	Ph.D.	Research Professor Professor	Neurobiology	Yerkes
		Associate Professor	Psychology	Emory Univ.
		Assistant Professor	Ophthalmology	Emory Univ.
R.Buddington	Ph.D.	Administrative Associate	Administration	Yerkes
K. Gould	D.V.M. Ph.D.	Research Professor and Chief, Division of Reproductive Biology	Reproductive Biology	Yerkes
		Adjunct Professor	Biology	Emory Univ.
J. Herndon	Ph.D.	Associate Research Professor	Neurobiology	Yerkes
		Adjunct Assistant Professor	Biology	Emory Univ.
		Adjunct Assistant Professor	Psychology	Emory Univ.
C. Lin	B.S.	Computer Services Coordinator	Computer Services	Yerkes
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes

Computer Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
E. Smith	Ph.D.	Associate Research Professor	Behavioral Biology	Yerkes
		Associate Professor	Anthropology	Emory Univ.
		Adjunct Associate Professor	Biology	Emory Univ.
K. Wallen	Ph.D.	Associate Research Professor	Behavioral Biology	Yerkes
		Associate Professor	Psychology	Emory Univ.

5) Library Committee

This committee provides guidance with regard to the library needs of the scientific and veterinary staff, and makes recommendations on journal and volume purchases, and library policies and procedures. The composition of this committee is as follows:

Library Committee

Name	Degree	Academic Titles	Department or Division	Institution
E. Smith (Chair)	Ph.D.	Associate Research Professor	Behavioral Biology	Yerkes
		Associate Professor	Anthropology	Emory Univ.
		Adjunct Associate Professor	Biology	Emory Univ.
J. Herndon	Ph.D.	Associate Research Professor	Neurobiology	Yerkes
		Adjunct Assistant Professor	Biology	Emory Univ.
		Adjunct Assistant Professor	Psychology	Emory Univ.

Library Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
N. Johns		Librarian	Administration	Yerkes
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes
B. Swenson	D.V.M.	Associate Research Professor and Chief of Veterinary Medicine	Animal Resources	Yerkes
M. Wilson	Ph.D.	Associate Research Professor	Reproductive Biology	Yerkes
		Associate Professor	Medicine	Emory Univ.
		Associate Professor	Psychology	Emory Univ.

6) Affirmative Action Committee

The three main areas of responsibility of this committee include: (1) serve as a vehicle for the proper disposition of complaints or grievances by employees concerning discrimination on the basis of race or sex; (2) to monitor the Center's implementation of Policies for Faculty Appointments and Promotions as approved by the Office of Equal Opportunity Programs; and (3) to provide for communication between the administration of the Center and the Office of Equal Opportunity Programs with regard to University policies on hiring, promotion and personnel matters. The composition of this committee is as follows:

Affirmative Action Committee

Name	Degree	Academic Titles	Department or Division	Institution
D. Anderson (Chair)	D.V.M.	Associate Research Professor	Pathobiology and Immunobiology	Yerkes
D. Houseworth		Asst. Superintendent	Animal Care	Yerkes
K. Pralinsky	B.A.	Superintendent	Main Station	Yerkes

Affirmative Action Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
J. Magnotta (ex officio)	B.A.	Associate Director for Administration	Administration	Yerkes

7) Task Force on 1992 Budget

This task force is charged with the responsibility of critically and thoroughly evaluating all aspects of the Center's operating costs, with recommendations made to the Director concerning the allocation of funds in the most efficient manner. The composition of this task force is as follows:

1992 Budget Task Force

Name	Degree	Academic Titles	Department or Division	Institution
J. Magnotta (Chair)	B.A.	Associate Director for Administration	Administration	Yerkes
T. Gordon	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
		Adjunct Professor	Psychology	Emory Univ.
H. McClure	D.V.M.	Associate Director for Scientific Programs; Research Professor and Chief, Division of Pathobiology and Immunobiology	Pathobiology and Immunobiology	Yerkes
		Assistant Professor	Pathology	Emory Univ.
B. Swenson	D.V.M.	Associate Research Professor and Chief of Veterinary Medicine	Animal Resources	Yerkes

8) Animal Records Committee

The committee's charge is to develop an animal records system that can be adapted for computer use to facilitate storage, retrieval and processing of animal records relating to husbandry and mangagement, medical history and research utilization. The composition of this committee is as follows:

Animal Records Committee

Name	Degree	Academic Titles	Department or Division	Institution
R. Buddington (Chair)	Ph.D.	Administrative Associate	Administration	Yerkes
R. Boothe	Ph.D.	Research Professor	Neurobiology	Yerkes
		Associate Professor	Psychology	Emory Univ.
		Assistant Professor	Ophthalmology	Emory Univ.
S. Klumpp,	D.V.M.	Associate Scientist and Veterinary Pathologist	Pathobiology and Immunobiology	Yerkes
S. Setzekorn	---	Supervisor Animal Records	Animal Resources	Yerkes
B. Swenson	D.V.M.	Associate Research Professor and Chief of Veterinary Medicine	Animal Resources	Yerkes
D. Vinson	---	Secretary I	Field Station	Yerkes
W. Hultgren	B.S.	Software Development Coordinator	Computer Services	Yerkes

9) Biohazard Safety Committee

The Biohazard Safety Committee was formed in 1986 to monitor the use, storage and disposal of hazardous materials at the Primate Center to insure that all Yerkes laboratories are in full compliance with OSHA and EPA regulations governing safety in the laboratory. The composition of this committee is as follows:

Biohazard Safety Committee

Name	Degree	Academic Titles	Department or Division	Institution
M. Wilson (Chair)	Ph.D.	Associate Research Professor	Reproductive Biology	Yerkes
		Associate Professor	Medicine	Emory Univ.
		Associate Professor	Psychology	Emory Univ.
D. Anderson	D.V.M.	Associate Research Professor	Pathobiology and Immunobiology	Yerkes
K. Pralinsky	B.A.	Superintendent	Main Station	Yerkes
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes
J. Roberts		Chief Superintendent	Main Station	Yerkes

10) Ophthalmology Research Laboratory Building Use Committee

The responsibility of this committee is to consider and make assignments of space in the Ophthalmology Research Laboratory Building on the Yerkes premises to assure cooperation and smooth coordination of scientific projects conducted by Yerkes core faculty and members of the Emory University Department of Ophthalmology. In matters in which the committee cannot reach agreement among the members, these are taken to the Director of the Yerkes Center and the Chairman of the Department of Ophthalmology for adjudication. The composition of this committee is as follows:

Ophthalmology Building Use Committee

Name	Degree	Academic Titles	Department or Division	Institution
H. McClure	D.V.M.	Associate Director for Scientific Programs; Research Professor and Chief, Division of Pathobiology and Immunobiology	Pathobiology and Immunobiology	Yerkes
		Assistant Professor	Pathology	Emory Univ.

Ophthalmology Building Use Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
J. Magnotta	B.A.	Associate Director for Administration	Administration	Yerkes
B. McCarey	Ph.D.	Affiliate Scientist	Pathobiology and Immunobiology	Yerkes
		Associate Professor	Ophthalmology	Emory Univ.
M. Riemann	---	Department Administrator	Ophthalmology	Emory Univ.

11) Summer Internship Committee

This committee is charged with the responsibility of evaluating applicants for the Yerkes summer internship program; selection of the most outstanding applicants for which positions are available and making recommendations to the Director concerning the selected applicants and the Yerkes Division or investigator to whom the applicants could most appropriately be assigned. The composition of this committee is as follows:

Summer Internship Committee

Name	Degree	Academic Titles	Department or Division	Institution
L. Byrd (Chair)	Ph.D.	Research Professor and Chief, Division of Behavioral Biology	Behavioral Biology	Yerkes
		Associate Professor	Pharmacology	Emory Univ.
		Adjunct Professor	Psychology	Emory Univ.
		Adjunct Professor	Psychology	Ga. Tech.
D. Anderson	D.V.M.	Associate Research Professor	Pathobiology and Immunobiology	Yerkes
M. Tigges	Ph.D.	Associate Research Professor	Neurobiology	Yerkes
		Associate Professor	Anatomy and Cell Biology	Emory Univ.

12) Primate Enrichment Committee

This committee was established in 1990 with a mandate to provide improvements in housing and other types of enrichment for Yerkes nonhuman primates. The committee will evaluate enrichments such as manipulanda; food varieties; food distribution devices; "toys"; climbing devices; opportunity of choice of visual, auditory, and other sensory stimulations; opportunities for increased socialization; and other related changes that may enhance normal behaviors. The committee is expected to not only conceptualize enrichment opportunities, but to implement them through discussions and arrangements with the appropriate units of the Center, and evaluate them objectively as to their effectiveness.

Primate Enrichment Committee

Name	Degree	Academic Titles	Department or Division	Institution
E. Strobert (Chair)	D.V.M.	Associate Veterinarian	Veterinary Medicine	Yerkes
F. de Waal	Ph.D.	Research Professor	Behavioral Biology	Yerkes
		Associate Professor	Psychology Department	Emory Univ.
J. Ellis	Ph.D.	Research Associate	Behavioral Biology	Yerkes
T. Gordon	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
		Adjunct Professor	Psychology	Emory Univ.
D. Gust	Ph.D.	Research Associate	Behavioral Biology	Yerkes
K. Paul	D.V.M.	Research Associate	Pathobiology and Immunobiology, and Veterinary Medicine	Yerkes
K. Pralinsky	B.A.	Superintendent	Main Station	Yerkes

13) Research Advisory Committee

The Research Advisory Committee is responsible for the review of all research proposals involving the Center's facilities or resources that will not be peer-reviewed by a funding agency. This committee is advisory to the Center Director and makes recommendations to the Director concerning the scientific merit of non-peer reviewed proposals and the appropriateness of conducting such studies at the Center, as well as recommendations concerning the overall research program of the Center and the use of Center resources.

Research Advisory Committee

Name	Degree	Academic Titles	Department or Division	Institution
H. McClure (Chair)	D.V.M.	Associate Director for Scientific Programs; Research Professor and Chief, Division of Pathobiology and Immunobiology	Pathobiology and Immunobiology	Yerkes
		Assistant Professor	Pathology	Emory Univ.
L. Byrd	Ph.D.	Research Professor and Chief, Division of Behavioral Biology	Behavioral Biology	Yerkes
		Associate Professor	Pharmacology	Emory Univ.
		Adjunct Professor	Psychology	Emory Univ.
		Adjunct Professor	Psychology	Ga. Tech
K. Gould	D.V.M. Ph.D.	Research Professor and Chief, Division of Reproductive Biology	Reproductive Biology	Yerkes
		Adjunct Professor	Biology	Emory Univ.
T. Gordon	M.S.	Associate Director for Field Station and Associate Research Professor	Behavioral Biology	Yerkes
		Adjunct Professor	Psychology	Emory Univ.

Research Advisory Committee (Cont'd)

Name	Degree	Academic Titles	Department or Division	Institution
J. Tigges	Ph.D.	Research Professor and Chief, Division of Neurobiology	Neurobiology	Yerkes
		Professor	Anatomy and Cell Biology	Emory Univ.
		Professor	Ophthalmology	Emory Univ.

D. DISSEMINATION OF INFORMATION

As in past years, the Center has continued to use the following mechanisms for the dissemination of information:

1) Brochures and literature are distributed to Yerkes staff, all officers and departments of Emory University, other universities, institutions, public mailing list, legislators, professional societies and associates.

2) Articles are published in NIH and Emory University publications and in newspapers and magazines.

3) Lectures and videotape and slide presentations are presented at other institutions and to the public, as well as at scientific and professional meetings.

4) Seminars by investigators who conduct research at the Center and the Yerkes visiting speaker series are scheduled throughout the year.

Additional documents on Center research programs, the conduct of research and animal care at the Center, the importance and benefits of animals to human health, and primate contributions to human health have been developed for distribution to faculty and staff, the news media and the general public, as needed.

A detailed packet of information concerning research at the Center has been developed and is provided to all investigators interested in initiating research projects at the Center. This application includes information on research opportunities at the Center, criteria for the use of primates in research, Center access policy, standards and procedures for working with nonhuman primates, guidelines for experimental surgery and procedures and guidelines for the preparation and submission of research proposals.

DIVISION OF BEHAVIORAL BIOLOGY

Larry D. Byrd, Ph.D., Chief

Core Faculty:

L.D. Byrd
F.B.M. de Waal
T.P. Gordon
H.T. Gouzoules
E.S. Savage-Rumbaugh
E.O. Smith
K. Wallen

Associate, Affiliate and Collaborative Faculty:

F. Aureli	Yerkes Regional Primate Research Center, Emory University
I.S. Bernstein	Department of Psychology, University of Georgia
G.G. Berntson	Departments of Psychology and Pediatrics, The Ohio State University
S.T. Boysen	Department of Psychology, The Ohio State University
D.T. Cerutti	Language Research Center, Georgia State University
C.L. Ehardt	Department of Anthropology and Linguistics, University of Georgia
J.E. Ellis	Yerkes Regional Primate Research Center, Emory University
D.L. Forthman	Atlanta/Fulton County Zoo, Inc.
D.M. Fragaszy	Department of Psychology, University of Georgia, Athens, GA
S.M. Gouzoules	Yerkes Regional Primate Research Center, Emory University
D.A. Gust	Yerkes Regional Primate Research Center, Emory University
S.G. Holtzman	Department of Pharmacology, Emory University
W.D. Hopkins	Yerkes Regional Primate Research Center, Emory University
L.L. Howell	Yerkes Regional Primate Research Center, Emory University
P.G. Judge	Yerkes Regional Primate Research Center, Emory University
D. Maestripieri	Yerkes Regional Primate Research Center, Emory University
T.L. Maple	School of Psychology, Georgia Institute of Technology, and Atlanta/Fulton County Zoo, Inc.
E.W. Menzel	Department of Psychology, State University of New York at Stony Brook
D.L. Molfese	Departments of Psychology, Physiology, and Behavioral and Social Sciences, Southern Illinois University at Carbondale
R.D. Morris	Department of Psychology, Georgia State University
M.A. Romski	Department of Communication, Georgia State University
D.M. Rumbaugh	Department of Psychology, Georgia State University
K.F. Schama	Yerkes Regional Primate Research Center, Emory University
R.A. Sevcik	Department of Psychology, Georgia State University
W.M. Tomasello	Department of Psychology, Emory University
E. Visalberghi	Primate Laboratory Unit, Institute of Psychology (CNR), Rome, Italy
S.L. Williams	Language Research Center, Georgia State University

Visiting Scientist:

E.C. Spada	Institute of Marine Sciences, University of California at Santa Cruz

SECTION ON PSYCHOBIOLOGY AND BEHAVIORAL PHARMACOLOGY

Larry D. Byrd, Ph.D., Section Head

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: The Development of Numerical Competence in Chimpanzees

AXIS I: 1a

AXIS II: 34, 36, 41

PRC UNIT: Behavioral Biology

INVES1: Boysen, Sarah T.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Berntson, Gary G.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Pan troglodytes
NUM1: 5

SPECIES2: Cebus apella
NUM2: 1

NON-HOST INST: The Ohio State University

ABSTRACT: The present studies of the mechanisms supporting numerical and counting skills in the chimpanzee will provide direction for further study of complex information processing in a nonhuman primate model. Previous studies have documented the acquisition of a range of numerical abilities, the capacity for numerical symbol manipulation and strategies for implicit counting in apes. Exploration of these number-related skills suggests that the requisite cognitive processes for complex manipulation of numerical representations are within the capacity of this species. Chimpanzees have demonstrated the ability to label quantities with Arabic numerals from 0 to 8, to respond receptively in tests of number comprehension, and to exhibit spontaneous addition with objects or Arabic numerals. Evidence for an understanding of ordinality and transitivity with numerical stimuli, as well as the use of fractions (1/2, 1/4), has also been established. The same animals have also exhibited the ability to construct arrays from collections of objects, in response to displayed numbers. Together, these skills and capacities indicate that the chimpanzee, like human children, derives a "sense of number" from a variety of counting schemas. Since time, space and number are significant features of the adaptive domain of many species including the great apes, studies of the potential for numerical abilities may provide new insights into the evolution of cognition in apes and humans.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Recall and Recognition in Aged Rhesus Monkeys

AXIS I: 1a, 2, 9, 21, 25b

AXIS II: 30, 36, 46, 50b, 72

PRC UNIT: Behavioral Biology

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

INVES2: Ellis, Jane E.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 6

NON-HOST INST: NA

ABSTRACT: Studies of memory typically have involved linguistically-competent human subjects; therefore, studies of memory processes have been confounded with linguistic ability. Studies on human and animal memory have demonstrated remarkable similarities in human and nonhuman memory processes, and they indicate that findings derived from animal experiments, which are not confounded by linguistic ability, can enhance our understanding of human memory. The present, ongoing project has developed the rhesus monkey as a model for studying human memory by examining the performances of old, mid-age and young animals on a delayed-recall task which is similar to tasks commonly used to study human memory. The methodology used in this study is based on a touch-sensitive cathode ray tube (CRT) upon which a microcomputer displays visual stimuli that a subject must acknowledge, then recall and reproduce after an intervening period of time (delay) has elapsed. High levels of accuracy on the recall task following very brief delays are characteristic of all three age groups. Accuracy levels declined with increasing delays for all age groups, although the decline was more pronounced for the oldest animals. Similar results are obtained with humans performing analogous tasks. Several pharmacologic compounds were tested to determine their potential effect on test performance and to enhance our understanding of the neuropharmacology of memory and aging. The long-range objective of the research is to characterize the neuropharmacology of memory so that decrements in memory can be prevented or treated therapeutically.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Chronic Cocaine Exposure during Gestation

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

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

PRC UNIT: Behavioral Biology

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

INVES2: Ellis, Jane E.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

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

NON-HOST INST: NA

ABSTRACT: Cocaine use has increased dramatically among Americans, and users now include young adults of child-bearing age and pregnant women. Clinical reports have indicated that a pregnant woman and her fetus are subjected to a host of potential problems due to cocaine use. However, few studies have examined the consequences of cocaine use during pregnancy under highly controlled laboratory conditions. Therefore, cocaine's effects on maternal, fetal and neonatal behavior and on development are poorly understood. This project is studying in rhesus monkeys the effects of cocaine administration during gestation to characterize effects on the pregnant female, the developing fetus and the resulting offspring. Several doses of the drug are being administered in order to determine differences in effects as a function of dose and to determine the most appropriate dose to use in subsequent experiments. The drug is being infused via chronically-implanted osmotic pumps, and drug levels in maternal blood and in amniotic fluid are being monitored. In control monkeys, saline is substituted for cocaine solution and infused. In utero growth and activity of the fetus are being measured using diagnostic ultrasound. Neonates are being tested and studied postnatally using selected visual, psychomotor and developmental tasks to characterize differences in

behavioral development and physical growth. Infant monkeys will also be monitored for evidence of tolerance or sensitization to the presence of cocaine, and adult monkeys will be studied for evidence of withdrawal following birth of the infant and subsequent removal of the infusion pump from the adult. The research will characterize a nonhuman primate model of prenatal cocaine exposure in order to understand better the risks of cocaine use during pregnancy in humans.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Behavioral and Physiological Concomitants of Drug Abuse

AXIS I: 1a, 2, 13, 21

AXIS II: 36, 50b, 54b, 72, 87

PRC UNIT: Behavioral Biology

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

INVES2: Howell, Leonard L.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

INVES3: Schama, Kevin F.
DEGREE3: Ph.D.
DEPT3: Behavioral Biology
STAFF3: O

SPECIES1: Saimiri sciureus
NUM1: 24

NON-HOST INST: NA

ABSTRACT: The primary goal of this research is to characterize the effects selected drugs can have on the central nervous system of nonhuman primates by studying the effects of these drugs on operant behavior. In addition, studies will determine the effects the drugs can have on heart rate, arterial blood pressure and core temperature at doses that have effects on behavior mediated via the central nervous system, and determine whether the behavioral, cardiovascular or thermoregulatory effects are enhanced, diminished or blocked by other drugs or by behavioral procedures. Methods used include the direct measurement of arterial blood pressure and heart rate as indices of cardiovascular activity, the direct measurement of colonic temperature as an index of thermoregulatory activity, and schedule-controlled behavior as an index of central nervous system activity. Through the use of various dopaminergic, serotonergic, adrenergic and cholinergic agonists and antagonists, this laboratory has demonstrated the involvement of specific neurotransmitter systems in the behavioral and reinforcing effects of selected drugs having high abuse liability. In addition to developing appropriate animal models for studying the effects of drugs, the project also uses animal models to generate a better understanding of the effects certain types of drugs can have in humans and animals and to identify ways in which undesirable effects of the drugs can be attenuated. The long-range objective is to characterize the behavioral, cardiovascular and thermoregulatory effects of various drugs that may have abuse liability or may have therapeutic value in treating drug abuse.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Behavioral and Respiratory Effects of Methylxanthines

AXIS I: 1a, 21, 24

AXIS II: 50b, 87

PRC UNIT: Behavioral Biology

INVES1: Howell, Leonard L.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 8

NON-HOST INST: NA

ABSTRACT: Caffeine and related methylxanthines are behaviorally-active drugs used clinically in the management of several breathing disorders including respiratory depression, neonatal apnea and bronchial asthma. Because nicotine is a widely-used behavioral stimulant frequently co-administered with caffeine, studies during the past year have focused on altered sensitivity to the respiratory effects of caffeine and changes in caffeine pharmacokinetics during acute and chronic nicotine administration. Ventilation in unanesthetized monkeys was monitored continuously using a pressure-displacement head plethysmograph. Drug effects were determined on ventilation during exposure to normal atmospheric conditions and on ventilation stimulated by increased concentrations of CO_2 (hypercapnia) or decreased concentrations of O_2 (hypoxia) in inspired air. Acute administration of nicotine alone had no effect during hypoxia but had modest respiratory-stimulant effects during hypercapnia. However, nicotine administration in combination with caffeine enhanced the respiratory-stimulant effects of caffeine during hypoxia but not during hypercapnia. Subsequently, nicotine was administered on a chronic, daily basis for 28 consecutive days via osmotic minipumps, and the respiratory effects of caffeine were redetermined. Chronic nicotine administration alone did not alter the ventilatory response to hypercapnia or hypoxia. However, in contrast to the acute interactions of nicotine and caffeine, chronic nicotine administration attenuated the respiratory-stimulant effects of caffeine under all conditions. Moreover, the metabolism of caffeine to paraxanthine was enhanced in all subjects during the 28-day period of chronic nicotine administration. Paraxanthine is a major metabolite of caffeine in humans, and the enhanced conversion of caffeine to paraxanthine in the present study established the rhesus monkey as an acceptable model for investigating altered pharmacokinetics associated with chronic nicotine administration. Additionally, the interactions obtained with caffeine and nicotine suggested that modulation of caffeine's effects during acute and chronic nicotine administration likely involved separate and distinct pharmacological mechanisms.

SECTION ON BEHAVIORAL ENDOCRINOLOGY AND SOCIAL BEHAVIOR

Thomas P. Gordon, M.S., Section Head

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Calculated Reciprocity in Chimpanzees

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Behavioral Biology

INVES1: de Waal, Frans B. M.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

SPECIES1: Pan troglodytes
NUM1: 17

NON-HOST INST: NA

ABSTRACT: Spontaneous food-sharing in chimpanzees (Pan troglodytes) housed outdoors is being studied by subjecting the colony to food trials in which all individuals are present and by conducting experiments which increase the optional nature of sharing. The latter is achieved through the temporary separation of particular individuals while they receive food and are presented the choice either of rejoining the group or of consuming the food undisturbed. Previous research using the same group indicated a high level of reciprocity in food-sharing. The present study is designed to investigate the extent to which food-sharing is voluntary and how it is affected by the perceptions of others. Due to the close taxonomic relationship between humans and chimpanzees, the reciprocity system of chimpanzees may depend upon emotions, social pressures and cognitive evaluations that are fundamentally similar to those underlying human reciprocity.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Pilot Research on Capuchin Social Behavior and Cognition

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Behavioral Biology

INVES1: de Waal, Frans B. M.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

SPECIES1: Cebus apella
NUM1: 14

NON-HOST INST: NA

ABSTRACT: A series of pilot studies are being conducted on two social groups of brown capuchin monkeys (Cebus apella). This project is intended to be a starting point for further research and is designed to collect preliminary data necessary for applications for outside funding. The primary focus of the research is on post-conflict interactions (i.e. reconciliation behavior), the sharing of food and social reciprocity. Particular attention is being paid to the social cognition involved in these processes. The methods used are largely observational, i.e. data collection on spontaneous behavior in the groups. Food-sharing is also being studied by conducting brief tests on pairs of monkeys separated from their group. The monkeys, which recently came to the Yerkes Center from the Wisconsin Regional Primate Research Center, are housed and studied in a newly-constructed indoor/outdoor facility.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Housing Conditions and Psychological Well-being of Chimpanzees

AXIS I: 1a

AXIS II: 36

PRC UNIT: Behavioral Biology

INVES1: de Waal, Frans B. M.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Aureli, Filippo
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Pan troglodytes
NUM1: 25

NON-HOST INST: NA

ABSTRACT: One of the most important considerations in animal management is to determine the optimal captive environment for the physical and psychological well-being of a particular species. This can be accomplished by comparing the behavior and health of animals maintained under different living conditions. The present study is designed to develop an optimal captive environment for the chimpanzee (Pan troglodytes), a species that is very important to research at the Yerkes Regional Primate Research Center. The planned construction of a new outdoor compound for chimpanzees at the Field Station of the Yerkes Center will provide an excellent opportunity to compare two housing conditions. Twenty-five chimpanzees maintained in small groups in indoor/outdoor runs in the Center's Great Ape Wing have been observed, and data have been collected on aggression, affiliation (e.g. social grooming), stereotypical behavior and behavioral stress-indicators. Approximately twelve of these chimpanzees will be transferred to the Field Station to form a large group in the new compound, and the remaining subjects will continue to live under the same small-group conditions. Following relocation of the animals, data will continue to be collected on all subjects. Comparison of the data sets will show how chimpanzee behavior differs under the two environmental conditions, and how these apes adjust to a new physical and social environment.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Relation between Space and Aggression in Rhesus Macaques

AXIS I: 1a

AXIS II: 36

PRC UNIT: Behavioral Biology

INVES1: de Waal, Frans B. M.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Judge, Peter G.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 64

NON-HOST INST: NA

ABSTRACT: Rhesus monkeys (Macaca mulatta) were observed under five degrees of spatial crowding, from groups maintained in small cages to free-ranging monkeys, in order to test models which predict the effect of higher population densities on aggressive and affiliative behaviors in primates. A "spatial density" model predicts that as density increases, aggression will also increase. A "coping model" predicts that as density increases, animals may increase aggression slightly but will compensate for the likelihood of increased aggression by performing tension-reducing, affiliative and appeasement behaviors. Preliminary analyses indicate that the "coping model" is a more accurate predictor. General rates of aggression did not differ significantly across spatial conditions, while appeasement and affiliative behaviors, such as grooming, were more frequent at higher population densities. The findings are of theoretical importance because they contrast with the commonly-held, but often unsupported, assumption that primates are more aggressive at higher population densities. The findings also have theoretical significance because they show the capacity of primates to adapt to environmental conditions, such as relative crowding, by modifying their social behavior. The results have applied and practical significance because studies that reveal how animals respond to their various captive environments will provide guidelines for maintaining animals under social conditions which optimize psychological well-being.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Post-occupancy Evaluation of Gorilla Exhibits

AXIS I: 1a

AXIS II: 36, 54b

PRC UNIT: Behavioral Biology

INVES1: Forthman, Debra L.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Maple, Terry L.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Gorilla gorilla gorilla
NUM1: 17

NON-HOST INST: Atlanta/Fulton County Zoo, Inc.

ABSTRACT: The continuing, post-occupancy evaluation of the naturalistic gorilla habitats at Zoo Atlanta has entered another phase. In an effort to facilitate reproduction in some of the females which have not recently given birth, to promote pairings in accordance with the gorilla Species Survival Program, and to continue efforts to produce offspring sired by Zoo Atlanta's founder male, Willie B., a series of gorilla moves was initiated by the Yerkes Center and Zoo Atlanta. The process of acclimation during these changes was monitored by the methods used during the previous phases of this long-term project. First, Molly, the female acquired from the Audubon Zoo, was gradually introduced to Rann's group. Next, three of the groups were shifted among exhibits: Willie B.'s group was moved to Rann's habitat (I), Rann's group was moved to Calabar's habitat (IV), and Calabar's group was moved to Willie B.'s habitat (II). Ozoum's group remained in habitat III. Following these moves, selected females were exchanged among groups, simulating natural female emigration. All introductions were accomplished in gradual stages. To date, Choomba and Shamba have been moved to Willie B.'s group with Katoomba and Kinyani. Since the introduction of Choomba, Willie B. has mated with her during each estrus. Kuchi and Stadi were moved to Rann's group, and Taz, Shamba's infant, remained in Rann's group when his mother was transferred to Willie B.'s group. The only remaining, scheduled moves are Katoomba to Rann's group and Banga to Ozoum's group.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Managed Breeding Program in Support of AIDS Animal Model Project

AXIS I: 1a, 17, 23

AXIS II: 31, 36, 58

PRC UNIT: Behavioral Biology

INVES1: Gordon, Thomas P.
DEGREE1: M.S.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Gust, Deborah A.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Cercocebus atys
NUM1: 100

SPECIES2: Macaca mulatta
NUM2: 100

SPECIES3: Macaca nemestrina
NUM3: 100

NON-HOST INST: NA

ABSTRACT: The principal objective of this project is to maintain 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 and ensure long-term colony survival. In association with these activities, various supportive programs are in place to provide for behavioral management, serum banking and genetic analyses. Breeding productivity was excellent in sooty mangabeys (Cercocebus atys) and rhesus monkeys (Macaca mulatta), but suboptimal in the pigtail macaques (Macaca nemestrina) which exhibited higher than normal levels of neonatal loss. The recently-acquired pigtail macaques showed reproductive rates which were superior to the long-held subgroup. Consequently, the first priority in the genetics area will be to characterize the differences between these populations to determine whether variability may be low in the pigtail macaques derived from the long-term resident group. A private laboratory has been consulted to conduct DNA analyses of the pigtail macaques, and preliminary studies identifying effective probes for this species have been concluded. Similar studies will be initiated with the mangabeys, which have not been characterized previously. A serum bank has been established with samples collected from two of the three species. A number of other studies have been conducted with the breeding populations, and these have been summarized in separate reports.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Social Modulation of Stress Response to Separation in Adult Female Rhesus Monkeys

AXIS I: 1a, 15, 17

AXIS II: 31, 36, 64

PRC UNIT: Behavioral Biology

INVES1: Gordon, Thomas P.
DEGREE1: M.S.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Gust, Deborah A.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: Human epidemiological studies have been the basis for the concept that social variables can modulate the effects of stress on the immune system, and this theory has been gaining increasing attention with positive results emerging from empirical studies using nonhuman primates over the last two decades. The objective of this study was to determine if social separation induces a stress response in adult, female rhesus monkeys and to assess whether the presence of familiar social partners modulates such effects. The subjects were members of a stable social group housed in an outdoor compound. In a counterbalanced design, each subject was removed from the group twice, at 6-week intervals, and was housed either alone or with a familiar partner for a 4-day period. Blood samples were obtained prior to and at 2 hours, 24 hours and 4 days following each separation and assayed for cortisol and absolute numbers of T-cell subsets. Removal to individual housing resulted in significant increases in cortisol levels and significant decreases in the numbers of CD4+ and CD8+ T cells. Differences from baseline values were evident at 2 hours and 24 hours, with recovery evident at 4 days following separation. Separation to housing with a companion also produced evidence of stress which, however, was significantly modulated in the majority of subjects. Behavioral data analysis did not reveal a specific pattern that was predictive of modulation. These results extend the separation stress paradigm to adults and provide an additional, but not conclusive, demonstration that social support modulates physiological response to stress.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Housing Change Affects Cortisol Levels & T Cell Subsets in Juvenile Rhesus Monkeys

AXIS I: 1a, 15

AXIS II: 31, 36, 64

PRC UNIT: Behavioral Biology

INVES1: Gordon, Thomas P.
DEGREE1: M.S.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Gust, Deborah A.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

INVES3: Wilson, Mark E.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: C

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

INVES5: Ansari, Aftab A.
DEGREE5: Ph.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: A growing literature has provided compelling evidence that factors associated with social life, and changes in the social environment, may lead directly to alterations in immune function and, thus, to increased susceptibility to pathogens. Furthermore, steroid hormones, acting as immunoregulators, are known to affect immune function. Psychosocial stress associated with the transfer of six naive, juvenile rhesus monkeys from their natal social group to peer housing resulted in increased basal cortisol secretion and significant decrements in the absolute numbers of the T lymphocyte subsets in the peripheral blood. Six subjects matched for age and social rank remained in the group of 80 animals serving as controls. Baseline immune and cortisol measurements were obtained before the six test subjects were removed from the group and housed together in an outdoor, circular enclosure. Blood samples

were taken 24 hours following removal of the test subjects from the group and at intervals thereafter through 11 weeks. Compared to controls, test subjects showed a significant decrease in the absolute numbers of CD4+ (-56.9%) and CD8+ T cells (-57.6%) and a significant increase in basal cortisol levels (+43.9) 24 hours following removal to peer housing. Group difference in the absolute numbers of most immune cells persisted through 11 weeks, whereas cortisol differences lasted only through 2 weeks. These data, when compared to an earlier study employing an identical protocol except that subjects were housed in indoor, individual cages following separation, fail to demonstrate a modulating effect of randomly chosen peer-mates on the stress effect produced by social separation.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Ontogeny and Function of Primate Vocal Signatures

AXIS I: 1a

AXIS II: 36, 40

PRC UNIT: Behavioral Biology

INVES1: Gouzoules, Harold T.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Gouzoules, Sarah, M.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Macaca nemestrina
NUM1: 45

NON-HOST INST: NA

ABSTRACT: Previous research by these investigators revealed that acoustically-distinct macaque screams, which elicit support from allies in the group during agonistic encounters, encode specific information about an opponent (such as its relative dominance rank and, in the case of rhesus macaques, its relatedness to the caller) and the intensity of the attack. In order for a monkey to use a contextually-correct call, it must have knowledge about the network of kinship and dominance relationships within its group. The same is true for an ally hearing the call. Consistent with these requirements, it was found that gradual attainment of proficiency characterizes both scream usage and scream production. Individual vocal recognition of callers is critical to this system of agonistic recruitment. Vocalizations are likely to have multiple referents; therefore, pigtail macaque screams were analyzed for evidence of vocal signatures that might characterize and, perhaps, serve to identify matrilineal kin groups. In addition to information about the external agonistic context, these calls can also convey information about kinship. Matrilineal kinship is often a major factor underlying primate agonistic alliance formation, and evidence from this research indicates a recognition system in the recruitment screams of pigtail macaques. This work will focus on the source of morphological detail that characterizes these vocal signatures in pigtail macaque screams. The screams of foster-reared and natural infants will be studied to establish the developmental origins of the vocal signatures. The overall goal of the program is to understand the function and ontogeny of nonhuman primate vocal communication in complex social contexts. The long-term aim is to explore cognitive dimensions of primate behavior that ultimately may provide insights into the evolutionary origins of human language. These studies will also contribute to a better understanding of the criteria for appropriate primate models for studies of language acquisition.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Conflict Resolution and Social Dominance Structure in the Sooty Mangabey

AXIS 1: 1a, 15, 23

AXIS 2: 36

PRC UNIT: Behavioral Biology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

SPECIES 1: Cercocebus atys
NUM1: 80

NON-HOST INST: NA

ABSTRACT: Sooty mangabeys exhibit a dominance hierarchy unrelated to matrilineal kinship except during the first years of life. A cross-sectional analysis showed that mangabeys from infancy to approximately three years of age rank just below their mothers, but subsequently achieve higher rank than their mothers. Although males and females typically begin to attain higher rank at the same age, males between the ages of 5-6 years ultimately rank above all females. A multiple-regression analysis showed that sex, age and maternal rank significantly predicted rank (multiple correlation coefficient = 0.73). No relationship existed between dominance rank of adult females and age or weight, nor between ranks of adult females and their younger, adult sisters. Consequently, the dominance system in this species initially depends on maternal rank, and later, upon sex and other unknown factors.

Behavior associated with conflict and conflict resolution and the individuals involved (kin versus non-kin) provide an important means for comparing social systems of different primate species. Aggression and its sequelae were studied in a captive group of sooty mangabeys for a total of 307 agonistic episodes. Most aggression did not involve contact (53%), and contact that did occur was controlled. Aid to victim was recorded during 4.4% of episodes in sooty mangabeys and 15.6% in rhesus monkeys in a comparison study. For mangabeys, victims involved in heavy aggression received aid more frequently than victims involved in light aggression. Interaction with opponents was initiated following aggression during 55% of post-conflict sessions versus 2% of controls. The most common victim-initiated interaction was returning to or remaining within 1 m of the aggressor (94%). Kinship did not influence frequency of interactions following aggression. Thus, sooty mangabeys do not inhibit damaging aggression under stable, social conditions, aid to the victim is infrequent, and non-aggressive interactions between opponents occur following most agonistic episodes without regard to kinship.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Response of Juvenile Sooty Mangabeys to Maternal Reunion

AXIS 1: 1a, 15, 23

AXIS 2: 36

PRC UNIT: Behavioral Biology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES 1: Cercocebus atys
NUM1: 20

NON-HOST INST: NA

ABSTRACT: The return of six juvenile sooty mangabeys to their social group following an absence of one year resulted in increased basal cortisol secretion for both the offspring and the mothers and in significant decrements in the absolute number of lymphocyte subsets for the offspring. Six 9-month-old sooty mangabeys were removed from their socially-housed mothers, subsequently peer-housed, and then returned to the maternal social group one year later. The offspring showed a significant increase in cortisol levels 24 hours following reunion (48 $\pm$ 6%), and this difference persisted through one month, while the mothers showed a significant increase only at the 24-hour sample point (18 $\pm$ 3%). Moreover, the offspring, but not the mothers, showed a significant decrease in lymphocyte subsets which were evident through the one-month sample point. Behavioral data revealed a significant positive correlation between the percent of total scan samples the offspring were with their mothers (proximity, contact, huddle) on the day of return and the offspring's percent change from baseline in total T cells 24 hours later ($r = 0.84$). All mother-offspring pairs, with the exception of one, exhibited frequent affiliative behaviors toward one another by six days following the return. These data demonstrate that the reunion of juvenile mangabeys with their mothers after a year's absence is an acute stressor for the mothers and a relatively longer-term stressor for the offspring, and that behavioral interactions which characterize the return of individual subjects to the natal group can predict acute physiological responses.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Relationship between Social Variables and Pituitary Adrenocortical Activity

AXIS 1: 1a, 15

AXIS 2: 36, 64

PRC UNIT: Behavioral Biology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Wilson, Mark E.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: C

SPECIES 1: Macaca mulatta
NUM1: 16

NON-HOST INST: NA

ABSTRACT: Psychosocial stress in humans has been related to the occurrence or progression of certain diseases, and a positive social environment has been shown, in some cases, to ameliorate this effect. This study was designed to determine the specific social behaviors which can affect an endocrine-defined stress response, i.e. changes in serum cortisol. Subjects were members of one of two social groups of rhesus monkeys. One group was an established, long-term (eight years) group consisting of members that had from one to many kin, and the second group, consisting initially of unfamiliar animals, was formed five months prior to initiation of the present study. Blood samples were collected weekly, and a total of 16 hours of behavioral data were collected on each subject. For analyses, the year-long study was organized according to quarters (three months) with cortisol concentrations averaged and behavioral categories cumulated. Interestingly, when regression techniques were applied, neither group nor dominance rank was a predictor of cortisol levels, although when groups were analyzed separately, rank significantly correlated with cortisol levels in the established group, but not in the recently-formed group. Behavioral categories which combined to account for a significant proportion of the variance in cortisol levels were not identical over four quarters. Three of four quarters analyzed included an affiliative behavioral category in addition to aggressive, submissive and other behavioral categories. Results showed that reconciliatory behaviors occurred significantly more often following dyadic agonistic episodes in the recently-formed versus the long-term group. These data demonstrate that cortisol levels are influenced not only by negative interactions (receiving bites), but also by positive interactions (receiving grooms). Moreover, the tendency for reconciliatory behaviors to follow a larger percentage of aggressive interactions in the recently-formed group may account for the lack of a dominance rank/cortisol relationship.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Group Formation of Female Pigtail Macaques (Macaca nemestrina)

AXIS 1: 1a, 15

AXIS 2: 36, 64

PRC UNIT: Behavioral Biology

INVES1: Gust, Deborah A.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Wilson, Mark E.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: C

INVES4: Ansari, Aftab A.
DEGREE4: Ph.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

INVES5: McClure, Harold M.
DEGREE5: D.V.M.
DEPT5: Pathobiology and Immunobiology
STAFF5: C

SPECIES 1: Macaca nemestrina
NUM1: 16

NON-HOST INST: NA

ABSTRACT: Human epidemiological studies have suggested that social variables can modulate the effects of stress on the immune system. This concept has gained increasing attention with positive results emerging from empirical studies using nonhuman primates over the last two decades. Results from a previous study using rhesus monkeys suggested that receiving grooming positively affected recovery of T-helper and T-suppressor cells following initial stress associated with group formation, and this co-varied with high dominance rank. Thus, the present study was undertaken to determine (1) whether the stress effect of group formation could be replicated in another species and (2) given that formation is a stressor, whether social behaviors or dominance rank might correlate independently with physiological recovery from the stressor. Eight adult, female pigtail macaques were moved from individual cages and introduced into an outdoor enclosure along with an adult male, while eight weight-matched

controls remained in individual caging. Behavioral data were collected during the introduction and over four weeks thereafter. Blood samples were collected prior to and at intervals for four weeks following group formation. Compared to control subjects, test subjects showed an increase in basal cortisol secretion (+28.9%) and a significant decrease in T-helper cells (-33.6%), T-suppressor cells (-30.8%) and B cells (-22.5%), while there was a significant increase in white blood cells (+29.5%) 24 hours following group formation. When dominance rank and seven behavioral categories were analyzed, only frequency of receiving grooming significantly predicted change; animals that received a greater frequency of grooms showed a lesser negative percent change from baseline in absolute number of T-helper cells one week following group formation. Establishment of a dominance hierarchy, apparent within one week following group formation, was accomplished with no serious fighting and a complete absence of wounding or trauma, suggesting that psychosocial stress was responsible for the physiological changes observed.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Male Migration in Yellow Baboons in the Tana Primate Reserve

AXIS I: 1a

AXIS II: 34, 92 (behavioral ecology)

PRC UNIT: Behavioral Biology

INVES1: Smith, Euclid O.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

SPECIES1: Papio cynocephalus
NUM1: 78

NON-HOST INST: NA

ABSTRACT: During the past year, continuing behavioral observations were conducted on a troop of 78 yellow baboons (Papio cynocephalus) in the Tana River National Primate Reserve. The focus of attention has been on the evolution of male reproductive strategies, especially with regard to patterns of male dispersal. It is known that male dispersal is the hallmark of many mammalian species, but it is poorly understood as a life-history strategy. This study is attempting to collect detailed behavioral data on all adult males in the main study group and to make less intensive observations on two adjacent troops in the hope of documenting factors that influence males' first migration from their natal troop as well as factors that influence prime, aged males to move between groups. In addition, work is in progress to determine factors that may precede as well as follow a migratory event. To date, nearly 2,000 hours of focal observations have been collected on 12 adult males through December, 1992, This study is in the process of entering the last of the behavioral data, and plans for the coming year are to continue to analyze data collected previously.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Social Learning of Tool Use by Great Apes and Human Children

AXIS I: 1a

AXIS II: 36

PRC UNIT: Behavioral Biology

INVES1: Tomasello, W. Michael
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

SPECIES1: Pongo pygmaeus
NUM1: 8

NON-HOST INST: NA

ABSTRACT: In this study, orangutans (Pongo pygmaeus) were presented a rake-like tool and a desirable but out-of-reach object. The tool could be used in either of two ways: a simple but inefficient way, or a complex but efficient way. Subjects assigned to the Partial Model condition observed a human demonstrator perform the simple but inefficient procedure. Subjects assigned to the Full Model condition observed a human demonstrator perform the complex but efficient procedure. The results were compared with those obtained from chimpanzees and human children in a previous study. A follow-up study using a slightly different apparatus was also conducted. Results show that apes and humans learn socially from one another in different ways,. This may have implications for the way atypical children (e.g., autistic children) are able to learn from others.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: The Gestural Communication of the Yerkes Field Station Chimpanzees

AXIS I: 1a

AXIS II: 36

PRC UNIT: Behavioral Biology

INVES1: Tomasello, W. Michael
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

SPECIES1: Pan troglodytes
NUM1: 18

NON-HOST INST: NA

ABSTRACT: Common chimpanzees (Pan troglodytes) were observed during natural interactions while in their enclosure at the Yerkes Field Station. This is the third longitudinal time point on this group. Data were analyzed to determine whether chimpanzees "transmit" their gestures across generations, or whether each individual conventionalizes its own gestural repertoire. Results show that chimpanzees do not culturally transmit gestures across generations. The implication suggests that humans have special abilities to learn and use communicative symbols, and the processes by which they do so may be specified so as to have implications for children who have difficulty learning language.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Social Integration of Adult Male and Female Rhesus Macaques: Role of Female Hormonal Status

AXIS I: 1a, 15, 23

AXIS II: 36

PRC UNIT: Behavioral Biology

INVES1: Wallen, Kim
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

SPECIES1: Macaca mulatta
NUM1: 10

NON-HOST INST: NA

ABSTRACT: The role of female hormonal status in social integration was investigated in a social group of ten adult male and six adult, ovariectomized female rhesus monkeys. The group was formed three years prior to initiation of the present study. The females had lived as a unit since birth and were removed from their natal social group three years before introduction of the males. All males were from the same natal group, were removed as a unit and housed with the ovariectomized females at 3.5 years of age, and were six years old at the start of the study. After 2.5 years of social housing, males and females were not socially integrated. Although affiliative interactions occurred within each sex group, the only interactions across sexes were female agonistic behaviors and male avoidance behaviors. After three years of social housing, the ovariectomized females received either daily injections of estradiol or estradiol-bearing silastic capsules. Either treatment elevated serum estradiol levels to the mid-follicular range (125-175 pg/ml). Within three days after initiation of estradiol treatment, social integration of the sexes occurred. Heterosexual affiliative behavior (grooming; sitting in proximity) and copulatory behavior were seen for the first time. Females received two three-week periods of estradiol treatment during the spring, summer and fall, with predictable increases in sexual behavior with each treatment period. Six months after the last estradiol treatment, affiliative behavior remained significantly elevated over pretest levels and was not significantly lower than during estradiol treatment. Rate of sexual behavior was significantly lower without estradiol treatment. These results support a role for female hormonal status in heterosexual integration. The finding that affiliation remained elevated months after cessation of hormonal therapy suggests that social integration is a permanent or semi-permanent social change. Hormones facilitate its occurrence, but social mechanisms are responsible for its maintenance.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Influence of Social Factors on the Acquisition of Learning Set Formation

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Behavioral Biology

INVES1: Wallen, Kim
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Drea, Christine
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 55

NON-HOST INST: NA

ABSTRACT: An innovative technique was used to investigate learning in subsets of a 55-member social group. The group, having six matrilines with comparable numbers of subjects in the three top and three bottom matrilines, was trained to split upon command into two halves between the third- and fourth-ranking matrilines, enabling study of the complete group, high-ranking matrilines and low-ranking matrilines separately. Subjects were trained on two color-discrimination problems either in their matrilineal groups or in the whole group. Subjects trained under one social condition were subsequently tested on a given color discrimination under the other social condition to determine how social rank influences acquisition of color discrimination. Low-ranking subjects acquired color discrimination as rapidly as high-ranking subjects when high-ranking subjects were not present, but showed no color-discrimination learning when given a task in the whole group. When low-ranking subjects were tested in the presence of high-ranking subjects on the discrimination learned without high-ranking animals, low-ranking subjects performed at chance level. When tested on the color discrimination to which they were exposed in the whole group without the high-ranking animals, low-ranking animals showed clear evidence of having learned the discrimination. These results show that social conditions can influence performance of color discrimination but do not appear to influence discrimination learning. Furthermore, they demonstrate that low-ranking animals learned the color discrimination in the whole group but never expressed this learning until tested in the absence of high-ranking animals. Since aggression and harassment were infrequent between high- and low-ranking animals, these results suggest that failure to perform resulted from low-ranking animals' knowledge that they would be prevented from interacting with goal boxes and their acceptance of this social condition.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Steroid Binding, Estrogen Availability and Female Sexuality

AXIS I: 1a, 15, 23

AXIS II: 36, 62

PRC UNIT: Behavioral Biology

INVES1: Wallen, Kim
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: C

INVES2: Wilson, Mark E.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 9

NON-HOST INST: NA

ABSTRACT: The role of androgens in female primate sexual behavior is unclear. Evidence from humans and rhesus monkeys suggests that adrenal androgens are important for female sexual interest. Recent work in this laboratory has demonstrated that adrenal function is not required for normal sexual behavior in group-living female rhesus monkeys; however, a role for ovarian androgens cannot be ruled out. Studies of steroid replacement therapies in ovariectomized human females strongly suggest that androgens are needed to reinstate female sexual desire. Research is underway to test the hypothesis that levels of bioavailable estradiol are dynamically modulated by levels of sex hormone-binding globulin (SHBG) and the androgens, testosterone and dihydrotestosterone (DHT). The role of DHT in displacing SHBG-bound estradiol was investigated by comparing the effects of administering injections of oil, 10.0 μg/kg DHT or 7.5 μg/kg estradiol to seven ovariectomized females bearing silastic estradiol capsules that produced about 125.0 pg/ml blood levels of estradiol. In a counterbalanced manner, each female received all hormonal treatments during the course of the study. All females lived in a 75-member social group in which they had been born and raised. Female sexual behavior was reinstated by all of the hormonal treatments. The estradiol capsules partially restored female sexual behavior; however, both the estradiol injection and the DHT injection significantly increased female sexual initiation above the level produced by the estradiol capsule alone. These data support the hypothesis that DHT can increase the bioavailable estrogen and support a role for endogenous androgens in regulating estradiol bioavailability.

SECTION ON LANGUAGE, COGNITION AND NEUROPSYCHOLOGY

Duane M. Rumbaugh, Ph.D., Section Head

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

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: 40

SPECIES2: Pan paniscus
NUM2: 11

SPECIES3: Pongo pygmaeus
NUM3: 9

SPECIES4: Macaca mulatta
NUM4: 36

NON-HOST INST: NA

ABSTRACT: Two studies were conducted to assess hand preference as a function of bipedal or quadrupedal posture in 40 chimpanzees, 9 orangutans and 11 bonobos. Results indicate a significant shift toward population-level right-handedness when subjects reached from a bipedal versus a quadrupedal posture. Analysis of a larger data set revealed a strong heritability effect for hand preference in the chimpanzees. Predicting offsprings' hand preference was highly significant. This effect was evident for offspring reared both with and apart from the biological mother. A developmental study of hand preference for simple reaching was performed on 39 infant chimpanzees aged 2-5 years. Results indicated a significant rearing effect, with nursery-reared chimpanzees showing higher levels of right-handedness than mother-reared chimpanzees. Moreover, younger infants showed higher percentages of right-handedness.

In a study of hand use and throwing in 36 chimpanzees, significantly more chimpanzees threw with the right hand, and right-handed throwing was almost exclusively linked to a bipedal posture while throwing. Hand preference in joystick manipulation was studied on 36 rhesus monkeys. Results indicate an even distribution of left- and right-handedness for joystick use, but right-handed monkeys learned faster and performed significantly better on two psychomotor tasks. Data are being analyzed on the relation between hand preference and object manipulation in chimpanzees.

An examination of laterality in processing meaningful and non-meaningful symbols in language-trained chimpanzees was completed. Subjects processed and

responded faster when meaningful symbols were presented to the left rather than the right hemisphere. Another study using a recognition paradigm showed that meaningful symbols were processed better by the left hemisphere. Asymmetries in facial expressions was examined in eight chimpanzees; preliminary data analysis indicates clear asymmetries in facial morphology and facial expression. Finally, six experimentally-naive chimpanzees were trained on the joystick-testing paradigm prior to initiating neuropsychological testing.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Bio-behavioral Studies of Language and Cognition: Program Project

AXIS I: 1a, 5a, 5b

AXIS II: 36, 40, 41, 92 (comparative psychology)

PRC UNIT: Behavioral Biology

INVES1: Rumbaugh, Duane M.
DEGREE1: Ph.D.
DEPT1: Behavioral Biology
STAFF1: O

INVES2: Savage-Rumbaugh, E. Sue
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Romski, Mary Ann
DEGREE3: Ph.D.
DEPT3: Behavioral Biology
STAFF3: O

INVES4: Morris, Robin D.
DEGREE4: Ph.D.
DEPT4: Behavioral Biology
STAFF4: O

SPECIES1: Pan troglodytes
NUM1: 5

SPECIES2: Pan paniscus
NUM2: 4

SPECIES3: Homo sapiens
NUM3: 43

NON-HOST INST: Georgia State University (DMR, MAR, RDM)

ABSTRACT: In effect, all operations of the Language Research Center that had been supported, in part, by the Yerkes Center base grant (RR00165) were transferred from Emory University to Georgia State University on June 1, 1992. That date was the occasion for the transfer of Grant #HD06016 from the Yerkes Regional Primate Research Center of Emory University to the College of Arts and Sciences, Georgia State University. Support of the Language Research Center's program by Grant #P51RR00165 terminated at that time.

Because only five months of research conducted during 1992 received partial support from the Yerkes Center base grant, a conventional progress report is not feasible. Notwithstanding, a list of publications which have appeared since last year's report and which credit Grant #RR00165 is provided. Other publications which credit Grant #RR00165 and that are scheduled to appear in the future will be forwarded to the Yerkes Center in future reports.

DIVISION OF NEUROBIOLOGY

Johannes Tigges, Ph.D., Chief

Core Faculty:

R. G. Boothe
J. G. Herndon
F. A. King
J. W. Tigges
M. H. Tigges
J. R. Wilson

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R. A. E. Bakay	Department of Neurological Surgery, Emory University
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K. L. Boyer	Department of Neurological Surgery, Emory University
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M. L. Feldman	Department of Anatomy, Boston University
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J. B. Justice	Department of Chemistry, Emory University
P. R. Kennedy	Bioengineering Center, Georgia Institute of Technology
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Consultants:

H. M. Eggers	Department of Clinical Ophthalmology, Columbia University
H. Warner	Consultant, Biomedical Engineering
J. P. Wilmeth	Anderson Eye and Ear Associates, Anderson, South Carolina

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Safety and Efficacy of Neural Grafting for the Treatment of Parkinsonism

AXIS I: 1a, 1d, 6, 9, 19, 21

AXIS II: 30, 36, 46, 50a, 64, 88

PRC UNIT: Neurobiology

INVES1: Bakay, Roy A.E.
DEGREE1: M.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Watts, Raymond L.
DEGREE2: M.D.
DEPT2: Neurobiology
STAFF2: O

INVES3: Iuvone, P. Michael
DEGREE3: Ph.D.
DEPT3: Neurobiology
STAFF3: O

INVES4: Ansari, Aftab A.
DEGREE4: Ph.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: The objective of this study is to determine if transplantation of fetal neural tissue into the central nervous system can be safely used in primates to correct the fixed neurological deficits associated with parkinsonism. The successful CNS transplantation requires anatomical integration of the graft with the host which results in a permanent clinically significant behavioral improvement. At the present time we do not know the relative degree of risk for immunological rejection. Human studies are unable to answer the sophisticated questions required to determine the potential for rejection of CNS grafting and therefore nonhuman primate studies are needed.

MPTP-induced Parkinson-like syndrome in nonhuman primates is an excellent model to test both the surgical technique and immunological tolerance of central nervous system grafts. Behavioral and biochemical assessments are made on each animal prior to administration of MPTP subsequent to stabilization of a parkinson-like state, and following grafting. Control studies using trauma or non-dopaminergic tissue have also been initiated. At the conclusion of these behavioral studies, anatomical assessment is performed to determine the effectiveness of the graft host integration, severity of the

induced Parkinson disorder, and determination of the immunological response. In addition to anatomical studies, lymphocytotoxic assays of host vs. graft (fetal immortalized cultures) are used to assess both systemic (blood, spleen, and lymph nodes) and local (brain tissue) evidence for rejection.

Preliminary results suggest that there is no systemic or local immunological response to fetal tissue grafts that is any different from control needle injuries. Attempts at secondary rejection through systemic presentation of fetal tissue is currently being tested.

If the mechanism of rejection in nonhuman primates can be defined, techniques developed to prevent rejection can then be developed. If neurological deficits can be successfully improved in this model with little risk to the host, the implications are extremely important not only for potential treatment of parkinsonism but also for other neurological diseases that have neurochemical deficiencies correctable by central nervous system grafting.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: CNS Grafting for Parkinsonism

AXIS I: 1a, 1d, 6, 9, 19, 21

AXIS II: 30, 36, 46, 50a, 64, 88

PRC UNIT: Neurobiology

INVES1: Bakay, Roy A.E.
DEGREE1: M.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Byrd, Larry D.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Watts, Raymond L.
DEGREE3: M.D.
DEPT3: Neurobiology
STAFF3: O

INVES4: Iuvone, P. Michael
DEGREE4: Ph.D.
DEPT4: Neurobiology
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 18

NON-HOST INST: NA

ABSTRACT: The objective of this research project is to determine whether central nervous system grafts can be successfully transplanted into the central nervous system of nonhuman primates and improves its neurological deficits. The model uses the administration of MPTP to selectively destroy dopaminergic cells in the substantia nigra which results in a movement disorder which is analogous to parkinsonism. The MPTP-induced Parkinson-like syndrome is an excellent model for testing CNS transplantation in nonhuman primates in order to identify factors which can produce behavioral improvement. Preliminary studies have demonstrated the potential for correcting the parkinsonian-like symptoms using either adrenal medullary tissue or fetal mesencephalic tissue. It is, however, not at all clear which of these tissues produces the greatest degree of improvement. This is the first side-by-side comparison of behavior improvement resulting from these two different types of tissue.

Specifically, we are evaluating cografting technique which uses both adrenal medullary and peripheral nerve tissue. The peripheral nerve tissue, when cografted with the adrenal medullary tissue, greatly enhances the adrenal medullary tissue survival and conversion to a neuronal morphology.

Stereotactic techniques are being employed to place the grafts in multiple locations in the caudate and putamen. These grafts will be compared to fetal mesencephalic grafts implanted in the same areas, using the same techniques. The surgical controls will have the needed passages without deposition of tissue. The behavior comparative studies are anticipated to start on April 1, 1993.

This study should have sufficient number of animals to predict statistical determination of the difference between the two grafting techniques. The results of this comparison should have important implications for future clinical studies.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Naturally Occurring Strabismus in Primates

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

INVES2: Eggers, Howard M.
DEGREE2: M.D.
DEPT2: Neurobiology
STAFF2: O

INVES3: Tychsen, Lawrence
DEGREE3: M.D.
DEPT3: Neurobiology
STAFF3: O

INVES4: Hoffmann, Klaus-Peter
DEGREE4: Ph.D.
DEPT4: Neurobiology
STAFF4: O

SPECIES1: Macaca nemestrina
NUM1: 8

NON-HOST INST: Columbia University (HME), Washington University School of Medicine (LT), Ruhr Universitat Bochum, Germany (KPH)

ABSTRACT: Strabismus, or crossed eyes, is a very prevalent disorder in human children. It would be very advantageous to have an animal model with which to study this disorder. In previous years we have identified a number of monkeys that have a naturally occurring strabismus. However, one of the limitations we have encountered in trying to extrapolate results from this animal model to humans is that it is difficult to classify strabismic monkeys into groups that can be related to common syndromes that occur in humans. A major effort of this laboratory over the past several years has been put into making this classification. That task was completed during the past year in regard to characteristics of convergence misalignment. We have been able to relate the particular type of strabismus that is present in each of our animals to a human clinical syndrome. These results are now published (Quick, Eggers, and Boothe, 1992). We have now turned our efforts towards relating the accommodative errors that are present in these same animals to human syndromes involving accommodative convergence errors.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Induced Strabismus in Monkeys

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: In addition to studying monkeys that have a naturally occurring strabismus, we have been examining monkeys that were raised under various conditions of visual deprivation in order to determine whether an induced strabismus occurs similar to the deprivation-induced strabismus syndrome that occurs in human children who are subjected to visual deprivation from conditions such as cataracts, ptosis, eye infections, or injury. At last year's vision meetings we presented our results regarding the developmental time course of induced strabismus (Boothe and Gong, 1992). In addition, Michael Quick, a graduate student working in this laboratory, completed a doctoral dissertation on this topic. His dissertation titled "Experimentally induced monkey models of infantile strabismus" has been accepted by the graduate program in neuroscience at Emory University. The major results will now be prepared for publication in a refereed journal.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Aphakic Amblyopia Treatments that Involve Extended-Wear Contact Lenses

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

INVES2: Wilson, James R.
DEGREE2: Ph.D.
DEPT2: Neurophysiology/Neurobiology
STAFF2: C

INVES3: Tigges, Margarete
DEGREE3: Ph.D.
DEPT3: Neural Ultrastructure/Neurobiology
STAFF3: C

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

INVES5: Eggers, Howard M.
DEGREE5: M.D.
DEPT5: Neurobiology
STAFF5: O

SPECIES1: Macaca mulatta
NUM1: 8

NON-HOST INST: Columbia University (HME)

ABSTRACT: Our current studies of aphakic amblyopia are focused on trying to find optimal treatments that could be provided to human children that have an aphakic eye secondary to infantile cataract surgery. We are currently trying out a number of experimental groups that we think might be effective based on theoretical grounds. One experimental treatment group that we are studying involves using defocusing lenses instead of patching of the fellow eye. The rationale for these groups is that the monkey will be forced to use the aphakic eye, the same as when the fellow eye is patched, but the forced usage will depend on viewing distance instead of on whether or not the fellow eye is wearing the patch. We are rearing monkeys in two groups along these lines. One group is forced to use the aphakic eye to see close objects, and the fellow eye for focusing on distant objects. The opposite case is true for the

other group. Our hope, based on theoretical expectations from physiological optics, is that these treatment conditions may be less disruptive to binocular vision than patching. The reason for this expectation is that low spatial frequencies that are present at intermediate distances will be equally visible to both eyes. It is possible that this low spatial frequency stimulation will be sufficient to stimulate binocular function, and thus maintain orthophoria. The results obtained from animals in this group continue to be encouraging. Two monkeys that have completed testing exhibit acuity that is about 0.5 log units poorer than normals in their aphakic eyes and have essentially normal vision in their fellow eyes. These results are as good as those we have obtained previously from animals treated with 75% patching of the fellow eye. We are continuing to raise and test additional animals in these treatment groups.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Aphakic Amblyopia Treatments that Involve Intraocular Lens Implants

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

INVES2: Tigges, Margarete
DEGREE2: Neural Ultrastructure/Neurobiology
DEPT2: Ph.D.
STAFF2: C

INVES3: Lambert, Scott R.
DEGREE3: M.D.
DEPT3: Neurobiology
STAFF3: O

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

SPECIES1: Macaca mulatta
NUM1: 15

NON-HOST INST: NA

ABSTRACT: During the past year our laboratory has been collaborating with Dr. Scott Lambert on a study that involves using surgical methods to treat aphakic infants with intraocular implants instead of with extended wear contact lenses. Our lab has been involved in the behavioral assessment of the functional outcomes of animals reared in treatment groups that involve implants either with or without patching. Preferential looking results indicate that functional outcome over the first postnatal year compares favorably with the results obtained from our previous groups of animals treated with contact lenses. Preliminary results from this project were presented at last year's vision meetings (Lambert, Tigges, Boothe, Grossniklaus, 1992). This project is continuing, and we are now conducting long-term operant testing on these same animals.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Disruption of Binocular Vision by Alternating Monocular Defocus

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

INVES2: Harwerth, Ronald S.
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 3

NON-HOST INST: College of Optometry, University of Houston (RSH)

ABSTRACT: Our laboratory has been involved in a collaborative project with Dr. Ron Harwerth at the University of Houston College of Optometry for the past year. We are rearing infant monkeys with a -6 Diopter extended wear contact lens that is alternated between the left and right eyes on alternate days. The rationale for this treatment is that it will disrupt binocular functions without causing any amblyopia. Our measures of acuity and of stereopsis using preferential looking procedures confirm that the rearing condition has succeeded in disrupting binocular functioning but has led to equal acuity in each eye.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Establishing the Appropriateness of the Animal Model

AXIS I: 1a, 21, 25b

AXIS II: 36, 44, 60

PRC UNIT: Neurobiology

INVES1: Boothe, Ronald G.
DEGREE1: Ph.D.
DEPT1: Neuropsychophysics/Neurobiology
STAFF1: C

INVES2: Bard, Kim A.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 6

SPECIES2: Pan troglodytes
NUM2: 10

NON-HOST INST: NA

ABSTRACT: Our goal in all of these studies with animals is to establish and use an animal model in order to better understand and treat visual disorders that afflict humans. In order to accomplish that goal it is important to also include studies that establish that the animal studies do in fact provide an adequate model of the human condition. One step in establishing an animal model is to include normative studies. Previous studies in our laboratory have established that development of vision in infant monkeys is very similar to development of vision in human infants except that monkeys develop about four times faster. These results have resulted in what we refer to as the "weeks to months rule", which states that it is possible to extrapolate developmental results from monkeys to human infants by assuming that what happens at a particular age in weeks in monkeys will happen at a comparable age in months in humans. During the past year our lab has been working on this project in two ways.

First, we have been conducting a major statistical data analysis of monocular data that have been collected from normal monkeys over the past several years. This analysis is not trivial due to the fact that we collected the data on unassigned infants in the nursery on an "as available" basis. This design had the advantage that it allowed us to obtain a large normative sample that would not have been available if we had used animals more directly under our control. However, this design also had a disadvantage in that the data had to be collected at different ages in different subjects. This unbalanced design is not amenable to standard statistical methods of analysis and a major effort over the past year has been to work out the complicated procedures for analyzing these data in a statistically appropriate manner.

That data analysis is now almost complete, and it is expected that the results will be published within the next year.

Second, we have embarked on a project to assess longitudinal acuity development in chimpanzees in collaboration with the laboratory of Dr. Kim Bard. It is expected that chimpanzees should show a time course that falls in between that found in humans and in monkeys.

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TITLE: Seasonal Control of Behavior in Male Rhesus Monkeys

AXIS I: 1a, 2, 15

AXIS II: 36, 92, Neuroendocrinology

PRC UNIT: Neurobiology

INVES1: Herndon, James G.
DEGREE1: Ph.D.
DEPT1: Neuropsychobiology/Neurobiology
STAFF1: C

INVES2: Turner, Jane J.
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 22

NON-HOST INST: NA

ABSTRACT: Recent studies focused on mechanisms that control seasonality of reproductive events in the male rhesus monkey. The question being addressed is whether the seasonal cycle of reproduction is an endogenous one or whether it is driven directly by exogenous factors. The males were moved from outdoor housing (where they had exhibited normal seasonal breeding) to indoor quarters where more control of environmental variables was possible. Males were placed on both short (breeding) and long (nonbreeding) day photoperiods, the specific questions addressed included: (1) Whether interaction with females was necessary for the expression of physiological indices of sexual activation (e.g., testosterone elevations, increased testis size) normal to the mating season, and (2) Whether the absence of behavioral opportunities to males with females influenced the magnitude and timing, or even the expression of, subsequent behavioral and physiological seasonality. Work to date supports the possibility that the reproductive cycle in males is an endogenous one, that is, that the basic cyclic mechanism is little influenced by external factors. Supporting this view are: (1) the fact that the cycle was unaffected by the absence of females, and (2) the finding that artificial manipulations of the photoperiod were without effect upon the male reproductive cycle. We are now examining the effect of elimination of the post-mating lengthening of photoperiod on subsequent mating seasonality. This effort may contribute to an understanding of whether or not lighting conditions have a subtle influence on timing of the internal seasonal cycle. These studies are significant because they address fundamental issues in reproductive biology. They focus on the mechanisms for neuroendocrine control of reproduction in a species which shares many features of reproductive endocrinology with humans. Although the human reproductive seasonality which was evident in records prior to the Industrial Revolution has waned in the modern world, it remains possible that humans are subtly influenced by the same factors which influence rhesus breeding seasonality.

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TITLE: Delay of Stereoacuity Development in Monkeys by Full-time Alternate Occlusion

AXIS I: 1a, 21, 25b

AXIS II: 60, 62

PRC UNIT: Neurobiology

INVES1: Jampolsky, Arthur
DEGREE1: M.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Brown, Rick J.
DEGREE2: B.A.
DEPT2: Neurobiology
STAFF2: O

INVES3: Boothe, Ronald G.
DEGREE3: Ph.D.
DEPT3: Neuropsychophysics/Neurobiology
STAFF3: C

INVES4: Wilson, James R.
DEGREE4: Ph.D.
DEPT4: Neurophysiology/Neurobiology
STAFF4: C

INVES5: Tigges, Margarete
DEGREE5: Ph.D.
DEPT5: Neural Ultrastructure/Neurobiology
STAFF5: C

INVES6: Norcia, Anthony
DEGREE6: Ph.D.
DEPT6: Neurobiology
STAFF6: O

INVES7: Fernandes, Alcides
DEGREE7: M.D.
DEPT7: Neurobiology
STAFF7: O

SPECIES1: Macaca mulatta
NUM1: 2

NON-HOST INST: The Smith-Kettlewell Eye Research Institute (AJ, AN)

ABSTRACT: Purpose. To test the hypothesis that neonatal, full-time alternate monocular occlusion (AMO) is a "no-stimulus" condition for the binocular system, allowing developmental delay with normal binocular development upon

subsequent normal binocular visual experience. Methods. Stereoacuity was measured with preferential looking techniques. The stereo target consisted of vectographic random dot stereograms. Newborn rhesus monkeys were raised with AMO produced by opaque contact lenses changed from one eye to the other every 24 hrs starting from birth and lasting from 21-24 days of age. Results. Normal monkeys exhibit stereoacuity of 1760 arc secs by 21-28 days of age. This improves to 22 arc secs by about 70 days of age. One monkey with AMO exhibited stereoacuity of 1760 arc secs by 45 days of age. Stereoacuity improved to 22 arc secs by 84 days of age. A second monkey with AMO exhibited stereoacuity of 1760 arc secs by 56 days of age. Stereoacuity then improved to 22 arc secs by 77 days of age. Thus, two monkeys that had AMO from birth through a substantial part of the period of normal stereo development were able to, upon restoration of normal visual experience, develop normal stereoacuity. Monkeys reared with AMO for 112 days developed strabismus and had no stereopsis. Conclusions. The development sequence of stereopsis can be delayed relative to normal by short-term AMO. The 21-28 day age of onset of stereopsis in normal animals was delayed until 45-56 days after birth. The 70 day age to attainment of adult stereoacuity was delayed until 77-84 days of age. Thus, the rate of stereoacuity development was more rapid in the AMO monkeys. Longer periods of AMO in monkeys result in strabismus.

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TITLE: Long-Term Recording of Neural Signals from Monkeys

AXIS I: 1

AXIS II: 21

PRC UNIT: Neurobiology

INVES1: Kennedy, Philip R.
DEGREE1: M.D., Ph.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Tigges, Johannes
DEGREE2: Ph.D.
DEPT2: Neuroanatomy/Neurobiology
STAFF2: C

INVES3: Bakay, Roy A.E.
DEGREE3: M.D.
DEPT3: Neurobiology
STAFF3: O

INVES4: Howell, Leonard
DEGREE4: Ph.D.
DEPT4: Behavioral Biology
STAFF4: O

INVES5: Mirra, Sue
DEGREE5: M.D.
DEPT5: Pathobiology & Immunobiology
STAFF5: O

SPECIES1: Macaca mulatta
NUM1: 3

NON-HOST INST: Georgia Institute of Technology (PRK), VA Medical Center (SM)

ABSTRACT: The objectives are to determine (1) if neurotrophic substances can be used in the monkey to produce neural signals from the electrode, and (2) if single units can be controlled by the monkey. The significance of this research in primates is that it will allow monitoring of neural signals over long time periods for the study of motor control, sensory responses, sensori-motor integration, plasticity experiments in the motor and sensory systems with its attendant questions of learning and memory, the effects of pharmacological agents on cortical activity, and, not least, its possible role as a neural prosthetic controller. Eight electrode implants were made with a combination of neurotrophic substances (Matrigel and Nerve Growth Factor) inside the cone. Happily, signals were recorded from these implants. One electrode was implanted in a monkey here at Yerkes and prominent signals were

obtained that yielded separable single units. The other implants were made in two raccoons in another institution. In the first raccoon, four electrode implants produced signals in two of them, and in the second all three implanted electrodes produced signals. The technique of filling the electrodes with the factors was modified for the second implant. The monkey recordings were followed carefully every day until experiment termination. In this preparation, there was a stimulating electrode (two wires) placed within 1 cm of the cone electrode. This produced stimulation and/or inhibition of the recorded activity. For example, when given caffeine (3 mg/kg bolus, IM), the stimulation revealed a prominent single unit that fired only during and for a short period after stimulus offset. It did not fire in the control experiment the previous day, and only rarely when the monkey was at rest. These results suggest that the effects of various pharmacological agents on cortical activity can be measured directly.

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TITLE: Correction of Neonatal Monocular Aphakia with IOLS

AXIS I: 1a, 25b

AXIS II: 86

PRC UNIT: Neurobiology

INVES1: Lambert, Scott R.
DEGREE1: M.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Boothe, Ronald G.
DEGREE2: Ph.D.
DEPT2: Neuropsychophysics/Neurobiology
STAFF2: C

INVES3: Tigges, Margarete
DEGREE3: Ph.D.
DEPT3: Neural Ultrastructure/Neurobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 18

NON-HOST INST: NA

ABSTRACT: Monocular congenital cataracts are usually associated with a poor visual outcome. Factors which continue to limit the visual rehabilitation of these eyes after cataract removal include the less than ideal optical correction of the induced aphakia and amblyopia. This research project is a controlled study using a nonhuman primate model to evaluate the efficacy and safety of treating infants that have monocular congenital cataracts with intraocular lenses (IOLs). Its major objectives are to assess the effect of this treatment modality on: (1) visual acuity and contrast sensitivity using operant testing; (2) ocular growth; (3) long-term ocular complications evaluated clinically and histopathologically; and (4) neuroanatomical changes in the geniculostriate system using cytochrome oxidase histochemistry and parvalbumin and GABA immunoreactivity. These effects are being assessed in 5 groups of monkeys who are monocularly pseudophakic: 2 groups with monofocal IOLs, 2 groups with multifocal IOLs, and 1 group of monkeys treated with a new paradigm (i.e., a higher powered multifocal IOL with no additional optical correction of the pseudophakic eye or occlusion therapy of the fellow eye). One of the two monofocal IOL groups and one of the two multifocal IOL groups also receive occlusion therapy of the fellow eye. Correlations between clinical, behavioral and neuroanatomical outcomes will be assessed and compared across the treatment groups.

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TITLE: Comparative Neuropathological Study of Aged Primate Brains

AXIS I: 1a, 21

AXIS II: 30

PRC UNIT: Neurobiology

INVES1: Mirra, Suzanne S.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Gearing, Marla
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: O

INVES3: Tigges, Johannes
DEGREE3: Ph.D.
DEPT3: Neuroanatomy/Neurobiology
STAFF3: C

SPECIES 1: Pan troglodytes
NUM1: 3

SPECIES2: Macaca mulatta
NUM2: 4

NON-HOST INST: VA Medical Center (SSM, MG)

ABSTRACT: Aged primates provide important models for the investigation of aging changes and Alzheimer's disease in humans. Although there have been many studies of the brains of aged mammals, neuropathological studies of aged great apes have been limited. We had the opportunity to examine the brains of three elderly chimpanzees: a male aged 45 years, a female aged 56 years, and a 59-year-old female, the oldest known chimpanzee. We compared the brain changes to those seen in four female rhesus monkeys aged 20 to 30 years. Gross examination of the brains of the older chimpanzees and rhesus monkeys revealed discoloration in the globus pallidus and substantia nigra, corresponding to iron deposition and swollen axons previously described in macaques (Bronson et al., J. Neuropath. Exp. Neurol. 1980;39:181); the dentate nuclei in a 30-year-old rhesus monkey showed similar changes. Silver stains and immunohistochemistry revealed βA4 amyloid deposition in plaques in cortex and hippocampus, and in meningeal and cortical blood vessels, more striking in the older animals of both species. The brains of the older chimpanzees exhibited prominent amyloid angiopathy by light and electron microscopy as well as occasional diffuse plaque-like structures on silver and amyloid stains. In contrast, the cortex of the elderly rhesus monkeys displayed numerous neuritic plaques with dense bodies and mitochondria in swollen neurites often associated with fibrillar amyloid; amyloid angiopathy was also seen in some animals. The neuritic plaques in the rhesus monkey demonstrated

considerably more APP (amyloid precursor protein) immunoreactivity than the diffuse plaque-like structures observed in the chimpanzees. Neurofibrillary tangles and/or paired helical filaments were not observed in any animals. Although the number of elderly chimpanzee brains thus far examined is small, this preliminary study suggests that species differences may modulate amyloid deposition and plaque formation. Understanding these differences may help us to understand related changes in human aging and Alzheimer's disease.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Monocular Enucleation Effects on Calbindin 28 kD in the LGN of Rhesus Monkey

AXIS I: 1a, 21, 25b

AXIS II: 60, 62

PRC UNIT: Neurobiology

INVES1: Mize, R. Ranney
DEGREE1: Ph.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Luo, Qian
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: O

INVES3: Tigges, Margarete
DEGREE3: Ph.D.
DEPT3: Neural Ultrastructure/Neurobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 11

NON-HOST INST: Louisiana State University Medical Center (RRM, QL)

ABSTRACT: The calcium-binding proteins calbindin (CaBP) and parvalbumin (PV) are important in regulating intracellular calcium in brain cells. PV immunoreactivity is reduced by enucleation in the lateral geniculate nucleus (LGN) and by enucleation and visual deprivation in the striate cortex of adult monkeys. The effects of enucleation and visual deprivation on CaBP immunoreactivity in the LGN are not known. We therefore have studied cells and neuropil in the LGN that are labeled by antibodies to CaBP in normal and visually deprived rhesus monkeys. In normal monkeys, CaBP-immunoreactive neurons were found throughout the LGN. They were sparsely distributed within the layer S and the interlaminar zones (ILZ). The labeled ILZ neurons had a distinct morphology, with fusiform somata and elaborate dendritic trees that were confined primarily to the ILZ. Most CaBP-labeled neurons in the main layers had dendrites that radiated in all directions from the soma. ILZ and main layer cells labeled by CaBP thus probably represent two different cell types. Monocular enucleation with or without occlusion produced a significant reduction in antibody labeling in the deafferented laminae. Field measures revealed an average 11.5% reduction in optical density in each deafferented lamina compared to its adjacent, nondeprived layer. The differences in field optical density between deprived and nondeprived layers were statistically significant. CaBP neurons were still visible, but the optical density of antibody labeling in these cells also was reduced. Occlusion without enucleation had no effect. Thus, deafferentation, but not light deprivation,

reduces concentrations of CaBP in monkey LGN. This effect is different than that seen in striate cortex of adult monkeys, where visual deprivation as well as enucleation alters CaBP immunoreactivity. All animals have also been used in neuroanatomical studies of the striate cortex and SC, in behavioral testing by Dr. R. Boothe and in axial length measurements of the eye to investigate postnatal eye growth.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: NPY in the Visual Cortex of Chimpanzee

AXIS I: 1a, 21

AXIS II: 30

PRC UNIT: Neurobiology

INVES1: Mori, Shiro
DEGREE1: M.E.
DEPT1: Neurobiology
STAFF1: O

INVES2: Tigges, Johannes
DEGREE2: Ph.D.
DEPT2: Neuroanatomy/Neurobiology
STAFF2: C

INVES3: Tigges, Margarete
DEGREE3: Ph.D.
DEPT3: Neural Ultrastructure/Neurobiology
STAFF3: C

SPECIES1: Pan troglodytes
NUM1: 4

NON-HOST INST: NA

ABSTRACT: The purpose of this study was to determine the distribution and morphology of NPY+ neurons and fibers in area 17 of 4 chimpanzees (15 to 56 years old) and to compare the results with those in other primates. The NPY+ neurons are nonpyramidal cells, which are either multipolar, bipolar, or bitufted in shape. They occur most frequently in layer 6 and the subjacent white matter, are sparser in the supragranular layers, and are few in layer 4. The somata of NPY+ cells in the supragranular layers are significantly smaller than those in infragranular layers. The axon originates either from the NPY+ soma or from a primary dendrite. The distribution and morphology of NPY+ neurons are similar in the youngest and the oldest chimpanzee. The shape of NPY+ neurons, however, changes slightly with aging. The density of NPY+ fibers varies with laminar position. A distinct plexus extends through the upper part of layer 4 and the lowest aspect of layer 3. In the lowest part of layer 4, a thin fiber band is found. In the superficial layers, "snarls" of fibers appear. These results show that the morphology and distribution of NPY+ neurons and processes in chimpanzees are, in general, similar to that seen in rhesus monkeys and humans. Note: No chimpanzee was specifically sacrificed for this project.

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TITLE: Neural Substrates of Cognitive Decline in Aging Monkeys

AXIS I: 1a

AXIS II: 30, 41

PRC UNIT: Neurobiology

INVES1: Moss, Mark B.
DEGREE1: Ph.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Rosene, Douglas L.
DEGREE2: Ph.D.
DEPT1: Neurobiology
STAFF2: O

INVES3: Herndon, James G.
DEGREE3: Ph.D.
DEPT3: Neuropsychology/Neurobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 20

NON-HOST INST: Boston University School of Medicine (MMB, DLR)

ABSTRACT: This project centers exclusively on the behavioral changes that accompany aging in the monkey. It will be focused primarily on the cognitive domains of cognitive flexibility ("executive function") and memory. These two areas are known to undergo significant decline in normal human aging and to a greater extent in several types of dementia. The anatomical loci that underlie these functions are believed to be the prefrontal association cortex and the temporal lobe limbic system, respectively. Our overall hypothesis, that impairments in these functions result from synaptic dysfunction or disconnection rather than overt cell loss, are being tested by correlating age-dependent cognitive decline in the two identified behavioral domains with the anatomical, neurochemical and metabolic measures that will be obtained from the dorsolateral prefrontal cortex and the temporal lobe limbic system in the same monkeys. Accordingly, in this project, all monkeys (except five "pilot" animals) are undergoing a battery of behavioral tests designed to assess cognitive flexibility and memory function as well as other cognitive areas. In our attempt to parallel closely our studies in aged monkeys to those in aged humans, many of the tasks to be used are derived from those administered clinically to geriatric patients. Similarly, one of the tests in monkeys developed in our laboratory is now used widely as an early measure of early memory dysfunction in aged adults with suspected dementia. In another phase of this project, we are assessing cognitive function longitudinally in a group of five young (5-9 yrs) monkeys and compare their course to a group of five middle aged (20-24 yrs) monkeys.

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TITLE: Neural Substrates of Cognitive Decline in Aging Monkeys

AXIS I: 1a, 21

AXIS II: 30, 36, 41, 46

PRC UNIT: Neurobiology

INVES1: Peters, Alan
DEGREE1: Ph.D.
DEPT1: Neurobiology
STAFF1: O

INVES2: Rosene, Douglas L.
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: O

INVES3: Moss, Mark B.
DEGREE3: Ph.D.
DEPT3: Neurobiology
STAFF3: O

INVES4: Abraham, Carmela
DEGREE4: Ph.D.
DEPT4: Neurobiology
STAFF4: O

INVES5: Hyman, Brad
DEGREE5: M.D., Ph.D.
DEPT5: Neurobiology
STAFF5: O

INVES6: Kemper, Thomas
DEGEEE6: M.D.
DEPT6: Neurobiology
STAFF6: O

INVES7: Tigges, Johannes
DEGREE7: Ph.D.
DEPT7: Neuroanatomy/Neurobiology
STAFF7: C

INVES8: Volicer, Lavislav
DEGREE8: M.D., Ph.D.
DEPT8: Neurobiology
STAFF8: O

SPECIES1: Macaca mulatta
NUM1: 4

NON-HOST INST: Boston University School of Medicine (AP, DLR, MBM, CA, BH, TK, LV)

ABSTRACT: Monkeys of various ages, but largely 5-10 years of age, and over 25 years of age are behaviorally tested to determine if there is any memory loss or change in executive function. The brains of the monkeys are then examined to ascertain if there are any features that can be correlated with the behavioral results. Although some senile plaques develop with age, results so far suggest that there are no losses of neurons with age in the visual, motor and prefrontal cortices, or in the hippocampus. The brain stems are now being examined and assessments are also being made of alterations in the levels of neurotransmitters, and of amyloid. We have just completed the second year of funding of this program project, which is being supported by NIA.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Synapses Deep in the Dentate Gyrus Throughout Adulthood of Rhesus Monkey

AXIS I: 1a, 21

AXIS II: 30

PRC UNIT: Neurobiology

INVES1: Tigges, Johannes
DEGREE1: Ph.D.
DEPT1: Neuroanatomy/Neurobiology
STAFF1: C

INVES2: Herndon, James G.
DEGREE2: Ph.D.
DEPT2: Neuropsychology/Neurobiology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 9

NON-HOST INST: NA

ABSTRACT: The aim was to determine whether there are age-associated changes in the deep dentate gyrus. This portion of the hippocampal formation is involved in cognition and memory, and its decline may be the structural basis for age-associated loss of memory. The brains of 9 rhesus monkeys (4-35 y) were perfused with aldehydes. Pieces of the right or left dentate gyrus were embedded for routine electron microscopy. A sequence of 10 exposures per each ultrathin section were taken deep in the stratum moleculare along a line just above and parallel to the layer of granule cells. This photographic procedure was repeated in an additional 9 ultrathin sections, leading to a total of 100 exposures per monkey. On the photographic prints, with a final magnification of X 28,500, each axon terminal was counted, and its length of apposition to a dendrite or spine, and length of synaptic membrane specializations were measured. The cross-sectional area of each terminal was also determined. The statistical analysis of the morphometric will begin soon. It should be emphasized that the monkeys used for this study have been used for a previous study and will be used in future work, a move to conserve precious resources.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Parvalbumin Immunoreactivity in the LGN of Visually Deprived Rhesus Monkeys

AXIS I: 1a, 21, 25b

AXIS II: 60, 62

PRC UNIT: Neurobiology

INVES1: Tigges, Margarete
DEGREE1: Ph.D.
DEPT1: Neural Ultrastructure/Neurobiology
STAFF1: C

INVES2: Tigges, Johannes
DEGREE2: Ph.D.
DEPT2: Neuroanatomy/Neurobiology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 11

NON-HOST INST: NA

ABSTRACT: Research projects pursued in this lab have 2 goals: One is an inquiry into basic organizational principles of visual information processing the influence of the environment on postnatal maturation of the visual system. The other one uses the same monkey models to design and test treatments to preserve vision in human babies with congenital visual system disorders, like monocular cataracts, myopia, and strabismus. Newborn rhesus monkeys were raised under monocular (lid suture, aphakia, aphakia corrected optically with contact lenses, occlusion with opaque occluder lenses) and under binocular visual deprivation conditions (aphakia combined with occlusion or optical undercorrection of the fellow eye). Routine immunohistochemical methods with an antibody to the calcium-binding protein parvalbumin (PV) were used to examine the distribution of PV+ neurons and PV+ processes in the LGN of these monkeys. Under all rearing conditions, we found no obvious difference in PV density in neurons in any lamina, although in all monocularly deprived and in 2 of the 3 binocularly deprived monkeys neurons connected to the deprived eye were of reduced size. Furthermore, PV immunoreactive processes in the neuropil of deprived laminae were as numerous and of the same morphologies as those in nondeprived laminae or as in normal controls. Thus, the calcium-binding protein parvalbumin is resistant to monocular as well as binocular visual deprivation. All animals have also been used in neuroanatomical studies of the striate cortex and SC, in behavioral testing by Dr. R. Boothe and in axial length measurements of the eye to investigate postnatal eye growth.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Anatomical Effects of Long-term Alternate Occlusion on the Developing Visual System of Rhesus Monkeys

AXIS I: 1a, 21, 25b

AXIS II: 60, 62

PRC UNIT: Neurobiology

INVES1: Tigges, Margarete
DEGREE1: Ph.D.
DEPT1: Neural Ultrastructure/Neurobiology
STAFF1: C

INVES2: Fernandes, Alcides
DEGREE2: M.D.
DEPT2: Neurobiology
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 4

NON-HOST INST: NA

ABSTRACT: Research projects pursued in this lab have 2 goals: One is an inquiry into basic organizational principles of visual information processing the influence of the environment on postnatal maturation of the visual system. The other one uses the same monkey models to design and test treatments to preserve vision in human babies with congenital visual system disorders, like monocular cataracts, myopia, and strabismus. A previous study demonstrated that alternate occlusion (AO) of macaque monkeys from birth to 36 weeks of age resulted in stereoblindness, motion processing asymmetries, and strabismus (Tychsen et al., ARVO, 1991). The current study was done to determine the effects of long-term AO on postnatal eye growth and on the geniculostriate system. Four newborn rhesus monkeys were raised for 12 to 16 weeks with AO produced by switching an opaque contact lens from one eye to the other every 24 h. Outcome measures included A-scan ultrasonography, refraction, and cytochrome oxidase (CytOx) histochemistry. Postnatal axial eye elongation and refraction for each eye were not different from those of normal age-matched monkeys. In the LGN, all 4 parvocellular laminae exhibited equal CytOx reactivity. CytOx levels were also identical for the 2 magnocellular laminae, but they were more reactive than the parvocellular ones. In striate cortex, layers 4C and 4A were densely and uniformly reactive for CytOx. Layers 2/3 exhibited distinct arrays of blobs in rows, and the blobs were of equal size. Thus, CytOx staining in LGN and striate cortex appeared normal. Long-term AO neither interferes with normal postnatal axial eye elongation and refraction, nor does it affect CytOx levels in LGN and striate cortex. We will compare these data with those from previous studies of infant monkeys raised from birth with continuous monocular occlusion.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Review of the Literature on the Primate's LGN

AXIS I: 1a, 21, 25b

AXIS II: 92, Neuroscience

PRC UNIT: Neurobiology

INVES1: Wilson, James R.
DEGREE1: Ph.D.
DEPT1: Neurophysiology/Neurobiology
STAFF1: C

SPECIES1: Macaca mulatta
NUM1: 0

NON-HOST INST: NA

ABSTRACT: There has been no review of the anatomy of the lateral geniculate nucleus in twenty years. Such a review is important to update many neuroscientists as to the current state of this well-studied nucleus and to determine what research is needed in this area. The introduction for that review follows. The dorsal lateral geniculate nucleus (dLGN) is a prominent thalamic region for processing visual information. It has the major research advantages of clear anatomical separation from other thalamic nuclei with direct, separate, and easily manipulated inputs from each eye, plus a wealth of anatomical and physiological data on it. Approximately 2500 studies concerning the dLGN have been published since 1966. Following the 1971 review by Guillery, pathway tracing using horseradish peroxidase, immunohistochemical staining techniques, and other markers have greatly expanded our knowledge of the inputs to the dLGN and ability to selectively label neurons and their processes. The present review provides an update on efforts to analyze the circuitry of the cat's and monkey's dLGN beyond that of Guillery, 1971. New data on the neurons and circuitry of the visual part of the reticular nucleus of the thalamus also is covered because of the clear relationship and importance to the dLGN. No attempt has been made to be exhaustive, and those areas already covered by Guillery's review will not be referenced, i.e., those prior to 1971. As prerequisites to this review, the general features of the dLGNs of cats and primates can be found in reports by Guillery (1970) and Kaas et al. (1978). Other reviews that have emphasized different species, physiology, development, or the effects of abnormal visual inputs should be consulted for those aspects of the dLGN.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Review of Primate LGN

AXIS I: 1a, 21, 25b

AXIS II: 92, Neuroscience

PRC UNIT: Neurobiology

INVES1: Wilson, James R.
DEGREE1: Ph.D.
DEPT1: Neurophysiology/Neurobiology
STAFF1: C

SPECIES1: Macaca mulatta
NUM1: 4

NON-HOST INST: NA

ABSTRACT: This is a continuation of an ongoing project to determine the brainstem pathways to the dorsal lateral geniculate nucleus (dLGN) in the monkey. Injections of horseradish peroxidase into the dLGN are used to retrogradely label cells in assorted nuclei in the brainstem. Immunohistochemical techniques are also being used to determine what neurotransmitters these cells use for each nucleus. This data will provide the basis for determining the functional relevance of the brainstem projections to this visual thalamic center.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Morphological/Physiological Relationships in Primate LGN

AXIS I: 1a, 21, 25b

AXIS II: 92, Neuroscience

PRC UNIT: Neurobiology

INVES1: Wilson, James R.
DEGREE1: Ph.D.
DEPT1: Neurophysiology/Neurobiology
STAFF1: C

SPECIES1: Saimiri sciureus
NUM1: 2

NON-HOST INST: NA

ABSTRACT: This is a continuation of a 4-year grant from NIH/NEI to study the anatomy of the squirrel monkey's lateral geniculate nucleus using electron microscopic immunohistochemical, and behavioral methods. The year's research was mostly analyzing individual cells that had been injected with horseradish peroxidase for monkeys monocularly deprived. These are to be compared with similar cells in normally reared monkeys. In this way, a determination can be made of synaptic variations in the LGN caused by the deprivation.

DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY

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DIVISION OF PATHOBIOLOGY AND IMMUNOBIOLOGY
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M. Isahakia	Director, Institute for Primate Research, Kenya
V. Nassar	Surgical Pathology, VA Hospital; Dept. Pathology, Emory
J. Richardson	Consultant in Biosafety, Emory University (Retired)
R. Weaver	Consultant in Microbiology, Centers for Disease Control

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Optimization of In Vitro Anti-SIV Antibody Synthesis

AXIS I: 1d, 2, 7b, 9

AXIS II: 31, 56, 64, 66,

PRCUNIT: Pathobiology & Immun

INVES1: Ansari, Aftab A.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: C

INVES2: Villinger, Francois
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: O

SPECIES1: Cercocebus atys
NUM1: 12

SPECIES2: Macaca mulatta
NUM2: 8

SPECIES3: Macaca nemestrina
NUM3: 8

NON-HOST INST: NA

ABSTRACT: An in vitro B-cell stimulatory assay for antibody production was further analysed. This assay not only yields antibodies from actively secreting B cells but also reactivates memory B cells polyclonally to produce antibodies against the antigen for which they had been primed. As such, B cells from seropositive mangabeys and macaques were found to produce SIV-specific antibodies, mainly of the IgG subtype. While B cells of uninfected seronegative macaques failed to secrete SIV-specific antibodies, B cells from a large majority of seronegative mangabeys were found to secrete detectable levels of SIV-specific antibodies, mainly of the IgM subtype. While mainly mature B cells from seropositive monkeys secrete antibodies in vitro, the subpopulation responsible for in vitro antibody production in seronegative mangabeys is restricted to memory IgD^- B cells, suggesting possible peripheral tolerance induction in these animals. SIV-reactive antibody secretion was further found to be greatly regulated by autologous $CD8^+$ T cells.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Characterization of Peripheral T-Cell Clones in Nonhuman Primates

AXIS I: 1a, 1d, 2, 9, 15

AXIS II: 31, 39, 64

PRC UNIT: Pathobiology & Immun

INVES1: Ansari, Aftab A.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: C

INVES2: Villinger. Francois
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: O

INVES3: Findley, H.
DEGREE3: Ph.D.
DEPT3: Pathobiology & Immunobiology
STAFF3: O

SPECIES1: Cercocebus atys
NUM1: 15

SPECIES2: Macaca mulatta
NUM2: 10

SPECIES3: Macaca nemestrina
NUM3: 10

NON-HOST INST: NA

ABSTRACT: Functional CD4$^+$ and CD8$^+$ T cell subsets can be classified according to the cytokine they secrete upon activation. Th1 cell subsets secrete mainly IL-2, IFNγ, GM-CSF and IL-3 and are mainly involved in delayed-type hypersensitivity response. Th2 cell subsets secrete IL-4, IL-5, IL-6, IL-10, CSF-3, and GM-CSF and provide help for B cells. Skews in T-cell profiles have been correlated with clinical response to various pathogens and prompted the question whether disease susceptibility and/or resistance in macaques versus mangabeys may rely on differences in T-cell profiles. Using cytokine assays developed in our laboratory, peripheral T-cell clones isolated by limiting dilution analysis from macaques and mangabeys were characterized. Analysis of about 150 such clones suggests that macaques have a vast majority of Th1 type T cells in the periphery, but mangabeys' circulating T cells are primarily of the Th2 type. Additional numbers of T cell clones are currently being evaluated, as well as SIV-specific T-cell clones.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: In Vivo Stimulation of B Cells from Occultly Infected Mangabeys

AXIS I: 1a, 3, 7b

AXIS II: 31, 56, 64, 66

PRC UNIT: Pathobiology & Immun

INVES1: Ansari Aftab A.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: C

INVES2: Villinger, Francois
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: O

SPECIES1: Cercocebus atys
NUM1: 4

NON-HOST INST: NA

ABSTRACT: In vivo B-cell stimulation was attempted in 4 seronegative mangabey monkeys previously isolated and whose B cells produced SIV antibodies when stimulated in vitro. Stimulation of memory B cells was achieved using massive doses of mouse monoclonal antibody specific for human IgD. Within a period of 4-8 weeks, all 4 animals not only seroconverted, with serum antibodies reacting to core, envelope and pol proteins, but SIV isolation attempts were successful from PBMC of all 4 mangabeys, confirming the infection status of these animals. Titration of infected PBMC yielded up to $1x10^3$ circulating PBMC in these animals. These data clearly prove (i) that a good number of seronegative mangabeys are latently infected with SIV; (ii) that the virus in these animals, while not replication-competent in vitro (prior to seroconversion), is nevertheless present in a replication-competent form in vivo; and (iii) that immune parameters yet to be elucidated are present in these animals that are capable of maintaining viral latency for extended periods of time. A similar experiment is currently being repeated with additional control animals; the results are pending.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Standardized Radiographs for Quantitative Digital Subtraction Radiography in Monkeys

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Braswell, L.D.
DEGREE1: D.D.S.
DEPT1: Pathobiology and Immunobiology
STAFF1: 0

INVES2: Reddy, M.S.
DEGREE2: D.D.S.
DEPT2:
STAFF2: 0

INVES3: Fritz, M.E.
DEGREE3: D.D.S., M.S., Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: 0

INVES4: Jeffcoat, M.K.
DEGREE4: D.D.S.
DEPT4:
STAFF4: 0

INVES5: Eke, P.I.
DEGREE5: Ph.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: 0

SPECIES1: Macaca mulatta
NUM1: 4

NON-HOST INST: NA

ABSTRACT: The purpose of the present study was to develop and validate a method for the standardization of film geometry suitable for use in monkeys. Computer software was used to correct errors due to film tilt eliminating the need for an occlusal stent. A stainless steel head holder incorporating ear-rods and an occipital pointer was bolted to a movable examination table that contained an attachment to permit repeatable placement against the wall. The method was validated in four monkeys. Pairs of radiographs were subtracted following correction for contrast, density and film tilt. The mean standard deviation of the gray level histogram of these no change images was $3.3 \pm .81$. The usefulness of the method for quantitative subtraction radiography was validated using small bony chips less than 25 mg in size. The chips were placed in the monkey's mouth and the first radiograph exposed. The second

radiograph was taken following removal of the chips. A morphologic image processing method was used to estimate the mass of the chip from the subtraction image. There was an excellent correlation between calculated and actual lesion mass (r^2>.92, p<.01). These data indicate that the present method can provide repeatable radiographic images for quantitative digital subtraction radiography.

P51RR00165-32 1/1/1992 - 12/31/1992 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: Pathobiology & Immun

INVES1: Collins, William E.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 8

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

ABSTRACT: Studies have been continued to infect chimpanzees with malaria parasites to obtain blood-stage parasites for (1) development of monoclonal antibodies to blood stages, (2) preparation of genomic libraries, (3) extraction of m-RNA for genetic engineering studies, (4) antigen for serologic tests, (5) 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 (6) production of immune sera. During the current year, the following parasites and animals were inoculated: Plasmodium ovale - MORT (C-423), SUZANNA (C-0514), SABRINA (C-0536); Plasmodium vivax - ARTIFEE (C-0510), CHUCK (C-359), SABRINA (C-0536): Plasmodium malariae - BRENT (C-415). Following the development of patent infections and the collection of blood from infected animals for in vitro studies, the animals are treated and cured of the malaria infection. These studies will be continued in support of the development of vaccines for human malarias.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Opiates and AIDS: A Monkey Model

AXIS I: 1a, 7b, 15, 17, 19

AXIS II: 31, 36, 50b, 64, 66, 77, 79, 87

PRC UNIT: Pathobiology & Immun

INVES1: Donahoe, Robert M.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

INVES3: Byrd, Larry D.
DEGREE3: Ph.D.
DEPT3: Behavioral Biology
STAFF3: C

INVES4: Ansari, Aftab A.
DEGREE4: Ph.D.
DEPT4: Pathobiology & Immunobiology
STAFF4: C

INVES5: Fultz, Patricia N.
DEGREE5: Ph.D.
DEPT5:
STAFF5:

SPECIES1: Macaca mulatta
NUM1: 26

NON-HOST INST: NA

ABSTRACT: This study was conducted to determine the effect of morphine on the immunological status of rhesus monkeys in the presence and absence of infection with the sooty mangabey strain of simian immunodeficiency virus (SIV_{SM}). Opiate dependency was maintained by injections of 3mg/kg morphine per monkey, every 6 hr. Controls received saline placebo. Opiates caused temporally variable alterations in all aspects of immune status examined: T - cell proliferative responses; NK-cell cytotoxicity; T, B and PMN cell trafficking; immunoglobulin production. However, tolerance to the variable immunological effects of opiates occurred at varying times during the study. Once tolerance developed, opiate-dependent animals placed under stress responded differently, immunologically, from controls, especially when subjected to opiate withdrawal which severely depressed immunoresponsiveness. Surprisingly, opiate-dependent animals seemed to be protected from the

sequelae of SIV_{smm} infection, except when subject to opiate-withdrawal. That is, latent SIV_{smm} appeared to be activated by opiate withdrawal in virus-infected animals in which virus expression had entered a stage of persistent latency. Thus, these studies corroborate previous reports on the immunomodifying properties of opiates and extend them by showing that animals adapt to immunomodifying changes induced by opiates as pharmacological tolerance is established and that disruption of this adaptive state by stress, particularly the stress of opiate withdrawal, can be extremely disruptive in immunological and virological terms. Such data suggest that a well-compensated heroin addict may be protected from the sequelae of AIDS while a destabilized addict may be very vulnerable to these sequelae. This conclusion suggests a practical need for drug replacement therapy to stabilize street heroin addicts. Such findings also have basic relevance for psychoneuroimmunology by suggesting that stress reduction may be a useful therapeutic goal to help reduce the sequelae of HIV-1 infection.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Primates as Hosts for Onchocerca volvulus

AXIS I: 1a, 7c, 14, 17

AXIS II: 64, 66, 77, 91

PRC UNIT: Pathobiology & Immun

INVES1: Eberhard, Mark L.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 7

SPECIES2: Cercocebus atys
NUM2: 8

NON-HOST INST: Centers for Disease Control and Prevention

ABSTRACT: The primary purpose of this project has been to continue to characterize the primate model for the study of onchocerciasis, a blinding disease of people in Africa and Central America. Chimpanzees and mangabey monkeys continue to be the only experimental hosts available for study, and the responses seen in these primates mimic closely that seen in man. We have been able to demonstrate that an inocula of 200 third-stage larvae (L3) is as acceptable as an inocula of 400 L3 to initiate infection, and that the immunological and parasitological outcome will be the same. We have been able to show in experimental primates that an antibody response to several recombinant antigens appear as early as three months after inoculation and as much as 10 months before the onset of microfiladermia, and that there is a unique antibody which appears just before microfilariae appear in the skin. These responses, which were documented in primates with known exposure times and histories, have verified similar responses detected in humans living in endemic areas, and validated the usefulness of these assays for use in epidemiological studies. These immunological assays also have been useful in verifying that a large percentage of inoculated mangabey monkeys are actually infected, even though no microfilariae are detectable on skin snips. This observation has confirmed the usefulness of this primate as a model for the study of cryptic (occult) filariasis. It also has been possible to develop standardized survival, growth, and molting curves for O. volvulus larvae contained in implantable diffusion chambers. This has permitted us to begin vaccine trials using larvae contained in chambers as an in vivo procedure to assay the immunological status of an animal.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: The Microbiology of Initial Implant Placement in Rhesus Monkeys

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Eke, P.I.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Braswell, L.D.
DEGREE2: D.D.S.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Fritz, M.E.
DEGREE3: D.D.S., M.S., Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

SPECIES1: Macaca mulatta
NUM1: 40

NON-HOST INST: NA

ABSTRACT: The microflora associated with different stages of dental implants in rhesus monkeys were studied. This report presents the microflora (1) before first stage implant placement and (2) before and one month after second stage implant placement. We examined the microflora by darkfield microscopy, selective and non-selective culture, and characterizations of culture isolates by primary phenotypic properties. After the 1st month of 2nd stage implant placement, the proportion of the aerobic flora declined at implant site, while proportions of the capnophilic flora increased steadily. The Black Pigmented Bacilli (BPB) were not detected around implants placed in monkeys with low proportions (< 0.01%) of BPB before implantation. In contrast, the proportions of BPB (mainly P. intermedia) increases significantly around implants in monkeys with pre-implantation levels of BPB > 0.01%. The corroding fastidious asaccharolytic gram negative rods were not detected at implant sites but were detected at non-implant sites. A.a. levels around exposed 1st stage implants were relatively low and increases significantly one month after 2nd stage placement. A complex strictly anaerobic microbiota was detected from one receptor space after the 1st stage of implant was uncovered, otherwise all unexposed 1st stage implants were culture negative. Our results demonstrate important quantitative and qualitative changes, and differences from the normal subgingival flora, at different stages of implant placement in rhesus monkeys.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Chronic Immunologic Activation and SIV-Induced Disease

AXIS I: 1a, 7b

AXIS II: 31, 64, 66

PRC UNIT: Pathobiology & Immun

INVES1: Folks, Thomas M.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

INVES3: Ansari, Aftab A.
DEGREE3: Ph.D.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 12

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

ABSTRACT: Varying periods of latency between viral infection and development of disease and death have been noted for both human HIV-1 infection and in nonhuman primates experimentally infected with various simian immunodeficiency virus isolates. It has been shown that only 1 per 100,000 cells (approximately) are infected with HIV-1 at any given time. However, activated cells from infected subjects, when analyzed, demonstrate a frequency of 1 per 10,000 and even as high as 1 per 1000. These findings imply that activation in vitro and perhaps in vivo may contribute to an increase in virus replication and exacerbation of disease. To test this hypothesis, it is the objective of these studies to determine if controlled exogenously induced T-cell activation in vivo may alter and accelerate SIV-induced disease induction in rhesus macaques. Rhesus macaques will be administered 1 x 10^4 $TCID_{50}$ SIVsmm9. One group will be administered adjuvant alone (Freund's incomplete) subcutaneously and not be infected with virus (N=3). Following virus infection the second group will be administered KLH, tetanus toxoid, or allogeneic cells incorporated in adjuvant and given subcutaneously at monthly intervals (N=3) and the third group will be given allogeneic cells alone (intravenously) at monthly intervals (N=3). The fourth group will serve as a control (N=3) and be infected with virus but will not receive any immune stimulation. All monkeys are being monitored for total numbers of CD4 and CD8 cells and CD4/CD8 ratios and clinical disease.

P51RR00165-32 1/1/1992 - 12/31/1992 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: Pathobiology & Immun

INVES1: Fritz, Michael E.
DEGREE1: D.D.S., M.S., Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Braswell, Laura D.
DEGREE2: D.D.S
DEPT2: Pathobiology & Immunobiology
STAFF2: O

INVES3: Kutner, Michael H.
DEGREE3: Ph.D.
DEPT3:
STAFF3: O

INVES4: Eke, Paul I.
DEGREE4: Ph.D
DEPT4: Pathobiology & Immunobiology
STAFF4: O

INVES5: Winter, Marvin
DEGREE5: D.D.S.
DEPT5:
STAFF5: O

INVES6: Slosberg, Robert
DEGREE6: D.D.S.
DEPT6:
STAFF6: O

INVES7: Lemons, Jack E.
DEGREE7: Ph.D.
DEPT7:
STAFF7: O

SPECIES1: Macaca mulatta
NUM1: 40

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

ABSTRACT: The present study integrates the disciplines of biomaterials, clinical dentistry, digital radiology, and biomechanics to study the behavior of dental implants. Root-form fixtures and blade-vent dental implants have been produced under stringent conditions in a Department of Biomaterials, and

biology of these are being assessed in a partially edentulous monkey model system, utilizing 40 rhesus monkeys. Non-loaded dental implants have been examined in 4 monkeys and both root-form and blade-vent implants have displayed approximately the same percentage of osseointegration. In 36 monkeys that remain in the study, implants have been placed in 32, and 30 bridges of the total of 72 have been placed. Routine scalings are being performed in the monkeys on a once monthly basis to prevent periodontitis. Microbiological data demonstrate that the gingival sulci are colonized by microbiological species that resemble the putative pathogens of periodontal disease. Periodontitis and peri-implant disease will be created by the use of silk ligatures being tied around teeth or implants (fixtures) for 6 months. Clinical, microbiological and radiological measurements, and computer modeling will be performed. The data produced will provide a comparison of 2 types of implants and/or fixtures, and the natural teeth in both non-diseased and diseased environment in a monkey model. These data are not in existence, and will be important as they provide immediate application to patient care. Implant dentistry will become more prevalent in our society as technology is improving rapidly and our population ages, and this population has a high percentage of partially or fully edentulous individuals.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Use of SGTAM in Treatment of Large Alveolar Ridge Defects in Monkeys - Pilot Study

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Fritz, Michael E.
DEGREE1: D.D.S., M.S., Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Jeffcoat, Marjorie, K.
DEGREE2: D.D.S.
DEPT2:
STAFF2: O

INVES3: Malmquist, Jay P.
DEGREE3: D.M.D.
DEPT3:
STAFF3: O

INVES4: Lemons, Jack E.
DEGREE4: Ph.D
DEPT4:
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 3

NON-HOST INST: University of Oregon (JPM) and University of Alabama, Birmingham (MKJ, JEL)

ABSTRACT: Recently, the concept of Guided Tissue Regeneration (GTR) has been used to regenerate periodontal and bony defects both in animals and humans. Briefly, granulation tissue originating from the fibrous connective tissue is mechanically separated from the region in which regeneration is desired by the use of a biocompatible membrane. The membrane serves as a passive barrier which both creates a space into which regeneration can occur and prevents undesirable tissues such as fibrous connective tissue (scar) and epithelium from participating in the healing events in the space. Presently the most commonly used materials in GTR procedures are made from GORE-TEX (TM) expanded polytetrafluoroethylene (e-PTFE).

W. L. Gore and Associates, Inc. has developed reinforced forms of GORE-TEX Augmentation Material which allow molding and shaping to a desired configuration along with additional stiffness for spacemaking in situations where bone morphology does not provide adequate support. These materials have been

successfully utilized to treat large surgically created (acute) mandibular alveolar ridge defects in dogs (W. L. Gore and Assoc., Inc. unpublished data). However, this technique has not been tested with chronic alveolar ridge defects or in a model which is phylogenetically more closely related to humans.

The purpose of the study has been to test the ability of a reinforced form of GORE-TEX Augmentation Material to maintain a suitably configured space for an appropriate healing period and to regenerate bone in chronic alveolar ridge defect in rhesus monkeys. Three adult male rhesus monkeys were used in this study. The monkeys were made previously edentulous in the mandibular posterior regions, dental implants placed bilaterally, and 1 cm^2 block sections of implant and surrounding bone removed. Reinforced GORE-TEX Augmentation Material was used as a mechanical barrier to create and preserve a space adjacent to the alveolar bone in the region of the defect and to prevent fibrous connective tissue from interfering with bone healing.

In each monkey mandibular alveolar ridge defects were surgically created as noted above and allowed to heal for a minimum of three months to produce chronic lesions. Standardized radiographs were taken to the time of defect creation to serve as a baseline for the evaluation of the position of the defects and any spontaneous healing and bone remodeling. Standardized radiographs were taken at the end of the healing period and immediately prior to the placement of the reinforced GORE-TEX Augmentation Material. The reinforced GORE-TEX Augmentation Material was shaped, adapted, and fixed to the bone surface in the region of the defect in such a way that a space in the approximate form of the intact alveolar ridge was created by the membrane and the membrane isolated the defect space from the fibrous connective tissue of the overlying gingiva.

Two membranes (out of a total of 6) were removed because of infection within 1 month. The remaining 4 membranes (in 3 animals) remained in place for one year, at which time they were removed with one <u>en bloc</u>. Initial histologic sections show bone growth of over 1 cm^2 in these defects. This is reinforced by radiological data. The histophotometry and radiological data are presently being analyzed.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: In vivo Platelet Interactions with Adhesive Glycoproteins: Role of Platelet Glycoprotein Ib Receptor for von Willebrand Factor

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 5

NON-HOST INST: NA

ABSTRACT: Platelet adhesion and aggregation are mediated, at least in part, through the platelet glycoprotein (GP) Ib receptor for von Willebrand factor (vWF). Platelet thrombus formation in a number of models has been closely correlated with the local wall shear rate. To determine the role of GP Ib on thrombus formation and the shear dependency of this mechanism, we studied thrombus formation on 2 cm long Type I collagen-coated tubing segments having diameters of 2,3, and 4 mm. These segments, placed in a baboon arteriovenous shunt system with blood flow rates maintained at 100 ml/min, model the hemodynamic conditions associated with normal arteries and produce wall shear rates of 265, 630, and 2120 sec^{-1}, respectively. The devices were exposed for 2 hours to whole blood flow without anticoagulation. The effects of a recombinant vWF GP Ib binding domain peptide and a monoclonal antibody against the GP Ib binding domain of vWF were studied. Platelet thrombus formation was measured by ^{111}Indium-platelet scintillation camera imaging. In control studies there was a rapid increase in platelet thrombus formation on collagen leading to occlusion of the 2 mm i.d. collagen tubes within 30 min. The rate of platelet deposition correlated directly with increasing wall shear rate, and was strongly inhibited by the vWF peptide (by > 70%) at the highest shear rate, but not at the intermediate shear rate (< 30% inhibition) or low shear rate (<20% inhibition). Similarly, the monoclonal antibody was quite effective in reducing thrombus formation (by> 80%) and preventing occlusion, but only under high shear conditions. Thus, blocking platelet GP Ib with

peptides based on the vWF binding domain for this receptor may prove useful for inhibiting thrombus formation under conditions of high fluid shear, as are associated with high grade arterial stenoses.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: In vivo Platelet Interactions with Adhesive Glycoproteins: Role of Platelet GP Ib and Platelet GP IIb/IIIA Receptor in Thrombus Formation

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 5

NON-HOST INST: NA

ABSTRACT: To evaluate the role of both the platelet GP Ib and platelet GP IIb/IIIa receptor in thrombus formation under conditions of high fluid shear, we examined thrombus formation at the throat of fluid mechanically well-characterized high grade stenoses. The stenoses were constructed from Type I collagen-coated tubes, and exhibited reductions in cross-sectional area of 50%, 75%, and 90%, corresponding to local wall shear rates of 1250, 4300, and 20,000 sec^{-1}, respectively. The devices were exposed to nonanticoagulated whole blood for 2 hours in baboons. In control studies, platelet deposition at the stenosis apex was strongly correlated with shear rate. Interestingly, under comparable shear conditions, platelet deposition at the stenotic sites, per unit surface area, was markedly higher than observed with straight collagen tubes. This result suggests that the stenosis geometry *per se* is predisposed to enhanced thrombus formation. The 75% and 90% stenoses tended to rapidly occlude over 2 hours, while the 50% stenoses remained patent. Platelet deposition was strongly inhibited (60-80%), and occlusion prevented, by the recombinant vWF peptide at all shear rates examined. Comparable effects were observed following administration of an R-G-D (Arg-Gly-Asp) peptide inhibitor of platelet GP IIb/IIIa, as well as with a potent inhibitor of thrombin enzymatic activity, PPACK (Phe-Pro-Arg chloromethylketone). These results suggest that platelet thrombus formation at arterial stenotic sites is regulated by multiple factors including platelet GP Ib, GP IIb/IIIa, and the actions of thrombin.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: In vivo Platelet Interactions with Adhesive Glycoproteins: Role of Thrombin

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 5

NON-HOST INST: NA

ABSTRACT: To more fully elucidate the role of thrombin in platelet thrombus formation, we used the baboon model to evaluate the effects of specifically blocking the recently described platelet receptor for thrombin. The peptide antagonist employed in these studies was based on the thrombin receptor neoterminal activating sequence, and has recently been described (Scarborough et.al., J Biol Chem, 268:1066, 1993). In preliminary studies, infusion of the peptide into baboons has blocked by > 50% platelet deposition onto arterial Dacron vascular grafts and Type I collagen-coated tubings, both exposed to blood flow at moderate arterial wall shear rates (265 sec^{-1}). These studies provide the first evidence that thrombin mediates platelet thrombus formation in vivo, at least in part, through cleavage of the platelet thrombin receptor as opposed to other possible substrates. Studies with this peptide in the stenosis model, and under variable shear conditions, are in progress. Overall, these studies are intended to define the relative importance of platelet receptor-mediated pathways of thrombus formation in vivo, and how these reactions are regulated by flow conditions relevant to clinical arterial disease.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evaluation of Small Vessel Prostheses: Graft Chemical Properties

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 20

NON-HOST INST: NA

ABSTRACT: In collaboration with Dr. H. Yasuda, University of Missouri-Columbia, we have continued to evaluate the healing characteristics of small caliber grafts modified by plasma polymerization. Since the surface chemistry of prosthetic grafts markedly affects their thrombogenicity, we postulated that graft chemical properties could also mediate their healing responses. Therefore, conventional polytetrafluoroethylene (PTFE) grafts (Gore-Tex, 30-60 μ porosity) have been coated by vapor phase deposition of ultra-thin (<30 nm) polymers which did not alter the graft morphology (by SEM) but which selectively altered the graft surface chemistry, as shown by surface spectroscopy. To date, the following grafts have been placed as aorto-iliac interposition grafts (4 mm i.d., 4-6 cm in length) in baboons: 1) 10 control 30 μ grafts, 2) 8 control 60 μ grafts, 3) 8 grafts (30 μ) coated with polymer based on hexafluoroethane, 4) 10 grafts (30 μ) coated with polymer based on methane, 5) 8 grafts (30 μ) coated with polymer based on tetramethyl disiloxane, and 6) 8 grafts (60 μ) coated with polymer based on hexafluoroethane. After 3 months implantation of 30 μ control grafts, neointimal thickening was equivalent at proximal and distal anastomoses and averaged 1.3 $\pm$ 0.3 mm^2. This result, as well as patency rates (> 80% in all

cases), was unaffected by the coating of 30 μ grafts with methane, hexafluoroethane, or tetramethyl disiloxane ($p > 0.2$ in all cases). While both control and treated 60 μ grafts which were placed for 1 month are presently being evaluated morphometrically, initial results suggest no marked differences in intimal cell proliferation. All grafts (whether 30 μ or 60 μ porosity) were completely covered by confluent endothelium overlying smooth muscle cells. These results suggest that strategies for modifying graft chemistry alone may be ineffective for limiting the development of anastomotic intimal hyperplasia.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evaluation of Small Vessel Prostheses: Inhibition of Graft-Platelet Interactions

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 20

NON-HOST INST: NA

ABSTRACT: Since platelets can cause acute thrombo-occlusion of very small caliber grafts, we determined the effect of blocking the platelet GP IIb/IIIa receptor for fibrinogen by bolus infusion of the murine monoclonal antibody LJ CP-8 against the GP IIb/IIIa complex in baboons. In this study, 1 cm segments of 4 mm i.d. PTFE graft were placed in the common carotid arteries of 5 control and 4 treated baboons. ^{111}Indium-platelet imaging showed that antibody therapy reduced graft platelet deposition acutely (0-90 min) after grafting ($p<0.006$), at 24 hours ($p<0.01$), and at 48 hours ($p<0.1$) postoperatively. After 30 days 4/4 (100%) of grafts were patent in treated animals, while only 2/5 (40%) of grafts were patent in control animals ($p=0.06$). Since this antibody produces systemic antithrombotic effects for only 24-48 hours (J Clin Invest 81:149, 1988), these results suggest that the earliest platelet reactions may be an important determinant of late graft patency, and that short-term antiplatelet therapy during this period may produce a lasting benefit.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evaluation of Small Vessel Prostheses: Role of Thrombin in Intimal Hyperplasia

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 20

NON-HOST INST: NA

ABSTRACT: We have developed a method for locally infusing antithrombotic agents through the porous wall of surgically placed PTFE grafts, so that these agents achieve high local concentrations only in the fluid boundary layer at the blood graft interface and along the distal vessel wall. This approach was used to evaluate the role of the procoagulant enzyme thrombin in vascular lesion formation. Recombinant hirudin, a potent antithrombin, was infused continuously (1.4 mg/kg-day) through porous graft devices placed proximal to sites of carotid artery balloon angioplasty in 4 baboons, thereby achieving a high local concentration (> 10 μg/ml) at the vessel injury sites without increased systemic bleeding. In collaboration with Dr. Josiah Wilcox, vessels were harvested after 3 days and proliferating smooth muscle cells (SMC) were identified by cyclin/PCNA (proliferating cell nuclear antigen) staining. Local hirudin therapy reduced SMC proliferating SMC by 80% (4.3 ± 0.3% cyclin positive SMC) as compared to the contralateral control arteries injured in the same manner (20.7 ± 1.8% positive SMC, $p < 0.01$). These studies provide the first evidence that thrombin is a key mediator of early SMC proliferation following arterial injury in the primate, and that the hemostatic mechanism may be important in the development of vascular restenotic lesions.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evaluation of Small Vessel Prostheses: Role of von Willebrand Factor (vWF) in Graft Thrombosis

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Hanson, Stephen R.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Harker, Laurence A.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 20

NON-HOST INST: NA

ABSTRACT: While it is well established that vWF plays an important role in the reactions of platelets with subendothelial collagen, its role in blood reactions with artificial surfaces is less well established. Therefore, a murine monoclonal antibody (BB3 BD5) against the platelet glycoprotein Ib binding domain of vWF was infused into 5 baboons having Dacron vascular grafts (4 mm i.d.) placed as extension segments of chronic femoral arteriovenous shunts (since the exposure of graft material in this manner excludes reactions mediated by vessel injury). Following antibody infusion, the tendency for hemostatic bleeding was markedly increased. Over a one hour blood exposure period with continuous ^{111}Indium-platelet imaging, antibody therapy reduced platelet deposition onto 5 grafts by an average of only 37% vs. studies in 6 control animals ($p = 0.04$). Therefore, despite interruption of platelet hemostatic functions, therapeutic targeting of vWF inhibited graft thrombus formation only modestly.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Antithrombotic Therapy in Experimental Thrombosis: Effects of Direct Antithrombins

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 19

NON-HOST INST: NA

ABSTRACT: The importance of thrombin in high blood-flow, platelet-dependent thrombotic and hemostatic processes is evident from studies in baboons measuring the relative anti-thrombotic and antihemostatic effects of hirudin. Many direct antithrombins, including recombinant hirudin, the irreversible antithrombin peptide D-Phe-Pro-Arg chloromethylketone (D-FPRCH_2Cl), the competitive antithrombin peptide D-Phe-Pro-boroArginine (D-FPRBOH), the bifunctional antithrombin peptide (BAP) combining the catalytic site inhibitor sequence D-FPR and the carboxy-terminal dodecapeptide of hirudin, benzamidine-based and arginine-based (argipidine) synthetic direct antithrombins, interrupt platelet and fibrin deposition and thrombotic occlusion in a dose dependent manner that is profound at the highest doses for all thrombogenic surfaces tested.

However, all of these direct antithrombins concurrently inhibit platelet hemostatic function in concert with their antithrombotic effects (bleeding times show intermediate prolongation by doses that reduce thrombus formation by half (ID_{50}). We conclude that platelet-dependent thrombotic and hemostatic processes are thrombin mediated and that direct antithrombins produce a potent dose dependent inhibition of arterial thrombus formation that greatly exceeds the minimal antithrombotic effects produced by heparin (even ten fold the therapeutic dose), but cause an equivalent impairment of hemostatic function with corresponding risks of abnormal bleeding. Thus, while direct antithrombins exhibit antithrombotic efficacy for heparin resistant thrombosis, they achieve this benefit with an equivalent hemostatic burden.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Antithrombotic Therapy in Experimental Thrombosis: Inhibition of Thrombin Production

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 19

NON-HOST INST: NA

ABSTRACT: Protein C undergoes catalytic activation by thrombin when complexed with thrombomodulin. Activated protein C (APC) inhibits subsequent thrombin production by inactivating the cofactor activities of fVa and fVIIIa in the autoamplification pathway. We have shown that infusions of human plasma-derived or recombinant APC (rAPC) inhibit VTF in a dose dependent manner without significantly impairing primary hemostasis in baboon models of carotid endarterectomy and thrombogenic segments incorporated into chronic AV shunts. As opposed to the direct antithrombins, antithrombotic doses of APC prolong the bleeding time only at the highest dose studied. Consequently, surgical bleeding is substantially less for APC than for equivalent antithrombotic doses of the antithrombin D-FPRCH$_2$Cl, although APC significantly increases surgical bleeding compared with untreated control endarterectomies. APC also enhances the antithrombotic effects of urokinase, but fails to increase circulating plasma markers of fibrinolysis when administered alone. Thus, exogenous APC interrupts heparin resistant VTF while sparing HPF.

Since exogenous APC produces useful and safe antithrombotic effects, we have also examined the possibility that useful antithrombotic effects will result from inducing activation of endogenous PC in baboons. Endogenous APC was generated by infusing purified human α-thrombin intravenously at doses of 1 or 2 U/kg/min for 1 hr (concentration in the main pulmonary artery estimated to

be 0.08 nM). These doses did not affect circulating concentrations of either platelets or fibrinogen. Circulating APC, measured by an enzyme immunocapture assay, attained antithrombotic levels of 280 ± 44 ng/mL ($P < 0.01$), and 613 ± 159 ng/ml ($P < 0.01$) for 1 and 2 U/kg/min, respectively. Thrombus formation was assessed using the low-flow thrombogenic device consisting of a platelet-rich Dacron graft component and a fibrin-rich chamber of disturbed flow incorporated into chronic AV shunts for 1 hr. Thrombus formation in the fibrin-rich chamber was abolished by both doses of infused thrombin, and was significantly decreased in the platelet-rich component of the device with the higher dose of thrombin. The antithrombotic effects are attributable to the elevation of APC because inhibiting the activation of protein C by prior injection of the monoclonal antibody HPC-4 (5 mg/kg bolus) eliminated the elevation in circulating APC and abolished the antithrombotic effects in the device. Bleeding times remained within the normal range (3-5 min). At 1 hr, APTT values were prolonged by 29 sec at 1 U/kg/min and by 117 sec at 2 U/kg/min doses of thrombin. Thus, the infusion of low-dose thrombin produces an antithrombotic state in vivo by inducing endogenous activation of protein C. These results imply that thrombin analogs may be useful in generating antithrombotic levels of endogenous APC for preventing and treating thrombosis. In preliminary studies we have also evaluated the capacity of protein S, the cofactor for APC, to enhance the antithrombotic effects of APC. Recombinant protein S, provided by Dr. Brian Grinnel, was infused by the boundary infusion device in combination with equimolar APC in a calcium-containing buffer, to achieve a local concentration of 5 nM for 1 hr in baboons. Whereas 5 nM APC detectably decreased thrombus formation, the addition of protein S significantly enhanced the antithrombotic effect. Protein S alone at 3 orders of magnitude greater concentration (5μM) exhibited no detectable antithrombotic effect; APC at 5μM abolishes thrombus formation. Baboon and human protein S activity and antigenic concentrations and C4b binding protein (C4BP) levels are comparable and readily measurable using the same assay systems (J.H. Griffin, unpublished data).

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Antithrombotic Therapy in Experimental Thrombosis: Safe Interruption of Thrombus Formation

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Papio cynocephalus
NUM1: 19

NON-HOST INST: NA

ABSTRACT: The relative antithrombotic efficacy and hemostatic safety of inhibiting fXa have been examined by comparing the dose response effects for two different natural potent and specific polypeptide inhibitors of fXa, antistasin and tick anticoagulant peptide (TAP), and contrasting their effects with hirudin, a comparably potent and specific natural inhibitor of thrombin. Acute arterial thrombus formation in baboons was measured in vivo as ^{111}In-platelet deposition and ^{125}I-fibrin accumulation onto segments of Dacron vascular graft, collagen-coated tubing, and homologous endarterectomized aorta, interposed as extension pieces into exteriorized arteriovenous shunts under arterial flow conditions using gamma camera imaging. Platelet hemostatic function was assessed by determining template bleeding times and coagulation was evaluated by measuring coagulation tests. Antistasin or TAP were administered intravenously for 60-120 min. Platelet deposition and fibrin accumulation were interrupted in concert in a dose-dependent manner with a half-maximal inhibitor dose (ID_{50}) of 2 μg/kg per min and 6 μg/kg per min, respectively, and corresponding inhibitor concentrations (IC_{50}) of 1.2 ± 0.04 μg/mL and 4.3 ± 0.39 μg/mL, respectively. Bleeding times remained normal (4.3 ± 0.4 min and 4.0 ± 0.6 respectively). APTT's were 199 ± 37 sec and 31 ± 2 secs. Thrombus formation on the segments of vascular graft was prevented for at least 24 hrs despite clearance of antistasin and TAP from the blood (t_{50}=2.3 hrs and 48 min, respectively). By contrast, hirudin infused for an equivalent time inhibited thrombus with an ID_{50} of 6.6 mg/kg per min, IC_{50} of

5.75 μg/mL and bleeding times of 13 ± 3 min and APTT's of 130 ± 2 sec. Moreover, thrombus formed after discontinuing hirudin infusion after 1 hr, resulting in shunt occlusion. TAP (18 μg/kg per min) also abolished thrombus formation at sites of endarterectomy with markedly reduced surgical blood loss compared with hirudin.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Endarterectomy: Prevention of Thrombosis and Restenosis: Development of Baboon Models of EA, Characterization of VLF and Local Drug Infusion

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 11

NON-HOST INST: NA

ABSTRACT: Detailed description of the endarterectomy procedure, its thrombogenicity with respect to imagable platelet deposition, and responsiveness of the thrombotic response to antithrombotic interventions are now well established. The methodology for documenting the initial proliferative responses of medial SMCs, accumulation of mononuclear leukocytes and the extent and composition of the subsequent mature vascular lesion formed at sites of EA are also well in hand. In addition, the ICC and ISH techniques for characterizing the growth factors, receptors, and modulating molecules and cells in VLF are in place in the laboratory.

We have also developed a local drug delivery system for infusing inhibitors of thrombin activity or its production into the blood fluid boundary layer at sites of vessel wall injury. This method achieves very high drug concentrations locally while minimizing total drug requirements and circulating drug levels, and allows for the efficient design and interpretation of studies in primates with agents that are available in

limited amounts or that might produce cardiovascular side-effects. We have now completed: a) a formal theoretical analysis of the convective diffusion problem for the local infusion flow geometry; b) in vitro studies with measurements of wall drug concentrations distal to infusion sites; c) studies with a baboon ex vivo shunt system using the local delivery device to block distal thrombus formation; and d) in vivo studies with local infusion of hirudin at sites of carotid artery angioplasty. The experimental studies document that the local infusion devices are remarkably efficient, deliver agents uniformly, and can be successfully used to block in vivo thrombus formation and modulate vascular healing. These studies document the reproducibility and efficiency of the method.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Endarterectomy: Prevention of Thrombosis and Restenosis: Immediate Reconstitution of Confluent Autologous Endothelium at Sites of EA

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 11

NON-HOST INST: NA

ABSTRACT: We have established the capability of forming confluent endothelium at sites of endarterectomy using cultured endothelial cells derived from mature arteries and veins. In baboons autologous EC (>10^6 cells) are harvested from surgically removed segments (5-6 cm each) of autologous cephalic vein by collagenase treatment, and expanded as much as 100 fold in culture. In situ incubation of fresh 1-cm carotid EA sites with 10^6 EC in suspension and rotational repositioning for 30 min results in acute attachment of EC in saturation density (3 x10^5 cells/cm^2). After restoring flow through the operated artery the attached ECs undergo subsequent spreading to confluence, despite exposure to arterial shear rates. This acute restoration of confluent endothelium abolishes subsequent ^{111}In-platelet deposition and maintains confluence when examined by SEM one week later. Thus, we have confirmed the feasibility of immediately restoring confluent EC at sites of mechanical vascular injury using autologous cultured cells.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Endarterectomy: Prevention of Thrombosis and Restenosis: Transduction of Tissue Plasminogen Activator (tPA) Gene Constructs into Cultured EC

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Harker, Laurence A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Hanson, Stephen R.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Kelly, Andrew B.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Lumsden, Alan
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 11

NON-HOST INST: NA

ABSTRACT: In collaboration with Dr. David Dichek, NIH, Bethesda MD, we have studied EC gene transfer experiments. Cultured baboon cephalic vein EC are transduced with tPA construct, using the techniques reported previously (Dichek, DA: Retroviral vector-mediated gene transfer into endothelial cells. Mol Biol Med 8:257-266, 1991). The transduced cells express high levels of plasminogen activator activity in the supernatant media (Lee SW, Kahn ML, Dichek DA: Expression of an anchored urokinase in the apical endothelial cell membrane. J Biol Chem, in press). We have evaluated these cells for their antithrombotic effects in the baboon by attaching cells at subconfluent density of 2.5 and 5.0 x10^4 EC/cm^2 onto collagen-coated segments of vascular graft. The segments are then incorporated as extension pieces into exteriorized chronic femoral AV shunts in baboons with flow rates controlled at 40 mL/min, and ^{111}In-platelet deposition is measured on the EC-treated segments over 1 hr. Whereas, segments bearing normal non-transduced cells accumulate platelets at intermediate values on the segments with somewhat greater deposition in the propogated tail extending downstream, the segments

in 3 sets of paired studies at two different densities of attached transduced cells showed substantially reduced platelet deposition on the graft ($<1 \times 10^9$ plat/cm) for both the graft and tail components. Thus, we have demonstrated the feasibility of performing experiments with autologous cultured ECs that have been transvected with the gene construct of tPA resulting in the secretion of the gene product in sufficient amounts to interrupt thrombus formation.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Peripheral Blood Stem Cells for Allogenic Transplantation: Development of An Animal Model: Initial Phase Investigations

AXIS I: 1d, 9, 17

AXIS II: 76b, 88

PRC UNIT: Pathobiology & Immun

INVES1: Hillyer, Christopher D.
DEGREE1: M.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Hart, Kim K.
DEGREE2: R.N.
DEPT2:
STAFF2: O

INVES3: Stanford, Margaret E.
DEGREE3:
DEPT3: Fenwal Division, Baxter Healthcare Corp., Deerfield, IL
STAFF3: O

INVES4: Swenson, R. Brent
DEGREE4: D.V.M.
DEPT4: Veterinary Medicine
STAFF4: C

INVES5: Winton, Elliott F.
DEGREE5: M.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: O

SPECIES1: Macaca mulatta
NUM1: 20

NON-HOST INST: NA

ABSTRACT: Some white blood cells in the circulating blood have the capability to restore bone marrow function after marrow ablative therapy and are called peripheral blood stem cells (PBSC). PBSC transplants have been accomplished in humans but questions as to the long term efficacy, dose and optimal product composition remain. This study allowed us to evaluate 8 unstimulated and 4 growth factor stimulated adult male rhesus monkeys that underwent a single large volume leukapheresis (LVL; >3 blood volumes processed) to define an animal model for future PBSC transplantation. Stimulated monkeys received 2.5 μg/kg GM-CSF days -12 to -5, 2.5 μg/kg IL-3 days -4 to -1, and large volume leukapheresis on day 0. Unstimulated animals did not receive growth factors. In unstimulated animals, LVL was similar to human PBSC leukapheresis in MNC/kg/hr harvested. In stimulated animals there was a >5-fold increase in

CFU-GM collected and an increase in circulating CFU-GM/MNC. The procedure was well tolerated, allows excellent collection of MNC, CFU-GM and $CD34^+$ progenitors and will allow future investigations of important questions in PBSC transplantation.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: CD34^{+} Progenitor Cell, Colony Forming Unit-Granulocyte/Macrophage (CFU-GM) and Burst Forming Unit-Erythroid (BFU-E) Analysis in SIVsmm Infected Rhesus Macaques (RM); Functional Bone Marrow Abnormalities Without Evidence of Direct Stem Cell Infection

AXIS I: 1d, 17

AXIS II: 31, 62, 66

PRC UNIT: Pathobiology & Immun

INVES1: Hillyer, Christopher D.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Lackey, Dixon A. III
DEGREE2:
DEPT2:
STAFF2: O

INVES3: Villinger, Francois
DEGREE3: D.V.M
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Winton, Eliott F.
DEGREE4: M.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

INVES5: Ansari, Aftab A.
DEGREE5: Ph.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: C

INVES6: McClure, Harold M.
DEGREE6: D.V.M.
DEPT6: Pathobiology & Immunobiology
STAFF6: C

SPECIES1: Macaca mulatta
NUM1: 23

NON-HOST INST: NA

ABSTRACT: CFU-GM and BFU-E were cultured from iliac crest bone marrow aspirates of RM infected with SIVsmm9 (Macaca mulatta; n=15) and of SIV^{-} RM (n=8). Each culture plate contained $1x10^{5}$ MNC/ml in 0.9% methylcellulose with 30% fetal calf serum, 5% rhesus PHA-LCM, 1 U/ml erythropoietin, $5x10^{-5}$ M mercaptoethanol, penicillin and streptomycin. CFUs were counted on day 10,

plucked and pooled for polymerase chain reaction (PCR) using an SIVsmm9 primer. CD34+ progenitor cells were identified by incubation with "12.8" monoclonal antibody and phycoerythrin staining. After plastic adherence, MNC underwent T-cell depletion (CD2/CD4 coated magnetic beads; Baxter) and were cultured. The infected animals were assigned to either Group A (SIV+ "well"; n=10; with lymphadenopathy and/or hepatosplenomegaly) or Group B (SIV+ "sick"; n=5; who had, in addition, weight loss, diarrhea, severe hematologic abnormalities and/or atypical infection). Mean ± standard deviation shown (* $p<.05$); CFU-GM and BFU-E are *per plate* and Lymphs, Hct and Plts are peripheral blood counts:

	CFU-GM	BFU-E	%CD34+ (n)	Lymphsx10^9/L	Hct %	Pltsx10^9/L
Cntrls	48±8	18±6	2.5±1.3 (3)	3.8	40.0	428
Grp A	34±8*	15±12	5.3±1.2 (7)	3.6	39.9	350
Grp B	6±5*	4±4*	0.09±.07 (4)*	1.2*	30.9	334

PCR did not demonstrate SIV infection of CFUs and T-cell depletion did not lead to a significant change in CFUs cultured. A profound decrease in CD34+ cells, CFU-GM and BFU-E is demonstrated, is similar to humans with HIV and may be important in the development of the hematologic abnormalities in SIV infection.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evidence for Autoimmune Hemolysis in All Macaques Studied With End Stage Simian Immunodeficiency Virus (SIV) Infection: An Important Etiology of Anemia

AXIS I: 1a, 17

AXIS II: 31, 66

PRC UNIT: Pathobiology & Immun

INVES1: Hillyer, Christopher D.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Ansari, Aftab A.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 74

NON-HOST INST: NA

ABSTRACT: Forty-nine SIV infected rhesus macaques (RM) were evaluated for autoimmune hemolytic anemia (AIHA); 25 SIV⁻ RM served as controls (Group A). The SIV⁺ RM were divided into 2 groups; Group B (n=35) were "well" with lymphadenopathy and/or hepatosplenomegaly only and Group C (n=14) were "sick" with weight loss, diarrhea, severe hematologic abnormalities and/or atypical infection. Hematocrit (Hct) and reticulocyte (retic) counts were determined. Direct antiglobulin tests (DAT) were done using mouse-anti-human IgG and complement (C') (Immucor) antisera after initial experiments confirmed DAT findings with goat-anti-monkey (Sigma) antisera. All animals had normal Hct preinfection. Mean values ± s.d. below:

Group (n=)	Hct %	Retic %	# + C' DAT	# + IgG DAT
A (25)	41.0±3.0	1.0±0.5	0	0
B (35)	38.7±3.4	2.1±1.4	4	9 (p=.007)
C (14)	25.6±11.8	5.5±4.4	7	14 (p=.001)

Polychromatophilia, anisocytosis and/or spherocytes were seen in all Group C RM; three had nucleated red blood cells (nRBC). Mean lactate dehydrogenase (LDH) was 426 U/L (n=13; Group A) and 1372 U/L (n=9; Group C). Erythroid hyperplasia was noted. Three Group C RM developed severe anemia (Hct < 10%) with retic > 16% and nRBC (13-18/100 WBC) on blood smear; evidence of cold

agglutinins was also present including RBC agglutination in the blood sample and smear, and agglutination (immediate spin; room temperature) in screening cell preparations (removed by 0.01M dithiothreitol). AIHA appears to occur often in "sick" SIV infected RM, may account in part for the anemia observed in these SIV infected animals and may be a good model for the study of lentivirus induced autoimmune phenomena.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Molecular Characterization of Simian Immunodeficiency Virus Isolated from Sykes' Monkeys

AXIS I: 1a, 7b

AXIS II: 31, 66

PRC UNIT: Pathobiology & Immun

INVES1: Hirsch, Vanessa M.
DEGREE1: D.V.M., Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Johnson, Philip R.
DEGREE2: M.D.
DEPT2: Pathobiology & Immunobiology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

SPECIES1: Cercopithicus mitis albogularis
NUM1: 1

SPECIES2: Macaca mulatta
NUM2: 4

SPECIES3: Macaca nemestrina
NUM3: 4

SPECIES4: Macaca fascicularis
NUM4: 4

NON-HOST INST: NIAID, NIH (VMH) and Ohio State University (PRJ)

ABSTRACT: Sykes' monkeys (Cercopithicus mitis albogularis) are African primates that are naturally-infected with SIV. Virus has been previously isolated from a seropositive Sykes' monkey (CM173) and this virus designated SIVsyk. The objectives of this study were to: (1) molecularly characterize SIVsyk, and (2) to determine the infectivity and virulence of SIVsyk in experimental infection of macaques. During the previous reporting period, full-length molecular clones of SIVsyk were generated by PCR amplification of half genomes and reconstruction in plasmid vectors. One full length, infectious clone (SIVsyk 1.2) was sequenced in its entirety and the predicted protein products compared with those of other primate lentiviruses. Comparisons of gag protein sequences revealed 50% identity between the gag proteins of SIVsyk and other primate lentiviruses, including HIV-1. Thus, SIVsyk is the prototype for a fifth group of primate lentiviruses. The other

four groups of primate lentiviruses previously identified are: (i) HIV-1, including SIVcpz from a chimpanzee; (ii) HIV-2, SIVsmmSIVmac; (iii) SIVagm; and, (iv) SIVmnd. The genomic organization of SIVsyk is similar to that of SIVmnd and SIVsyk is unique in lacking an identifiable NF-kB binding site in the LTRs. Cell-free virus stocks of SIVsyk were used to inoculate three species of macaques. All three species became persistently infected but immunologic parameters have remained normal and all animals are healthy. The clinical features and hematologic, virologic and immunologic parameters will continue to be monitored for these animals.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Effect of Two Adjuvants (OMPC and Interferon Gamma) on Immune Response in Neonatal Rhesus

AXIS I: 1a, 2

AXIS II: 64, 66, 91

PRC UNIT: Pathobiology & Immun

INVES1: Keyserling, Harry L.
DEGREE1: M.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 20

NON-HOST INST: NA

ABSTRACT: The human neonate is deficient in responding to antigenic stimuli to protein and polysaccharide antigens during the first two years of life. Many serious infections occur perinatally (Herpes simplex, hepatitis B, HIV, enteroviruses, listeria, gram negative enteric bacteria, and group B streptococcus) or during the first two years of life (respiratory syncytial virus, varicella, meningococcus, streptococcus pneumoniae and haemophilus influenzae).

To provide optimal protection against common infectious agents during the first two months of life, potent vaccines could be administered to the newborn at birth. Vaccines or adjuvants that accelerate the primary immune response either by more rapid production of antibody or a higher maximal antibody response would be beneficial.

We hypothesize that mixing various antigens with OMPC will result in an augmented immune response since OMPC has intrinsic adjuvant activity documented by its success as a carrier protein for the human HIB vaccine. Several studies in mice have demonstrated the adjuvant activity of interferon gamma. The infant rhesus monkey is a good model to predict human response to the vaccines.

Four groups consisting of five newborn rhesus monkeys in each group were immunized with three vaccines: A - OMPC-HIB(MSD); B - hepatitis B(MSD); C - inactivated polio (Connaught). Group 1 received vaccines A, B, and C at separate sites. Group 2 received vaccines A, B, and C combined at one site. Group 3 received vaccines A, B, and C at separate sites with 5,000 units of interferon gamma-1b added to each vaccine. Group 4 received vaccines A, B, and C and 5,000 units of interferon gamma-1b combined at one site. At six

weeks, all animals received booster doses of vaccines A, B, and C. Blood was collected at birth, and at 1 week, 2 weeks, and 8 weeks of age. The immune response of each animal to the various vaccine regimens is currently being evaluated using ELISA assays.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Human Infection with Simian Immunodeficiency Virus (SIV)

AXIS I: 1a, 4, 7b

AXIS II: 31, 66

PRC UNIT: Pathobiology & Immun

INVES1: Khabbaz, Rima F.
DEGREE1: MD
DEPT1:
STAFF1: O

INVES2: Murphey-Corb, M.
DEGREE2: PhD
DEPT2:
STAFF2: O

INVES3: Heneine, Walid
DEGREE3: PhD
DEPT3:
STAFF3: O

INVES4: George, Richard
DEGREE4: PhD
DEPT4:
STAFF4: O

INVES5: Burakh, P.
DEGREE5: PhD
DEPT5:
STAFF5: O

INVES6: McClure, Harold M.
DEGREE6: D.V.M.
DEPT6: Pathobiology & Immunobiology
STAFF6: C

INVES7: Folks, Thomas M.
DEGREE7: Ph.D.
DEPT7: Pathobiology & Immunobiology
STAFF7: O

SPECIES1: Macaca mulatta
NUM1: 2

SPECIES2: Macaca nemestrina
NUM2: 2

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

ABSTRACT: Susceptibility of humans to infection with the simian counterpart of HIV-2, SIV, has remained a question. A researcher working with SIV seroconverted in April 1990 and has shown increasing antibody titers to HIV-2/SIV 2.5 years later. On culturing, SIV was isolated from CD8-depleted PBMCs. The isolate bears a 40-44 bp depletion in the LTR, characteristic of SIV. Env sequences from the isolate and from a day-0 amplification from another time point are identical and closest (94% homology) to the SIV_{B670} strain this individual primarily worked with, and only 76%-81% and 50%-55% homologous to other representative SIV and HIV-2 strains, respectively. We conclude that this researcher is infected with SIV from exposure in the laboratory. This is the first isolation of an SIV strain from a human; the isolate has been designated SIV_{Mne}. To further evaluate this SIV, and to document any changes which may have occurred in the virus after passage through a human, two rhesus and two pig-tailed macaques have been inoculated intravenously with 10 ml of blood from the SIV positive individual. These animals are being monitored for signs of clinical disease and blood is collected periodically for immunologic evaluation, virus isolation and serologic evaluation. The molecular characteristics will be determined for any virus isolate obtained from these animals.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Animal Model for Pediatric AIDS: Pathology in Infant Rhesus Monkeys Infected with SIV_{smm} Through Maternal Transmission

AXIS I: 1a, 7b, 28 (Multisystemic)

AXIS II: 31, 66, 77, 92 (Pathology)

PRC UNIT: Pathobiology & Immun

INVES1: Klumpp, Sherry A.
DEGREE1: D.V.M., M.S.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Anderson, Daniel C.
DEGREE2: D.V.M.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

INVES3: Novembre, Francis J.
DEGREE3: Ph.D.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Pathobiology & Immunobiology
STAFF4: C

SPECIES1: Macaca mulatta
NUM1: 12

NON-HOST INST: NA

ABSTRACT: Cases of pediatric acquired immunodeficiency syndrome (AIDS) are increasing due to the rising incidence of HIV infection in women of child-bearing age. The literature suggests that disease progression and manifestations of pediatric AIDS are different from adult AIDS. Twenty-five percent (3 of 12) of infant rhesus monkeys born to mothers infected with simian immunodeficiency virus (SIV_{smm}) during the first, second or third trimester developed SIV antibodies between the ages of 9 to 12 months. The intervals between seroconversion and death were 7, 16 and 20 months. All infants were hypergammaglobulinemic early in the course of disease. Elevation of serum beta-2-microglobulin (B2M), which is an indicator of immune activation and a marker for monitoring disease progression, increased during the course of SIV_{smm} infection in rhesus infants. Absolute numbers of total T cells and the $CD4^+/CD8^+$ cell ratio declined with disease progression. Consistent gross necropsy findings included lymphadenopathy and splenomegaly, The two infants with a longer duration of illness were also emaciated. The infant which died 7 months after seroconversion had a severe hemolytic anemia with hemoglobinuria, renal hemosiderosis and extramedullary hematopoiesis.

The infant dying 16 months following seroconversion had SIV splenitis and lymphadenitis, interstitial pneumonia, CMV meningitis and radiculoneuritis, cryptosporidiosis of the gallbladder, bile duct and trachea and glial nodules in the cerebrum and spinal cord. The third infant had SIV meningoencephalomyelitis, cerebral glial nodules, progressive multifocal leukoencephalopathy confined to the spinal cord, pulmonary pneumocystosis, SIV interstitial pneumonia, cryptosporidiosis of the bile duct, pancreatic duct, stomach and small intestine, and adenoviral pancreatitis with adenoviral inclusion bodies in the gastric epithelial cells. Lesions of the two older SIV-infected rhesus infants resemble those of human pediatric AIDS in that pulmonary and CNS lesions were predominant and opportunistic infections were common.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Tissue/Implant Interfaces in Root and Plate Form Dental Implants

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

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

PRC UNIT: Pathobiology & Immun

INVES1: Koth, D.L.
DEGREE1: D.D.S.
DEPT1:
STAFF1: O

INVES2: Lemons, J.E.
DEGREE2: Ph.D.
DEPT2:
STAFF2: O

INVES3: Fritz, M.E.
DEGREE3: D.D.S., M.S., Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Kilpati
DEGREE4: Grad. Student
DEPT4:
STAFF4: O

SPECIES1: Mongrel dogs (UAB)
NUM1: 4

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

ABSTRACT: The purpose of this study was to evaluate the quantity of hard and soft tissue in contact with the surface of root and plate form implants as a first phase in a 60 month multicenter program project. The root and plate form implants were manufactured from the same materials (CPTi) and the plate form implant was designed to have the same tissue contacting area as the root form. Sixteen implants were placed in 4 mongrel dogs using specialized atraumatic surgical techniques. The implants were covered with soft tissue as in a first phase surgery and were not loaded. After 3 and 6 months the animals were euthanized. Using non-decalcified techniques the implants and adjacent tissues were prepared in mesial-distal and buccal- lingual sections. Samples were fixed in Pen-Fex (alcohol and formalin), stained with Sandersons rapid bone stain (Toluidine blue and Van Seison), placed in Methyl Methacrylate, cut with an Isomet saw to 100 micrometers and ground to approximately 40 micrometers. Tissue/implant interfaces were analyzed using computer aided optical microscopy. The root form implants showed a 56.5 mean percent of direct bone contact and the plate forms a mean percent of 62.35. Analysis by ANOVA revealed no statistical difference between the percent of bone in contact with root and plate form implants ($p=0.5487$). These favorable results support the continuation to further studies concerning prosthodontics and periodontics. These studies were conducted at UAB in preparation for the use of dental implants in nonhuman primates at the Yerkes Center.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Intravesical Injection of Teflon for Vesicoureteral Reflux

AXIS I: 1a, 27

AXIS II: 48, 62, 86

PRC UNIT: Pathobiology & Immun

INVES1: Malizia, Anthony A.
DEGREE1: M.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Woodard, John R.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Newton, Nancy E.
DEGREE3: M.D., Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Anderson, Daniel C.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

INVES5: Wyly, J. Bradley
DEGREE5: M.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: O

SPECIES 1: Macaca mulatta
NUM1: 1

NON-HOST INST: NA

ABSTRACT: Polytef paste injections (intravesical/subureteric) have been used to treat vesicoureteral reflex in children, although only limited animal studies have been performed, and our previous studies in monkeys demonstrated distant migration of Polytef particles and the development of large foreign body granulomas at all injection sites. The results of our previous studies in monkeys, through three years post-injection of the Polytef paste, have been reported and included in previous annual reports. As an adjunct to these studies, monitoring of one Polytef injected monkey has been continued to document changes in the granulomatous reaction and to monitor the potential carcinogenic effects of Polytef paste. This animal is being followed radiographically by CT scanning and magnetic resonance imaging. Plans are to monitor this animal for up to 15 years. There were no additional adverse findings during the current year.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: SIVsmm Infection via Amniotic Fluid Inoculation

AXIS I: 1a, 7b

AXIS II: 31, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Klumpp, Sherry A.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Anderson, Daniel C.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

SPECIES1: Macaca mulatta
NUM1: 14

NON-HOST INST: NA

ABSTRACT: Since preliminary studies failed to demonstrate intrauterine/ transplacental transmission of SIV in the rhesus macaque, this study was initiated to determine the effects of SIV infection via inoculation of the amniotic fluid. The ultimate goal is to develop a model that can be used to treat intrauterine lentivirus infection or that can be used to design strategies (immune system modulation or treatment) for the prevention of intrauterine, intrapartum, or postpartum infection. Accordingly, seven timed pregnant rhesus monkeys received amniotic fluid inoculations of SIVsmm at various stages of gestation. SIVsmm has been inoculated into the amniotic fluid (guided by ultrasound) of two rhesus macaques at 80 days gestation, two at 100 days gestation, two at 120 days gestation, and one animal received an amniotic fluid inoculation of virus at 147 days gestation. All seven rhesus females delivered clinically normal, term infants. Four of these females seroconverted and three animals continue to be seronegative, up to 8 months post-partum. Three of the seven infants were seropositive when first checked within the first week after birth, and one additional infant was seropositive at six weeks of age. One infant was virus positive within the first week of life and a second infant was virus positive at 7.5 months of age. Virus has

not been isolated from the other two seropositive infants (through 3.5 and 8 months of age). The other three infants continue to be seronegative at 3, 5, and 8 months of age. One of the seronegative infants has a virus positive mother; mothers of the other two seronegative infants are also seronegative. One seropositive and virus positive infant has a seronegative mother (through 7.5 months post-partum). The virus positive infants include one whose mother was inoculated (via the amniotic fluid) at 80 days gestation, one inoculated at 100 days gestation, one inoculated at 120 days gestation, and one inoculated at 147 days gestation. One infant that was seropositive and virus positive at birth showed a progressive anemia, hyperglobulinemia and immunosuppression and died at 15 months of age.

These preliminary observations indicate that intrauterine infection with SIV can be accomplished by inoculation of virus into the amniotic fluid. This route of infection should prove to be an appropriate model for pediatric AIDS that can be used to study the pathogenesis of lentivirus infection in fetuses and neonates, as well as a model for evaluation of prophylactic or therapeutic treatment regimens.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Serologic Survey of the Yerkes Great Ape Colony for Evidence of Retrovirus Infection

AXIS I: 1a, 7b

AXIS II: 31, 66

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis, J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 191

SPECIES2: Pan paniscus
NUM2: 13

SPECIES3: Pongo pygmaeus
NUM3: 30

SPECIES4: Gorilla gorilla
NUM4: 21

NON-HOST INST: NA

ABSTRACT: Since a number of chimpanzees in Africa and Europe have been found to be seropositive for antibodies to HIV-like viruses, with HIV-like viruses isolated from at least 3 of these seropositive chimpanzees, this serologic survey of the great apes in the Yerkes colony was undertaken to determine if any of these animals showed serologic evidence of retrovirus infection. In a previous survey in 1986, 139 chimpanzees, 20 gorillas and 37 orangutans in the Yerkes colony were found to be negative by IFA for antibodies to HIV. In the present survey, 191 chimpanzees, 13 pygmy chimpanzees, 30 orangutans and 21 gorillas were evaluated by ELISA for antibodies to HIV-1, HIV-2 and HTLV-1 (STLV-1). All seropositive animals were subsequently checked by Western blot.

Twenty-one of 191 chimpanzees were seropositive by ELISA for antibodies to either HIV-1, HIV-2 or HTLV-1/STLV-1; nine chimpanzees were positive by ELISA for HIV-1, one was positive for HIV-2, 10 were positive for HTLV-1/STLV-1, and one was ELISA-positive for HIV-1 and HTLV-1/STLV-1. However, none of the HIV-1 or HIV-2 positive animals were confirmed by Western blot. Ten of the eleven HTLV-1/STLV-1 ELISA positive animals were confirmed as positive by Western blot. Nineteen of 21 gorillas were seronegative for antibodies to HIV-1,

HIV-2 and HTLV-1/STLV-1. One gorilla was ELISA positive but Western blot negative for HIV-1 antibodies, and one gorilla was ELISA positive and Western blot positive for antibodies to HTLV-1/STLV-1. Twenty-six of 30 orangutans were ELISA negative for antibodies to HIV-1, HIV-2 and HTLV-1/STLV-1. Four orangutans were ELISA positive but Western blot negative for antibodies to HIV-2. Eight of 13 pygmy chimpanzees were ELISA negative for antibodies to HIV-1, HIV-2 and HTLV-1/STLV-1. One pygmy chimpanzee was ELISA positive but Western blot negative for antibodies to HIV-1 and four pygmy chimpanzees were ELISA positive for antibodies to HTLV-1/STLV-1. Three of these pygmy chimpanzees were confirmed as HTLV-1/STLV-1 positive by Western blot. These observations indicate that there are no natural infections with HIV-1 or HIV-2 in the Yerkes great ape colony, but that a small number of chimpanzees (5.2%), gorillas (4.8%) and pygmy chimpanzees (23.1%) show evidence of infection with HTLV-1/STLV-1.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Transmission of SIV_{SM} by Feeding Virus-Containing Infant Formula

AXIS I: 1a, 7b

AXIS II: 31, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Anderson, Daniel C.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

INVES4: Klumpp, Sherry A.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Macaca mulatta
NUM1: 9

NON-HOST INST: NA

ABSTRACT: This study was initiated to determine whether SIV_{SM} can be transmitted to infant rhesus monkeys by ingestion of virus-containing infant formula. The ultimate goal is to provide additional information on the potential importance of breast feeding in the transmission of HIV or SIV. Any infections that result would be monitored to document the characteristics and pathogenesis of SIV infection in the rhesus neonate to further develop and characterize the SIV-infected macaque as a model for pediatric AIDS.

For this study, six infant rhesus macaques (approximately 30 days of age) were moved to cages in an SIV containment area and placed on an SMA formula diet. Each of these infants received 1,000 $TCID_{50}$ of cell-free SIV_{SM} once daily for a period of one month. This was administered by adding the virus to the morning SMA feeding. Prior to initiating virus administration by this route, studies were done in the laboratory to show that SMA did not inactivate the virus. In addition, to demonstrate viability of the virus used for these feeding experiments, three juvenile rhesus monkeys were inoculated intravenously with the same virus dose (1,000 $TCID_{50}$) at different time points during the feeding studies.

Each animal in the study was examined at 6 and 12 weeks after the initial virus exposure, and at quarterly intervals thereafter. At each examination, blood was collected for a CBC, immunology and virus serology and culture. Each of the three juvenile macaques became virus-positive following intravenous inoculation. However, monitoring of the infant rhesus exposed to virus in the SMA formula has failed to demonstrate infection in any of the animals through approximately one year following the initial virus exposure. These observations indicate that SIV is not readily/easily transmitted by oral ingestion of cell-free virus, and suggest that virus-infected cells may be necessary for transmission by this route.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: SIV Infection in Feral Baboons in Kenya: Attempts to Isolate SIV from an SIV-Seropositive Baboon

AXIS I: 1a, 7b

AXIS II: 31, 66

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Chege, Gerald
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Isahakia, Mohamed
DEGREE4: Ph.D.
DEPT4: Pathobiology and Immunobiology
STAFF4: O

SPECIES1: Papio cynocephalus
NUM1: 2

SPECIES2: Macaca nemestrina
NUM2: 5

NON-HOST INST: Institute of Primate Research, Kenya (GC, MI)

ABSTRACT: In ongoing serologic surveys of feral nonhuman primates in Kenya, a small number of baboons have been found to be seropositive by ELISA and Western blot for antibodies to SIV. As part of our ongoing collaborative studies with the Institute of Primate Research in Nairobi, Kenya, one seropositive and one seronegative baboon have been shipped to the Yerkes Center to facilitate the isolation of an SIV from this seropositive animal. Although this baboon (#1621) is strongly seropositive by ELISA and shows multiple bands on Western blot, initial attempts to isolate SIV by culture of peripheral blood mononuclear cells were negative. This included coculture of baboon PBMC with human PBMC, PBMC from a seronegative baboon, pig-tailed macaque PBMC and multiple cell lines (MOLT 4, clone 8; CEMX174; CEMss, U937). DNA prepared from stimulated PBMC from animal 1621 was used as a template for two separate nested PCR amplifications. Conserved primers were derived from the gag and LTR sequences of SIVsmm/mac/HIV-2. Results gave a positive reaction with the LRT primers, but not with the gag primers. This was repeated and confirmed using PBMC and lymph node cells taken at a later date.

In order to improve the chances of isolation of an SIV from this baboon, 10 ml of heparinized blood from the baboon was inoculated intravenously into each of three juvenile pig-tailed macaques. These animals were subsequently monitored at periodic intervals for evidence of seroconversion and by culture of their PBMC. One of these animals was sacrificed 7 weeks following receipt of the baboon blood due to other health problems and its PBMC and various tissues were negative for SIV. The other two pig-tailed macaques have been monitored for 8 months and continue to be seronegative and virus negative. In further attempts to isolate a virus from the baboon, an inguinal lymph node was surgically removed from the baboon and aliquots of mononuclear cells from the lymph node were cultured or inoculated intravenously into two additional pig-tailed macaques; each macaque received 10^8 cells. For culture, aliquots of mononuclear cells from the lymph node were stimulated with PHA and placed in culture with the following cell types: CEMx174; CEMss; Molt 4, Clone 8; and baboon PBMC. Duplicate cultures of these contained 100 units/ml TNFa to try and stimulate virus replication. These two macaques have been monitored for 6 weeks post-inoculation and are still seronegative and virus-negative. Although this baboon appears to be clearly SIV-positive, all efforts, to date, to isolate a virus from this animal have been unsuccessful. Virus isolation attempts are continuing, and efforts are also underway to characterize SIV sequences from uncultured mononuclear cells from this animal by polymerase chain reactions. Isolation and characterization of a baboon SIV will provide further information on the apparently diverse family of nonhuman primate lentiviruses, and may help to further delineate the origin of the human AIDS viruses.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Serological Survey of Nonhuman Primates in Kenya

AXIS I: 1a, 7b

AXIS II: 31, 64, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Isahakia, Mohamed
DEGREE3: Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

SPECIES1: Cercopithecus mitis
NUM1: 120 (feral)

SPECIES2: Cercopithecus aethiops
NUM2: 606 (feral)

SPECIES3: Papio cynocephalus
NUM3: 682 (feral)

NON-HOST INST: Institute of Primate Research, Kenya (MI)

ABSTRACT: Serological surveys are being conducted on serum samples from feral nonhuman primates (baboons, Sykes monkeys, African green monkeys) in Kenya to determine the incidence of infection with HIV-1, HIV-2/SIV and HTLV-1/STLV-1 in various nonhuman primate species from different geographical regions of Kenya. Previous analyses showed a high prevalence of antibodies to SIV in Sykes (59% seropositive) and African green monkeys (51% seropositive). A somwhat lower prevalence of antibodies to SLTV-1 was observed (30% of Sykes monkeys and 43% of African green monkeys). These observations in feral Sykes and African green monkeys are similar to seroprevalence rates detected in the Yerkes mangabey breeding colony, suggesting that at least in these three African species of nonhuman primates, SIV infection is widespread. In these initial studies, the incidence of antibodies to SIV and STLV-1 was considerably lower in baboons; 0.2% of baboons were found to have antibodies to SIV and 5% had antibodies to STLV-1.

During the current year, serum samples were received from an additional 85 baboons and an additional 27 African green monkeys. All 85 baboons were negative when checked for antibodies to SIV/HIV-2 by Western blot. An evaluation of these samples for antibodies to HIV-1 and HTLV-1/STLV-1 has not been completed. The 27 African green monkey serum samples were received late in the year and have not yet been evaluated.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Post-Partum SIVsmm Infection via Breast Feeding

AXIS I: 1a, 7b

AXIS II: 31, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Klumpp, Sherry A.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Anderson, Daniel C.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

SPECIES1: Macaca mulatta
NUM1: 14

NON-HOST INST: NA

ABSTRACT: This study was designed to further characterize the potential for transmission of SIVsmm by breast feeding. In preliminary studies which demonstrated maternal-infant transmission of SIV in the experimentally infected rhesus macaque, transmission appeared to have occurred by breast feeding. In addition, recent studies with pediatric AIDS suggest that transmission of HIV by breast feeding may be a more important mechanisms for maternal-infant transmission than is generally believed. To further address this question, seven rhesus macaques were infected with SIVsmm following delivery of their offspring; the infants will remain with their mothers and allowed to breast-feed for a minimum of one year. Seven rhesus macaques were infected with SIVsmm at 5, 6, 8, 29, 37 and 102 days post-partum. All seven adult females seroconverted and were virus positive by six weeks post-inoculation. Following virus inoculation, the mothers and infants were monitored at bi-monthly intervals for evidence of virus infection in the infants (by serology and culture of PBMC). To date, the infants have been monitored for 9-16 months following SIV infection of the mother. All infants have remained seronegative and virus negative. Based on these observations, to date, and with small numbers of animals, it appears that SIV is not readily transmitted by breast feeding from infected mothers to their offspring.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Activation of Latent Malaria in SIV-Infected Immunosuppressed Pig-tailed Macaques

AXIS I: 1a, 7b, 7c, 17, 19

AXIS II: 31, 64, 66

PRC UNIT: Pathobiology & Immun

INVES1: McClure, Harold M.
DEGREE1: D.V.M.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Novembre, Francis J.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Klumpp, Sherry A.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: O

INVES4: Daniel C. Anderson
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

INVES5: Collins, William E.
DEGREE5: Ph.D.
DEPT5: Pathobiology and Immunobiology
STAFF5: O

SPECIES1: Macaca nemestrina
NUM1: 36

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

ABSTRACT: Acute clinical malaria was diagnosed in a pig-tailed macaque two years after importation from Indonesia and nine months after infection with SIV (smH4/PBj6.6 env chimera). Following infection with SIV, the animal showed a progressive decrease in the total WBC count, platelet count, and numbers of $CD4^+$ and $CD8^+$ T cells. At nine months post-SIV infection the animal was severely anemic (RBC: 1.35 x 10^6/ul, Hgb: 3.7 g/dl and Hcrt: 13.1%) and blood smears revealed large numbers of malaria parasites in the RBC. The parasites were present in all stages of development (ring forms of early trophozoites to mature schizonts) and were identified as Plasmodium inui. The animal was treated with chloroquine and follow-up at two and three weeks post-treatment revealed marked improvement in red cell parameters (RBC: 3.88 x 10^6/ul, Hgb: 11.8 g/dl and Hcrt: 34.9%) and the absence of malarial parasites,

although the animal continued to be immunosuppressed and thrombocytopenic. Following the occurrence of this clinical case, 35 other imported pig-tailed macaques were carefully examined and evidence of sub-clinical, chronic malaria infection was found in 37% (13 of 35) of the animals. Other SIV-infected animals, when they became immunosuppressed, subsequently developed variable degrees of anemia associated with increased numbers of malaria parasites in the RBCs in peripheral blood smears. These observations indicate that a significant number of wild-caught pig-tailed macaques have subclinical, latent malaria infection and that acute, clinical malaria with severe anemia may occur in these animals when they become immunosuppressed following SIV infection. These observations also suggest that HIV infection in humans may exacerbate subclinical malarial infection when these individuals become immunosuppressed.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Immunological and Molecular Studies of Primate Antigens

AXIS I: 1a, 2, 3, 4, 6, 9

AXIS II: 1b,e; 39; 60; 64; 74a,h; 76 a,b; 91

PRC UNIT: Pathobiology & Immun

INVES1: Metzgar, Richard S.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

SPECIES1: Pan troglodytes
NUM1: 2

NON-HOST INST: Duke University Medical Center

ABSTRACT: The overall goals of this project are to continue to define selected antigens of human secretory epithelial cells and to use chimpanzees for evaluating potential human tumor vaccines. The uniqueness of the study is that it utilizes the immunologic perspectives of a species remarkably similar to man to recognize epitopes on human antigens that may not be seen by non-primate mammalian species. The antigenic focus during the current and continuation year is on peptide determinants of human tumor and normal cell apomucins. We have cloned the human pancreatic tumor mucin gene at Duke University and are currently evaluating in chimpanzees the immunogenicity of various synthetic peptides derived from the predicted amino acid sequence of the human gene product and prokaryotic expressed recombinant human apomucin proteins. Other preclinical and clinical studies currently being conducted at Duke University have indicated that mucin peptides may be important antigenic molecules for active immunotherapy of breast and pancreatic cancer patients, and that tolerance is to the native glycosylated protein and not to peptides devoid of glycosylation sites.

These immunological studies of human tumor antigens in higher apes are unique and important preclinical models to evaluate immunogenicity of selected tumor antigens and justify active immunotherapy trials with these antigens. In addition, the chimpanzee antibodies may be useful as diagnostic and/or clinical management aids for patients with certain types of mucin producing adenocarcinomas. There is considerable evidence that tumor mucins are aberrantly glycosylated compared to their normal cell counterparts, so that antibodies to either carbohydrate or peptide determinant could detect the post-translational modifications of these tumor antigen molecules.

Two chimpanzees have been immunized and are currently being utilized for these studies. One animal received the recombinant human apomucin protein and the other was injected with a synthetic peptide representing the cytoplasmic tail portion of the membrane glycoprotein. The polyclonal antibody response of these animals is directed to peptide determinants in the tandem repeat segment of the mucin protein. A collaborative agreement has been reached with

Stratacyte Corporation to evaluate their new method for creating human and, in this case, chimpanzee monoclonal antibody expression libraries, using their patented bacteriophage lambda expression vector. Since chimpanzee and human immunoglobulins have virtually identical sequences, the human immunoglobulin primers should work well in PCR amplification of immunoglobulin mRNA. In the past, we have been unable to produce stable IgG hybridomas that secrete the desired chimpanzee monoclonal antibodies to human tumor antigens. The new technology described above to produce combinatorial libraries expressing monoclonal antibodies should solve the problem of an appropriate fusion partner and other shortcomings of primate hybridoma technology. The results of these studies will be of paramount importance in the design of future protocols utilizing higher apes in human tumor diagnostic and therapeutic strategies.

The T cell cellular immune responses of the immunized chimpanzees to mucin peptide epitopes is also being evaluated and the animals tested for autoimmune pathologic effects in their normal mucin expressing tissues.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Infection of Pig-tailed Macaque Monocytes with $SIV_{smm}PBj$

AXIS I: 1d, 7b

AXIS II: 31, 66

PRC Unit: Pathobiology & Immun

INVES1: Narayan, Opendra
DEGREE1: D.V.M., Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

SPECIES1: Macaca nemestrina
NUM1: 3 (PBMC only)

NON-HOST INST: University of Kansas (ON)

ABSTRACT: PBj is an extremely virulent virus that causes hyperacute fatal infection in pig-tailed macaques. Lymphadenopathy and multinucleated giant cell formation are found frequently in lymph node, spleen and lungs from fatally infected animals. Many of the cells in the multinucleated giant cells (MGC) appear to be macrophages. Although it has been well established that $SIV_{smm}PBj$ causes mitogenic infection in PBM cultures with lytic outcome, the effect of the virus on purified monocyte-macrophages has not been evaluated. We inoculated virus into such cultures and after one week, failed to observe any obvious CPE, unlike the fusion effect of the virus in macrophages in vivo during a similar time frame. We therefore resorted to a protocol that we had used previously to simulate fusion of macrophages observed in chronic diseases such as tuberculosis and rheumatoid arthritis. These experiments have shown that lymphokines obtained from PHA-stimulated PBM, together with antibodies to MHC Class 2, added to monocytes, caused rapid fusion. Using this protocol and $SIV_{smm}PBj$ grown in CEM x 174, we inoculated monocytes with virus alone or virus plus anti MHC Class 2 or virus plus anti MHC Class 2 plus PHA induced lymphokine. Only the last method resulted in MGC formation. We then used supernatant fluids from PBj-infected PBM and in another culture, this supernatant plus anti-MHC Class 2 to inoculate monocytes. The latter procedure resulted in massive MGC formation. We then repeated this experiment using anti-MHC Class 2 and a filtrate of the PBj-PBM supernatant fluid, separating the lymphokines from the virus so as to inoculate the monocytes with only the antibodies and the lymphokines, but not virus. This procedure resulted in MGC formation within two days. We speculate therefore that MGC formation observed in PBj infected animals may be caused by interaction of lymphokines, produced during the infection in lymphocytes, and minimal amounts of anti-MHC Class 2 that may be produced during the hyper acute disease.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: HIV Infection in Pig-tailed Macaques

AXIS I: 1a, 7b

AXIS II: 31, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: Narayan, Opendra
DEGREE1: D.V.M., Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

SPECIES1: Macaca nemestrina
NUM1: 3

NON-HOST INST: University of Kansas (ON)

ABSTRACT: Animal models of pathogenesis and neuropathogenesis by HIV are desperately need to determine what genes of the virus are important for infection and disease. In this study, we used a molecular clone of HIV [Virus 89.6 reported by Dr. Ron Collman, University of Pennsylvania School of Medicine]. A stock of this virus was prepared in CEM x 174 cells in our lab and this was used for inoculation of pig-tailed macaque monkeys. We followed a protocol of experimental infection that we had used previously to derive neurovirulent SIV_{MAC} from non-neurovirulent parental virus $SIV_{MAC}239$ in rhesus macaques. Virus 89.6 was to be inoculated intracerebrally (IC) into one pig-tailed macaque and after infection had been established, bone marrow cells from this animal were to be inoculated IC into 2 other animals. Brain tissue was subsequently to be evaluated.

One week after inoculation of the first pig-tailed macaque, viremia developed with a titer of 10^4 $TCID_{50}$/ml in plasma and infection in more than 1 in 500 PBMC. This highly productive infection continued for more than 16 weeks. At the six week point, bone marrow cells from this animal were used for IC inoculation into two other pig-tailed macaques. These 2 animals also became severely infected. This result was highly unusual, given the great difficulty other investigators have had in duplicating the positive infection in pig-tailed macaques with HIV, reported from the Washington Primate Center. We therefore performed a thorough examination of the virus used for inoculation of the first animal and virus obtained from all 3 inoculated animals, using immunocytochemical and molecular techniques. These studies showed that the inoculum virus was predominantly HIV, with a trace of cross-reacting SIV_{MAC}. However, virus that came out of the animals was purely $SIV_{MAC}239$. In retrospect, our "normal" cell culture line of CEM x 174 had apparently become contaminated with $SIV_{MAC}239$ without developing obvious cytopathic effects

typical of this viral infection. The animals, being more susceptible to infection with SIV_{MAC} than HIV, amplified the SIV.

Since $SIV_{MAC}239$ in earlier studies in rhesus macaques had mutated to a neurovirulent strain after IC inoculation, we will terminate the present study in the two surviving pig-tailed macaques (one died from nonlentiviral related disease) after one year and euthanatize the animals to determine molecular sequence of virus 239 in different tissues. We will thus be able to take advantage of the contamination problem and obtain useful results.

We will continue this investigation but will use only purified infectious DNA as inoculum. The infectivity of this material will be confirmed in tissue culture, but only DNA and not virus, will be used as the inoculum. The protocol for evaluation of infection in plasma and PBMC will be followed using virus isolation, immunocytochemistry and molecular (PCR) techniques to identify with certainty the virus in such tissue samples.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Molecular Analyses of SIVsmmPBj

AXIS I: 1a, 1d, 7b

AXIS II: 31, 39, 66, 77

PRC UNIT: Pathobiology and Immun

INVES1: Novembre, Francis J.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Hirsch, Vanessa M.
DEGREE2: D.V.M., Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Macaca nemestrina
NUM1: 20

NON-HOST INST: National Institute of Allergy and Infectious Diseases, NIH (VMH)

ABSTRACT: SIVsmmPBj induces a rapidly fatal disease when inoculated into pig-tailed macaques. This syndrome, in contrast to the protracted immunodeficiency ordinarily associated with SIV, is characterized by a fulminant diarrhea and acidosis leading to death in 5 to 14 days. Previously we had generated two full-length molecular clones of SIVsmmPBj which produce virus capable of reproducing the disease in inoculated animals. These molecular clones have been utilized to construct chimeric clones with SIVsmH4 to deliniate the genetic determinants responsible for acute pathogenesis of SIVsmmPBj. Results using these chimeras have shown that multiple determinants contribute to the pathogenesis of this acute disease. Specifically undefined regions in the gag and env genes of PBj are necessary for the induction of the acute disease. Also, sequences present in the regulatory gene region have also been found to be important. Interestingly, the LTR region, which contains a duplicated enhancer element, is not required for development of acute disease. In vitro studies utilizing viruses derived from these molecular clones have shown an association of the ability of a virus to cause disease and its ability to induce the proliferation of pig-tailed macaque peripheral blood mononuclear cells. While the LTR may not be important in the disease progression of SIVsmmPBj, elements contained within the LTR are necessary for efficient replication of SIVsmmPBj in macrophages. These investigations are important for understanding the molecular mechanisms involved in the pathogenesis of an acutely lethal lentivirus.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: HIV-1 Infection of Pig-tailed Macaque Cells In Vitro

AXIS I: 1a, 1d, 7b

AXIS II: 31, 39, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: Novembre, Francis J.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

SPECIES1: Macaca nemestrina
NUM1: 4

NON-HOST INST: NA

ABSTRACT: The most useful animal model for AIDS and HIV-1 infection currently available is the SIV/macaque model system. However, critics argue that SIV is only distantly related to HIV-1 and may not be truly indicative of disease in humans. Thus, animal models utilizing HIV-1 infection are routinely investigated. While the chimpanzee is readily infected with HIV-1, no disease or clinical symptoms have emerged suggesting that this is not a good model system. Recently investigators at the Washington Regional Primate Center have reported infection of pig-tailed macaques with HIV-1. We thus undertook these studies to possibly provide a new animal model for AIDS. Our in vitro experiments utilized peripheral blood mononuclear cells (PBMC) from pig-tailed macaques to try and establish HIV-infection. To date all of our efforts have failed to demonstrate that HIV-1 can infect pig-tailed macaque PBMC. We have utilized the following virus strains for these studies: HIV-1_{MN}, HIV-1_{SF2}, and HIV-1_{NL4-3}, two of which were used with success at the Washington Regional Primate Center. These results demonstrate that HIV-1 infection of pig-tailed macaques is not an easy task and thus may not be an appropriate, readily reproducible model system for human AIDS.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Molecular Cloning of SIV from Stump-tailed Macaques

AXIS I: 1a, 1d, 7b

AXIS II: 31, 39, 66, 77

PRC UNIT: Pathobiology & Immun

INVES1: Novembre, Francis J.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: C

INVES2: Hirsch, Vanessa M.
DEGREE2: D.V.M., Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Macaca nemestrina
NUM1: 10

SPECIES2: Macaca mulatta
NUM2: 10

NON-HOST INST: National Institutes of Allergy and Infectious Diseases, NIH (VMH)

ABSTRACT: SIV from stump-tailed macaques (SIVstm) is unusual in that it has been associated with outbreaks of infection characterized by aggressive spread within stump-tailed macaque colonies at two separate primate centers. To characterize this virus at the molecular level we have derived six biologically active molecular clones. Nucleotide sequence analysis of one of these clones (37.16) showed that SIVstm was indeed a member of the HIV-2/SIVmac/SIVsmm group of primate lentiviruses. Data indicate that SIVstm is equidistantly related to SIVs from macaques and SIV from African sooty mangabeys. These findings suggest that SIV in captive macaques may have originated from several cross-species transmissions from imported sooty mangabeys. Virus derived from uncloned stock of SIVstm and from two of our clones (37.16 and 29.11) was used for inoculation of macaques (pig-tailed and rhesus) to investigate whether AIDS-like disease would develop. Of 8 animals that received the uncloned virus, 4 have been euthanatized due to AIDS-like illness. Of 8 animals that received either molecular cloned virus, 3 have succumbed to AIDS. These studies indicate that our cloned viruses have similar characteristics to the uncloned stock with respect to induction of AIDS. Also, our results further implicate the spread of SIV by cross-species transmission. These studies are important in helping to define the origin of primate lentiviruses and understanding development of AIDS-like disease.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Magnetic Resonance Imaging and Spectroscopy in Rhesus Monkey (Macaca mulatta) Placenta and Fetus

AXIS I: 1a, 9, 21, 28 - placenta

AXIS II: 44, 50 - cocaine, 63c, 80, 87

PRC UNIT: Pathobiology & Immun

INVES1: Panigel, Maurice
DEGREE1: M.D., Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Nahmias, Andre J.
DEGREE2: M.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

INVES4: Swenson, R. Brent
DEGREE4: D.V.M.
DEPT4: Veterinary Medicine
STAFF4: C

INVES5: Dixon, Tom
DEGREE5: Ph.D.
DEPT5:
STAFF5: O

INVES6: Constantinidis, Ioannis
DEGREE6: Ph.D.
DEPT6:
STAFF6: O

INVES7: Long, Robert
DEGREE7: Ph.D.
DEPT7:
STAFF7: O

INVES8: Shepherd, Scott
DEGREE8: Ph.D.
DEPT8:
STAFF8: O

SPECIES1: Macaca mulatta
NUM1: 2

NON-HOST INST: NA

ABSTRACT: This research group has applied magnetic resonance technology to detect the effects of drugs and infectious agents on placental hemodynamics, fetal development and maternal fetal exchange. Evaluations have been made in pilot studies of the changes in the uteroplacental hemodynamics of two pregnant rhesus monkeys at different stages of gestation.

Fast scan dynamic magnetic resonance imaging demonstrated the maternal blood circulation in the placenta of two pregnant rhesus monkeys (Macaca mulatta) examined several times at different stages of gestation. Jets of maternal blood spurting intermittently into the intervillous space were observed without the use of any contrast medium. They were not seen during the first 2 months of pregnancy, and were observed in the later stages of pregnancy - from 114 days on.

Cumulative doses of cocaine hydrochloride, starting with 0.2 mg/kg were injected intravenously every 20 minutes for 2 hours. Changes due to cocaine infusion were observed in the sequence of imaging obtained without contrast. As anticipated by previous studies on rhesus monkeys, no side effects were noted in the monkeys or their offspring.

This method is applicable for the detection of the effects of other drugs and infectious agents on placental hemodynamics and maternal fetal exchange.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Synthesis and Biotransformation of Anti-HIV Prodrugs

AXIS I: 1a, 2, 28 Pharmacokinetics

AXIS II: 31, 50b

PRC UNIT: Pathobiology & Immun

INVES 1: Schinazi, Raymond F.
DEGREE 1: Ph.D.
DEPT 1: Pathobiology and Immunobiology
STAFF1: O

INVES 2: McClure, Harold M.
DEGREE 2: D.V.M.
DEPT 2: Pathobiology and Immunobiology
STAFF2: C

SPECIES1: Maccaca mulatta
NUM1: 3

NON-HOST INST: NA

ABSTRACT: Racemic 2',3'-dideoxy-5-fluoro-3'-thiacytidine (FTC) was recently shown to have potent and highly selective activity against HIV-1, HIV-2, and SIV in various cell culture systems (e.g., $EC_{50} \leq 0.01$ μM in HIV-1-infected human lymphocytes). This compound also had potent anti-hepatitis B virus activity in transfected HepG2 cells (2.2.15 cells). We subsequently determined that the more potent enantiomer was the (-)-b-L-enantiomer [(-)-FTC] against both viruses. FTC and its enantiomers were nontoxic to peripheral blood mononuclear cells (PBMC) and other cell lines at concentrations up to 200 μM. Studies with human bone marrow cells indicated that FTC had an $IC_{50} \geq 30$ μM. (-)-FTC was less toxic to human bone marrow cells than the (+)-FTC. FTC-TP competitively inhibited HIV-1 reverse transcriptase (RT) with a K_i of 0.2 μM using a poly(I)·oligo(dC) template-primer. Sequencing analysis demonstrated that FTC-TP was a potent DNA chain terminator when HIV-RT was used (C-stops).

The sensitivity to (-)-FTC of a pretherapy isolate when compared to a post-therapy AZT-resistant HIV-1 in PBMC was not substantially increased. Similar results were obtained with a BI-RG 0587-resistant HIV-1. (-)-FTC-resistant variants were cross-resistant to (-)-FTC, (-)-BCH-189, and their (+)-congeners, but remained susceptible to DDC, AZT, 3'-fluoro-3'-deoxythymidine, DDI, PFA, and the TIBO compound R82150. HIV-1 RT derived from drug-resistant viral particles was 25- to 50-fold less susceptible to the 5'-triphosphates of FTC and BCH-189 compared with enzyme from parental drug-susceptible virus. DNA sequence analysis of the RT gene amplified from resistant viruses consistently identified mutations at codon 184 from Met (ATG) to Val (GTG or GTA) or Ile (ATA). Sequencing analysis of amplified RT from a patient who had received (-)-BCH-189 therapy for 5 months demonstrated the Met^{184} to Val (GTG) mutation, indicating that this change can occur *in vivo*. The Met^{184} residue lies in a

highly conserved polymerase motif (Tyr-Met-Asp-Asp) adjacent to the putative catalytic site of the HIV-1 RT comprised of the carboxylate triad Asp^{110}, Asp^{185}, and Asp^{186}. Substitution of the Met^{184} residue appears to markedly affect the anti-HIV activity of oxathiolane-cytosine analogs. These findings should permit effective monitoring for the emergence of resistance to these drugs.

(-)-FTC-TP was the major intracellular metabolite in human PBMC. The intracellular half-life of FTC-TP was about 12 h, and at 24 h more than 2 μM FTC-TP could still be detected. 2'-Deoxycytidine prevented the anti-HIV-1 activity of (-)-FTC and no intracellular phosphorylation of FTC occurred in 2'-deoxycytidine kinase deficient cells. These results suggest that this compound is initially phosphorylated by this enzyme. Chronic treatments of FTC were not toxic to rodents, even at doses of 85 mg/kg per day. The pharmacokinetics of racemic FTC in rhesus monkeys indicated an oral bioavailability of 73 ± 6% and a plasma half life of 1.34 ± 0.18 h. Partial deamination of FTC occurred in monkeys, but not in rats. Racemic FTC was slowly deaminated in human PBMC and HepG2 cells only to (+)-FTU. In contrast, (-)-FTC was not deaminated in these cells, nor was it a substrate for cytidine/deoxycytidine deaminase. FTC and its deaminated product were not substrates for thymidine phosphorylase. More recent pharmacokinetic studies with radiolabeled (-)-FTC in rhesus monkeys indicated that (-)-FTC was the main metabolite found in the serum and urine. The formation of glucuronide and the two sulfoxides of (-)FTC was detected as minor metabolites. On the basis of these results the development of (-)-FTC is warranted as an antiviral agent for infections caused by HIV and HBV.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: In Vitro and In Vivo Disposition and Metabolism of 2', 3'-Didehydro-2', 3'-Dideoxythymidine (D4T).

AXIS I: 1a, 2, 28 Pharmacokinetics

AXIS II: 31, 50b

PRC UNIT: Pathobiology & Immun

INVES1: Sommadossi, J.-P.
DEGREE1: Ph.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Kidd, L.B.
DEGREE2: M.S.
DEPT2:
STAFF2: O

INVES3: McClure, Harold M.
DEGREE3: D.V.M.
DEPT3: Pathobiology & Immunobiology
STAFF3: C

INVES4: Kaul, S.
DEGREE4: Ph.D.
DEPT4:
STAFF4: O

INVES5: Hitchcock, M.J.M.
DEGREE5: Ph.D.
DEPT5:
STAFF5: O

INVES6: Cretton, E.M.
DEGREE6: Ph.D.
DEPT6:
STAFF6: O

SPECIES1: Macaca fascicularis
NUM1: 3

NON-HOST INST: University of Alabama at Birmingham (JPS, LBK, MJMH, EMC) and Bristol-Myers Research Institute (SK)

ABSTRACT: The disposition and metabolic fate of 2', 3'-didehydro-2', 3'-dideoxythymidine (D4T) was evaluated both in isolated hepatocytes and in nonhuman primates. Rapid formation of thymine and b-aminoisobutyric acid (BAIBA) occurred following incubation of hepatocytes with 10 uM [5-^{3}H]D4T. Substantial levels of tritiated water were also detected. Exposure of cells to D4T in the presence of either 1 mM thymine or 10uM benzyloxybenzyluracil, an inhibitor of dihydropyrimidine dehydrogenase, decreased intracellular BAIBA

levels by approximately 89% and 63% respectively. Concurrently, ^{3}H-thymine levels increased 2- to 5-fold. These results are consistent with D4T being cleaved to thymine which is then degraded to BAIBA. A similar metabolic disposition was observed in monkeys following administration of 25 mg [5-^{3}H]D4T per kg of body weight, BAIBA, thymine and tritiated water were identified in plasma and urine. Approximately 50% of the administered dose was recovered in urine within 24 hours, with the majority of the radioactivity representing unchanged drug. After administration intravenously or orally of 25 mg [4-^{14}C]D4T per kg body weight to monkeys, a novel metabolite designated X_2 was also detected in addition to unchanged D4T, thymine and BAIBA. The sum of the three metabolites and unchanged drug accounted for virtually all of the radioactivity in plasma and urine. Thymine and X_2 exhibited kinetic profiles similar to D4T with plasma elimination $T_{1/2}$ of 2-3 hr whereas BAIBA levels remained constant for extended time periods and declined slowly; this metabolite could be detected 24 hr after drug administration. Mean oral bioavailability of D4T was high at approximately 70%. As observed in the [5-^{3}H]-D4T study performed in monkeys, approximately half of the administered [4-^{14}C]D4T was recovered unchanged. The remainder was not recovered in urine or feces collected up to 30 days after drug administration. These data suggest that D4T metabolites may be further metabolized by salvage pathways and/or converted to biological macromolecules.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Catabolism of 2', 3'-Didehydro-2', 3'-Dideoxythymidine (D4T) in Isolated Hepatocytes and in Rhesus Monkeys

AXIS I: 1a, 2, 28 Pharmacokinetics

AXIS II: 31, 50b

PRC UNIT: Pathobiology & Immun

INVES1: Sommadossi, J.-P.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVES2: Zhou, Z.
DEGREE2: Ph.D.
DEPT2:
STAFF2: O

INVES3: Hitchcock, M.J.M.
DEGREE3: Ph.D.
DEPT3:
STAFF3: O

INVES4: McClure, Harold M.
DEGREE4: D.V.M.
DEPT4: Pathobiology and Immunobiology
STAFF4: C

INVES5: el Kouni, M.
DEGREE5: Ph.D.
DEPT5:
STAFF5: O

INVES6: Cretton, E.M.
DEGREE6: Ph.D.
DEPT6:
STAFF6: O

SPECIES1: Macaca mulatta
NUM1: 3

NON-HOST INST: University of Alabama at Birmingham (JPS, ZZ, MJMH, MEK, EMC)

ABSTRACT: The present study evaluated the in vitro and in vivo catabolic fate of D4T, a novel anti-HIV agent. Following a 2 hour exposure of hepatocytes to 10 uM [^{3}H]-D4T, the predominant intracellular catabolite was B-aminoisobutyric acid (BAIBA) representing 16% of the radioactivity by 90 min. Thymine levels decreased to 0.5% by 90 min. Increasing levels of tritiated water [^3H_2O] were also detected. In the presence of 1 mM thymine, 10 uM BBU (an inhibitor of dihydrouracil dehydrogenase), BAIBA was inhibited by 100% and

50% respectively. Following subcutaneous administration of 25 mg/kg [^{3}H]-D4T in rhesus, a similar catabolic profile was observed. The D4T Cmax averaged 14.3 ug/ml with an apparent plasma $T_{1/2}$ of about 1 hr. Levels of thymine and BAIBA were detected in biological fluids as early as 0.5 hr post administration with plasma Cmax values averaging 0.45 ug/ml and 0.60 ug/ml respectively. In addition, ^3H_2O was also detected. Urinary recovery of total radioactivity was approximately 50%, 24 hours after administration. Preliminary studies showed that D4T is a substrate for purified human thymidine phosphorylase. These results suggest that D4T catabolism involves a sequential degradation to thymine and BAIBA.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Analysis of Resistance-Associated Human Immunologic Responses to Onchocerca volvulus Infection

AXIS I: 5a, 5b, 7c

AXIS II: 64, 66, 91

PRC UNIT: Pathobiology & Immun

INVEST 1: Tsang, Victor C.W.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: O

INVEST2: Eberhard, Mark L.
DEGREE2: Ph.D.
DEPT2: Pathobiology and Immunobiology
STAFF2: O

INVES3: Pieniazek, Norman
DEGREE3: Ph.D.
DEPT3:
STAFF3: O

SPECIES1: Homo sapiens (serum)
NUM1: 1,032

NON-HOST INST: Centers for Disease Control and Prevention

ABSTRACT: The primary objectives of this study, which is being done in parallel with infection studies in nonhuman primates, is to complete expression and purification of 11 unique, immune-associated, O. volvulus recombinant antigens in the maltose binding protein (pMal) vector system and to quantify specific IgG3 and IgG1 reactivities of onchocerciasis patients to all recombinant antigens to confirm that putatively immune individuals react to these antigens with high IgG3 levels while infected individuals react with high IgG1 levels. To accomplish these goals, the isotypic responses to O. volvulus infection of 1,032 patients from hyper-, meso-, and hypoendemic plantations in Guatemala were examined.

Eighty-two residents in meso- and hyperendemic areas, in spite of constant, lifelong exposure to O. volvulus, were found to have never developed any O. volvulus infection. These individuals with no nodules, no microfilaria and no infection histories were classified as resistant. These putatively immune individuals react differently to O. volvulus nodular antigens than do infected individuals. Most infected individuals were found to produce levels of specific IgG1 much higher than that of IgG3, whereas immune individuals have much higher specific IgG3 levels, often equal to or higher than their IgG1 levels. The high specific IgG3/IgG1 ratio strongly correlates with the state of resistance to O. volvulus in all populations where prevalence of onchocerciasis is moderate to high. In addition, individuals with clinical

histories of onchocerciasis, but who are no longer infected, also show high IgG3/IgG1 ratios, suggesting that they may be in the process of acquiring immunity. The IgG3 from individuals with high specific IgG3/IgG1 ratios appears to be specific for a group of nodular glycoprotein antigens with a molecular weight of 18K-20K (GP20). In contrast, GP20 is almost exclusively recognized by IgG1 of infected individuals whose specific IgG1 levels are higher than IgG3, suggesting that IgG1 blocking antibody is present in susceptible individuals. Recent data from selected immune and infected individuals also indicate that Km/Gm allotypes do not influence immunity.

These studies have resulted in a more complete characterization of the immune response associated with onchocerciasis. Continued studies of this type, done in parallel with immunologic studies in experimentally infected nonhuman primates, should contribute to the eventual development of an effective vaccine for onchocerciasis.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Onchocerca volvulus Antigens Inducing a Cellular Immune Response.

AXIS I: 1a, 7c

AXIS II: 66, 91

PRC UNIT: Pathobiology & Immun

INVEST 1: Unnasch, Thomas R.
DEGREE1: PhD
DEPT1:
STAFF1: O

INVEST2: Chakravarti, Deb N.
DEGREE2: PhD
DEPT2:
STAFF2: O

SPECIES1: Pan troglodytes
NUM1: 3

NON-HOST INST: University of Alabama at Birmingham

ABSTRACT: Onchocerciasis is caused by infection with the parasite Onchocerca volvulus. Onchocerciasis is the second largest cause of infectious blindness worldwide. The lack of a drug to treat the adult form of the parasite has made chemotherapeutic strategies to control onchocerciasis difficult to implement. An alternative approach to chemotherapy is the development of a vaccine. The goal of our research is to identify parasite antigens which may induce protective immunity. In related helminthic parasites for which animal models are available, inoculation with irradiated infective larvae (*L3) results in the development of a protective immune response. Cellular immune responses are thought to be instrumental in this process. The only known non-human host for O. volvulus is the chimpanzee. Based upon the success of irradiated infective larvae in other helminthic parasitic systems, our efforts have concentrated on the purification of parasites that induce a cellular immune response in chimpanzees immunized with *L3. To accomplish this goal, parasite extracts were fractionated by gel filtration and anion exchange FPLC. Fractions containing antigens recognized by the cellular immune system of *L3 immunized chimpanzees were identified based on their ability to induce a lymphoproliferative immune response. Active fractions were further characterized based upon their ability to induce a proliferative response in cells collected from a chimpanzee with a patent O. volvulus infection. One pool of fractions was recognized by cells from the *L3 immunized chimpanzees, but not by cells from a patently infected chimpanzee. Further fractionation of these proteins by cation exchange, hydrophobic interaction and gel filtration HPLC yielded three apparently homogeneous antigens which exhibited significant blastogenic activity. Currently, efforts are underway to isolate cDNA clones encoding these antigens, with the eventual goal of producing enough of the purified parasite proteins to allow assessment of their value as candidate vaccine antigens.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Quantification and Detection of Nonhuman Primate Cytokines

AXIS I: 1a, 1d, 2, 9, 15

AXIS II: 39, 64

PRC UNIT: Pathobiology & Immun

INVES1: Villinger, Francois
DEGREE1: D.V.M.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Ansari Aftab A.
DEGREE2: Ph.D.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

SPECIES1: Cercocebus atys
NUM1: 10

SPECIES2: Macaca mulatta
NUM2: 10

SPECIES3: Macaca nemestrina
NUM3: 10

NON-HOST INST: NA

ABSTRACT: The fact that sooty mangabeys naturally infected with SIVsmm remain clinically asymptomatic whereas rhesus or pig-tailed macaques experimentally infected with SIVsmm develop disease which invariably results in death, combined with the plethora of studies that show an important role of cytokines in human and nonhuman primate lentivirus infections, prompted us to examine the spectrum of cytokines secreted by cells from these two species.

Toward this goal, our laboratory has screened commercially available EIA kits and set up biological assays and PCR techniques for the detection of cytokines and their mRNA in these two species. Results show that the commercially available cytokine EIA kits for IL1β, IL-2, IL-4, IL-6, and TNFα successfully detect these cytokines from the two species. The biological assays for IL-1, IL-2, IL-4, IL-6, TNF, and IFN-γ have been established. In addition, PCR techniques for the detection of mRNA for IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-6, IFN-γ, TNF-α, TNF-β, and IL-10 for the two species have been successfully established.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Role of Nef in Natural SIV Infection

AXIS I: 1a, 1d, 7b,

AXIS II: 31, 59, 66

PRC UNIT: Pathobiology & Immun

INVES1: Villinger, Francois
DEGREE1: D.V.M.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

INVES2: Ansari Aftab A.
DEGREE2: Ph.D.
DEPT2: Pathobiology & Immunobiology
STAFF2: C

SPECIES1: Cercocebus atys
NUM1: 16

SPECIES2: Macaca mulatta
NUM2: 3

SPECIES3: Macaca nemestrina
NUM3: 1

NON-HOST INST: NA

ABSTRACT: Based on the finding that the Nef gene was indispensable for the development of SIV-induced disease, the objective was to analyze the Nef gene found in naturally infected mangabeys. The SIV Nef has been isolated ex vivo from several naturally and experimentally infected mangabeys as well as for control purposes from experimentally infected macaques. Sequence analysis of 12 Nef clones suggests that mangabeys naturally infected with SIVsmm appear to have have two Nef families based on sequence homology. At the peptide level, however, while SIV Nef found in macaques appear to code for a full-length protein, Nef clones from mangabeys have all early termination codons, resulting in truncated and most likely nonfunctional protein. The database is currently being enlarged to allow more firm conclusions.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Cytokine Effects on Post-Chemotherapy Immunohematopoietic Regeneration Using a Nonhuman Primate Model

AXIS I: Ia, Id, 2, 17

AXIS II: 50a, 76b, 88

PRC UNIT: Pathobiology and Immun

INVES1: Winton, Elliott F.
DEGREE1: M.D.
DEPT1: Pathobiology & Immunobiology
STAFF1: O

SPECIES1: Macaca mulatta
NUM1: 9

NON-HOST INST: NA

ABSTRACT: High dose chemotherapy, with or without hematopoietic stem cell rescue, has become an important part of curative treatment strategies for patients with malignancies. Damage to the hematopoietic system with resultant low blood counts is the major, dose-limiting toxicity of high dose chemotherapy. The purpose of these studies is to define the optimal use of the newly available recombinant hematopoietic growth factors to lessen chemotherapy induced hematopoietic suppression. In 1992, we developed a high dose chemotherapy model in the rhesus monkey employing hepsulfam which results in predictable severe suppression of circulating platelets, granulocytes, and erythrocytes. The hepsulfam is administered by a single intravenous infusion, and the following day cytokine(s) are administered subcutaneously over 3 weeks. Post chemotherapy blood counts are obtained 3 times per week, and marrow samples to assay for primitive hematopoietic cells (progenitors, CD34+ cells) are obtained weekly. The animals are supported with prophylactic antimicrobials, and administered blood or platelet transfusions as needed to treat low platelet or red cells counts. We have determined the effects of single cytokine (rhIL-3, rhIL-6, GM-CSF) and combination cytokine (rhIL-3 plus rhIL-6; rhGM-CSF plus rhIL-3) on the depth and duration of the cytopenias. We have been able to prevent the severe low platelet counts following hepsulfam with rhIL-6 or rhIL-6 plus rhIL-3, and with rhGM-CSF plus rhIL-3 administration. In addition, the duration and severity of post-hepsulfam granulocytopenia has been lessened by the same cytokines and combinations. Further combinations and schedules of cytokines are planned for future studies.

DIVISION OF REPRODUCTIVE BIOLOGY

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P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Neurobehavioral Responsivity of Neonatal Nursery-Reared Chimpanzees

AXIS I: 1a, 21, 25

AXIS II: 36, 60, 71

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

INVES2: Platzman, Kathleen A.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: 0

INVES3: Suomi, Stephen J.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: 0

INVES4: Swenson, R. Brent
DEGREE4: D.V.M.
DEPT4: Veterinary Medicine
STAFF4: C

INVES5: Lester, Barry M.
DEGREE5: Ph.D.
DEPT5:
STAFF5: 0

SPECIES1: Pan troglodytes
NUM1: 7

NON-HOST INST: NICHD, Laboratory of Comparative Ethology (SJS); Bradley Hospital and Brown University (BML)

ABSTRACT: From January, 1992 through December 31, 1992, 7 chimpanzee infants were placed in the nursery, due to inadequate maternal care and their neurobehavioral integrity was assessed with the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton, 1984). When comparisons are made with human infants striking similarities are found in the following areas: capacity for attention to visual and auditory, social and nonsocial stimuli; motor activity, coordination, and muscle control; autonomic nervous system stress. Significant differences between the species were found in two clusters of behavior related to infant state. Human infants reach a higher level of arousal and undergo more behavior state changes during the course of the examination than do chimpanzee neonates. Chimpanzee infants maintain a quiet alert state throughout the examination. Moreover, chimpanzee neonates utilize their own behaviors, or those of the examiner, to regulate their state to a greater extent than do human infants.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Cognitive Development and Temperament in Young Nursery-Reared Pan troglodytes

AXIS I: 1a, 21, 25

AXIS II: 36, 41, 60, 71

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Platzman, Kathleen A.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: O

INVES3: Suomi, Stephen J.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: O

INVES4: Swenson, R. Brent
DEGREE4: D.V.M.
DEPT4: Veterinary Medicine
STAFF4: C

SPECIES1: Pan troglodytes
NUM1: 10

NON-HOST INST: NICHD, Laboratory of Comparative Ethology (SJS)

ABSTRACT: Each nursery-reared chimpanzee infant was tested once a month, from the age of 3 months to 12 months, using the Bayley Scales of Infant Development. Tests were conducted on 10 infants, 4 infants began testing during this period and 6 infants were given continuing assessments. This human-based test is used to assess temperamental responsiveness and manipulative abilities. This research is ongoing. Two scores were obtained from each chimpanzee's test: a human age equivalent and a mental development index (MDI). Chimpanzees, 3-7 months of age, performed at higher cognitive levels than humans at the same age, whereas the same chimpanzees at 8-12 months of age performed at lower levels than humans. The value of this study is to provide species comparisons of cognitive competence, to provide data on individual difference in emotional responsivity, and to provide a normative database to evaluate the effectiveness of behavioral interventions. These data from chimpanzees are important in order to assess the effect of standardized environmental variables on cognitive development.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Attachment in Nursery-Reared Pan troglodytes: Ainsworth Strange Situation

AXIS I: 1a

AXIS II: 36, 60, 71

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Swenson, R. Brent
DEGREE2: D.V.M.
DEPT2: Veterinary Medicine
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 6

NON-HOST INST: NA

ABSTRACT: The quality of attachment in six nursery-reared chimpanzees was assessed using the Ainsworth Strange Situation. This research is ongoing. Each individual was tested with his or her favorite caregiver as the 'mother', and a completely unknown female as the stranger. The distribution of major attachment classifications in previously tested nursery-reared chimpanzees was similar to that found in human infants by Ainsworth. Specifically, 17 chimpanzees were classified as securely attached to their favorite caregiver, 9 were classified with insecure attachments. Attachment mechanisms in chimpanzee infants parallel those in human infants. Research from other cultures suggest that minimal exposure to novelty, frequency of separations from caregivers, and multiple attachments may all influence attachment at 1 year. These data from chimpanzees will be used to assess social competence and coping capacity, and to evaluate the validity of using this variable as a predictor of later competence. This study can not be conducted as easily in humans due to extraneous environmental variables.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Social Learning of Tool Use in Pan troglodytes

AXIS I: 1a

AXIS II: 36, 41, 60

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

INVES2: Visalberghi, Elizabetta
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: 0

INVES3: Fragaszy, Dorothy
DEGREE3: Ph.D.
DEPT3: Behavioral Biology
STAFF3: 0

SPECIES1: Pan troglodytes
NUM1: 6

NON-HOST INST: CNR, Instituto di Psicologia (EV); University of Georgia (DF)

ABSTRACT: This study was designed to investigate 1) the development of the ability to use a simple tool; 2) the cognitive substrate necessary for tool use; and 3) a comparison of the learning process when the task is learned by individual trial-and-error and when the task is learned through social observation. To date, the acquisition and understanding of a tool-using problem was investigated in a total of six chimpanzees, aged 2-4 years. One of each age-matched pair was exposed to a model performing the task successfully. Increasing age and the presence of a model affected the ease of acquisition. Following acquisition, subjects were tested with more complex versions of the task to evaluate comprehension. Age, rather than exposure to a model, affected comprehension. These results indicate that young chimpanzees, once they reach a minimum age, are capable of benefiting from exposure to a model in the acquisition of a novel and complex behavior. Chimpanzees are used in this study, rather than humans, because their experience with imitating models is standardized and minimal. In future studies different amounts of modeling experience will be given to chimpanzees and, in this way, the independent contribution of social learning to performance of tool use can be assessed.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Development of Self-Recognition in Pan troglodytes

AXIS I: 1a

AXIS II: 36, 41, 60

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 10

NON-HOST INST: NA

ABSTRACT: The goals of this study are to determine the age at which chimpanzees recognize their mirror image and to document mirror-directed behavior that many develop concurrently with this ability. Chimpanzees have been tested with the Gallup self-recognition paradigm (i.e., a colored mark applied to the forehead which is touched while looking in the mirror). Clear evidence for self-recognition was found in 5-year olds, in three out of four 4-year olds, and in 2 1/2 year old chimpanzees. There was no compelling evidence for self-recognition in any of the four 2-year old chimpanzees. It is tentatively concluded that both self-directed behavior and contingent movement developmentally precede self-recognition. Self-recognition in chimpanzees appears to be consolidated between 2 and 2 1/2 years of age, a slightly older age than human infants. In humans, self-recognition is linked with other cognitive abilities. The current results conform to the general pattern of great apes exhibiting many cognitive skills comparable to 2 year old chimpanzees. In the current year an additional 10 subjects have been videotaped in front of the mirror. The data have not yet been analyzed. This study is designed to evaluate the development of self-recognition when environmental conditions are standardized. Basic scientific information is being gathered, but the age at which chimpanzees develop self-recognition remains unknown.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Foundations of Parenting in Pan troglodytes: Intuitive Parenting

AXIS I: 1a

AXIS II: 36, 60, 71

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Papousek, Hanus
DEGREE2: M.D.
DEPT2:
STAFF2: O

INVES3: Suomi, Stephen J.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: O

SPECIES1: Pan troglodytes
NUM1: 2

NON-HOST INST: NICHD, Laboratory of Comparative Ethology (SJS); Center for Social Pediatrics, Munich FRG (HP).

ABSTRACT: In order to investigate the foundations of intuitive parenting, mother-reared chimpanzees have been videotaped from birth through 3 months of age. In addition, historical records have been analyzed. Maternal behavior in chimpanzees is not instinctual. Maternal behaviors must be learned, and it is likely that direct individual learning is most effective. Early experience, i.e., whether an individual herself experienced adequate maternal care, is no guarantee of maternal competence. An equal proportion of mother-reared and nursery-reared chimpanzees exhibited insufficient maternal behavior when they became new mothers. Maternal competence in chimpanzees is initially dependent on cradling and support of the infant. Early mother-infant interaction in chimpanzees includes play, exercise, and grooming. Chimpanzee mothers spend some time assessing their infant's behavioral state, muscle tone, and fingers and toes. Chimpanzee mothers gaze at their infants's face and infants gaze at their mother's face. There is mutual gaze in chimpanzees, but it is brief. Neonatal chimpanzees clearly have the capacity for sustained face-to-face interactions; it is evident as early as the second day of life when nursery-reared chimpanzees interact with human adults. In the nursery, behavioral interventions are designed to maximize maternal competence. Natural learning conditions are approximated by giving juvenile chimpanzees monitored and limited exposure to younger infants. Chimpanzees living under known environments can provide important information on the development of parenting that has important implications for humans.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Cortisol Levels in the Saliva of Young Pan troglodytes

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 14

NON-HOST INST: NA

ABSTRACT: Baseline cortisol values were obtained on 14 individuals ranging in age from 2 days to 12 months. These levels are similar to the levels found in human infants. Cortisol samples were obtained pre- and post-tests on neonatal neurobehavior (NBAS) for 8 subjects. Cortisol samples were obtained pre-and post-tests of cognitive/manipulative ability (i.e., the Bayley Scales of Infant Development) for 10 subjects. Preliminary data suggests physiological changes are minimal in response to these behavioral tests. This research is in progress. Chimpanzees are a useful animal model. Because environmental conditions are known and standardized, physiological responses can be pinpointed more specifically to experimental variables than is possible in humans.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Social Competence in Pan troglodytes

AXIS I: 1a

AXIS II: 36

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 6

NON-HOST INST: NA

ABSTRACT: Primates show some of the most complex social interactions. Many behavioral studies show the strong social relations are beneficial to individuals in a changing environment. The main goal of this study, in progress, is to develop a coding system (1) to describe social interactions in a group of young chimpanzees; (2) to describe the social competence of each individual within the group; and, (3) to describe individual differences in personality or social style. Use of this coding system will facilitate continuity in the assessment of individual differences from birth throughout the juvenile period. This study may provide a methodology applicable to the study of social competence in human children.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Early Social Responsivity

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 25

NON-HOST INST: NA

ABSTRACT: Previous testing of the social responsiveness of neonatal chimpanzees revealed performance comparable to that of neonatal humans. These tests were conducted with chimpanzees raised under standard nursery conditions at the Yerkes Research Center. The flexibility of very early social learning is explored by comparing these nursery-reared chimpanzees to another group of chimpanzees: i.e., those reared with 20 hours per week of responsive caregiving in addition to standard nursery care. Analyses reveal that significant differences exist by the end of the neonatal period at least between the standard nursery-reared group and the biological mother-reared chimpanzees (data collected elsewhere). Higher, more human-like, levels of social responsiveness were found in the standard nursery-reared chimpanzees. That differential responses are not evident at 2 days of age but are evident at 30 days of age points to the very early effects of these different environments on social responsiveness in young chimpanzees. Further analyses comparing responsive nursery-reared with standard nursery-rearing will explore additional flexibility in neonatal chimpanzees' social responsivity. This study is valuable in the scientific search for the contribution of environmental and genetic factors to behavioral expression.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Focal Distance of Infant Pan troglodytes

AXIS I: 1a

AXIS II: 36

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVEST2: Boothe, Ronald
DEGREE2: Ph.D.
DEPT2: Neurobiology
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 13

NON-HOST INST: NA

ABSTRACT: The preferential looking technique was used to assess visual acuity in 13 nursery-reared chimpanzees from 1 week to 52 weeks of age. This technique, widely used to assess visual acuity of human infants (Teller, 1979) and monkeys (Boothe, 1990), provides a noninvasive assessment of visual acuity that addresses the question of how well young chimpanzees see and allows for a projection of optimal focal distance. The hypothesis is that chimpanzee infants see better at a further distance compared with human infants. Neonatal chimpanzees exhibited acuity levels of about 1 cycle/degree which is similar to both human and monkey neonates. There are significant improvements in acuity during the first year, and the time course of development falls between that of monkeys and humans. Tests were conducted at three separate viewing distances and comparison of acuity values reveals increased acuity at far distances for young chimpanzees. This finding confirms previous observations regarding optional focal distances in chimpanzee neonates given neurobehavioral assessments. This study is furthering our knowledge of visual development by providing new information.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Ontogeny of Emotional Expression

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 30

NON-HOST INST: NA

ABSTRACT: Facial and vocal emotional expressions of 30 chimpanzees were studied. Emotional expressions were recorded during the NBAS, administered every other day from 2 days after birth through 30 days of age. All infants were given standard nursery care but 5 of the 30 neonates were given responsive caregiving 20 hours per week in addition. Facial expressions of happiness ("playface" and smiles), interest, anger (bulging and compressed lips), and distress (pout face and scream face) were given in response to contextual cues, i.e., animated examiners face, environmental stimuli, physical manipulations, lack of contact and elicitation of reflect items. In fact, many of the same NBAS items were responded to with the same emotional expression by both chimpanzee and human newborns (Bard et al., 1992; Field et al., 1984). Vocal expressions of activity (effort grunt), distress (hoo, whimper, and scream), greeting, anger (threat bark), and alarm were also found. Individual differences were noted. The emotional expressions that were found in neonatal chimpanzees are similar both in form and in emotional tone to those found in adult chimpanzees. In addition, most emotions are expressed in the same context and in response to the same type of stimuli for both neonates and adults. Learning and experience appear to be required in order for infant chimpanzees to use alarm calls and threats in the appropriate situations. Finally, the emotional tone or quality of expression found in neonatal chimpanzees is strikingly similar to the emotional tone of expressions found in human neonates. This study is important to further our scientific understanding of environmental and genetic contributions to emotional development. The study of laboratory-raised chimpanzees provides unique information as both environmental and genetic variables are known.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Ontogeny of Lateral Bias

AXIS I: 1a

AXIS II: 36

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

INVES2: Hopkins, W.D.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 28

NON-HOST INST: NA

ABSTRACT: This study extends previous documentation of behavioral asymmetries in hand-to-mouth self-calming behaviors of infant nursery-reared chimpanzees at the Yerkes Center. The underlying source of lateralized hand-to-mouth self-consoling behavior was investigated by comparing individual differences in neonatal arousal levels, regulatory ability, and motor performance with individual differences in the degree of laterality at 3 months. Asymmetrical hand-to-mouth self-calming behaviors at 3 months of age were significantly related to general arousal at 2 days of age (i.e., the Range of State cluster scores measured by the NBAS). Simply stated chimpanzees with a right-hand bias in hand-to-mouth behavior exhibited lower arousal at 2 days of age compared with non-right handed individuals. The only item of the range of state cluster to distinguish subjects was irritability: right-handed subjects were less irritable. Previously trend was reported with respect to sex differences in the laterality of hand-to-mouth behavior. With the greater number of subjects in the present study, we now find that females exhibited a significantly greater right hand bias for hand-to-mouth behaviors (12 out of 13) than did males (9 out of 15). We conclude that neonatal arousability, and not regulatory capacity or motor performance, predicts the degree of laterality found in hand-to-mouth self-calming behaviors in 3-month old chimpanzees. This study furthers our basic understanding of the neurobehavioral basis of laterality.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Behavioral Interventions

AXIS I: 1a

AXIS II: 36, 41

PRC UNIT: Reproductive Biology

INVES1: Bard, Kim A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

SPECIES1: Pan troglodytes
NUM1: 9

NON-HOST INST: NA

ABSTRACT: Standard nursery-rearing for chimpanzees at the Yerkes Research Center consists of groups of three to six peers formed as early as 6 weeks of age given human contact during caregiving activities. Normative data have been collected on infants raised under these standard nursery conditions. A behavioral intervention project, conducted during the last 2 years, is designed to (1) provide responsive caregiving to nursery-reared chimpanzees, which more closely approximates species-typical rearing; (2) to provide monitored and protected access to younger individuals, an experience that more closely approximates that which older siblings receive in species-typical family groups. Preliminary analyses indicate that the behavior and neurobehavioral integrity of infants, 2 to 30 days of age, does not differ in the two different conditions. Differences are found, however, in early emotional expressiveness. Changes in emotional responsiveness also appear to effect subsequent performance on standardized tests of cognitive and manipulative performance given to infants from 3 to 13 months of life. The second intervention has proven successful in providing older infants with hands-on experience with younger infants. We predict enhanced maternal competence in those individuals who had hands-on experiences as infants. The implications of this research relate to long-term effects of early experiences and early learning. Chimpanzees raised under known, documented and standard conditions provide a unique animal model to further our scientific knowledge.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Perineal Swelling of Pan troglodytes and Premenstrual Edema

AXIS I: 1a, 15, 23

AXIS II: 36, 62, 72, 93

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 20

NON-HOST INST: NA

ABSTRACT: It follows from the close resemblance between apes and humans that studies of ape reproduction, and reproductive pathology, are highly comparable to those of humans. Based on this premise, the work represents efforts to understand disease that affects women by controlled study of Pan. Daily monitoring of the primary pattern of perineal swelling in female P. troglodytes, using anatomical markers to define the follicular swollen phase, enables recognition of significant variation in the progress of the ovarian cycle and an ability to predict either the day of ovulation or luteal phases which are relatively brief and with low progesterone production. Continued monitoring and pattern analyses of anatomical changes, moreover, has yielded identification of additional variants to the two major patterns previously described:

1) Cycles with a secondary, luteal phase swelling or premenstrual edema. Temporal variation in this edema is similar to that of symptoms indicative of Late Luteal Phase Dysphoric disorder (and/or premenstrual syndrome) which severely effects about 5% of all adult women in the US;

2) That do not conform to either of the two major pattern types and which indicate that a subject exhibits a contraceptive behavior.

Furthermore, recognition of a normally fertile pattern in an infertile subject can indicate that the female has a physical abnormality of the reproductive tract; detailed genital monitoring is critical in differential diagnoses of reproductive disorders in Pan. The empirical basis for the monitoring method, which is the integrating basis for studies of artificial breeding, is being verified by quantifying swelling changes using spreading calipers (to detail size), and a compression manometer (to quantify tautness of the sex skin). Monitoring the external genitalia provides the bases for scheduling artificial insemination procedures, ultrasonographic evaluations, and remedial hormone therapies in the case of subjects with inadequate luteal phases. That the secondary edema may be an external marker for changes in water balance may prove particularly productive for examination of luteal phase and premenstrual pathologies that have proven particularly difficult to understand through studies of women.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Contraceptive Behaviors in Pan troglodytes: Lactational Infertility

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

AXIS II: 36, 62, 72, 93

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Pan troglodytes
NUM1: 20

NON-HOST INST: NA

ABSTRACT: The resemblance between apes and humans in female reproductive endocrinology provides the basis for understanding the mechanisms of lactational amenorrhea through study of apes; this has implications for human birth control and infertility and our fundamental understanding of human endocrinological mechanisms. It is clear that either allo- or auto-stimulation of the nipples, or nipple stimulation behaviors (NSBs), cause a prolonged post-partum amenorrhea in female Pan when the infant is absent. A program of observation coupled with careful monitoring of the perineal swellings of 20 subjects reveals, however, that NSB can occur during spontaneous intermenstrual intervals (IMIs) and IMIs induced by treating with pergolide mesylate. Pergolide is a dopamine receptor agonist that acts to depress the prolactin production (consequent to the NSBs) so that an ovarian cycle ensues and amenorrhea is terminated. Using three measures of NSB calculated from the results of 65 minute observation periods, five quantitatively and qualitatively distinct NSBs were documented. Some variation was associated with the progress of the ovarian cycle. NSBs were significantly higher during either the swollen (follicular) phase, or during the luteal phase. The variation in the behavior, and what is known of the luteolytic action of oxytocin (OT) in women, implicates OT in both the proximate reinforcement of the behavior, and as a disruptive influence on the luteal phase or the establishment of pregnancy. Direct investigation of the role of OT in women is logistically and ethically difficult, prompting use of this non-human model; the species can be studied under controlled conditions of housing, food supply, social environment and data on endocrinological variables are obtainable using uniform techniques. Moreover, recognition, and eventual treatment, of contraceptive behaviors are of considerable significance for stabilizing the captive population of Pan. This has consequences for improving the biomedical basis for research as well as the conservation effort.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Indexing Urinary Concentrations of Steroid Excretory Products

AXIS I: 1a, 2, 9, 15, 27.

AXIS II: 62, 74h

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Macaca fascicularis
NUM1: 13

SPECIES2: Pan troglodytes
NUM2: 6

NON-HOST INST: NA

ABSTRACT: To answer questions concerning the pathology of certain behaviors and/or conditions of infertility, Pan troglodytes can act as a productive model for both human and non-human primates. Blood withdrawal may be precluded during certain studies, however, and then urine is the most practicable source for quantifying steroid fluctuations. Use of urine in this way is possible because urinary concentrations of creatinine are used to index estrone, pregnanediol, and cortisol concentrations. The efficacy of this indexing process is critical for interpreting steroid fluctuations, and was evaluated in analyses of 485 urine samples from 13 Macaca fascicularis maintained in metabolism cages. The results indicate that the most efficacious factor to use as an index during laboratory studies is the Creatinine Coefficient (amount of creatinine produced in 24 hr/kg body weight). For example, cortisol concentrations were indexed to either creatinine concentration (μg cortisol/mg Cr) or Creatinine Coefficient (μg cortisol/mgCr/kg body weight). Use of the Creatinine Coefficient as an index altered the distribution of cortisol concentrations from a polynomial one to a single, positively skewed distribution in which a small group of high outliers was identifiable. It is expected that use of the Coefficient makes possible some significant advance in the level of acuity possible in studies of female reproductive physiology and behavior. It should be possible to identify subtle variation in reproductive steroid excretion associated with reproductive disorders; inter-individual comparisons are considerably more meaningful when the Coefficient is employed.

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TITLE: Morphometrics of the Male Reproductive Apparatus

AXIS I: 1a, 23

AXIS II: 46, 60, 62, 73

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Pongo pygmaeus
NUM1: 10

SPECIES2: Gorilla
NUM2: 7

NON-HOST INST: NA

ABSTRACT: It is possible to advance our understanding of reproductive health in humans, and normal ranges of development, through comparisons with an array of closely related species such as the apes and monkeys. Previous measures of both penes and testicles raise questions about normal or abnormal size (and the ability to identify degenerative conditions), and variations in structure and function. Morphometric techniques applied during routine medical survey yield a new picture of variation, and reveal some previously unrecognized character complexes. Results of measures taken from 5 genera (Cebus, Macaca, Pongo, Pan, and Gorilla) suggest functional questions about:

1) The mechanical role of the glans during copulation that (a) may enhance the process by which large quantities of sperm make contact with the ovum, and (b) may contribute to maintaining a clear passage along the fallopian tubes;

2) The dimorphic testicles of Gorilla, and similar dimorphism among human populations that may be sex-linked with dizygotic twinning frequency. This has been linked, in turn, with the incidence of breast cancer;

3) The dimorphic testicle size in Cebus. The significant variation in gross testicle size may associate with the influence of subordination on spermatogenesis and/or testosterone levels.

Such questions arise by appropriate consideration and refinements of sexual selection theory, particularly consideration of the sperm dilution effect. The work with Gorilla and Pongo contributes to our ability to diagnose male infertility consequent to degenerative spermatogenic tissue, important to our ability to manage the captive population.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Body Size, Heat Storage, and Comfort Levels for Monkeys and Apes

AXIS I: 1a, 25

AXIS II: 36, 54b(thermoregulation)

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: 0

INVES2: Burton, B.J.
DEGREE2: B.A.
DEPT2: Reproductive Biology
STAFF2: 0

SPECIES1: Pan troglodytes
NUM1: 9

SPECIES2: Macaca arctoides
NUM2: 29

NON-HOST INST: NA

ABSTRACT: The conduct of biomedical research with non-human primates requires high standards of empiricism and care, with special attention to the subjects' well-being; they should be studied and housed under environmental conditions that are reproducible and comfortable to the subjects. To further comprehend and identify the limits of comfortable conditions for apes and monkeys, a group of Pan troglodytes and of Macaca arctoides were studied in large indoor-outdoor enclosures during winter, spring, and summer conditions. This was an extension of studies on both behavior and on behavior and pelage coloration, all of which contributed to our understanding of physiological comfort for the wide morphological range that constitutes the Order Primates. The aim of the present study was to test whether large body size, and hence large heat storage capacity, was an advantage under both cold and hot conditions. Groups of 9 and 29 adults were observed when they had free access to both exterior and interior portions of their enclosures, and the interior was climatically controlled. If large size is advantageous then the 9 Pan would remain outside under both cooler and hotter conditions than the much smaller Macaca. Results suggest that the larger Pan were comfortable (stayed outside) under much cooler conditions than the Macaca, but they were uncomfortable (went inside) more than the Macaca when conditions were warmer. This result is consistent with a dynamic model of energy flow at the body surface rather than the more static, traditional model, and indicates statistically different comfort ranges (as measured by environmental cooling power) for non-human primates of different size. Appropriate application of data on thermal conditions by consideration of environmental cooling power, and the observed responses of animals of different size provide an ability to fine tune both the management and the study of primates housed in indoor/outdoor enclosures; this benefits both the animals and the researcher.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Conservation of Neotropical Forests and Populations of Ateles and Alouatta

AXIS I: 1a, 15, 23

AXIS II: 36, 40, 54b

PRC UNIT: Reproductive Biology

INVES1: Dahl, Jeremy F.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Gould, K.G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: C

SPECIES1: Alouatta pigra
NUM1: 20 (feral)

SPECIES2: Ateles geoffroyi
NUM1: 20 (feral)

NON-HOST INST: NA

ABSTRACT: A training program in tropical forest conservation was expanded, and a framework for studies of reproduction in two species of New World monkeys (Ateles geoffroyi and Alouatta pigra) was laid down. This program continued studies carried out in Belize, Central America, where:

1) Over 200 km² of forested habitat have been surveyed both North and South of the Mayan Divide and from lowland, coastal sites to 950 m. elevation;

2) Several groups of Alouatta observed at a low to mid-elevation site (250-450 m) were found to exhibit an unusual activity pattern (active at night as well as day times). Some females had conspicuous, pink genital swellings like those in other primates which act as external markers of the progress of the ovarian cycle. A low-elevation site for a study of several groups of habituated Alouatta is available, and a mid-high elevation site (450-750m) has been identified that probably supports both species. Additional training was offered to Forest Guards and students of conservation biology in both theoretical and practical aspects of reserve management. Both genera of monkeys face vulnerable or endangered status consequent to their relatively large size, and the preferences of hunters; even minimal disruption of habitat in Belize by illegal activities may have a major impact on the monkey populations. More effective patrolling can minimize these disruptions and studies of reproduction are central to our understanding of population dynamics and appropriate reserve management.

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TITLE: Hormone Parameters of the Adult Male Chimpanzee

AXIS I: 1a, 9, 23

AXIS II: 36, 60

PRC UNIT: Reproductive Biology

INVES1: Gould, Kenneth G.
DEGREE1: D.V.M., Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Young, Leona G.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: O

SPECIES1: Pan troglodytes
NUM1: 15

NON-HOST INST: NA

ABSTRACT: The chimpanzee, because of its similarities to the human, is especially valuable in studies of reproductive function. However, relatively little is known about the physiology of reproduction in the adult male chimpanzee. This study provided, for five adult male chimpanzees, baseline values for testicular volume without and with pressure and for cellular and biochemical characteristics of ejaculates collected by artificial vagina (AV). There was no correlation between body weight and testicular volume measured without or with pressure. The ratios of mean testicular volume without and with pressure were not statistically different among animals. Statistical analysis of penetration of denuded hamster oocytes by ejaculated chimpanzee sperm revealed no correlations between sperm count and percentage of eggs penetrated.

To monitor the relative secretory activity of different portions of the male reproductive tract, the seminal fluid from 30 chimpanzee ejaculates (N=5 x 6) was analyzed for protein, alpha-glucosidase, fructose, and acid phosphatase. Protein concentration of the 30 samples assayed showed a mean ±SE of 50 ±6.7mg/ml (Range 11-135) liquid fraction. Protein in the seminal fluid of ejaculates collected by AV showed relatively little intra- and inter-animal variability. Alpha-glucosidase activity in the seminal fluid of chimpanzee ejaculates collected by AV showed high intra- and inter-animal variability with a mean ±SE value of 3767 ±1521mIU/ml (Range 285-14269). Fructose concentrations varied significantly, especially within and among animals although analysis of the total sample population fails to demonstrate this, with mean ±SE value of 4.8 ±0.2mg/ml, but a range of 0.07 - 8.44mg/ml. Acid phosphatase activity in the seminal fluid was highly variable, with a mean value of 43551 ±2884 Sigma Units/ml (range 400 - 223000).

For an individual animal, sperm motility ranged between 70 and 97% motile. Sperm curvilinear velocity (VCL), the velocity of a sperm without regard to the direction of travel, ranged from 41 μm/sec to 62 μm/sec. Sperm straight line velocity (VSL), the velocity of a sperm measured as progress in a straight line between two points, ranged from 15 μm/sec to 24 μm/sec. The higher values associated with sperm VCL as opposed to VSL reflect the non-linearity of sperm swimming patterns. This convoluted swimming pattern is also reflected by the linearity, which ranged from 29 to 56. The alternating lateral deflection of the sperm head (ALH), characteristic of swimming sperm, ranged between 3.4 μm and 6.5 μm.

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TITLE: Tana River Primate Project

AXIS I: 1a, 8, 11

AXIS II: 34, 36, 54b

PRC UNIT: Reproductive Biology

INVES1: Gould, Kenneth G.
DEGREE1: B.Vet.Med., Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Else, James G.
DEGREE2: D.V.M., M.P.V.M.
DEPT2: Reproductive Biology
STAFF2: O

INVES3: Leakey, Richard E.
DEGREE3:
DEPT3: Reproductive Biology
STAFF3: O

INVES4: Struhsaker, Thomas
DEGREE4: Ph.D.
DEPT4: Reproductive Biology
STAFF4: O

INVES5: Njuguna, Stephen
DEGREE5: Ph.D.
DEPT5: Reproductive Biology
STAFF5: O

INVES6: Smith, Euclid O.
DEGREE6: Ph.D.
DEPT6: Behavioral Biology
STAFF6: C

SPECIES1: Colobus badius
NUM1: ≈800 (wild)

SPECIES2: Cercocebus galeritus
NUM2: ≈1600 (wild)

NON-HOST INST: University of Florida (TS); Kenya Wildlife Services (JE,RL); and National Museums of Kenya (SN)

ABSTRACT: The Tana River National Primate Reserve is the home for two highly endangered primate species, the Tana River red colobus (Colobus badius rufomitratus) and the Tana River crested mangabey (Cercocebus galeritus galeritus). Both species experienced dramatic declines in population which resulted in the establishment of the Tana River Project in 1987. Since that

time the population decline has been slowed, if not arrested. However, based upon the results of research findings published in 1990 and the planned implementation of a park management plan a World Bank sponsored EVA (Ecology Viability Analysis; part of a larger program of planned World Bank support) was undertaken in the latter part of 1991 in order to plan coordinated action to ensure the responsible development of the Tana Reserve with a goal of ensuring the continued survival of the endangered primate species. The Yerkes Center continues to support research in the area and additional, non-federal, funding is being sought to assist in these conservation efforts.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Artificial Breeding of Chimpanzees

AXIS I: 1a, 9, 23

AXIS II: 36, 60

PRC UNIT: Reproductive Biology

INVES1: Gould, Kenneth G.
DEGREE1: D.V.M., Ph.D.
DEPT1: Reproductive Biology
STAFF1 C

INVES2: Dahl, Jeremy F.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: O

SPECIES1: Pan troglodytes
NUM1: 15

NON-HOST INST: NA

ABSTRACT: Research directed to improvement of methods for artificial breeding of chimpanzees, with implication for both conservation of other primate species and for the human, has continued into a prospective study directed to identification of the 'normal fertile' cycle. Using previous data which suggested that monitoring of the perineal swelling could identify a 'fertile' subset of 'normal' menstrual cycles we have evaluated the use of this cycle monitoring method for artificial insemination. Physical monitoring has been supplemented by increased use of ultrasound monitoring of follicle development during the follicular phase of the cycle and during ovulation. Further clinical evaluation of females who did not become pregnant has identified physical reasons for infertility not reflected in altered patterns of endocrine change in the menstrual cycle. Retrospective analysis suggests that the method can provide information which will result in an 83% success rate (5/6) for artificial insemination. These data suggest methods for development of a predictive scoring system for the success of a given attempt at artificial insemination. Previous, suggestive, results that successful insemination is associated with higher linearity values, derived by CAMA, have been extended and confirmed. Work in the current year will be directed to prospective evaluation of success rate of artificial insemination using the predictive method currently available and to development of a scoring system directed to correct identification of the potential success of any given insemination attempt.

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TITLE: Evaluation of Thrombus Formation Rates

AXIS I: 1a, 3, 13, 17

AXIS II: 50, 52, 86

PRC UNIT: Reproductive Biology

INVES1: Hanson, S.
DEGREE1: Ph.D.
DEPT1: Pathobiology and Immunobiology
STAFF1: 0

INVES2: Anderson, J.
DEGREE2: M.A.
DEPT2:
STAFF2: 0

INVES3: Apkarian, Robert P.
DEGREE3: M.A.
DEPT3: Reproductive Biology
STAFF3: 0

SPECIES1: Papio
NUM1: 10

NON-HOST INST: NA

ABSTRACT: These studies represent continuation of an ongoing project directed to evaluation of Goretex graft material for control of thrombus formation when used as part of a vascular replacement. Goretex vascular grafts have been coated with various compounds such as freon, methane, silicone to evaluate cell proliferation. Grafts are 10 cm lengths placed in the baboon aorta-iliac position Goretex. These specimens were constructed to exhibit 60 micron pores.

In a separate study the effect of shear rate on thrombus formation in collagen coated ePTFE-grafts was studied in a baboon ex vivo shunt model. Grafts of 2mm, 3mm and 4mm diameter were used to create shear rates of 2100s-1, 630s-1, and 265s-1. SEM was used to document the deposition of blood platelets on the grafts, as well as to document the increased platelet deposition rate in grafts with the higher shear rates.

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TITLE: Evaluation of Cell-Substrate Interaction Using Crystalline Surfaces

AXIS I: 2, 7b

AXIS II: 51, 66

PRC UNIT: Reproductive Biology

INVES1: Robert L. Hunter
DEGREE1: M.D., Ph.D.
DEPT1:
STAFF1: 0

INVES2: Robert P. Apkarian
DEGREE2: M.A.
DEPT2: Reproductive Biology
STAFF2: 0

SPECIES 1: NA
NUM1:

NON-HOST INST: NA

ABSTRACT: It is well known that the toxicity of quartz and certain other minerals depends upon interaction of cells with a particular crystalline surface. We are evaluating the hypothesis that the virulence of tuberculosis involves similar mechanisms. Trehalose 6,6' dimycolate (TDM) is a glycolipid of mycobacteria whose toxicity depends upon presentation as a monolayer on hydrophobic surfaces. This project is designed to characterize the biologically active surface of the TDM monolayer. We previously investigated the structure of the TDM monolayer using real time kinetic microscopy, low magnification scanning electron microscopy and other methods. Monolayers of TDM formed concentric ring structures at an air-water interface which were rigid in the direction parallel to the rings but compressible perpendicular to them. The formation of the characteristic surface layer was found to depend upon the precise structure of the TDM molecule. These observations were used with previously published data to construct a model of the structure of TDM monolayer. This model provides testable hypotheses about the molecular basis of virulence of M. tuberculosis. We will investigate the structures formed by surface layers of TDM and selected analogues to evaluate these hypotheses. This project has the potential of establishing a new virulence mechanism of microorganisms and suggesting new approaches to therapy.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Effect of GnRH Analogues on Immune System Development in Male Rhesus Monkeys

AXIS I: 1a, 15, 23, 28 (immune system)

AXIS II: 60, 64, 65, 74e

PRC UNIT: Reproductive Biology

INVES1: Mann, David R.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Ansari, A.A.
DEGREE3: Ph.D.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 46

NON-HOST INST: Morehouse School of Medicine (DRM)

ABSTRACT: Two studies were performed: (1) neonates were treated with a GnRH agonist (Ag; Wy 40972; 10 ug/day; minipump; N=5) or vehicle (N=4) for the first 4 mo of life and FACScan's on whole-blood, mitogen challenges of lymphocytes (MCL) and antigenic challenges (tetanus toxoid) were performed at 7-8 yr of age; and (2) neonates were treated with vehicle (N=8) or a GnRH antagonist (Antide [A]; 15 mg/kg BW/wk sc; N=8) for the first 4 mo and FACScan's, MCL and antigenic challenge were performed at 4 mo, 6 mo and 1.5 yr of age, respectively. In study 1, numbers of T-helper cells (CD4) were unchanged, but T-suppressor cells (CD8) were elevated ($P<0.01$) and B cells were suppressed by Ag treatment ($P<0.05$). Lymphocytes from treated monkeys exhibited an increased response to T-cell mitogens (ConA, PHA; $P<0.001$) but their response to PWM and SLO was normal. Anti-tetanus antibody production did not differ between the controls and treated monkeys. In study 2, CD8 ($P<0.05$) and B cell numbers ($P<0.05$) were reduced at 4 mo in neonates treated with A. CD4 cell numbers were normal. At 6 mo, lymphocyte responses to ConA, PHA and PWM were normal, but the response to SLO was elevated ($P<0.001$) above control levels in A-treated monkeys. Anti-tetanus antibody production was normal in A-treated monkeys in response to the initial toxoid injection, but the response to a booster was increased ($P<0.05$) in the A-treated group. The data are summarized in the table below. N=normal, I=increased and D= decreased levels in GnRH analogue-treated vs controls.

Study	FACScan			MCL				TET Ab	
	CD4	CD8	B	PHA	ConA	PWM	SLO	1°	2°
1	N	I	D	I	I	N	N	N	N
2	N	D	D	N	N	N	I	N	I

These preliminary data suggest that early postnatal treatment of male monkeys with GnRH analogues may alter immunological parameters, but the significance of these changes and whether the immune system is permanently impaired will require further study.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Effect of Neonatal Treatment of Male Monkeys with a GnRH Analogue on Sexual Development

AXIS I: 1a, 15, 23

AXIS II: 60, 74e

PRC UNIT: Reproductive Biology

INVES1: Mann, David R.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Wallen, K.
DEGREE2: Ph.D.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Gould, Kenneth G.
DEGREE3: Ph.D., D.V.M.
DEPT3: Reproductive Biology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 40

NON-HOST INST: Morehouse School of Medicine (DRM)

ABSTRACT: There are two groups of animals being used in this study. The first group was treated neonatally with GnRH agonist during the birth season of 1984. The second group was treated with a GnRH antagonist alone or in conjunction with testosterone replacement therapy. Animals treated with a GnRH agonist as neonates have shown a delay (1 year) in the onset of puberty and as adults exhibit a mild hypogonadotropic-hypogonadal condition. The hypogonadal condition is associated with stunted growth and a reduced bone mineral density. In a paper recently accepted for publication in J. Clin. Endocrinol. Metab., we have shown that neonatal treatment with a GnRH agonist apparently alters development of CNS regulating GnRH secretion such that treated animals show a subnormal serum LH and testosterone response to excitatory amino acids (e.g. aspartate or glutamate). Thus, the critical period for sexual differentiation of CNS centers regulating gonadotropin secretion may extend beyond the prenatal period in primates to include the neonatal period as well.

Recent work related to the second group of animals was presented at the 1993 Endocrine Society Meeting. These animals are presently prepubertal, but should exhibit peripubertal changes during the 1993 and 1994 breeding season. This component of the study will intensify as the animals approach puberty.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Behavior and Physiology of the Gibbon

AXIS I: 1a, 15, 23

AXIS II: 36, 74e

PRC UNIT: Reproductive Biology

INVES1: Nadler, Ronald D.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Dahl, Jeremy F.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: O

INVES3: Gould, Kenneth G.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: C

INVES4: Collins, Delwood C.
DEGREE: Ph.D.
DEPT4: Reproductive Biology
STAFF4: O

SPECIES1: Hylobates lar
NUM1: 9

NON-HOST INST: NA

ABSTRACT: The objectives of this research are 1) to determine whether an hypothesis regarding the ultimate (evolutionary) causation of differences in reproductive behavior, anatomy and physiology of the polygamous great apes, extends to the monogamous gibbon, and 2) to determine the relationship among sex hormone levels, female genital swelling, duetting (vocalizations) and test conditions on the proximate activation of reproductive behavior in this lesser ape. The hypothesis is based on intermale competition for estrous females (and female choice of a male at estrus). Since intermale competition for estrous females in the gibbon is minimal or totally absent, similar to the gorilla, we hypothesized that the reproductive characteristics of the gibbon would be similar to the gorilla. Research on the gibbon permits us to assess comparatively, the relevance of a monogamous sexual relationship to the regulation of reproductive behavior, anatomy and physiology of the extant hominoids. During the reporting period, articles were published on the anatomy and cyclic pattern of female genital swelling and articles were accepted for publication on the hormonal correlates of the swelling and on testis size in the orang-utan. The results indicate that the female gibbon resembles other female primates that exhibit genital swelling during the menstrual cycle and is contrary to predictions based on intermale competition.

Our research suggests that the evolution of genital swellings which enhance a female's attractiveness to males is more complex than previously thought and that mechanisms as yet unclear contribute to this characteristic. The results on relative testis weight in orang-utans confirms relationships among the great apes and establishes the basis for comparison with the male gibbon.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Behavioral Effects of Oral Contraceptive in Chimpanzees

AXIS I: 1a, 15, 23

AXIS II: 36, 50b, 74e

PRC UNIT: Reproductive Biology

INVES1: Nadler, Ronald D.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Dahl, Jeremy F.
DEGREE2: Ph.D.
DEPT2: Reproductive Biology
STAFF2: O

INVES3: Gould, Kenneth G.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: C

INVES4: Collins, Delwood C.
DEGREE4: Ph.D.
DEPT4: Reproductive Biology
STAFF4: O

SPECIES1: Pan troglodytes
NUM1: 13

NON-HOST INST: NA

ABSTRACT: The behavioral and physiological effects of a combined oral contraceptive (OC) were studied in chimpanzees for comparative purposes related to 1) the ambiguity surrounding the effects of OCs on the sexuality of humans, 2) the close biological relationship between chimpanzees and humans, especially with respect to hormones and sexual behavior, and 3) the relatively greater behavioral sensitivity of the chimpanzee to changes in sex hormone levels such as those that accompany the use of OCs. Two different types of pair-tests were used to evaluate effects on female behavior imposed by the male. During the reporting period, one article was published on the genital effects of the OC, one article on the behavioral effects was accepted for publication and one article was submitted on the regulation of sexual behavior during the natural (control) cycles. The results on anogenital swelling revealed adverse effects due to low levels of endogenous estrogen consequent to OC use. The results on sexual behavior suggest that there is an overall reduction in sexual activity, but that this effect was related to the social relationship of the partners, i.e., more modest in compatible pairs. These studies focus attention on two possible sources of concern to couples in which women use OCs; the effects are clearly more pronounced in the chimpanzee, but may have relevance to some subset of women with high sensitivity to hormonal

influences. The study of sexual behavior during the natural menstrual cycle suggests that male dominance plays a preeminent role in the regulation of sexual activity in this species, similar to our earlier results on gorillas and orang-utans and comparable to data on human couples. The results have implications for both basic research on regulatory mechanisms and comparative extrapolation to studies on human sexual behavior.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Spermatogenesis in Rhesus Macaques Inoculated with SIV Prior to Puberty

AXIS I: 1a, 6, 15, 23

AXIS II: 31, 60, 66, 83

PRC UNIT: Reproductive Biology

INVES1: Nadler, Ronald D.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: McClure, Harold M.
DEGREE2: D.V.M.
DEPT2: Pathobiology and Immunobiology
STAFF2: C

INVES3: Anderson, Daniel C.
DEGREE3: D.V.M.
DEPT3: Pathobiology and Immunobiology
STAFF3: C

SPECIES1: Macaca mulatta
NUM1: 26

NON-HOST INST: NA

ABSTRACT: The objectives of the research are 1) to determine if the simian immunodeficiency virus (SIV) has a comparable effect on the reproductive tract of male rhesus macaques as that described for men who die of acquired immunodeficiency syndrome (AIDS), i.e., primarily azoospermia, and if so, 2) to determine if the condition develops as a direct result of (SIV) infection or as a result of the cachexia associated with the disease and 3) to determine the developmental and endocrine basis of the azoospermia. The experimental subjects were 13 rhesus macaques inoculated with SIV between 1.5 and 47 months of age and which died between the ages of 22 and 71 months of age. Thirteen control animals were selected on the basis of comparable age at death to the experimentals and noninvolvement in research on the endocrine system or SIV. During the reporting period, hormone assays were conducted to complement the data on spermatogenesis and to assess the value of endocrine markers in disease progression. A close relationship between spermatogenesis and body weight in both the SIV-infected animals and the controls suggests that SIV inhibits spermatogenesis indirectly, as a result of cachexia reflected by low body weight. Relatively low levels of testosterone in the older SIV-infected animals suggest that testosterone may be a useful marker of disease progression; longitudinal data are required to confirm this. The absence of elevated levels of luteinizing hormone in the older SIV-infected animals, which would be expected on the basis of reduced negative feedback by testosterone, also supports the proposal that azoospermia results from an overall depression of bodily function. No relationship was found between the

levels of dehydroepiandrosterone sulfate and any of the other parameters examined; this hormone has been implicated in some studies of HIV infection. The results overall support the use of the macaque as a model for research on HIV and suggest that further research on SIV-infected macaques may confirm the value of markers related to reproductive function for projection of disease progression.

P51RR00165-32 1/1/1992 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Reproductive Behavior in the Chimpanzee

AXIS I: 1a, 15, 23

AXIS II: 36, 74e

PRC UNIT: Reproductive Biology

INVES1: Nadler, Ronald D.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

SPECIES1: Pan troglodytes
NUM1: 6

NON-HOST INST: NA

ABSTRACT: The objective of the research is to determine the cause(s) of increased sexual behavior, in relation to the natural habitat, that frequently occurs in laboratory pair-tests of sexual behavior in chimpanzees and other nonhuman primates. The specific hypothesis to be tested states that greeting rituals which are a species-typical response to reunion following separation in chimpanzees account, in part, for sexual behavior that is temporally dissociated from the midcycle periovulatory phase of the menstrual cycle in laboratory pair-tests. The greeting rituals which are performed under natural conditions contain sexual components which may become conditioned to the test conditions in the laboratory. The hypothesis is tested by the use of two different types of pair-test, 1) an immediate access test in which the door separating the male and female is opened immediately upon introduction of the male into the cage adjoining the female and 2) a delayed access test in which the door is opened after a 5-minute interval. The prediction is that copulation will be less frequent in the delayed access test as a result of greeting rituals being completed during the delay, when the animals can see each other through the fence, and hence, do not stimulate sexual activity when the door is opened. The results have implications for increasing our knowledge of factors which influence the regulation of sexual activity in a close biological relative of humans. The study was initiated during the reporting period; data analysis for the initial phase of the study is underway.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Evaluation of Acute Thrombosis and Late Reendothelialization of Vascular Grafts and Carotid Stents in Swine

AXIS I: 1a, 2, 13, 17

AXIS II: 48, 50, 52, 70

PRC UNIT: Reproductive Biology

INVES1: Robinson, Keith A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Apkarian, Robert P.
DEGREE2: M.A.
DEPT2: Reproductive Biology
STAFF2: O

SPECIES1: Porcine
NUM1: 10

NON-HOST INST: NA

ABSTRACT: Thrombotic complications limit the efficacy of a variety of therapeutic vascular interventions, including vascular surgery and balloon angioplasty. Development of pharmacologic agents or other strategies to decrease thrombotic potential, while minimizing the adverse side effects of increased bleeding tendency, is therefore of considerable importance of the mechanisms of thrombus formation.

This project primarily relies on scintigraphic imaging of radiolabelled platelet deposition for quantitation of thrombus formation. However, scanning and transmission electron microscopy will be obtained of some specimens to allow morphologic documentation and correlation of gamma images and measurements. Dacron graft segments exposed to blood flow for 2 h in an exteriorized arteriovenous shunt, and carotid artery segments stented for 4 wk, will be fixed and examined primarily by conventional SEM. Comparisons will be made between grafts from animals treated with various antiplatelet agents or those receiving no treatment, with respect to overall thrombosis as well as specific platelet morphology.

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Leukocyte Adhesion to Endothelium in Early Atherogenesis: Role of Oxidant Stress

AXIS I: 1a, 13, 17

AXIS II: 50, 74f

PRC UNIT: Reproductive Biology

INVES1: Robinson, Keith A.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: O

INVES2: Apkarian, Robert P.
DEGREE2: M.A.
DEPT2: Reproductive Biology
STAFF2: O

SPECIES1: Rabbits
NUM1: 10

NON-HOST INST: NA

ABSTRACT: One of the earliest pathogenic events in atherosclerosis is adhesion of circulating monocytes to the arterial endothelium. This may be due in part to expression of specific endothelial-leukocyte adhesion molecules (ELAMs) at the luminal plasmalemma of the endothelial cells (ECs). Among the various stressors which may induce ELAM expression is oxidative stress. This study will therefore determine whether antioxidant therapy (dietary supplementation with the oxidant scavenger butylated hydroxytoluene) will inhibit monocyte adhesion to aortic endothelium early in diet-induced atherosclerosis. Fifteen rabbits will be fed a diet of regular chow supplemented with 1% cholesterol and 5% peanut oil; the control group will receive no other intervention, while the experimental group will also receive 1% BHT in the diet. After two weeks, the animals will be killed and the aortas perfusion fixed for SEM analysis. The numbers of adherent monocytes at three aortic segments will be determined using a quantitative scheme on the SEM. Between-groups difference will be tested using an unpaired two tailed student t test.

P51RR00165-32 1/1/92 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Prolonged Lactational Infertility During Adolescence

AXIS I: 1a, 2, 15, 23

AXIS II: 36, 60, 71,

PRC UNIT: Reproductive Biology

INVES1: Wilson, Mark E.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

SPECIES1: Macaca mulatta
NUM1: 13

NON-HOST INST: NA

ABSTRACT: Adolescent rhesus monkey mothers experience a prolonged period of lactational infertility following their first parturition. The mechanisms responsible for this difference between primiparous and multiparous mothers is not fully understood. Although differences in nursing behavior do not account for the age differences in the duration of lactational infertility, nursing behavior does suppress the reproductive system but only if the duration and frequency of suckling is of sufficient intensity. As the suckling stimulus diminishes, the reproductive system is re-activated. Previous work indicates that adolescent mothers are more sensitive to the nursing stimulus which translates to an increased sensitivity to estradiol negative feedback inhibition of gonadotropin secretion. Studies were continued this year to further characterize the physiological differences between lactating adolescent and lactating adult females. In addition to assessing nursing behavior, patterns of solid food intake were also monitored from 6 weeks post partum through the first post partum ovulation. Blood samples were collected throughout lactation in all mothers for the determination of serum lipids, insulin, glucose , and glucagon. Milk was collected for the determination of fat, protein, and lactose. Analyses of these data are still underway. It was predicted that there would be no differences in milk content between adult and adolescent mothers and that all infants, regardless of the age of their mother, would show the same developmental patterns in food intake. This prediction was based on the previous observation of a lack of difference in nursing behavior between adult and adolescent mothers. On the other hand, it was predicted that serum lipids and indices of glucose metabolism may be compromised in adolescent mothers. This is based on the hypothesis that "metabolic energy" may be preferentially diverted to maternal growth and lactational competence at the expense of reproduction in adolescent mothers. Consequently, sufficient energy would not be available to support the return to fertility in adolescent mothers. These studies will not only provide insight into basic mechanisms regulating the duration of lactational infertility but also what factors affect infant health.

P51RR00165-32 1/1/92 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: The Effect of a Human Growth Hormone (hGH) Analogue on IGF-I in Male Rhesus Monkeys

AXIS I: 1a, 2, 15, 26

AXIS II: 50b, 60

PRC UNIT: Reproductive Biology

INVES1: Wilson, Mark E.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Cronin, M.
DEGREE2: Ph.D.
DEPT2:
STAFF2: O

SPECIES1: Macaca mulatta
NUM1: 6

NON-HOST INST: NA

ABSTRACT: Studies were initiated this year to test the effectiveness of new growth hormone analogues for increasing serum concentrations of insulin-like growth factor-I (IGF-I) in adolescent males. Since IGF-I mediates, in part, the effects of GH on growth, this approach will identify those compounds which may be useful clinically at improving growth rates in children. Data analyses are still underway. These studies will provide much needed information on the effectiveness of these compounds which may alleviate the need for daily injections for those children receiving treatment for growth disorders.

P51RR00165-32 1/1/92 - 12/31/92 Yerkes Regional Primate Research Center

TITLE: Common Neuroendocrine Mechanisms for Growth and Puberty

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

AXIS II: 60, 71

PRC UNIT: Reproductive Biology

INVES1: Wilson, Mark E.
DEGREE1: Ph.D.
DEPT1: Reproductive Biology
STAFF1: C

INVES2: Gordon, Thomas P.
DEGREE2: M.S.
DEPT2: Behavioral Biology
STAFF2: C

INVES3: Tanner, James M.
DEGREE3: M.D.
DEPT3:
STAFF3: O

SPECIES1: Macaca mulatta
NUM1: 34

NON-HOST INST: NA

ABSTRACT: Studies were continued this year to determine if there is a common neuroendocrine mechanism regulating both pubertal growth and reproductive maturation. Immature females were treated with a clinical grade somatostatin analogue ("Sandostatin", Sandoz) and their prepubertal growth patterns, as well as parameters of sexual maturation, were compared to age-matched controls. Treatment with Sandostatin suppressed growth hormone (GH) and insulin-like growth factor-I (IGF-I) and lowered growth rates. All females exhibited an adolescent growth spurt and, since bone age was delayed in Sandostatin-treated females, this peak growth velocity occurred at the same bone age in all females but at an older chronological age in treated females. Age at menarche was not affected but first ovulation occurred at a significantly older age in treated females. These data suggest that the GH - IGF-I axis not only regulates skeletal growth but also is involved in the control of reproductive maturation. Additional studies are in progress to determine how long-term administration of IGF-1 and the opioid antagonist naltrexone may alter the tempo of growth and the development of gonadotropin secretion. Treatment with IGF-1 accelerated skeletal growth. Furthermore, the hypersensitivity to estradiol negative feedback inhibition of LH secretion, which characterizes the final stages of puberty and thus the timing of first ovulation, was decreased at an earlier age in IGF-I-treated females. These data compliment those from the Sandostatin study, underscoring the importance of the GH - IGF-I axis in regulating the timing of puberty. On the other hand, treatment with the opioid antagonist naltrexone did not affect growth rates of the development of gonadotropin secretion. These studies have described how reproductive maturation and skeletal growth are linked and have provided insight into how puberty may be affected in children with growth disorders.

DIVISION OF ANIMAL RESOURCES AND VETERINARY MEDICINE

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

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Research Associate

K.S. Paul, D.V.M., Assistant Veterinarian, Division of Animal Resources and Research Associate, Division of Pathobiology and Immunobiology, Yerkes Center

P51RR00165-32 1/1/1992 - 12/31/1992 Yerkes Regional Primate Research Center

TITLE: Establishment of A Chimpanzee Breeding and Research Program

AXIS I: 1a, 23

AXIS II: 36,60, 92 (Breeding)

PRC UNIT: Veterinary Medicine

INVES1: Swenson, R. Brent
DEGREE1: D.V.M.
DEPT1: Veterinary Medicine
STAFF1: C

INVES2: Gould, Kenneth
DEGREE2: Ph.D., D.V.M.
DEPT2: Reproductive Biology
STAFF2: C

INVES3: Bard, Kim A.
DEGREE3: Ph.D.
DEPT3: Reproductive Biology
STAFF3: O

INVES4: Gordon, Thomas P.
DEGREE4: M.S.
DEPT4: Behavioral Neuroendocrinology
STAFF4: C

INVES5: Strobert, Elizabeth A.
DEGREE5: D.V.M.
DEPT5: Veterinary Medicine
STAFF5: C

SPECIES1: Pan troglodytes
NUM1: 91

NON-HOST INSTITUTION: NA

ABSTRACT: This colony is a part of a cooperative program which includes 4 other institutions. The object of the program has been to establish and maintain a self-sustaining population of chimpanzees which can also supply subjects for AIDS and other health-related research. Fourteen livebirths were produced in 1992. The success of the program has resulted in a shortage of housing space and required a managed reduction of breeding. To this end, a reversible contraceptive implant [Norplant (R)] had been used in 3 program females and will be considered in others until additional space and demand for offspring in research programs comes about. Indoor-outdoor caging which will accommodate 40 additional animals is currently being assembled at the Field Station.

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: XXX OTHER:

NAME	TYPE	AGENCY	GRANT/CONTRACT	TOTAL FUNDS	% RPRC USED
Ansari, Aftab A.	FED	NIH	AI-27057-05	$222,970	25
Boothe, Ronald G.	FED	NIH	EY-05975	132,535	100
Byrd, Larry D.	FED	NIDA	DA-01161	224,135	100
	FED	NIDA	DA-06264	272,727	100
	FED	NIDA	DA-07805	20,960	100
	FED	NIDA	DA-06264-S2	3,260	100
de Waal, Frans B.M.	FED	NCRR	RR-05276-04	66,834	100
	FED	NIMH	MH-49475	49,900	100
Gould, Kenneth G.	FED	NIH	HD-26423-01	23,376	100
	FED	NIH	HD-26076-02	75,820	100
	FED	NIH	RR-03587-05	119,137	100
	FED	NIH	RR-05994-02	130,645	100
McClure, Harold M.	FED	NIH	RR-00165(S)	1,598,891	100
	FED	NIH	HL-42125 (UAB Subcontract)	104,847	100
	FED	NIH	RR-06753 (Johns Hopkins Subcontract)	9,695	100
Swenson, R. Brent	FED	NIH	RR-03591-0	677,020	100
Tigges, Johannes	FED	NIA	AG-00001	94,356	100
Tigges, Margarete	FED	NIH	EY-09737	115,085	100
Wilson, James R.	FED	NIH	EY-04976	74,592	100
	FED	NIH	EY-04976-S1	1,340	100
Wilson, Mark E.	FED	NICHD	HD-16305	107,000	100
	FED	NICHD	HD-18120	95,153	100

TOTAL PHS SUPPORT This page: $ 4,220,278
Grand (Cumulative) Total: $ 4,220,278

PART II, SECTION B1 GRANT NUMBER: P51RR00165-32

INVESTIGATORS WITH PUBLIC HEALTH SERVICE SUPPORT

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT/CONTRACT	TOTAL FUNDS	% RPRC USED
Bakay, Roy A.E.	FED	NIH	NS-24340	$ 66,661	80
Bard, Kim A.	FED	NIH/DRR	RR-06158-01	121,580	100
Fritz, Michael E.	FED	NIH	DE-08917-03	586,832	20
	FED	NIH	DE-08917-03S1	33,306	20
Gust, Deborah A.	FED	NIMH	MH-46676	49,311	100
Hanson, Stephen R.	FED	NIH	HL-31469	184,154	45
	FED	NIH	HL-31950	139,617	20
	FED	NIH	HL-31950	86,113	100
Harker, Laurence A.	FED	NIH	HL-41619	179,866	45
	FED	NIH	HL-31950	129,073	20
Hopkins, William D.	FED	NINDS	NS-29574	78,256	100
Howell, Leonard L.	FED	NIDA	DA-05346	70,401	100
Lambert, Scott R.	FED	NIH	EY-08544	99,623	100
Mann, David R.	FED	NIH	HD-26423-04	163,386	34
Moss, Mark B.	FED	NIH	P01AG00001-19 (Subproject)	9,471	50
Peters, Alan Boston University	FED	NIH	2T32 NS07152	185,834	5
	FED	NIH	R01 NS07016	136,165	35
	FED	NIH	P01AG00001-19	99,456	25
Rumbaugh, Duane M.	FED	NICHD	HD-06016	693,223	17

TOTAL PHS SUPPORT

This page: $ 3,112,328
Grand (Cumulative) Total: $ 3,112,328

PART II, SECTION B1 GRANT NUMBER: P51RR00165-32

INVESTIGATORS WITH SUPPORT OTHER THAN PUBLIC HEALTH SERVICE

CORE: XXX OTHER:

NAME	TYPE	AGENCY	GRANT/CONTRACT	TOTAL FUNDS	% RPRC USED
Gouzoules, Harold	FED	NSF	IBN-9209844	$ 33,520	100
Herndon, James G.	FED	NSF	BNS-90-071701	27,357	100
McClure, Harold M.					
		Pharmaceuticals			
Nadler, Ronald D.	FED	NSF	BNS-91-09441	34,536	100
Tigges, Margarete					
Wallen, Kim	FED	NSF	BNS-8919888	15,052	100
Wilson, Mark					
TOTAL NON-PHS SUPPORT					

INVESTIGATORS WITH SUPPORT OTHER THAN PUBLIC HEALTH SERVICE

CORE: OTHER: XXX

NAME	TYPE	AGENCY	GRANT/CONTRACT	TOTAL FUNDS	% RPRC USED
Bakay, Roy A.E.	FED	VA	Merit Award	$125,180	60
Eberhard, Mark L.					
Forthman, Debra L. and Maple, Terry L.					
Hillyer, Christopher					
Kennedy, Philip R.					
Malizia, Anthony A.					
Metzgar, Richard					
Tomasello, W. Michael					
Unnasch, Thomas R.					
Winton, Elliott F.					

PART II, SECTION C BOOKS/PAPERS/ABSTRACTS GRANT NUMBER:P51RR00165-32

CORE: XXX OTHER:

Number Published:	Books:	0	Papers:	30	Abstracts:	37
Number in Press:	Books:	0	Papers:	42	Abstracts:	3

*Ansari, A.A., Mayne, A., Hunt, D. and Villinger, F.: Analysis of the frequencies of TH0, TH1, and TH2 subsets of cloned lymphoid cells in mangabeys and macaques, based on cytokine profiles. Tenth Annual Symposium on Nonhuman Primate Models for AIDS, San Juan, Puerto Rico, Nov. 17-20, 1992 (Abstract).

*Boothe, R.G. and Gong, W.: Development of binocular alignment in normal and visually deprived monkeys. Invest. Ophthalmol. Visual Sci. Suppl. 33:871, 1992 (Abstract).

*Boothe, R.G., Tigges, M., Wilson, J., Fernandes, A., Gammon, J.A. and Eggers, H.: A monkey model of patching treatment for unilateral aphakia. Congenital Cataract Symposium, London, England, June 18-19, 1992 (Abstract).

*Boothe, R.G., Tigges, M., Wilson, J. and Fernandes, A.: Selective defocus and penalization as alternatives to patching therapy. Congenital Cataract Symposium, London, England, June 18-19, 1992 (Abstract).

*de Waal, F.B.M.: Aggression as a well-integrated part of primate social relationships: A critique of the Seville Statement on Violence. In: Aggression and Peacefulness in Humans and Other Primates, J. Silverberg and J.P. Gray, eds., Oxford University Press, New York, pp. 37-56, 1992.

*de Waal, F.B.M.: Appeasement, celebration, and food sharing in the two Pan species. In: Topics in Primatology, Vol. 1, Human Origins, T. Nishida, W.C. McGrew, P.R. Marler, M. Pickford and F.B.M. de Waal, eds., University of Tokyo Press, Tokyo, Japan, pp. 37-50, 1992.

de Waal, F.B.M.: The chimpanzee's sense of social regularity. In: The Sense of Justice: Biological Foundations of Law, R. Masters and M. Gruter, eds., Sage, Newbury Park, pp. 241-255, 1992.

de Waal, F.B.M.: Coalitions as part of reciprocal relations in the Arnhem chimpanzee colony. In: Coalitions and Alliances in Humans and Other Animals, A.H. Harcourt and F.B.M. de Waal, eds., Oxford University Press, Oxford/New York, pp. 233-257, 1992.

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*de Waal, F.B.M.: Fighting and reconciliation. Bull. Chic. Acad. Sci. 15:14, 1992 (Abstract).

*de Waal, F.B.M.: Food-sharing, reciprocity, and moralistic aggression in chimpanzees. Bull. Chic. Acad. Sci. 15:11, 1992 (Abstract).

*de Waal, F.B.M.: Group specific behavior. Bull. Chic. Acad. Sci. 15:22, 1992 (Abstract).

*de Waal, F.B.M.: Intentional deception in primates. Evol. Anthropol. 1:86-92, 1992.

de Waal, F.B.M.: Separating the men from the apes. Review of The Third Chimpanzee by Jared Diamond. New York Times Book Review (March 15):10-11, 1992.

*de Waal, F.B.M.: A social life for chimpanzees in captivity. In: Chimpanzee Conservation and Public Health: Environments for the Future, J. Erwin and J.C. Landon, eds., Diagnon/Bioqual, Rockville, MD, pp. 83-87, 1992.

de Waal, F.B.M. and Harcourt, A.H.: Coalitions and alliances: A history of ethological research. In: Coalitions and Alliances in Humans and Other Animals, A.H. Harcourt and F.B.M. de Waal, eds., Oxford University Press, Oxford/New York, pp. 1-27, 1992.

*de Waal, F.B.M. and Johanowicz, D.L.: Modification of reconciliation behavior through social experience. In: Abstracts of the XIVth Congress of the International Primatological Society, Strasbourg, France, August 16-21, p. 104, 1992 (Abstract).

*Gordon, T.P., Gust, D.A. and McClure, H.M.: Social modulation of stress response to separation in adult female rhesus monkeys. In: Abstracts of the XIVth Congress of the International Primatological Society, Strasbourg, France, August 16-21, p. 300, 1992 (Abstract).

*Gordon, T.P., Gust, D.A., Wilson, M.E., Ahmed-Ansari, A., Brodie, A.R. and McClure, H.M.: Social separation and reunion affects immune system in juvenile rhesus monkeys. Physiol. Behav. 51:461-472, 1992.

*Gould, K.G. and Dahl, J.F.: Assisted reproduction in great apes. Presented at a Serono Conference "In Vitro Fertilization and Embryo Transfer in Primates", Beaverton, Oregon, May 28-31, 1992 (Abstract).

*Gould, K.G. and Dahl, J.F.: Reproduction in chimpanzees: With reference to problems of fertility and infertility. In: Abstracts of the Symposium, The Role of the Chimpanzee in Research, Immuno AG, Vienna, Austria, May 22-24, pp. 85-89, 1992 (Abstract).

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*Gouzoules, H.: Review of The Sociobiological Imagination (M. Maxwell, ed.). Am. J. Phys. Anthropol. 89:403-404, 1992.

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**Kelly, A.B., Maraganore, J.M., Bourdon, P., Hanson, S.R. and Harker, L.A.: Antithrombotic effects of synthetic peptides targeting different functional domains of thrombin. Proc. Nat. Acad. Sci. 89:6040-6044, 1991.

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*King, F.A.: The emergence of the chimpanzee in research. In: Abstracts of the Symposium, The Role of the Chimpanzee in Research, Immuno AG, Vienna, Austria, May 22-24, pp. 123-127, 1992 (Abstract).

*King, F.A.: Suggestions and cautions for successful media visits to your laboratory. Lab Animal, Jul/Aug, pp.36-37, 1992.

King, F.A. and Yarbrough, C.J.: Animal Use in Research. In: Encyclopedia of Learning and Memory, L.R. Squire, ed., MacMillan Publishing Company, New York, pp.36-41, 1992.

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*McClure, H.M., Anderson, D.C., Ansari, A.A. and Klumpp, S.A.: The simian immunodeficiency virus infected macaque: A model for pediatric AIDS. Path. Biol. 40:694-700, 1992.

*McClure, H.M., Anderson, D.C., Gordon, T.P., Ansari, A.A., Fultz, P.N., Klumpp, S.A. Emau, P. and Ishahakia, M.: Natural simian immunodeficiency virus infection in nonhuman primates. In: Topics in Primatology, Vol. 3, Evolutionary Biology, Reproductive Endocrinology and Virology, S. Matano, R.H. Tuttle, H. Ishida and M. Goodman, eds., University of Tokyo Press, Tokyo, Japan, pp. 425-438, 1992.

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*McClure, H.M., Novembre, F.J., Hirsch, V.M., Lockwood, E., Saucier, M., Hamm, T., and Johnson, P.R.: Non-sexual horizontal transmission of SIVsmm. Tenth Annual Symposium on Nonhuman Primate Models for AIDS, San Juan, Puerto Rico, November 17-20, 1992. (Abstract).

*Nadler, R.D.: Estrus and mating of the great apes. In: Perspectives in Primate Biology, Vol. 4, P.K. Seth and S. Seth, eds. Today and Tomorrow's Printers and Publishers, New Delhi, pp. 71-78, 1992.

*Nadler, R.D.: Proximate and ultimate mechanisms in the regulation of mating in great apes. In: Abstracts of the XIVth Congress of the International Primatological Society, Strasbourg, pp. 247-248, 1992 (Abstract).

*Nadler, R.D.: Sexual behavior and the concept of estrus in the great apes. In: Topics in Primatology, Vol 2, Behavior, Ecology, and Conservation. N. Itoigawa, Y. Sugiyama, G.P. Sackett and R.K.R. Thompson, eds. University of Tokyo Press, Tokyo, Japan, pp. 191-206, 1992.

*Nadler, R.D., Dahl, J.F., and Collins, D.C.: The anomalous female genital swelling of the monogamous gibbon. In abstracts of the Second International Conference on Advances in Reproductive Research in Man and Animals, Institute of Primate Research, National Museums of Kenya, Nairobi, Kenya, pp. 13-14, May 3-9, 1992 (Abstract).

*Nadler, R.D., Dahl, J.F. and Collins, D.C.: Sexual characteristics of the monogamous gibbon: A useful model for the human? In abstracts of the Eighteenth Annual Meeting of the International Academy of Sex Research, Prague, Czechoslovakia, 1992 (Abstract).

*Nadler, R.D., Dahl, J.F., Collins, D.C., and Gould, K.G.: Hormone levels and ano-genital swelling of female chimpanzees as a function of estrogen dosage in a combined oral contraceptive. Proc. Soc. Exp. Biol. Med. 201:73-79, 1992.

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* Center Support Acknowledged
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* Center Support Acknowledged.
** (Not previously reported).

PART II, SECTION C BOOKS/PAPERS/ABSTRACTS GRANT NUMBER: P51RR00165-32

PUBLICATIONS SUPPORTED BE RECEIPT OF SPECIMENS: XXX

Number Published:	Books:	0	Papers:	15	Abstracts:	5
Number in Press:	Books:	1	Papers:	8	Abstracts:	1

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* Center Support Acknowledged
** (Not previously reported).

PART III - SECTION A -- PROGRAM SPECIFIC DATA — REGIONAL PRIMATE RESEARCH CENTERS

GRANT NUMBER P 5 1 R R 0 0 1 6 5 - 32 — REPORT PERIOD: January 1, 1992 TO: December 31, 1992

COLONY STATISTICAL TABLE

Fill out separate Colony Statistical Table for each of the following: Check one only. Do not include statistics on more than one table.

■ RESEARCH COLONY ONLY ☐ BASE BREEDING COLONY ONLY 1/ ☐ NON-BASE BREEDING COLONY 2/

SPECIES	POPULATION JAN 1st	LIVE BIRTHS	OTHER 3/ ADDITIONS	REDUCTIONS: EXPERIMENTAL USE	4/ OTHER	SOLD OR 5/ TRANSFERRED	TRANSFERRED 6/ WITHIN CENTER	POPULATION DEC 31st
Saimiri sciureus	27	0	2	3	0	0	0	26
Macaca mulatta	1349	242	0	44	72	5	0	1470
Macaca nemestrina	77	0	117	11	8	0	0	175
Macaca arctoides	62	6	0	0	2	7	0	59
Macaca fascicularis	35	0	0	0	4	0	0	31
Cercocebus atys	26	0	0	0	0	0	0	26
Papio spp.	57	0	27	43	0	0	0	41
Hylobates lar	16	0	0	0	1	2	0	13*
Pan troglodytes	120	1	3	0	3	6	0	115*
Pan paniscus	15	2	0	0	0	0	0	17
Gorilla gorilla	26	0	0	0	0	0	0	26*
Pongo pygmaeus	36	2	0	0	0	0	0	38*
Hylobates-Siamang Hyb.	1	0	0	0	0	0	0	1
Cercopithecus mitis	10	0	0	0	1	0	0	9
Cebus apella	14	8	0	0	1	0	0	21
TOTALS	1871	261	149	101	92	20	0	2068

1/ ARP Supported
2/ Supported by other than ARP sources
3/ Purchased from outside Center or transferred from another colony within the Center
4/ Includes deaths due to intercurrent diseases and other causes
5/ Permanent transfer or sale to outside the Center
6/ Transferred from another colony within the Center
*/ Includes some animals on loan to other institutions (see page 316)

PART III-SECTION A--PROGRAM SPECIFIC DATA
GRANT NUMBER P51RR00165 - 32
COLONY STATISTICAL TABLE

REGIONAL PRIMATE RESEARCH CENTERS
REPORT PERIOD: January 1, 1992 TO: December 31, 1992

ATTACHMENT PAGE FOR RESEARCH COLONY ONLY

* INCLUDES ON LOAN TO:

SPECIES	AMOUNT	FACILITY
Hylobates lar	1	Sequoia Park Zoo, Eureka, CA
Pan troglodytes	2	Ohio State University
	1	Central Washington University
Gorilla gorilla	2	Toledo Zoo, Toledo, OH
	16	Zoo Atlanta, Atlanta, GA
	3	Audubon Zoo, New Orleans, LA
	5	Busch Gardens, Tampa, FL
Pongo spp.	1	Monkey Jungle
	11	Zoo Atlanta, Atlanta, GA
	3	Metro Zoo, Toronto, Ontario, Canada
	2	Sedgwick County Zoo

PART III - SECTION A -- PROGRAM SPECIFIC DATA — REGIONAL PRIMATE RESEARCH CENTERS

GRANT NUMBER P 5 1 R R 0 0 1 6 5 - 32 — REPORT PERIOD: January 1, 1992 TO: December 31, 1992

COLONY STATISTICAL TABLE

Fill out separate Colony Statistical Table for each of the following: Check one only. Do not include statistics on more than one table.

☐ RESEARCH COLONY ONLY ■ BASE BREEDING COLONY ONLY 1/ ☐ NON-BASE BREEDING COLONY 2/

SPECIES	POPULATION JAN 1st	LIVE BIRTHS	OTHER 3/ ADDITIONS	REDUCTIONS: EXPERIMENTAL USE	REDUCTIONS: 4/ OTHER	REDUCTIONS: SOLD OR 5/ TRANSFERRED	REDUCTIONS: TRANSFERRED 6/ WITHIN CENTER	POPULATION DEC 31st
Macaca mulatta	204	73	0	0	6	0	0	271
Saimiri sciureus	165	38	0	0	22	13	2	166
Macaca nemestrina	149	61	0	0	18	0	43	149
Cercocebus atys	172	34	0	0	15	35	0	156
TOTALS	690	206	0	0	61	48	45	742

1/ ARP Supported
2/ Supported by other than ARP sources
3/ Purchased from outside Center or transferred from another colony within the Center
4/ Includes deaths due to intercurrent diseases and other causes
5/ Permanent transfer or sale to outside the Center
6/ Transferred from another colony within the Center

PART III - SECTION A -- PROGRAM SPECIFIC DATA — REGIONAL PRIMATE RESEARCH CENTERS

GRANT NUMBER P 5 1 R R 0 0 1 6 5 - 32 — REPORT PERIOD: January 1, 1992 TO: December 31, 1992

COLONY STATISTICAL TABLE

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☐ RESEARCH COLONY ONLY ☐ BASE BREEDING COLONY ONLY 1/ ■ NON-BASE BREEDING COLONY 2/

SPECIES	POPULATION JAN 1st	LIVE BIRTHS	OTHER 3/ ADDITIONS	REDUCTIONS				POPULATION DEC 31st
				EXPERIMENTAL USE	4/ OTHER	SOLD OR 5/ TRANSFERRED	TRANSFERRED 6/ WITHIN CENTER	
Pan troglodytes	86	14	0	0	6	0	3	91
TOTALS	86	14	0	0	6	0	3	91

1/ ARP Supported
2/ Supported by other than ARP sources
3/ Purchased from outside Center or transferred from another colony within the Center
4/ Includes deaths due to intercurrent diseases and other causes
5/ Permanent transfer or sale to outside the Center
6/ Transferred from another colony within the Center

ADMINISTRATIVE STATISTICS

1. PERSONNEL	NUMBER
A. Core Personnel	159
Doctoral Level Scientists	23
Other Personnel	136
B. Collaborative or Affiliate Scientists	120
C. Visiting Scientists	10
D. Graduate and Undergraduate Students	118

2. REGIONALITY	
A. Scientists Provided with Specimens	83
B. Number of Specimens Provided	4,914
C. Scientists Touring the Center	51
D. Other Visitors	592

3. PERCENT OF TOTAL FUNDS FOR EACH RPRC UNIT

UNIT	PERCENT	
Administration		
Director's Office	4%	
Associate Director for Administration	1%	
Business Office	3%	
Human Resources	1%	
		9%
Institutional Services		
Physical Plant	5%	
Information Services	1%	
General Office Services	1%	
General Shop	1%	
		8%
Research Services		
Diagnostic Pathology	6%	
Library	1%	
Biomedical Engineering	1%	
Photography	1%	
Computer Services	3%	
RIA	1%	
		13%
Division of Animal Resources		33%
Division of Behavioral Biology		4%
Division of Neurobiology		3%
Division of Pathobiology and Immunobiology		3%
Division of Reproductive Biology		3%
AIDS Animal Model Development Supplement		24%
TOTAL YRPRC		100%

APPENDIX TO INSTRUCTIONS
NCRR SCIENTIFIC CLASSIFICATION

AXIS I

RESEARCH AREAS (Max. 6 codes)

code

1 Animals, Whole
  a. Vertebrates, Mammal
  b. Vertebrates, Non-Mammal
  c. Invertebrates
Animals, Cell/Membrane/Tissue/Organ
  d. Vertebrates, Mammal
  e. Vertebrates, Non-Mammal
  f. Invertebrates
2 Biological/Chemical Compounds
3 Biomaterials
4 Human, Cells Only
5 Human, Adult
  a. Female b. Male
Human, Infant/Child
  c. Female d. Male
6 Human, Membrane/Tissue/Isolated Organ
7 Microorganisms
  a. Bacteria b. Viruses
  c. Parasites d. Other
8 Plants/Fungi
9 Technology/Technique Development
11 Facility Construction/Improvement

ANATOMICAL SYSTEM

12 Clinical Trials
  a. Multicenter b. Single Center
13 Cardiovascular System
14 Connective Tissue
15 Endocrine System
16 Gastrointestinal System
  a. Esophagus b. Gallbladder
  c. Intestine d. Liver
  e. Pancreas f. Stomach
17 Hematologic System
18 Integumentary/Skin System
19 Lymphatic and Recticulo-Endothelial System
20 Muscular System
21 Nervous System
22 Oral/Dental
23 Reproductive System
24 Respiratory System
25 Sensory System
  a. Ear b. Eye c. Taste/Smell d. Touch
26 Skeletal System
27 Urinary System
28 Other (SPECIFY)

AXIS II

RESEARCH AREAS (Max. 6 codes)

code

30 Aging
31 AIDS, SAIDS
32 Anesthesiology
34 Anthropology/Ethnography
35 Arthritis
36 Behavior/Psychology/Social Sci
38 Bioethics
39 Biotechnology (rDNA, CDNA, hydridoma)
41 Cognition/Learning
40 Communication/Speech
42 Computer Science
44 Congenital Defects or Malformations
45 Deafness/Hearing
46 Degenerative Disorders
48 Device, Prostheses, Intra/Extracoporeal
49 Diabetes
50 Drug/Therapeutic Agent Studies
  a. Toxic b. Other c. Orphan Drugs
51 Education
52 Engineering/Bioengineering
54 Environmental Sciences
  a. Toxic b. Other
56 Epidemiology
57 Fitness, Physical
55 Gene Therapy
58 Genetics, Including Metabolic Errors
59 Genome
60 Growth and Development
62 Health Care Applications
63 Imaging
  a. CT e. PET i. Microscopy
  b. Laser f. Spect j. Near Infrared
  c. MRI,MRS g. Radiography
  d. NMR h. Ultrasound
64 Immunology/Allergy/Inflammation

65 Infant Mortality
66 Infectious Diseases
68 Information Science
70 Instrument Development
69 International Hlth
71 Maternal & Child Hlth
72 Mental Disorders/Psychiatry
73 Mens Health
74 Metabolism/Biochemistry/Physiology/Structur
  a. Carbohydrate e. Hormone
  b. Electrolyte/Mineral f. Lipid
  c. Enzymes g. Nucleic Acid
  d. Gases h. Protein/Amino Ac
75 Minority Hlth
  a. Asian/Pacific Is. b. Black c.Hispanic
  d. Native American e. Other
77 Model Dvlmt
76 Neoplasms/Oncology/Cancer
  a. Benign b. Malignant
78 Nutrition
79 Pain
80 Radiology/Radiation Nuclear Medicine
81 Rare Disease
82 Rehabilitation
83 Sexually Transmitted Disease
85 Sleep Research
84 Statistics/Mathematics
89 Structural Biology
87 Substance Abuse
86 Surgery
88 Transplantation
90 Trauma/Burns/Injury
91 Vaccine
93 Womens Health Research
92 Other (SPECIFY)