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National Center for Research Resources

INTRODUCTION

The National Center for Research Resources (NCRR) develops and supports critical research technologies and shared resources that underpin research to maintain and improve the health of the Nation's citizens. NCRR supports the development and use of sophisticated instrumentation and technology, animal models for studies of human disease, and clinical research environments, as well as the enhancement of research capacity for underrepresented groups.

International cooperation provides opportunities to achieve a wide range of research and resource objectives and offers access to biological resources available only in foreign countries. Through cooperation and collaboration with national and international organizations, NCRR plans biomedical research programs in support of National Institutes of Health (NIH) activities.

NCRR sponsors international activities through four extramural components: Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NCRR supports the Cambridge Crystallographic Data Centre, England, which builds and maintains the Cambridge Structural Database, the largest searchable database of crystal structures that have been determined by biomedical researchers. This database contains crystal structure information for more than 190,000 organic and metal organic compounds and is the only available file of x-ray crystallographic coordinates for compounds of low molecular weight. The Cambridge Crystallographic Data Centre distributes the database and software to more than 600 academic and commercial users worldwide.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Activities With International and Multinational Organizations

International Adoptees

Studies of children from foreign countries who were adopted by U.S. residents during the past 6 years suggest devastating short-term effects caused by previous neglect. The incidence, severity, and chronicity of these problems are of critical interest to adoptive families and the medical professionals who care for these children. The General Clinical Research Center (GCRC) at the University of Minnesota, Minneapolis, participates in ongoing studies of adoptees from Asia, the Caribbean, and Central and South America, to determine the nature of short- and long-term medical and developmental problems resulting from institutionalization in early childhood. The investigators use history, physical examination, developmental evaluation, and appropriate screening tests of international adoptees to obtain comprehensive information for assessment of these problems.

International Registries

The International Fanconi Anemia Registry is a repository for clinical, hematologic, and genetic information on patients with Fanconi anemia, a rare disease. The registry was established at Rockefeller University, New York City, New York, in 1982, to collect this information and to make it available to researchers. Patients with Fanconi anemia are seen at the Rockefeller University GCRC, New York City, where the registry is maintained. Active collaborative efforts continue with investigators at several centers in the United States, as well as the Hospital St. Louis, Paris, France; the University of Heidelberg, Germany; and the University of Parma, Italy.

In addition, NCRR provides support for specimen collection and biostatistics for the International Skeletal Dysplasia Registry through its GCRC at Harbor-UCLA (University of California, Los Angeles) Medical Center. Skeletal dysplasias are a heterogeneous group of disorders resulting in disproportionate short stature, skeletal deformities, or both. The data from this registry are from multidisciplinary investigations of the clinical, genetic, morphological, biochemical, and molecular characteristics of the skeletal dysplasias. In fiscal year 1999 (FY 99), studies resulted in the identification of the genes responsible for several dysplasias, including pseudoachondroplasia and achondrogenesis.

Hypertension Optimal Treatment International Study

The Hypertension Optimal Treatment International Study is being conducted in collaboration with investigators in Canada, China, England, Germany, Mexico, and Sweden. A substudy examining renal clearance is under way at 10 centers in the United States, including the GCRC at the University of Texas, Houston.

Hyperkinesia in Schizophrenia Not Treated With Neuroleptic Agents

NCRR supports a study that addresses long-standing questions about the nature and origin of hyperkinesia in schizophrenia. This study investigates the nature and origin of choreoathetoid movement disorders in schizophrenia. A group of Moroccans with schizophrenia who have a long duration of illness but have never received neuroleptic medication is being compared with matched groups of healthy control subjects who do not have schizophrenia and with patients at the GCRC, Oregon Health Sciences University, Portland, who have schizophrenia and have received long-term treatment with neuroleptic medication. The GCRC supports the study of patients with schizophrenia who are receiving long-term medication and healthy control subjects, in Portland.

Pathobiology and Treatment of Malaria in Africa

Children with severe malaria often present with a combination of lactic acidosis and hypoglycemia—complications that independently predict mortality. Treatment of lactic acidosis with dichloroacetate has improved survival in severely infected animals. Researchers at the University of Florida GCRC, Gainesville, participated in a study conducted at St. George's Hospital, University of London, England, and in Kumasi, Ghana, to determine whether dichloroacetate can help in the treatment of lactic acidosis in children with malaria. The investigators found that dichloroacetate, in combination with traditional malaria therapies, significantly enhanced lactate disposal in patients with hyperlactacidemia. The agent is now being tested in a large, placebo-controlled study to assess whether it improves survival.

Melatonin and Sleep Studies in Children With Developmental Disabilities

The University of Colorado GCRC, Denver, is participating in a study to document melatonin profiles in patients aged 3–21 years who have fragile X syndrome. The study includes control subjects with mental retardation (e.g., Angelman's syndrome, velocardiofacial syndrome, and Smith-Magenis syndrome) in addition to healthy control subjects, including normal siblings. The melatonin profiles will be determined by using saliva samples. Participants are enrolled from participating centers in Australia, France, and Colorado. Over a period of 3 years, this study also will evaluate the efficacy of melatonin compared with placebo in the treatment of sleep disturbances in patients with fragile X syndrome or other causes of mental retardation.

Herpes Simplex–*Candida* Vaccine

Researchers at the Medical University of South Carolina GCRC, Charleston, are collaborating with investigators in Australia, Canada, and New Zealand on a study to evaluate the safety and effectiveness of a vaccine for herpes simplex and *Candida*, to prevent the spread of genital herpes disease to noninfected partners. A total of 300 couples will participate in this international study.

Extramural Programs

Brazil

The Wisconsin Regional Primate Research Center (RPRC), Madison, continues to assist with a project on the social regulation of fertility in wild, free-ranging common marmosets (*Callitrichid spp.*) near Natal. This study has involved the development of novel fecal assays for noninvasive monitoring of reproductive events in marmosets in captivity and in the wild.

Joint studies were extended in FY 99 to include evaluation of bone biomarkers and bone pathophysiology in Brazilian marmosets. Marmosets are providing a novel understanding of bone loss due to estrogen depletion. Little is known about the bone physiology of marmosets living in their natural habitat, and these investigations are providing crucial information that will form the basis for future studies of captive marmosets. Before this collaboration between the Wisconsin RPRC and Universidade Federal do Rio Grande do Norte, Natal, such studies were limited to captive marmosets.

Wisconsin RPRC researchers are also working with Brazilian investigators on fertility assessment of wild, male *Muriqui* monkeys near Minas Gerais. Their research on the seldom-studied *Muriqui* is revealing how basic temperament affects testosterone levels, aggression, and breeding. The results may be useful in studying other primate species. Techniques developed at the Wisconsin RPRC for fecal assay for steroids were used in this study. These techniques also show promise for helping researchers to learn more about the breeding and behavior of other endangered monkeys.

This work is critical because habitats and populations of many nonhuman primates continue to shrink.

Canada

The Wisconsin RPRC also supports a collaborative study with scientists at the University of Victoria, British Columbia, which explores the evolution of molecular forms of gonadotropin-releasing hormone. The presence of different molecular forms of this hormone in the brain within a single species, from the tunicate to primates, has been described in the literature.

In a second Canadian study, researchers at the Rockefeller University GCRC, New York City, are participating in a molecular genetics study of human obesity. Obesity is the most prevalent nutrition-related problem in societies in industrial countries. In the United States, approximately one-third of adults and one-fifth of children are obese. Findings in adoption and segregation studies of twins show clear evidence of a substantial genetic basis for susceptibility to obesity, but the specific genes involved remain unknown. This project examines the role of human homologues of genes that produce obesity in rodents, as well as other candidate genes, by use of linkage mapping, mutation analysis, and direct measurement of the protein products of these genes. More than 15,000 affected persons and family members will be recruited to these studies, from 13 populations, including blacks, whites, Hispanics, and American Indians, in the United States and Canada.

Indonesia

The Washington RPRC, Seattle, continues to support international research, training, and the breeding of nonhuman primates in collaboration with the Primate Research Center at Bogor Agricultural University, which is Indonesia's only primate center. This program has successfully established and maintains a breeding colony of *Macaca fascicularis* that is free of specific pathogens. In the forests of the 600-hectare Tinjil Island, approximately 2,000 *M. fascicularis* range freely and provide progeny for research on acquired immunodeficiency syndrome (AIDS), at the Washington RPRC and other research facilities supported by the NIH. Additionally, the program has established and maintains a breeding colony of *Macaca nemestrina* at Bogor Agricultural University, which provides primates free of simian retrovirus for use in AIDS-related research. The Virology Laboratory at Bogor, an integral component of the collaboration, provides support facilities for all simian retrovirus screening procedures necessary for the colony. As part of the research and training mission of the program, more than 10 researchers from Bogor Agricultural University have come to the Washington RPRC as Visiting Scientists to receive specialized training in a variety of research areas.

Personnel from the Washington RPRC travel to Indonesia on a regular basis to engage in ongoing research projects and to conduct annual training courses in the field.

These 1-month courses, which accommodate both Indonesian and U.S. students, are conducted on Tinjil Island and at the Tangkoko Nature Reserve, in North Sulawesi. As part of the expanding collaboration with the Primate Research Center in Bogor, the Washington RPRC scientists are assisting with projects that help to promote primate conservation throughout Indonesia, such as the Orangutan Reintroduction Project at Wanariset Station, East Kalimantan, Borneo. The Indonesian program continues to serve as an excellent model of international collaboration in the development of primate resources and also serves as a prototype of natural habitat breeding facilities for future primate resources from other countries.

Italy

NCRR's Biomedical Technology area, Gruppo Biomed Mod, Padua, continues to support the development of new software that uses deconvolution to solve the problems of estimating input for biological–physiological systems. (In deconvolution, the system response and the input signal are used to produce an estimate of the system model.) To achieve this goal, researchers will develop the theory, numerical algorithms, and software tools through which input signals of these systems and the time course of the signals can be estimated from measured outputs. (Actual measurement of input signals is not possible.) Key to the success of this research effort is development of new numerical algorithms, without which new theories are useless. The combination of theory and novel algorithms will drive the development of software tools, permitting physiological and clinical investigators to solve real-world deconvolution problems.

In a second Italian collaboration, the Wisconsin RPRC provided training in performance of assays and support for research and development for the Istituto Superiore di Sanità, Rome. Studies were also initiated to establish assays of salivary cortisol as a noninvasive physiological indicator of stress in marmosets. This research will enable studies of cognitive function in marmosets.

A third joint project, between Wisconsin RPRC researchers and the Lazzaro Spallanzani Institute, Milan, Italy, has focused on the role of innate immunity in infectious diseases, particularly AIDS and tuberculosis. The main discovery has been that gamma–delta T cells are very potent killers of cells infected with human immunodeficiency virus (HIV) or simian immunodeficiency virus and also produce β-chemokines with potent antiviral activities. This knowledge may aid the development of vaccines for infectious diseases.

Mexico

NCRR supports the subcontract of Pangea Systems, Inc., Oakland, California, with Universidad Nacional Autonoma de Mexico, Mexico City, to maintain and expand the publicly accessible EcoCyc database on the World Wide Web. This database describes all known genes and metabolic pathways of *Escherichia coli* and other microbes.

Russia

The Washington RPRC continues to maintain a collaborative program with the Institute of Medical Primatology near Sochi, in southern Russia. This program has provided Russian-bred *M. nemestrina* for research and new sources of *Papio anubis cynocephalus* for the research needs of the Washington RPRC. The first shipment of *P. anubis* was received in October 1998, and the primates were used in joint research programs with the University of Washington School of Medicine, Seattle.

United Kingdom

The NCRR-supported Wisconsin RPRC continues its work with investigators at Oxford and Cambridge Universities, England, on the genetic basis of disease. In addition to identifying genes underlying risks for endometriosis, studies are beginning to examine risks for colon cancer.

The Wisconsin RPRC provides serum samples from prenatally androgenized female rhesus monkeys to the Medical Research Council Reproductive Biology Unit, University of Edinburgh, Scotland. The scientists are investigating common problems in women's health. These samples will enable development of assays for inhibins as serum biomarkers for impaired development of ovarian follicles. Other researchers, from the Wisconsin RPRC and the Mayo Clinic, Rochester, Minnesota, are using the prenatally androgenized female rhesus monkeys as models for polycystic ovarian syndrome and for ovarian hyperstimulation.

International Meetings

RCMI International AIDS Symposium

The 6th RCMI (Research Centers in Minority Institutions) International AIDS Symposium was held in San Juan, Puerto Rico, on November 15–18, 1998. This symposium provided a forum for scientists from Africa, Latin America, and the United States to present research findings from investigations on the AIDS epidemic among the general population and specifically among the African-American, African, and Hispanic populations. Recommendations from the symposium's more than 500 participants included increases in minority participation in basic and clinical AIDS research, the number of minority health care professionals, research collaborations in basic and clinical AIDS research, and dissemination of AIDS information among minority populations. Plans for the 7th symposium were also developed.

Synchrotron-Based Macromolecular Crystallography Research

The 6th International Conference on Biophysics and Synchrotron Radiation was hosted by Bio-CARS, the NCRR-supported Synchrotron Structural Biology Resource. This conference was cosponsored by and held at the Advanced Photon Source, in Argonne, Illinois, the only true third-generation synchrotron source in the United States. Held in August 1998, the meeting featured invited talks on synchrotron-based macromolecular crystallography and other technologies applied at the resource center. Countries represented included Australia, France, Germany, Japan, the Netherlands, Sweden, Switzerland, the United Kingdom, and the United States. Attendees participated in activities that provided cutting-edge information and new insights into the exciting field of biophysics and synchrotron radiation.