

# XIX.

## National Institute of Mental Health

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### INTRODUCTION

The National Institute of Mental Health (NIMH) is a scientific organization dedicated to the support and conduct of research focused on the understanding, prevention, and treatment of mental disorders and the promotion of mental health. NIMH is one of 25 Institutes and Centers of the National Institutes of Health (NIH), the principal biomedical and behavioral research agency of the U.S. Government and part of the U.S. Department of Health and Human Services (DHHS). Authorized in 1946, NIMH was one of the first NIH Institutes.

Mental illness is a serious burden for the global population; 5 of the 10 leading causes of disability are brain and behavioral disorders—unipolar major depression, alcohol use, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Depression is the leading cause of disability in the United States and in other established market economies. In the United States, depression affects 5% of the population over the course of their lives. Other global health-related issues that have a behavioral and mental health component include transmission of human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs), drug and tobacco use, intentional injuries, perinatal problems, and lifestyles contributing to chronic general medical illnesses.

Through research in basic neuroscience, behavioral science, and genetics, NIMH and the scientists it supports seek to gain an understanding of the fundamental mechanisms underlying thought, emotion, and behavior and an understanding of what goes wrong in the brain in mental illness. The Institute endeavors, at the same time, to hasten the translation of this basic knowledge into clinical research leading to interventions that will address appropriately and effectively the needs of diverse populations who seek and obtain treatment for mental illness, in a context of evolving health care systems.

### Research Areas

Key areas of NIMH-sponsored research include brain science, genetics, behavior, treatment, mental health of children and adolescents, brain imaging, and disparities in susceptibility to, prevalence of, and access to care for specific mental and behavioral disorders.

**Brain Science.** Neuroscientists are gaining the ability to determine how brain cells and circuits function to enable cognition, emotion, and behavior. This progress further challenges researchers to apply this fundamental knowledge—along with information about how the brain changes as it develops and ages—to reveal precisely which parts of the brain are disturbed in mental illness.

**Genetics.** The imminent completion of the Human Genome Project will provide enormous impetus to ongoing efforts to identify the genes responsible for vulnerability to mental and behavioral disorders. Combined with growing knowledge about the inheritance of these disorders in families and with information about the environmental triggers needed to activate vulnerability, the genetics revolution permits the anticipation of “cures” for mental illnesses.

**Behavior.** The explosion in new knowledge about the genetics, structure, and function of the brain challenges behavioral scientists to radically expand the traditional boundaries and methods of their discipline to determine how specific behaviors are directed and influenced by genes, how behavior can modify brain biology, how behavioral treatments for mental disorders can be strengthened, and how behavioral strategies for the prevention of diseases can be refined.

**Treatment.** With greater understanding about brain mechanisms involved in memory, decision making, and emotional responses to traumatic events, there is a growing need to revisit and redesign many of the current treatments. Translation of basic science findings into innovative behavioral

and pharmacological treatments that can either correct or compensate for brain dysfunctions will present immediate benefits to patients, family members, and clinicians.

**Mental Health of Children and Adolescents.** Childhood and adolescence are critical developmental periods that have lifelong ramifications for mental health. Among immediate challenges to researchers are recognizing the precursor forms of adult mental illnesses and how and when to intervene with preventive measures in high-risk situations; designing the most effective mental health care services for children and adolescents; and recognizing the biological, behavioral, and environmental roots of violence and aggression, to facilitate timely and effective intervention.

**Brain Imaging.** Advances in the temporal and spatial precision of brain-imaging technologies are being matched by reductions in cost and invasiveness of procedures. The net effect is to enhance the practicality of approaches that will image brain function in real time and over periods of development. The monumental challenge today is to link technological prowess to activation models capable of illuminating the complexities and subtleties of brain dysfunction at the onset and during the course of specific mental disorders.

**Disparities in Mental Health.** Globally, gender and social, cultural, or ethnic factors are known to increase the susceptibility of some groups of people to certain mental and behavioral disorders. Their access to and use of mental health care services, response to treatment, and resiliency also may be influenced by the same factors. NIMH is dedicated to broadening the diversity of mental health researchers with the expertise and commitment to identify and accommodate for these factors.

### Research Programs

The NIMH research enterprise has two major organizational and funding components.

Through its extramural research program, NIMH supports more than 2,000 grants and contracts at universities and other institutions across the country and overseas. The extramural research grant system is premised on *independence*, embodied in “investigator-initiated” research; on *self-governance*, evident in peer review of science by scientists, as the primary basis for judging the merits of research proposals and award of funding; and on the powerful incentive of *competition* among scientists. The Institute’s three major extramural components are the Division of Basic and Clinical Neuroscience Research; the Division of Mental Disorders, Behavioral Research, and AIDS (acquired immunodeficiency syndrome); and the Division of Services and Intervention Research.

NIMH also administers an Intramural Research Program consisting of approximately 500 scientists in 22 laboratories and branches on the NIH campus, Bethesda, Maryland. Intramural scientists include molecular biologists, geneticists, and behavioral scientists who conduct research on fundamental processes and clinical investigators who work with patients at the NIH Warren Grant Magnuson Clinical Center. The stable funding available through the Program makes possible long-term clinical studies that would be difficult for extramural researchers to accomplish. Also, because it involves basic science as well as clinical research, the Program is structured to facilitate interdisciplinary studies.

## **HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES**

### **Kenya**

NIMH provided supplemental funding to a team of U.S. investigators from the School of Medicine, Washington University, St. Louis, Missouri, to extend and broaden the scope of their ongoing epidemiologic studies of survivors of disasters. The research will now include a cross-cultural investigation focused on survivors of the bombing of the U.S. embassy in Nairobi, in August 1998.

The bombing provided a unique opportunity to conduct a cross-cultural investigation of disasters, through a comparison of this bombing with the bombing in Oklahoma City, Oklahoma, in 1995. Both bombings were devastating events of extraordinary

magnitude, but they provided unique opportunities to study the mental health consequences for victims and their responses to such events.

In the Nairobi bombing, approximately 250 people were killed and 5,000 were injured. Despite historically frequent trauma in Nairobi, mental health professionals have not been well trained in post-trauma work, and the infrastructure for emergency response is limited. In the immediate aftermath of the embassy bombing, Kenyan mental health professionals began to organize and provide services and to collect data. With additional support from NIMH, the U.S. investigators partnered with a group of physicians representing the Kenya Medical Association to perform the following functions:

- document the extent and nature of diagnosable psychopathology in direct victims of the blast and compare results with findings from research on victims of the 1995 Oklahoma City bombing;

- assess needs of community populations at risk for bomb-related psychosocial problems;

- provide technical assistance and training to professionals in Nairobi who have begun to gather data, to enhance the clinical and scientific sophistication of mental health interventions and their evaluation for effectiveness; and

- further develop a database to inform interventions in future terrorist incidents worldwide.

The U.S.-Kenyan investigative team has collected data on diagnosable psychiatric disorders, disability and functioning in a number of domains (e.g., family, work, and school), health status, treatment history, and physiological assessments for approximately 95 U.S. citizens and more than 100 Kenyans working for the United States in the foreign service. The investigators also have collected data on a large number of Kenyan volunteer rescue personnel. Finally, they are obtaining data on several hundred 11- to 12-year-olds from the community.

The investigators are preparing data for publication and are exploring the feasibility of evaluating the children of the U.S. embassy employees in Nairobi and the children of direct victims in Oklahoma City. Furthermore, they have obtained commitment from the U.S. Department of State to help

locate the families that will have moved by the time a subsequent follow-up is conducted.

### **Russia**

After the development of programs to treat depression in primary health care settings in four Russian cities (Dubna, Moscow, Tomsk, and Yaroslavl) in fiscal year 1998 (FY 98), the Health Committee of the U.S.-Russia Joint Commission on Economic and Technological Cooperation proposed a merger of several related programs. The program for treatment of depression in primary care settings was merged with other primary care programs directed at treatment of chronic medical conditions, such as hypertension, asthma, and diabetes mellitus. This component of the commission’s Health Committee, entitled Access to Quality Health Care, came under the purview of the Director of the Agency for Health Care Research and Quality, who serves as the DHHS Secretary’s point of contact to the Russian Minister of Health. The overall Health Committee is cochaired by the Secretary of DHHS and the Russian Minister of Health.

A major objective of merging the activities was to facilitate a greater coordination of management of chronic disease in primary health care settings. Hence, the Health Committee sponsored a primary care site in Tula, Russia, and a primary demonstration project to improve treatment of hypertension was selected to exchange its expertise in managing this chronic condition with one of the Moscow-based primary care sites treating depression. Facilitating all of these activities was a contribution from the U.S. Agency for International Development (USAID), to purchase and equip eight laptop computers for use in administering a computer-assisted diagnostic assessment interview for mental disorders—the *Composite International Diagnostic Interview (CIDI)*, which was developed by the World Health Organization (WHO). On the basis of its extensive USAID-sponsored work in Russia, the American International Health Alliance was of great assistance in facilitating the purchase and equipping of these computers for use in Russian-language settings. The computers are also useable for data management of demonstrations at each site and Internet-based communication of results to the coordinating center at the Moscow Research

Institute of Psychiatry. Implementation of a joint protocol for treatment of hypertension or depression in each site, with monitoring of patients by a common nurse-coordinator, is expected in FY 01.

### **South Africa**

A team of researchers from South Africa and the United States is studying the Psychiatric Effects of Apartheid and Torture. This 5-year research project involves epidemiologists from the University of Michigan, Ann Arbor; Harvard University School of Public Health, Cambridge, Massachusetts; the Dean of the National School of Public Health, Medical University of South Africa, Pretoria; the Chair of the Department of Psychiatry, University of the Orange Free State, Bloemfontein; and researchers at the University of Cape Town. The study will focus on 1,000 persons who testified at the hearings of the Truth and Reconciliation Commission and a random sample of 5,000 from all of South Africa. It will be the first study of the effects of torture on a population that will be conducted in the country in which it occurred. Other studies of the psychiatric consequences of torture have been limited to examining the effects on selected samples, and these effects could not be compared with the incidence of psychiatric illness in the general population. The project is proceeding at the University of Michigan and in South Africa through training of staff to conduct the interviews and translation of the instruments of the *International Classification of Diseases* into four South African languages, as well as validation of the measurement of disorders. In addition to studying the relationship between torture and mental illnesses, this study will provide the first national epidemiologic data on mental disorders in any country in Africa. The data will increase scientific knowledge and will be useful for policy development. Transformation of the health system to meet the needs of all the citizens of South Africa is a major goal of the new South African government.

In addition, the U.S.-South Africa Binational Commission met in Cape Town, in February 1999. The U.S. Surgeon General led the U.S. delegation in the meetings with the Minister of Health of South Africa; the Medical Research Council of South Africa; and the Dean of the National School of Public Health, Medical University of South

Africa, Pretoria. The Director of Mental Health and Substance Abuse, South Africa Department of Public Health, and NIMH staff discussed the research on mental illness and apartheid and torture and its implications for science and for policy. South Africa is changing its mental health system in two major ways. Mental health care for persons with severe mental illnesses had been provided almost entirely in long-term, largely custodial, mental hospitals, often by private contractors. The government of South Africa is trying to provide much more of this care in the community and is seeking ways to avoid the homelessness that has too often occurred in the United States and other countries as a result of deinstitutionalization. There is also a government plan to integrate mental health care with primary health care. These goals are similar to efforts being made in the United States and other countries. The question is how South Africa and the United States can learn from each other and thus provide more effective care. The new constitution of South Africa clearly states that health care, including mental health care, is a basic human right.

Consultation provided in 1998 by NIMH staff and consultants was cited by South African mental health officials for its usefulness in implementation of community care of persons who had been long-term patients in mental hospitals. This implementation has involved sharing research instruments, assessment tools, and models of care.

The Surgeon General and NIMH staff met with the Director of Health for the Eastern Cape and with university faculty from several schools in the Eastern Cape province to discuss health and mental health issues. With the assistance of funding by the USAID program, the \$50 million, 5-year EQUITY Project in the Eastern Cape province is developing new ways to provide health and mental health care.

A new National School of Public Health at the Medical University of South Africa, Pretoria, was dedicated in February 1999. At the dedication, the U.S. Surgeon General spoke on Disparities in Health, and NIMH staff lectured and met with faculty and students.

### **World Health Organization**

In FY 99, the Secretary General of WHO sponsored a consultation with leading men-

tal health consultants to establish a WHO agenda for mental health. The NIMH Associate Director for Epidemiology and Health Policy Research contributed to that consultation in April 1999, which led to a major policy announcement of WHO's mental health agenda, in a speech in Beijing, China, in November 1999. More recent follow-up consultations with the NIMH Director and other international consultants have led to the development plans for a focus on primary health care programs on treatment of depression and suicide prevention. In addition, international public health education programs about the nature of depression and the effectiveness of available treatments to prevent disability and suicide are in the planning stage. Also, models being developed in Australia, England, Norway, Russia, the United States, and other countries are being evaluated for their effectiveness and transportability to other sites.

### **Revision of *International Classification of Impairments, Disabilities, and Handicaps***

Throughout FY 99, the International Task Force on Mental Health and Addictive, Behavioral, Cognitive, and Developmental Aspects of the *International Classification of Impairments, Disabilities, and Handicaps (ICIDH)* actively contributed to the revision process for the WHO *ICIDH*. The charge of the International Mental Health Task Force continued to be focused (1) on the mental health aspects of the *ICIDH* revision, the unique contributions of mental functions and structure for which the task force has responsibility, and (2) on the impact of mental disorders on performance of activities and participation in society.

During FY 99, the field trials of the beta-1 version of *ICIDH-2* were completed, analyses of the five mandatory components were conducted by WHO, and the revised version, *ICIDH-2* beta-2, was published. The International Mental Health Task Force played a leading role in the revision process, especially in developing operational definitions of mental functions and of the activities that most characteristically reflect the limitations experienced by people with mental disorders, such as those related to work and social relations.

*ICIDH-2* beta-2 was published in July 1999. The International Mental Health Task

Force collaborated with WHO to conduct a pilot training for the beta-2 field trials in August. The task force also undertook to translate *ICIDH-2* beta-2 into six languages: Tamil and Hindi (India), Yoruba (Nigeria), Russian, Spanish, and Turkish.

The translation of *ICIDH-2* beta-2 into Spanish was conducted with use of an innovative method. Because Spanish languages and cultures are diverse across the many Spanish-speaking countries, it became necessary to develop a consensus on the version that would be acceptable and practical for all. To accomplish this, La Red de Habla Hispana en Discapacidades (La RHHD), with major support from NIMH, convened two meetings. At the first meeting, which was held in Santander, Spain, in 1998, the method of translation was developed, and responsibilities were identified for each of the participating countries. Initial translation was conducted by a core group in Spain, and each chapter and section was then sent to chapter leaders in different countries for correction, modification, and further circulation. Field trial materials were also translated in this fashion.

A second meeting of representatives of NIMH and La RHHD was held with members of the Ministry of Health, Santiago, Chile, in September 1999. The purposes were (1) to plan a meeting to train all members of La RHHD to conduct field trials and (2) to develop a network of potential users of *ICIDH-2* in Chile. One aspect of this meeting was to solidify the liaison and harmonize the revision process with a second Spanish-language network in Latin America (La Red de Discapacidades y Rehabilitación), which had been convened by the Pan American Health Organization and also worked on the revision of *ICIDH*.

Both the formal training for and the conduct of the *ICIDH-2* beta-2 field trials are planned as FY 00 activities. With the foundation laid by the International Mental Health Task Force and its collaboration with La RHHD, at least 22 countries are actively participating in the revision process and the field trials. During FY 99, in addition to support for the meetings described here, NIMH contributed funding as seed money for the conduct of the field trials for both the International Mental Health Task Force and La RHHD.

### **WHO-NIH Joint Project on Assessment of Disabilities**

In the WHO-NIH Joint Project on Assessment of Disabilities, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and NIMH are working with WHO to develop research instruments with versions to assess disabilities in epidemiologic and clinical investigations. In FY 99, the 4th of 5 years planned for this research effort, the project neared successful completion. The development of the *WHO Disability Assessment Schedule II* (*WHO DAS II*) has primarily focused on the structured epidemiologic version. The strategy is that the clinical version will essentially telescope from the foundation laid by the shorter epidemiologic version and will have a semistructured interview format. Preliminary work on the clinical version and on computer-assisted and proxy versions of the survey instrument was undertaken in FY 99.

The survey version of *WHO DAS II* queries six domains of disability—understanding and communicating; getting around; self-care; getting along with people; life activities (work and household); and participation in society. This questionnaire is designed to obtain data on both the amount and frequency of difficulty experienced in each area. Qualitative and quantitative field trials and testing of the instrument's psychometric properties were conducted in 21 centers in 19 countries, to ensure international applicability, relevance, and reliability. During FY 99, the field tests directed the final selection of questions, provided information on practicality of use (e.g., how much time the assessment takes), and guided the development of screener questions. Psychometric analyses of the 36-item instrument affirmed a general disability factor with excellent correlations to the six domains, and preliminary analyses for reliability and concurrent validity show sound psychometric properties. During FY 99, planning was started for pilot studies that will use *WHO DAS II* in research on health services.

A supplement to the Cooperative Agreement that supports this joint project is dedicated to development of a method for using an empirical base as a disability weight in assessment of the global burden of disease, a measure of worldwide disease created by WHO, the World Bank, and Harvard University, Cambridge. This disability weight

would be applied to determine the years lived with a disability (YLDs), which is a component of disability-adjusted life years. In the past, disability weights for YLDs have been determined through preference valuation techniques from the field of economics, but these techniques may not be sufficiently sensitive to changes in disability status in response to health care treatment and interventions. During FY 99, researchers in pilot studies in China, Colombia, the Philippines, and Tanzania collected data on disability by using WHO DAS II and simultaneously conducted preference valuation assessments. These data are being used (a) to develop a method that can apply an empirically based global measure of disability that is sensitive to change and (b) to compare relative disability weights across health conditions and assessment techniques.

### **Center for Mental Health Research on AIDS Prevention Program**

Prevention remains a critical priority of the NIMH Center for Mental Health Research on AIDS, in efforts to curtail the AIDS epidemic that is emerging worldwide. Few epidemics are stopped by treatment, and treatment certainly is the more expensive route. However, it is possible to mobilize behavioral prevention within a community, to address the major factors associated with the rapid development of an epidemic. NIMH has made a commitment to the development of an international prevention program for HIV and STDs. The bidirectional goals for this program are (1) to extend the generalizability of research findings to international settings; (2) to identify assumptions and cultural issues in prevention programs; and (3) to understand the situational determinants and dynamics of AIDS prevention in multicultural settings.

### **International Research Studies**

#### *NIMH Collaborative HIV/STD Prevention Trial*

The AIDS epidemic remains largely out of control in many areas of the world, particularly in developing countries with few economic resources, where there are large increases in HIV incidence. Rapidly increasing STD rates are also a widespread concern, because STDs can lead to infertility and increased risk of HIV. Approaches that change

behavior in one person at a time cannot be implemented rapidly enough to avert an epidemic. However, community-level interventions to achieve behavioral change have the potential to reach large numbers of people, to reinforce individual behavior change, and to be cost-effective and feasible, even in areas with limited resources.

The NIMH Collaborative HIV/STD Prevention Trial is a two-arm, randomized, community-level trial in six countries—China, India, Peru, Russia, Uganda, and Zimbabwe. This project will be the first international test of a community-level prevention program. The trial uses the Popular Opinion Leader program, which is based on the theory of diffusion of innovations through popular opinion leaders in the community. The intervention engages these leaders to serve as agents of behavior change to friends and neighbors in their community. The prevention program is expected to strengthen norms of safer sexual behavior and encourage risk reduction among at-risk populations.

The pairs of collaborating institutions conducting this trial in foreign countries are (1) the University of California, Los Angeles, and the Chinese Academy of Preventive Medicine, in Beijing; (2) Johns Hopkins University, Baltimore, Maryland, and the YRG Centre for AIDS for Research and Education (CARE), in Madras, India; (3) the University of California, San Francisco, and Cayetano Heredia University, in Lima, Peru; (4) the Medical College of Wisconsin and St. Petersburg State University and Biomedical Center, in St. Petersburg, Russia; (5) Columbia University, New York City, New York, Makerere University, in Rakai, Uganda; and (6) Battelle Centers for Public Health and University of Zimbabwe.

#### **Brazil**

Two NIMH-supported investigators are conducting HIV studies in Brazil. One investigator from Columbia University, New York City, is studying the use of combination antiviral therapies in the developing world. Brazil is the only developing country that makes drugs for combination therapies widely and freely available for persons who are HIV seropositive, and little is known about adherence to treatment protocols or the behavioral consequences of these therapies. The aims of this study are to measure

adherence to protocols for combination therapies in developing countries and to examine the relationship between administration of combination therapies and safer sexual behaviors and better quality of life in persons with HIV/AIDS. Another high-priority study in Brazil, conducted by an investigator at the University of California, San Francisco, will determine the frequencies of drug-resistant HIV subtypes present in recently HIV-infected persons and the behavioral and social factors associated with transmission of drug-resistant HIV subtypes. These data are critical to design of culturally appropriate HIV prevention programs.

#### **Dominican Republic, Mexico, and Puerto Rico**

An investigator from the University of Puerto Rico is conducting a multisite study in the Dominican Republic, Mexico, and Puerto Rico, focusing on the role of men in HIV/AIDS prevention with women. The specific aims of the study are to explore the social and cultural context of HIV risk behaviors in men, in efforts to develop interventions for male partners in prevention programs. In addition, a researcher at the National Development and Research Institute, New York City, New York, is working with a Mexican investigator to replicate a preventive intervention for parents and their children. The prevention program teaches parents how to talk about sexual behavior and AIDS with their children who are not yet sexually active. The goals of this study are to overcome AIDS stigma in young children and to delay the initiation of sexual debut in the children.

#### **India**

NIMH has made a major commitment to support intervention research to encourage behavioral change to prevent the spread of HIV in India. NIMH researchers are conducting four projects there. Researchers at Johns Hopkins University, Baltimore, and YRG CARE are implementing the NIMH Collaborative HIV/STD Prevention Trial, in Madras. Investigators at the University of California, Los Angeles, and the Indian Council on Medical Research are conducting a study to identify HIV/STD risk factors for Indian women in order to develop an intervention that will integrate disease prevention and reproductive health, for

use in clinics. Also, the first randomized clinical trial of an intervention for women in Calcutta will be conducted jointly by a researcher from the University of California, Los Angeles, and the Indian researcher who developed this comprehensive AIDS prevention program using empowerment for women. In addition, an investigator at the University of Syracuse, New York, is collaborating with an investigator at the National Institute of Mental Health and Neurosciences, Bangalore. The investigators will adapt and test an HIV/STD prevention program for persons who have serious mental illness.

#### **Indonesia**

A study by a researcher at the University of Michigan, Ann Arbor, is evaluating the effectiveness of two long-term HIV prevention programs for women in Bali. Interviews are being conducted to collect qualitative and quantitative data to elucidate the dynamics of HIV transmission in this vulnerable population. The presence of STDs is being evaluated at baseline and at 6, 12, and 18 months later. The results from this project can be used to develop long-term intervention programs for high-risk populations in developing countries.

#### **South Africa**

An investigator at Columbia University, New York City, will collaborate with mental health care providers in South Africa to develop and implement HIV prevention programs among persons with severe mental illness. The study is being performed in collaboration with a large public psychiatric institution in KwaZulu, Natal province, which has the highest HIV seroprevalence in South Africa. The goals are (1) to train mental health care providers in South Africa in basic knowledge of HIV/AIDS and in communication with patients about sexual issues and stigma and (2) to develop and adapt interventions for HIV prevention for persons with severe mental illness.

#### **Zimbabwe**

Zimbabwe is the site of two studies focused on populations at risk for HIV: orphans and patrons of beer halls. A small study of orphans of parents who died of AIDS is being conducted in Mutare by the AIDS Orphan's Project, a private African foundation, and

in New York City, New York, by a researcher from Einstein College of Medicine. The aims of this study are (1) to document the extent to which children have taken on adult responsibilities when parents with AIDS are ill and (2) to describe educational, health, mental health, and developmental consequences for children who assume these caregiving roles. These data will be used to develop an intervention to prevent the negative psychological and behavioral sequelae in these children.

Municipal social halls are a major feature of the social life of men living in Harare, and social halls are the setting for the high transmission rates of HIV/STDs. Frequent attendance at social halls in Harare is also a strong predictor of HIV seroconversion. Researchers from the University of California, San Francisco, are conducting the first study of HIV seroprevalence in male patrons of social halls in sub-Saharan Africa and are obtaining data on behavior risk that can be used to develop an intervention to prevent HIV transmission in this setting.

#### **AIDS Research Centers**

NIMH supports four AIDS Research Centers that actively promote collaborative international studies. The Center for AIDS Prevention Studies (CAPS) at the University of California, San Francisco, builds partnerships between CAPS scientists and scientists from Africa, Asia, Eastern Europe, and Latin America. Together these scientists are examining risk behavior patterns, in efforts to develop AIDS prevention programs that are appropriate for specific countries. Examples of research projects are a molecular epidemiology study in Brazil and an investigation of behavioral patterns related to HIV risk in men in Zimbabwe.

The HIV Center for Clinical and Behavioral Studies, at Columbia University, New York City, has a history of collaborative research in Brazil, Puerto Rico, and South Africa. Both NIMH and the Fogarty International Center are contributing to building infrastructure to conduct extensive epidemiologic studies on HIV and STDs. Specific programs focus on integrating pregnancy prevention and disease prevention in Brazil and prevention of HIV risk behaviors in the mentally ill in South Africa.

The Center for AIDS Intervention Research, in Milwaukee, Wisconsin, has been

cooperating in research training and the initiation of studies in St. Petersburg, Russia. The alarming prevalence of STDs among youth has prompted the initiation of a program for youth. St. Petersburg is one of the sites for the NIMH Collaborative HIV/STD Prevention Trial.

The Center for Early Detection, Prevention, and Treatment of HIV, at the University of California, Los Angeles, has also started an international program. The investigators are studying the risk patterns for vulnerable populations, such as homeless youth and disenfranchised women in Australia, China, and India.

#### **Meetings**

NIMH sponsors an annual conference on the Role of Families in Preventing and Adapting to HIV/AIDS. At the conference in Philadelphia, Pennsylvania, on July 21–23, 1999, the organizers invited international representatives to participate in a Workshop on AIDS Orphans, to develop a research agenda. Invited participants were from Guatemala, Thailand, Zambia, and Zimbabwe.

An NIMH delegation composed of eight prevention scientists and three NIMH staff members participated in the HIV Prevention Conference, in New Delhi, India, on January 9–11, 1999. This workshop was cosponsored by the Indian Council on Medical Research, the National AIDS Control Organization, and the NIH. This group drafted a joint Indo-U.S. Behavioral Prevention Research Agenda that would be implemented under a joint agreement to be signed by both governments. The first NIMH delegation went to India in September 1997. As a result of the 1999 conference, four studies of behavioral prevention are being conducted by Indo-U.S. research teams.

Staff from the Center for Mental Health Research on AIDS were invited to give an opening address and a presentation on behavioral prevention at the 7th Annual Russian Conference on AIDS, Cancer, and Related Diseases, in St. Petersburg, Russia, on May 21–23, 1999. AIDS staff also gave invited presentations at the 2nd Conference on Global Strategies for the Prevention of HIV Transmission From Mothers to Infants, in Montreal, Quebec, on September 3, 1999.

#### **Future International Activities**

The NIMH Collaborative HIV/STD Preven-

tion Trial has been invited to present a symposium on this international trial at the 8th National Russia Conference on AIDS, Cancer, and Related Diseases, in St. Petersburg, Russia, on May 23–26, 2000. The steering committee for this trial will also hold a meeting to review its progress at that time.

The NIMH Center for Mental Health Research on AIDS is sponsoring a booth at the XIIIth International AIDS Conference, in Durban, South Africa, in July 2000. The theme will be Behavioral Prevention Is Today's AIDS Vaccine. A modeling program is being developed by epidemiologists at the University of Oxford, England, to project the HIV/STD epidemics in different countries on the basis of the current prevalence of HIV and STDs and the risk patterns in different populations. Unique to this program will be the opportunity to examine the projections for spread of the epidemic that are based on the introduction of various effective behavioral programs for prevention.

### **SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES Activities With International and Multinational Organizations**

#### **International Cooperative Biodiversity Group Program**

For the past 5 years, the Neuropharmacology Program in the Molecular and Cellular Neuroscience Research Branch of NIMH has contributed funds to support international research on biodiversity and drug discovery of the International Cooperative Biodiversity Group (ICBG) Program. The ICBG Program is an innovative, interagency conservation and development effort administered by the Fogarty International Center, NIH. The goal of the Program is to promote biodiversity conservation and sustained economic activity through the discovery and development of therapeutic agents derived from natural products (e.g., plants, fungi, insects, and microbes). The ICBGs consist of diverse public and private institutions, including universities, environmental organizations, and pharmaceutical companies. The ICBG Program is jointly funded by a consortium of Federal agencies, including the Biological Sciences Directorate of the National Science Foundation, the Foreign Agriculture Service of the U.S. Department of Agriculture, and Institutes of the NIH—the National Institute of

Allergy and Infectious Diseases; the National Cancer Institute; the National Institute on Drug Abuse; the National Heart, Lung, and Blood Institute; and NIMH. The Neuropharmacology Program of NIMH contributes support to three of the ICBG projects.

The Program supports seven ICBG projects in 11 countries in Africa, Asia, and Latin America: Argentina, Cameroon, Chile, Laos, Madagascar, Mexico, Nigeria, Panama, Peru, Suriname, and Vietnam. Projects include the selection and acquisition of natural products derived from biological diversity, as potential therapeutic agents for disorders such as Alzheimer's disease, psychiatric disorders, drug addiction, cancer, AIDS, parasitic diseases, and heart disease, all of which are of concern to both developed and developing countries. Nearly 4,000 species of plants and animals have been examined for biological activity in 13 therapeutic areas.

Numerous publications in chemistry, ethnobiology, biodiversity policy, and conservation have been generated by the funded investigators. Broad public attention to the ICBG Program and its timing relative to international developments associated with the United Nations Convention on Biological Diversity have allowed the Program to offer useful working models for national and international policy discussions about biodiversity conservation incentive measures, technology transfer, intellectual property, and benefit sharing. Further information about the ICBG Program is available at the Web site <http://www.nih.gov/fic/opportunities/icbg.html>.

### **Organization for Economic Cooperation and Development**

Since 1996, the Associate Director, Office on Neuroinformatics, NIMH, has chaired the Neuroinformatics Subgroup, Biological Informatics Working Group, Megascience Forum, of the Organization for Economic Cooperation and Development (OECD). In the United States, the Human Brain Project/Neuroinformatics Program is supported by multiple agencies and multiple Institutes of the NIH. The supporting agencies are the NIH, the National Science Foundation, the U.S. Department of Energy, and the National Aeronautics and Space Administration. The supporting Institutes of the NIH are the Fogarty International Center; the National

Institute on Aging; the National Institute on Alcohol Abuse and Alcoholism; the National Cancer Institute; the National Institute of Child Health and Human Development; the National Institute on Deafness and Other Communication Disorders; the National Institute of Dental and Craniofacial Research; the National Institute on Drug Abuse; the National Heart, Lung, and Blood Institute; NIMH; the National Institute of Neurological Disorders and Stroke; and the National Library of Medicine.

The goal of this effort is to create a set of distributed databases and tools to advance the field of neuroscience research. The driving force for this initiative in the United States is the ever-increasing amount of empirical research data generated at greater levels of granularity and sophistication, from the 30,000 neuroscientists in the United States. There is a great need to create modern databases at all levels of neuroscientific analysis. Such an effort will conserve this great wealth of data and allow for integrating brain function across levels of analysis and modeling of brain structure, function, and development, to facilitate proper theoretical-experimental interplay. Because there are approximately 55,000 neuroscientists globally, all neuroscientists in all countries must participate to achieve the creation of an adequate knowledge management system. This goal provides the impetus for the OECD Megascience Neuroinformatics Subgroup.

The Neuroinformatics Subgroup of the OECD Megascience Forum issued its defining report as part of the full Biological Informatics Working Group Committee's report to the delegates in January 1999 (see [http://www.oecd.org/dsti/sti/s\\_t/ms/index.htm](http://www.oecd.org/dsti/sti/s_t/ms/index.htm)). The general recommendation is that the governments of OECD countries have the opportunity to play a crucial role in fostering biological informatics by eliminating the barriers that prevent cooperation and by providing incentives to potential participants. Actions that could be taken include the following:

- funding development of software or hardware capabilities that enable biological informatics;
- protecting the needs of scientific research and education in international agreements about intellectual property and biological information;

- making creation of a database and provision of information two conditions for government funding of biodiversity and neuroscience research projects;

- participating in international efforts to establish standards in several areas, including validation and description of data; and

- encouraging participation in the worldwide biological informatics effort by academia, private companies, publishers, and other segments of the private sector, through use of tax concessions, contracts, or other incentives.

The specific findings and recommendations of the Neuroinformatics Subgroup include the following:

1. Neuroinformatics combines neuroscience and informatics research to develop and apply advanced tools and approaches essential for a major advancement in understanding of the structure and function of the brain. Neuroinformatics research is uniquely placed at the intersections of medical and behavioral sciences, biology, physical and mathematical sciences, and computer science and engineering. The synergy from combining these approaches will accelerate scientific and technological progress, resulting in major medical, social, and economic benefits.

2. In the past, neuroscience has been dominated by the acquisition of experimental data. It is now propitious to facilitate the development of theoretical models and tools to help manage and use the data to yield new knowledge and understanding.

3. The scientific aim of neuroinformatics is to accelerate the progress of neuroscience and informatics by achieving the following goals:

- making better and more efficient use of neuroscience data by using informatics-based technologies, including computational approaches;

- generating and evaluating new hypotheses and computational theories about brain function to drive further experiments;

- developing and applying new tools and methods for acquiring, visualizing, and analyzing data important for understanding how the brain functions;

- ensuring that the accumulating knowledge of how the brain functions will be applied more efficiently to understanding brain dysfunction in disease; and

- creating computer systems and tech-

nological applications that simulate or emulate specific aspects of brain function.

4. The Megascience Forum should support establishment of a global neuroinformatics capability. This capability needs to be developed as a network of neuroinformatics facilities and approaches distributed across many research centers around the world. This diverse network should focus on developing the following resources:

- databases that are increasingly able to handle the full complexity and organization of the nervous system, from molecular to behavioral levels;
- powerful new tools for data acquisition, analysis, visualization, and distribution; and
- theoretical, computational, and simulation environments for modeling and understanding the brain.

5. International coordination, as well as national efforts, are needed to ensure that these steps are properly implemented and sustained. An international scientific coordinating body, the International Neuroinformatics Committee, and an associated secretariat should be established through the support of the participating countries.

At the January 1999 meeting of the Megascience Forum, the delegates affirmed neuroinformatics as a highly important emerging field of science, still in its formative stages. They agreed that neuroinformatics is an amalgamation of different fields and, as such, requires additional time for its maturation and that it is important for the neuroinformatics initiative to move forward in a coordinated manner. It was recommended that the Neuroinformatics Subgroup present interim recommendations to the Megascience Forum. The Neuroinformatics Subgroup concurred at its March 1999 meeting on the need to ensure that a lasting interface is established between the neuroscience field and the fields of information technology. There was also agreement on the following measures to achieve this goal:

- education of scientists and governments to support these collaborative activities;
- facilitation of this cooperation by focusing on the international components;
- increase in the visibility of neuroinformatics in the neuroscience community; and
- realization of the interoperability of tools and models.

To meet these needs and the recommen-

dations of the Megascience Forum, a committee from the Neuroinformatics Subgroup will develop a strategic interim plan for coordination of neuroinformatics activities.

#### **U.S.-European Commission**

The U.S.-European Commission (U.S.-EC) Task Force on Biotechnology Research was established in 1990 and is cochaired by the Assistant Director, Biological Sciences, National Science Foundation, and the Director, Life Sciences Coordination, Directorate of General Research, EC. A joint U.S.-EC Neuroinformatics Steering Committee was established in 1995, under the auspices of this task force, to monitor and promote interactions and communications about collaboration on neuroinformatics research between the United States and EC, across disciplines and national borders. The activities of this steering committee complement the activities of the Human Brain Project/Neuroinformatics Program and the Neuroinformatics Subgroup of the OECD Megascience Forum.

The joint meeting of the Neuroinformatics Steering Committee in March 1999 was cochaired by the Associate Director, Office on Neuroinformatics, NIMH, and the Principal Scientific Officer, EC. The steering committee made several recommendations for future joint activities, including additional workshops, demonstration projects, and training activities. The demonstration projects would attempt to facilitate vertical and horizontal integration of data. A joint U.S.-EC symposium, entitled Neuroinformatics: an Enabling Capability for Understanding and Integrating Data on Brain Function, has been accepted for the meeting of the Collegium Internationale Neuro-Psychopharmacologicum, in Brussels, Belgium, in July 2000.

EC collaborated with the German Presidency of the European Union to organize the second conference on New Vistas in Transatlantic Science and Technology Cooperation, held in Stuttgart, Germany, on June 21–22, 1999. The goals of the conference, which brought together 260 representatives from the two continents, were to promote and strengthen cooperation in a number of strategic areas, under the terms of the October 1998 agreement between the European Union and the United States on cooperation in science and technology. The agreement seeks to stimulate a much more

active cooperation based on initiatives jointly supported by the European Union's 5th Framework Program and leading U.S. scientific and technological agencies. Projects include creation of structures for the sharing of study data and results and the exchange of scientists. One meeting session was organized and chaired by the Associate Director, Office on Neuroinformatics. At the conference, many areas of future cooperation were identified as immediate, intermediate, or long-term goals. The recommendation for immediate action included the following:

- create cross-training facilities and organize workshops on common neuroinformatics issues, including problems in developing computational models and databases in neuroscience;
- organize demonstration projects for exchanging data among ongoing programs;
- provide annual U.S.-EC Summer Schools on Neuroinformatics at alternating sites in the United States and the European Union; and
- develop software simulators for the ensemble of neurons, neural circuits, and systems of neurons, for general use and similar to the standard simulators for single neurons.

#### **Extramural Programs Fellowships**

In FY 99, the extramural programs of the National Institute of Child Health and Human Development, NIMH, and the National Institute of Neurological Disorders and Stroke awarded contracts for a data coordinating center and seven pediatric study centers, to implement a 6-year study of normal brain development from birth through age 18 years. Neurovision Sciences, Inc., Montreal, Quebec, will serve as the data coordinating center and will analyze the brain-imaging data collected as part of this project. Seven U.S. institutions will serve as pediatric study centers, recruiting, testing, and performing brain scans on the children and adolescents. This study will use state-of-the-art techniques for magnetic resonance imaging (MRI) to characterize brain maturation from infancy through late adolescence. These techniques include conventional anatomic MRI scanning, as well as newer methods that use conventional MRI scanners to measure brain metabolites and methods that provide information on connecting

fibers in the brain. Approximately 500 subjects will be recruited to be representative of the population of the United States. They will be studied repeatedly at three time points, so that changes in brain structure can be measured. Also, they will simultaneously be studied with behavioral measures and tests, so that cognitive and behavioral development can be related to maturational changes occurring in the brain.

This project is expected to provide a better understanding of normal brain development and its variability, as well as a solid basis for detecting and understanding subtle abnormalities of brain development seen in a variety of developmental, neurological, and psychiatric disorders of childhood. It also is expected to yield new developmentally sensitive tools for image analysis. Ultimately, this research should provide normative data and useful tools for both clinicians and researchers. In view of the large scale of this project, it probably could not have been initiated without NIH support.

#### **Research Grants**

##### *Adult Psychopathology and Prevention Research Branch*

The Adult Psychopathology and Prevention Research Branch supports one foreign grant and eight domestic grants with foreign components. An investigator from Iowa State University, Ames, is conducting a longitudinal study of the effect of the postcommunist transformation on the well-being of families and individuals in the Czech Republic, as indicated by reports of physical health, emotional distress, and behavioral problems. The investigator is also examining the role of such factors as economic and job appraisal, family and social support, and psychological states, in mediating and moderating the relationship between transformation and well-being. Data on a series of three questionnaires have been collected in 1994–1996. The 740 households participating in the study are a representative quota sample of Czech households, one-half rural and one-half urban. The aims of the project are to refine the connection between the transformation and stress, to model the stress–distress process, and to compare the results with those in the United States.

Using the Department of Psychiatric Demography data systems in Denmark, a study at Johns Hopkins University, Baltimore,

Maryland, is analyzing the relationship of pregnancy and birth complication with hospitalization for mental disorder. One goal is to assess the relationship of pregnancy and birth complication to the psychiatric history of the mother, for 40,000 of 600,000 women giving birth. Another goal is to assess the effect of pregnancy and birth complication on the child's later hospitalization for mental disorder.

The University of Southern California is studying Schizophrenia in High-Risk Populations by examining data from 9,125 consecutive deliveries of infants in a perinatal cohort in Denmark. The "two-hit" working model to guide this research on the etiology of schizophrenia consists of a disruption of fetal neural development induced by genetic or teratogenic factors. The second hit may take the form of brain damage caused by delivery complications or stressful, nonoptimal circumstances related to child rearing. The tests will be conducted in three projects: the 1962 High-Risk Project, the Fetal Virus Project, and the project on Perinatal Disturbance and Adult Schizophrenia.

A researcher from Yale University, New Haven, Connecticut, initiated three ongoing investigations. The Collaborative Longitudinal Study of Personality Disorders was started in 1966, as a 5-year project. The five sites for this study are located in Denmark, Finland, and Norway. The research on Early Detection and Intervention in Schizophrenia was started in 1977 as a 4-year project, also in Scandinavia. The study entitled Delaying or Preventing Psychosis: a Clinical Trial of Treatment in Persons Prodromal to Psychosis was started in New Haven in late 1997.

A project at the Research Foundation for Mental Hygiene, New York State Psychiatric Institute, New York, is investigating the relationships among prenatal exposures, obstetric complications, neonatal health, heredity, and schizophrenia. The study is based on 92,000 pregnancies in Israel in 1966–1974, for which a wealth of prospective data was collected from early in gestation, for the Jerusalem Perinatal Study. The cohorts are now at the age of risk for schizophrenia.

A Scientist Development Award for Clinicians is enabling an investigator at Columbia Hospital, New York City, to develop expertise in epidemiology and a working

knowledge of neurobiology and neurodevelopment, so that he can independently conduct epidemiologic investigations of schizophrenia and prenatal exposures to viruses and other factors. The research plan for this study of the Epidemiology of Prenatal Exposures in Schizophrenia includes an extension of the previous study of prenatal influenza and schizophrenia in the Netherlands. The study is examining the effect of prenatal influenza exposure in schizophrenia, in urban versus rural settings.

The goal of the Longitudinal Studies of Partner Violence Perpetration, which is being performed by the University of Wisconsin, Madison, is to build a knowledge base about partner violence among adults, the peak risk group. Perpetration and victimization will be measured for both men and women in the longitudinal Dunedin Multidisciplinary Health and Development Study, which performs follow-up on a representative 1972 birth cohort of 1,000 New Zealand men and women to age 26 years. Results will be compared with findings in the longitudinal Pittsburgh Youth Study, which performs follow-up on a high-risk 7th-grade cohort of 250 urban black men and 250 urban white men in the United States to age 24 years. By comparing results across genders, races, and sites in two different nations, the project aims to document which findings about violence of young adult partners are sufficiently robust to inform theory, practice, and policy.

A student at Case Western Reserve University, Cleveland, Ohio, received dissertation support to conduct an ethnographic study of religious healing among labor migrants in the Altinagac squatter settlement, Ankara, Turkey. Past anthropological research has suggested that religious healing plays an important role both as a mental health care resource and in the process of negotiating new identities, but there have been no in-depth studies in the context of labor migration and resettlement. The overall objective of the study is therefore to understand the complex relationships among migration, identity, and religious healing within one community. This work will be accomplished through structured, semistructured, and in-depth interviews with the total population of 15 religious healers in the community and 60 religious healing partic-

ipants, as well as participant observation in a variety of settings.

### *Molecular and Cellular Neuroscience Research Branch*

The Psychopharmacology Program, Molecular and Cellular Neuroscience Research Branch, NIMH, supports two research projects. In the first project, an investigator at McGill University, Montreal, plays a central role in applying his model of maternal separation to examine, in adult rats, the effects of early postnatal experience on behavioral, neuroendocrine, and neurochemical responses to stress. The study examines the effects of prolonged maternal separation on susceptibility to adverse effects of stress in adult rats. In the second project, the Canadian investigator is exploring the effects of natural variations in maternal behavior on the development of behavioral responses to stress, patterns of maternal behavior in offspring, and the relationships among behavioral, hormonal, and neurochemical changes. Preliminary results showed that maternal care in infancy regulates the development of brain systems that activate behavioral, endocrine, and autonomic responses to stress. These studies will help to explain how early environment influences the development of neural systems underlying fearfulness and aspects of susceptibility to mental disorders.

The Neuropharmacology Program supports a scientist at the National Institute of Mental Health and Neurosciences, Bangalore, India, to study the metabolism of psychoactive drugs by the human brain enzymes, cytochromes P-450. The goals of the research are (1) to determine the capability of human brain cytochromes P-450 to metabolize psychoactive drugs and (2) to characterize and localize the multiple forms of these enzymes in the human brain. The novel hypothesis is that enzymatic activity in specific brain regions may play an important part in modulating the concentration and duration of the activity of drugs at their primary sites of action in the brain. The psychoactive drugs being studied include fluoxetine (Prozac); haloperidol (Haldol); clomipramine (Anafranil); and diazepam (Valium). The drugs are used clinically to treat depression, obsessive-compulsive disorder, schizophrenia, and anxiety disorders. These studies are important for

elucidation of how the human brain metabolizes psychoactive drugs and for development of new therapeutic interventions for neuropsychiatric disorders.

### *Genetics Projects*

Several large-scale human genetics projects funded by NIMH in FY 99 have major international collaborations. These projects are expected to greatly complement ongoing NIMH-funded human genetics projects that analyze pedigrees collected in the United States.

An investigator at the University of Queensland, Australia, has been funded to collect pedigrees containing multiple individuals affected with schizophrenia. This unique data collection effort will occur in the major Australian cities of Adelaide, Brisbane, Melbourne, and Sydney. This investigator is collaborating with eight research teams collecting data on schizophrenia pedigrees in the United States.

A researcher at the University of California, Los Angeles, is studying brain function and structure in Finnish twins with schizophrenia, by collaborating with researchers in Helsinki, Finland, at the National Public Health Institute, the University of Turku, and the University of Helsinki. Finland offers unique research resources for such genetic studies, because the population is genetically homogeneous and because the government maintains detailed registries of twins and of patients with schizophrenia.

An investigator at Virginia Commonwealth University, Richmond, is collaborating with researchers at the Health Research Board, Dublin, and Mater Hospital, Belfast, Ireland, to perform genetic studies of patients with schizophrenia and their parents. These subjects represent a unique research resource drawn from the genetically homogeneous Irish population. The current effort is a continuation and expansion of a set of studies in Ireland started a decade ago by this research consortium.

In collaboration with researchers at the Center for Neuroscience, University of Coimbra, Portugal, a researcher at the State University of New York, Buffalo, is conducting a genetics study of patients with bipolar disorder and their parents from the population of the Azores, a nine-island archipelago settled more than 500 years ago by the Portuguese. This population is uniquely suited

for a genetic study of bipolar disorder, because it is a relative genetic isolate and because the centralized health system will allow identification of all cases of bipolar disorder.

A researcher from the University of California, Irvine, is collaborating with scientists at the Dagestan Center of the Russian Academy of Sciences, Makhachkala, Dagestan, to study schizophrenia in very large, extended families from primary genetic isolates in this southwestern republic of the current Russian Federation. The sampling of families from large, genetically homogeneous, ethnic population groups in Dagestan represents a unique research resource and will greatly enhance efforts to find schizophrenia susceptibility genes.

The chief of the Genetic Basis of Neural Function Program in the Genetics Research Branch, Division of Neuroscience and Basic Behavioral Science, was one of the invited speakers at the Kazusa International Workshop on the Structural and Functional Analysis of Human cDNA (complementary DNA). His presentation, entitled The NIH Brain Molecular Anatomy Project, provided an up-to-date overview of this ongoing initiative of NIMH and the National Institute of Neurological Disorders and Stroke. The meeting was held at the Kazusa DNA Research Institute, in Chiba, Japan, in March 1999.

### *Trauma Studies*

A researcher from Harvard University, Boston, Massachusetts, is working with researchers at the University of Zagreb, Croatia, to conduct the first large-scale, general population study of the role of personal, environmental, and other risk factors in modification of the relationships among trauma, psychiatric symptoms, and functional status. The study will produce the first psychiatric data from follow-up of a refugee population that allows examination of dose-effect relationships between trauma, psychiatric symptoms, and functional status, and the ability to engage in economic activity before and after repatriation. A model of the impact of trauma on populations over time also will be developed.

The proposed research fills a major gap in understanding the effect of trauma on a person's ability to function and to participate in economic activity, by analyzing the dura-

tion and character of the dose–effect relationship. The design is a prospective cohort study in two time periods. Data on a cohort of 536 Bosnian refugees, collected in 1996, will be analyzed to establish baseline estimates of trauma, symptoms, functional status, and ability to participate in income-generating activities. Cohort members will be re-interviewed after repatriation, allowing prospective assessment of the psychiatric and functional outcomes of trauma. A standardized personal interview will be administered by using the previously validated Harvard Trauma Questionnaire and the Hopkins Symptom Checklist-25 to obtain retrospective reports of trauma, contemporaneous reports of trauma experienced during repatriation, and replicate measures of depression, post-traumatic stress disorder (PTSD), and functional outcomes. Concurrent measures of personal and environmental characteristics also will be obtained, along with measures of income-generating activity. These measures will be used (1) to assess change in the dose–effect relationship of trauma to mental and physical health outcomes and (2) to test hypotheses deriving from a conceptual model of the interaction between trauma and its psychiatric and functional outcomes over time. Quantitative analyses will use graphic methods, descriptive statistics, and structural equation models.

The ongoing Prospective Neurobiological Study of PTSD, at Hadassah University Hospital, Jerusalem, Israel, continues the prospective longitudinal research on functioning of the sympathetic nervous system in acutely traumatized subjects in Israel. No other study has performed follow-up on subjects from the point of trauma to the full development of PTSD. The study is expected to advance the theoretical understanding of the pathogenesis of this condition.

An investigator at Georgia State University, Atlanta, is collaborating with investigators at the University of Guadalajara and the National Institute of Anthropology, Oaxaca, Mexico, to examine the social and cultural dynamics of disaster recovery. This work was begun by studying the effects of Hurricane Andrew in a sample composed equally of Latinos, non-Hispanic whites, and non-Hispanic blacks. As part of that study, a Spanish-language instrument with known psychometric properties was developed. The goal of the current research is to conduct a

truly cross-cultural study by collecting post-disaster data in Mexico that is comparable with the data collected in the United States after Hurricane Andrew. Mexico provides a strikingly different cultural and economic context that will yield insights into disaster recovery in developing countries. Although the majority of disasters occur in the developing world, very little of the research has been performed there.

The study is taking place in four phases. In phase 1, survivors of past disasters will provide ethnographic data on the meaning and manifestation of the constructs to be studied. In phase 2, samples representative of three cities in Mexico will provide epidemiologic data on other types of trauma, PTSD, depressive symptoms, and “nervios.” In phase 3, victims of a recent disaster in Mexico will provide comparable data on the process of disaster recovery. In phase 4, the same participants will provide longitudinal data on the timing of disaster recovery. It is hypothesized that social, psychological, and material resources may mediate the relationship between the severity of trauma exposure and psychiatric outcomes. The investigators propose an ecological framework for the study of trauma that differentiates among invulnerable resources, which are impervious to the effects of trauma (e.g., social class); vulnerable resources, which are potentially damaged by trauma (e.g., appraised social, psychological, and material resources); and emergent resources, which arise in response to trauma (e.g., social support, coping efforts, and financial aid) and serve to protect or replace the vulnerable resources. The research team combines expertise in stress and trauma, Latino culture, and Mexican society. The disciplines of clinical psychology, social psychology, community psychology, social anthropology, and medical anthropology are represented. Two members of the team previously conducted survey research in Mexico.

#### *Consortium on Role of Stress in Psychopathology*

An international team of investigators will focus on future multidisciplinary collaborations on the role of stress and psychopathology. U.S. and British researchers will address the hypothesis that perinatal events can cause disorders in later life by altering the responsiveness of the brain’s systems to

stress. They will test the theory that stress causes permanent changes in the brain by changing the molecular composition of the receptor proteins for specific neurotransmitter systems. Such studies help to define vulnerable periods in development and how the brain changes to adapt to differing environments.

#### *Hippocampal Interneuronal Network*

In a research project on the hippocampal interneuronal network, an investigator at the Center for Molecular and Behavioral Neuroscience, Rutgers State University of New Jersey, New Brunswick, is examining the anatomy and physiology of inhibitory interneurons in the hippocampus, a structure critically involved in memory functions. His colleagues at the Institut Pasteur, Paris, France, and the Institute for Experimental Medicine, Budapest, Hungary, bring specific and unique expertise to this research. The study combines dual intracellular recording from functionally connected neurons in the hippocampus with intracellular staining and sophisticated double-labeling techniques of immunocytochemistry, to reveal the connectivity patterns of hippocampal inhibitory interneurons.

#### *Steroid–Catecholamine Interactions and Behavior*

An exceptionally productive international research team is examining the behavioral neuroendocrinology of mating. The use of the Japanese quail as a model to study the regulation of hormone-dependent behaviors has facilitated exploration of the interrelated roles of dopamine and aromatase at the cellular level. The scientists have reliably localized the protein and messenger RNA of brain aromatase, enabling a precise definition of the neural circuit mediating the behavior. They are now focusing on the interactions between dopamine and brain aromatase in this circuit, to specify the action of testosterone. The study of these mechanisms is relevant to understanding the differential regulation of appetitive and consummatory aspects of motivated behavior. The research on steroid-mediated changes in neural circuit function is an important extension of an area of traditional concern in behavioral neuroscience.

### *PET Imaging Studies of Schizophrenia*

Two investigators are conducting research on dopamine receptors in patients with schizophrenia, at Karolinska Institute, Stockholm, Sweden. These investigators are considered international leaders in the development of novel ligands (biological markers) for positron emission tomography (PET). They are using this skill to study the several classes of dopamine receptors in patients with schizophrenia. In complementary experiments to measure messenger RNA in dopamine receptors, the investigators are performing postmortem examination of brains of patients with schizophrenia and control subjects. Such studies will help to define the exact differences in the schizophrenic brain, a goal that has remained exceedingly difficult to achieve.

### **International Meetings**

NIMH staff participated as observers and commentators at a WHO workshop on the Worldwide Project on Sleep and Health, which was entitled Sleep and Cognitive Function: Research and Clinical Perspectives. The workshop was held in Cancún, Mexico, on March 1–4, 1999.

Staff from the Office on Neuroinformatics, NIMH, gave a presentation on Interoperable Neuroinformatics Management Systems for Understanding Functional Neuroanatomy, at the 5th International Conference on Functional Mapping of the Human Brain, in Düsseldorf, Germany, on June 21–25, 1999. The neuroscience field has benefited considerably from the application of the principles, methods, and technologies developed from the recent explosion of advanced technologies in the computer and information sciences (neuroinformatics research). The presentation provided an overview of the full array of current research projects and novel tools and methodological strategies used in the rapidly progressing interdisciplinary field of neuroinformatics and the various funding opportunities for new research and career development under this initiative. Two topics important to progress in this field were presented to the international scientific community. The first topic addressed the development of new databases, querying approaches, and information management systems in neuroscience, which can be used to better integrate diverse data on the brain and behavioral re-

search across multidimensional perspectives. The second topic explored the unprecedented opportunities offered by the creation of an international electronic collaborative infrastructure in neuroinformatics research, which can be used to rapidly meet the burdening challenges in medicine and health, in the prevention, diagnosis, and treatment of disease.

Staff from the Office on Neuroinformatics gave a presentation on Neuroinformatics Management Systems for Brain and Behavioral Analysis, at the meeting of the American College of Neuropsychopharmacology, in Acapulco, Mexico, on December 12–16, 1999. This presentation represented the primary mission of the Human Brain Project/Neuroinformatics Program, which is sponsored by 15 Federal agencies and NIH Institutes. The presentation gave an overview by citing key examples of currently funded projects, including research to develop novel tools and unique methodological strategies, in areas ranging from genetics to study of the whole brain and behavioral research, at varying stages of human development and conditions of health, including clinical trials in psychopharmacology. The presentation also dealt with the role of these methodological strategies worldwide in the promotion and improved prevention and treatment of psychiatric and neurological diseases and behavioral and addictive disorders of the nervous system. Finally, the presentation discussed the funding opportunities for new research, education, training, and career development that are offered under this initiative, for the training of future generations of basic and clinical neuroscientists in the fundamentals of neuroinformatics research.

Two meetings sponsored by NIMH included participants from foreign institutions: the Dynamical Neuroscience Satellite Conference of the Society for Neuroscience 28th Annual Meeting, held in Los Angeles, California, and Toward Replacement Parts for the Brain 1999, held in Washington, D.C.

In FY 99, a staff member in the Mental Health Economics Research Program (MHERP) served as a mentor for a young psychiatrist from the Czech Republic. During his 2-month stay at NIMH, the scientist prepared the first draft of a book on psychopharmacoeconomics, to be published in Central Europe.

The Health Department of Japan sought advice from MHERP about how to conduct a cost-effectiveness analysis of the planned deinstitutionalization of the mentally ill. A former graduate of the NIMH economics training grant program at the University of Wisconsin, Madison, served as a consultant for the study. A health economist with another Federal agency is now advising the researchers in Japan.

Also during FY 99, MHERP provided technical assistance to WHO and researchers from foreign countries.

### **Intramural Programs and Activities**

The NIMH Division of Intramural Research Programs plans and administers a comprehensive, long-term research program exploring the causes, diagnosis, prevention, and treatment of mental disorders, as well as the genetic, biological, developmental, environmental, and social factors that determine human behavior and development. The Division operates laboratories and clinical branches on the NIH campus in Bethesda and at the Poolesville Animal Facilities, both in Maryland. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year. Using a bench-to-bedside approach, Division scientists provide a critical link between basic and applied research on mental disorders.

During FY 99, scientists in the Division of Intramural Research were engaged in several projects with foreign scientists. The Division offered a broad range of research opportunities for foreign scientists, including 3 Guest Researchers, 8 Visiting Associates, 11 Visiting Volunteers, 15 Visiting Scientists, and 48 Visiting Fellows. The investigators are from Argentina, Australia, Bosnia, Brazil, Canada, China, Ethiopia, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Mexico, the Netherlands, New Zealand, Paraguay, Slovakia, Switzerland, the United Kingdom, and Taiwan.

The Division of Intramural Research Programs comprises 24 branches and laboratories. Selected examples of several collaborative research projects are highlighted here. These joint efforts illustrate the depth and diversity of the NIMH intramural projects.

## Child Psychiatry Branch

The Child Psychiatry Branch conducts clinical research that focuses on the causes, diagnosis, and treatment of psychiatric disorders with onset in childhood. International studies include the following:

- a prospective, longitudinal study of use of MRI brain scans for untreated subjects at high risk of mental illness and for control subjects (University of Melbourne, Australia);
- exploration of the use of an automated software system for analysis of anatomic MRI scans (Montreal Neurological Institute, McGill University);
- research into childhood-onset obsessive-compulsive disorder and tic disorders, in which 300 children aged 10–15 years and their primary caregivers are interviewed to assess neuropsychiatric symptoms, the course and periodicity of illness, and the association of the disorders with infection (Hospital Infantil de Mexico, Mexico City); and
- study of childhood-onset schizophrenia (Karolinska Hospital, Stockholm).

## Clinical Neuroscience Branch

The Clinical Neuroscience Branch conducts basic and clinical research on the molecular, cellular, and genetic aspects of inherited disorders involving the nervous system. The Branch maintains extensive international joint efforts in basic and clinical research with 17 institutions in 12 countries. Four scientists conduct international research in molecular genetics, molecular neurogenetics, molecular structures, and Gaucher disease, respectively.

### *Molecular Genetics*

In molecular genetics, collaborative studies of genetic mapping and gene isolation are being performed at the German Cancer Research Center, Heidelberg.

### *Molecular Neurogenetics*

In molecular neurogenetics, joint research is being conducted in the following areas:

- genetic mapping of the human genome for genes responsible for psychiatric disorders (National Public Health Institute, Helsinki, Finland);
- generation of animal models of human diseases, particularly those affecting the nervous system, including infantile ceroid neu-

rolipofuscinosis and aspartylglucosaminuria, the most common Finnish genetic disease (National Public Health Institute, Helsinki);

- chromosome mapping of clones having repeated trinucleotides, with use of fluorescent in situ hybridization (University of Helsinki);
- genetic mapping for bipolar affective disorder and other inherited disorders (Genethon, Evry, France);
- gene transfer as therapy for inherited diseases (Hôpital Robert Debré, Institut National de la Santé et de la Recherche Médicale, and Institut Pasteur, Paris, France);
- genetic studies of diseases affecting the nervous system (Brain Research Institute, Niigata, Japan); and
- electron microscope and immunopathological studies of transgenic animal models, including lysosomal diseases such as Gaucher disease (Erasmus University, Rotterdam, the Netherlands).

### *Molecular Structures*

In the study of molecular structures, collaborative research is being conducted in the following areas:

- structural studies of proteins from hibernating animals (Carleton University, Ottawa, Ontario);
- structural studies of stress proteins in plants (University of Toronto, Ontario);
- structural studies of *N*-hydroxylation enzymes (University of Waterloo, Ontario);
- research on crystallizing recombinant human glucocerebrosidase (University of Pierre and Marie Curie, Paris, France);
- studies on structure and function of allergens (Indian Institute of Science, Bangalore);
- structural studies of amyloid proteins and peptides in human disease (Heller Institute of Medical Research, Tel Hashomer, Israel); and
- studies on structure and function of neurotoxins from scorpions (Universidad Nacional Autónoma, Institute of Biotechnology, Cuernavaca, Mexico).

### *Gaucher Disease*

In the study of Gaucher disease, joint research is being performed in the following areas:

- neonatal Gaucher disease (The Adelaide Children's Hospital, North Adelaide, South Australia);

■ epidermal manifestations of glucocerebrosidase deficiency (University of Erlangen, Germany);

- unusual manifestations of Gaucher disease (Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel);
- unusual presentations of type 3 Gaucher disease (Ajou University School of Medicine, Suwon, Korea);
- a prenatal lethal form of Gaucher disease (Erasmus University, Rotterdam); and
- Gaucher disease and hydrops fetalis (University of Geneva, Switzerland).

## Laboratory of Brain and Cognition

The Section on Clinical and Experimental Neuropsychology, Laboratory of Brain and Cognition, conducts research (a) on factors in the central nervous system that underlie normal and abnormal behavioral states and (b) on the interaction between environmental and genetic effects on neuropsychiatric disorders, including schizophrenia. Scientists in Canada, Denmark, Ecuador, and Israel are cooperating in this effort. Collaborative research projects include the following:

- a large-scale investigation of familial genetic influences on attentional cognitive behavior in persons with absence epilepsy and schizophrenia (Montreal Neurological Institute);
- studies of occurrence of mental illness in the biological and adoptive families of 15,000 Danish adoptees in a national register (University of Copenhagen);
- assessment of attentional cognitive skills in a group of malnourished children, most of whom are infested with intestinal parasites, including neurocysticercosis, a parasitic infection of the brain (Ecuadorian Academy of Science, San Pablo del Laso); and
- a long-term, 25-year follow-up study of children who have parents with schizophrenia and of children who have healthy parents and who were reared in a town or kibbutz in Israel (Hebrew University, Jerusalem, and Oranim Institute for Research on Kibbutz Education, Haifa University).

## Other Studies

During FY 99, many other NIMH intramural collaborative research projects yielded scientific information of significance and merit to both U.S. and foreign scientists. Projects include the following:

■ The Biological Psychiatry Branch collaborated with McGill University, Montreal, on the effect of impaired function of type II glucocorticoid receptor in transgenic mice; with the University of Rome, Italy, on the neurobiology of noncompetitive NMDA antagonists; with Josai University, Saitama, Japan, on apoptosis in neurons; and with the Tokyo Dental and Medical University, Japan, on receptor regulation in neurohybrid cell lines.

■ The Clinical Brain Disorders Branch cooperated with McMaster University, Toronto, on MRI studies of brain anatomy, and with Service Hospitalier Frédéric Joliot, Orsay, France, on discovery and development of radioligands.

■ The Clinical Neurogenetics Branch worked with Institut National de la Santé et de la Recherche Médicale, Paris, on mapping of genes for schizophrenia, and with the Beersheva Mental Health Center, Israel, on scanning of mutations in candidate genes.

■ The Geriatric Psychiatry Branch is collaborating with Oxford Glycosciences, Inc., England, on a project using two-dimensional gel electrophoresis of cerebrospinal fluid in patients with Alzheimer's disease and healthy control subjects, to discover biological markers in the disease process.

■ The Laboratory of Cell Biology cooperated with Philipps University, Marburg, Germany, to study neuroendocrine secretory vesicle proteins, chemical coding of neurotransmission, and lentiviral neuropathogenesis, and with Royal Victoria Hospital, McGill University, Montreal, and Utrecht University, the Netherlands, on molecular biology of vasopressin and oxytocin receptors.

■ The Laboratory of Cellular and Molecular Regulation worked with the Weizmann Institute, Rehovot, Israel, on the structure and assembly of the acetylcholine receptor;

with the University of Bergen, Norway, on functional anatomy and regulation of signal molecules by neural activity; with the University of Santander, Spain, on the regulation of neurotransmission by receptors and transporters; and with Karolinska Institute, Stockholm, on neuroimmune interactions in infectious parasitic disease.

■ The Laboratory of Cerebral Metabolism collaborated with the Medical Research Council Cyclotron Unit, Hammersmith Hospital, London, England, and the PET Center, Hospital San Raffaele, Milan, Italy, on the kinetic modeling of PET radiotracers, and with the University of Rome, Italy, on studies of protein synthesis and amino acid compartmentalization. (The Laboratory Chief is a permanent external member of the Max Planck Society of Germany, and in that capacity, engages in frequent exchanges of information with members of the Max Planck Institute for Neurological Research, Cologne, on methods, strategy, and results of studies on cerebral blood flow and metabolism and on techniques for use of PET and nuclear magnetic resonance imaging).

■ The Laboratory of Clinical Science, Clinical Neuropharmacology Section, cooperated with the University of Würzburg, Germany, on animal models for the study of neuropharmacological effects and psychobiology and treatment of obsessive-compulsive disorder in adults, and with the Soroka Medical Center, Israel, and St. Radboud Hospital, Amsterdam, the Netherlands, on the neuropharmacology of neurotransmitter and neuroendocrine regulatory mechanisms.

■ The Laboratory of Clinical Science, Section on Pharmacology, worked with the University of Bern, Switzerland, on the role of neuropeptides and biogenic amines in neuroendocrine regulation of brain angiotensin receptor subtypes.

■ The Laboratory of Genetics collaborat-

ed with Merck Frosst Center for Therapeutic Research, Kirkland, Quebec, in research on ( $\gamma$ -aminobutyric acid (GABA) B receptors; with the Riken Institute, Saitama, Japan, on functional genetics; with Hôpital Ar-razi, Salé, Morocco, on the genetics of schizophrenia, and the National Institute of Hygiene, Rabat, Tunisia, on genetic traits; and with the Faculty of Medicine at Hôpital Ar-razi in Morocco and at the National Institute of Hygiene in Tunisia, on the genetics of schizophrenia.

■ The Laboratory of Molecular Biology, Unit on Neurobiology, worked with the University of Naples, Italy, on the compartmentalization of gene expression in the nervous system.

■ The Laboratory of Neurochemistry cooperated with the Oasi Institute for Research on Mental Retardation and Brain Aging, Troina, Sicily, Italy, in research on phenylketonuria and other diseases caused by defects in bipterin-dependent enzymes.

■ The Laboratory of Neuropsychology worked with Oxford University, England, on neural mechanisms of stimulus memory and habit formation, and with cognitive and MRI neuroscientists at the Institute of Child Health, University College, London Medical School, on studies of "developmental amnesia" in patients who had sustained relatively selective hippocampal damage as a result of hypoxic-ischemic episodes that occurred either neonatally or later in childhood.

■ The Laboratory of Socio-Environmental Studies collaborated with the Centre Régional de Médecine Traditionnelle, Bandiagara, Mali, on research on migration for work and on mental health and AIDS in Mali.

■ The Laboratory of Systems Neuroscience cooperated with the Hebrew University, Israel, on the neural mechanisms of motor learning and memory.