IX.
National Institute of Child Health and Human Development

INTRODUCTION

The National Institute of Child Health and Human Development (NICHD) focuses primarily on the reproductive, physiological, and behavioral processes thaat determine and promote the health of children, adults, and families. The Institute's programs are based on the concepts that adult health and well-being are largely determined by episodes early in life, that human development is continuous throughout life, and that reproductive processes and the management of fertility are major concerns to the individual and society. Medical rehabilitation has become an important research objective as the NICHD programs explore ways to restore the potential and functional capacities of individuals when disease, injury, or a chronic disorder intervenes in the developmental process.

Research at NICHD encompasses a unique and broad scope of laboratory, clinical, and epidemiologic studies. This work attracts international researchers to train in the NICHD laboratories and creates extensive opportunities for international collaboration. Many of the Institute's goals have global importance. These goals include the following:

- developing and evaluating methods for the regulation of fertility and research on reproductive health;
- advancing biomedical knowledge of pregnancy, fetal development, and birth;
- developing strategies to prevent infant and child mortality;
- identifying and promoting the prerequisites of optimal physical, mental, and behavioral growth and development in infancy, childhood, and adolescence;
- contributing to prevention and amelioration of mental retardation and developmental disabilities; and
- advancing knowledge of the pathogenesis, epidemiology, and natural history of the human immunodeficiency virus (HIV) and related retroviruses in pregnant women, mothers, infants, children, and adolescents.

Much of NICHD's research relies on the disciplines of cellular, molecular, and developmental biology to elucidate the mechanisms and interactions that guide a single fertilized egg cell through its development into a multicellular, highly organized, adult organism. These interests involve research as varied as molecular neurophysiology and vaccine development. The Institute's research also includes performance of applied studies and support of biomaterials development, which together form the core of medical rehabilitation science.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NICHD-funded investigators from France, Thailand, and the United States have shown that transmission of HIV from a mother to her child can be reduced with simpler and less costly treatments of zidovudine (AZT). The randomized, double-blind study, published in the *New England Journal of Medicine* (October 2000), included four treatment regimens of AZT, involving nearly 1,500 pregnant women from 27 hospitals in Thailand. The regimens included either short or long duration of treatment of the mother and the infant. The regimen involving short treatment for both the mother and the infant (short/short treatment) was found to be ineffective and was discontinued after the first interim analysis. The regimens involving long treatment of the mother and short treatment of the infant (long/short treatment) and short treatment of the mother and long treatment of the infant (short/long treatment) had efficacy equivalent to that of the regimen involving long treatment of both the mother and the infant (long/long treatment), which was similar to the standard treatment used in developed countries. Further analysis indicates how important it is that mothers receive the longer treatment—1.8% of infants whose mothers received the longer treatment were infected with HIV at birth, whereas 5.1% of infants whose mothers received the shorter treatment were infected at birth. On the basis of these findings, the researchers recommended that treatment for HIV-infected mothers start at the 28th week of pregnancy and continue until labor. In these cases, the infant can be treated for 3 days after birth, at one-fifth the usual cost. If treatment cannot begin until later in the pregnancy, the infant should be treated for the full 6 weeks used in the control treatment. The results of this study bring promise that, with the less costly and simpler AZT treatment option, greater numbers of children in the developing world will be born free from HIV infection.

In an NICHD-supported study that brought together investigators from Canada, Europe, and the United States as part of an International Perinatal HIV Group, the risk of vertical transmission of HIV from mother to infant was evaluated among women with a duration of ruptured membranes up to 24 hours. In this meta-analysis of data from 15 prospective cohort studies of more than 4,700 deliveries, a strong association was observed between duration of ruptured membranes (evaluated as a continuous variable with 1-hour increments) and risk of vertical transmission, after adjustment for other factors. Furthermore, the results also suggest that more advanced disease in the mother increases the effect of duration of ruptured membranes.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

NICHD, in partnership with the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) and the Office of Dietary Supplements, of the Na-

tional Institutes of Health (NIH), the Centers for Disease Control and Prevention, the U.S. Agency for International Development, and the Indian Council for Medical Research sponsored and coordinated the Indo-U.S. Workshop on Health and Nutrition in Women, Infants, and Children, which was held in Hyderabad, India, on February 10–12, 2000. This meeting (a) facilitated exchange of scientific information and development of shared research priorities for nutrition research and public health programs, including the role of micronutrients, and (b) helped to develop strategies for implementation of a cooperative research program and approaches for translation of that research into effective program and policy initiatives. Proceedings from the meeting will be published in *Nutrition Reviews* in 2001.

On June 13, 2000, the Indian Minister of Health and Family Welfare and the U.S. Secretary of Health and Human Services signed two joint statements to stimulate new cooperative efforts in the fields of research on (1) prevention of HIV and acquired immunodeficiency syndrome (AIDS) and (2) maternal and child health and human development. The implementing agencies are the NIH in the United States and the Indian Council for Medical Research in India. NICHD will serve as the Secretariat for the Indo-U.S. Joint Working Group on Maternal and Child Health and Human Development Research. The research efforts will focus on reduction of maternal, neonatal, infant, and pediatric mortality and morbidity in both countries.

On March 23, 2000, the NIH and the National Research Council of Italy signed an Exchange of Letters under the aegis of the Italy-U.S. Science and Technology Agreement, to establish a 3-year collaboration in basic biomedical and clinical research related to child health and human development. Scientists supported by NICHD and the National Research Council of Italy will participate in exchange of scientific information and materials and collaborate on joint research projects. Priority areas for research include physical and biochemical mechanisms regulating growth and differentiation of cells in multicellular systems, pathogenesis of HIV, molecular embryology, and developmental biology and genetics.

Through the Division of Epidemiology, Statistics, and Prevention Research (DESPR), NICHD continues to collaborate with the Vietnamese National Institute of Hygiene and Epidemiology, Ministry of Health, on a large-scale trial of the effectiveness of a locally produced, inactivated cholera vaccine. NICHD's medical team from DESPR and the Laboratory of Developmental and Molecular Immunity, in cooperation with the Vietnamese Ministry of Health, Institut Pasteur, Ho Chi Minh City, and Dong Thap Provincial Health Services, has also established a field site in Dong Thap Province for the evaluation of enteric vaccines, which have been developed by the Laboratory of Developmental and Molecular Immunity. The team has completed an epidemiologic study of typhoid fever and phase I and II evaluations of investigational Vi conjugate vaccines for typhoid fever. A phase III trial of the efficacy of the vaccines in children will be completed by fiscal year 2001 (FY 01).

NICHD staff is implementing a new joint research effort by scientists and public health officials from Africa, Europe, and the United States, to conduct a meta-analysis of several thousand mother–infant pairs, to estimate more precisely the proportion of vertical transmission of HIV that occurs during breast-feeding. This international meta-analysis also will attempt to determine as closely as possible the timing of such transmission, to improve the targeting, safety, efficacy, and feasibility of interventions.

Activities With International and Multinational Organizations

International Skeletal Dysplasia Registry

The International Skeletal Dysplasia Registry continues to grow as a major source of clinical, radiographic, morphological, biochemical, and molecular materials for research on skeletal dysplasias. It is supported in part by an NICHD-funded program project at Cedars-Sinai Medical Center, Los Angeles, California. The registry, which can be accessed via the World Wide Web (www.csmc.edu/genetics/skeldys), is a referral center for research into the diagnosis, management, and etiology of the skeletal dysplasias. It comprises a database containing more than 9,300 cases of many different skeletal dysplasias, as well as a comprehensive repository of ancillary material, including photographs and radiographs of patients, tissue samples for morphological and ultrastructural studies, cultured cells, and DNA. The registry maintains interactions with registries worldwide, collects information and materials from patients with skeletal dysplasias, and continues to provide diagnostic assistance to numerous clinicians throughout the world.

Reproductive Sciences of the Americas Network

The Reproductive Sciences of the Americas Network, initiated in 1995, fosters research collaboration among the participating countries of Argentina, Brazil, Canada, Chile, Mexico, and the United States. NICHD, together with organizations in the private sector, supports and coordinates the network's efforts, which include a monthly electronic bulletin to disseminate information on career and training opportunities, relevant scientific meetings, and the availability of reagents, in the North, Central, and South American countries. The Reproductive Sciences of the Americas Network course and the symposium on Frontiers in Reproduction continued to provide research training in this area. The course annually trains 16 selected scientists who are advanced postdoctoral fellows, early independent investigators, or midcareer scientists changing the direction of their research. Since 1998, participants from Argentina, Brazil, Chile, India, and Mexico have taken the course at the Marine Biological Laboratories, Woods Hole, Massachusetts. In FY 00, a symposium on The Oocyte and Human Reproduction was held in association with the course and attracted 145 scientists from the United States and foreign countries.

World Health Organization

Working with the World Health Organization (WHO) Regional Office for Europe and the international coordinating center in Edinburgh, Scotland, NICHD's DESPR sponsors U.S. research as part of a WHO project on Health Behavior in School Children (HBSC) in 30 countries. This quadrennial survey addresses the hypothesis that U.S. youth may have adopted lifestyles that place them at greater risk for certain health problems than their counterparts in other nations. It specifically examines the factors and causes of adolescent behaviors related to injury and violence. NICHD completed the

first of the quadrennial surveys in 1998, and selected summary results were released in a WHO International Report in February 2000 (EUR/ICP/VST 06 03 05[A], WHO-Euro, Copenhagen). Data from the 1998 survey were instrumental in testing and validating a revised system for classifying the causes of injury developed by the WHO International Collaborative Effort on Injury Statistics. DESPR scientists are collaborating with scientists of other countries to examine factors related to the incidence of injuries, the prevalence of interpersonal violence, the use of bicycle helmets and automobile seat belts, the prevalence of bullying behavior, and the prevalence of overweight in youth. NICHD plans to continue participation in the HBSC study through supplementation of the Maternal and Child Health Sponsorship of the next HBSC Survey in 2001–2002.

In August 2000, the proceedings of a symposium on Steroids and Endometrial Breakthrough Bleeding were published as a supplement to the journal *Human Reproduction*. The meeting, cosponsored by NICHD and WHO in May 1999, had reviewed current research on the mechanisms of endometrial bleeding in women using progestin-only contraceptives and hormone replacement therapy.

NICHD staff participated in a WHO-sponsored meeting, held in Geneva, Switzerland, on March 8–10, 2000, to update the landmark WHO publication, "Improving Access and Quality of Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use." This evidence-based document includes recommendations for use of contraceptives that are commonly available in many developed and developing countries. A revised version of the original 1996 document will be published in early 2001.

During FY 00, NICHD staff participated in one meeting, in Geneva, on January 12–14, 2000, and hosted a second meeting of the WHO Research Group on Post-ovulatory Methods for Fertility Regulation, in Washington, D.C.

Extramural Programs

NICHD supports extramural research with international components through grants to foreign investigators and institutions, as well as grants and contracts to domestic universities, hospitals, research institutes, and other facilities. Selected NICHD-funded research activities by country are described here, beginning with summaries of several multicountry studies.

Multicountry Studies

In Kenya and Malawi, an investigator from the University of Pennsylvania, Philadelphia, is conducting a study of the role of social interactions on diffusion of modern contraceptive methods, ideas about ideal family size, and knowledge about AIDS and AIDS prevention. She is also studying how patterns of social interaction help to shape husband–wife interactions regarding family planning and the autonomy of women.

Other researchers at the University of Pennsylvania have expanded the Mexican Migration Project database on populations migrating from Mexico to the United States to include migratory populations from nations in the Caribbean, Central America, and South America. Questionnaires originally developed for use in Mexico are being modified and applied to representative samples of four communities each, in Colombia, the Dominican Republic, El Salvador, Guatemala, Peru, and Puerto Rico. Community-level data, economic indicators, and oral histories are being added to the database and will be made available via the Internet.

The NICHD Pediatric/Perinatal HIV Clinical Trials Network has worked for more than one decade with the Pediatric AIDS Clinical Trials Group sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), NIH, on clinical trials related to prevention and treatment for HIV and AIDS in mothers, newborns, infants, children, and adolescents. In the past 2 years, the NICHD clinical trials network has expanded internationally to include one site in Nassau, the Bahamas, and two sites in Rio de Janeiro, Brazil. With technical assistance and support from NICHD and NIAID, these sites enrolled patients in a perinatal trial evaluating whether the addition of a two-dose regimen of nevirapine to standard antiretroviral prophylaxis would further reduce perinatal transmission. By 2001, three additional sites in Brazil will be added to this network and will participate in a study of enhanced versus standard formula feeding of infants born to HIV-infected mothers.

Additionally, NICHD is sponsoring an International Site Development Initiative in Latin America. Six to eight sites in Latin America will be selected to participate in a prospective observational study in HIV-infected pregnant women and their infants and an observational study of late outcomes among children born to HIV-infected women. These studies will better describe the demographics of the HIV-infected and HIV-exposed individuals who had follow-up at these sites and will provide follow-up to evaluate any consequences of (1) antiretroviral drug use during pregnancy for the woman or her infant or (2) long term use of such drugs in infected children. The studies will also provide clinical research training to Latin American sites with limited clinical trials experience, with a goal to have these sites join the NICHD clinical trials network and participate in future HIV prevention and treatment trials in collaboration with the Pediatric AIDS Clinical Trials Group and other relevant networks.

NICHD, in cosponsorship with FIC, NIAID, the National Cancer Institute, the National Institute of Dental and Craniofacial Research, the National Institute of Mental Health, and the National Center for Complementary and Alternative Medicine, NIH, and in partnership with the Bill and Melinda Gates Foundation, issued a solicitation during FY 00 to establish the Global Network for Women's and Children's Health Research. The Gates foundation has donated $15 million over a 3-year period to NICHD to help support the global network. Through cooperative agreements to be awarded in early 2001, collaborating teams of investigators from the United States and developing countries will conduct research related to critical and emerging health problems of women and children in resource-poor nations and regions of the world. Initial efforts will focus on safe pregnancy and birth outcomes. NICHD also contributes to the support of FIC's International Maternal and Child Health Research and Training program, which is designed to complement and facilitate the research on maternal and child health to be undertaken by the global network.

At the end of FY 00, several new training and research grants in population research sciences were awarded through the International Training and Research in Population and Health Program sponsored by FIC, in collaboration with NICHD and the National Institute on Aging, NIH.

Investigators from Northwestern University, Evanston, Illinois, are conducting studies in Argentina, Belgium, Italy, and Sweden, of infants and children acquiring different languages. The aim of these studies is to characterize the foundations of and linkages between language development and conceptual development. The investigators have obtained convergent evidence for phenomena involving noun and adjective usage in English, French, Italian, and Spanish that confirms predictions made from studies of adults. These cross-linguistic and developmental studies provide a more precise index of how infants' experiences augment their initial conceptions about word meaning and object categories. Additional studies are planned.

A researcher with Family Health International is conducting a pilot study to assess the feasibility of a randomized, controlled trial comparing the incidence of pelvic inflammatory disease in users of copper intrauterine devices with the incidence in users of injectable depot medroxyprogesterone acetate. One hundred subjects will be enrolled at each of four sites, located in Campinas, Brazil; Mansoura, Egypt; Guatemala City, Guatemala; and Hanoi, Vietnam.

NICHD is also supporting a study of the effect of oral and injectable contraceptive hormones on the risk of transmission of HIV in Thailand, Uganda, and Zimbabwe. A large, prospective, observational study of HIV seroconversion among women who used hormonal contraceptives and control subjects is expected to determine how a couple's current contraceptive use is predicted by concordant and discordant responses to specific survey questions. This project also involves two substudies, one examining the effect of different types of hormonal contraceptives on HIV genital shedding in primary HIV infection and the other a laboratory study analyzing HIV viral characteristics and host immune response in women with non–clade B human immunodeficiency virus type 1 (HIV-1).

Scientists at Johns Hopkins University, Baltimore, Maryland, are conducting an analysis of 23 demographic and health surveys from the 1990s in developing nations, including Bangladesh, Chad, Congo, Jordan, Kenya, Malawi, and Mozambique. The purpose of the study is to describe agreement or disagreement between husband and wife on current use of contraception and to determine unmet needs for family-planning services. The researcher also will determine how a couple's current contraceptive use is predicted by concordant and discordant responses to specific survey questions.

Investigators at Northwestern University, Evanston, Illinois, are coordinating the Hyperglycemia and Adverse Pregnancy Outcome Study, an international cooperative study involving 16 field centers, and are enrolling 25,000 pregnant women. Twelve centers are abroad in Australia, Canada, China, Israel, the Netherlands, Singapore, Thailand, the United Kingdom, and the West Indies. Four centers are in the United States. Overt diabetes mellitus is associated with significant risk of adverse pregnancy outcome. This epidemiologic investigation aims to clarify the association of various levels of glucose intolerance during the third trimester of pregnancy and risk of adverse outcomes. The study will examine glucose tolerance in a large heterogeneous, multinational, multicultural, ethnically diverse cohort of women in the third trimester of gestation. The study procedure is blinded in regard to the status of glucose intolerance. The data will be used to derive internationally acceptable criteria for the diagnosis and classification of outcomes. Important adverse outcomes include fetal hyperinsulinism, fetal obesity, cesarean section, and neonatal morbidity. The American Diabetes Association will fund an ancillary study to provide for measurement of concentrations of maternal plasma insulin during the oral glucose tolerance test that all subjects will have. Funds will be provided to extract and store DNA from samples of maternal and cord blood for future analyses at the conclusion of the study.

A researcher at Pennsylvania State University, University Park, has linked studies of sexual networks in Thailand, Uganda, and the United States to identify intervention strategies for preventing the spread of HIV and other sexually transmitted diseases. Results from Uganda show that sexual partnerships outside the village of residence are fairly common and that no one group (e.g., truck drivers or market sellers) acts as a bridge between communities. This finding suggests that targeting one such group for intervention would be insufficient. There also are significant differences between data for Thailand and Uganda. The median number of lifetime partners for men in Uganda was 6; the median in Thailand was 16. In Thailand, 45% of all partnerships were with commercial partners, and about 60% of respondents in Thailand, compared with 35% in Uganda, reported a concurrent partnership during the time they were associated with their last three partners. U.S. data are under analysis. Findings in a study of condom use suggest that condom promotion programs, which target travelers and their partners, may be an efficient method for spreading behavioral change into rural areas.

Investigators from the University of North Carolina, Chapel Hill, and the University of Witwatersrand, South Africa, are conducting a study of the impact of economic, demographic, and social change on child health in China, the Philippines, Russia, and South Africa. The study is examining the relationship of critical components of rapid economic and social change in each country to health-related behaviors such as physical activity, diet, and smoking, as well as the relationship of these behaviors and other factors to overweight and elevated blood pressure.

Australia

Scientists at Monash University, Clayton, Victoria, are participating in the National Cooperative Program on Mouse Sperm Cryopreservation, which is part of the Trans-NIH Mouse Genome Project. The goal of this program, supported jointly by NICHD and the National Center for Research Resources, NIH, is to develop inexpensive, easy, effective methods to preserve the tens of thousands of valuable new strains of genetically altered mice that are generated annually. This project will lead to improved methods for (1) obtaining mouse sperm through electro-ejaculation or pharmaco-ejaculation, (2) sperm preservation through evaporative or vacuum drying for storage at room temperature, (3) in vitro fertilization or intracytoplasmic sperm injection to initiate fertilization, and (4) verification that sperm manipulation will allow for the transmission of the genetic alteration to subsequent generations. Verification includes studies on histopathology, immunotype, gene expression, and behavior.

Bangladesh

An investigator at Columbia University, New York, New York, is using data from Matlab, Bangladesh, to explore the role of women's socioeconomic development in hastening health improvement and lessening health disparity. The study will consider the various determinants of health change, evaluate socioeconomic and gender disparities in a variety of health outcomes, and specify the mechanisms through which women's socioeconomic development influences health behaviors and outcomes.

Researchers from Massachusetts General Hospital, Boston, are studying the immune response to *Vibrio cholerae* in an endemic setting in Bangladesh, in collaboration with the NIAID International Collaboration in Infectious Disease Research (ICIDR) Program. The long-term goal of the study is to elucidate the role of mucosal immune responses in patients infected with cholera.

Botswana

Researchers from Harvard University, Boston, Massachusetts, are conducting studies in Botswana on the effects of different regimens of antiretroviral therapy to prevent intrauterine and intrapartum transmission of HIV from mother to child. These researchers will also compare the efficacy of prophylaxis with AZT in women who are breast-feeding and women who are feeding formula to their infants. Additional studies will be carried out to compare the risk for diarrheal disease among breast-fed and formula-fed infants, to determine whether the formula-feeding option is viable in the setting in Botswana.

Brazil

Investigators from Johns Hopkins University, Baltimore, are collaborating with investigators at Federal University, Rio de Janeiro, to study the use of β-chemokines as surrogate markers of disease progression in HIV-infected children.

A researcher from the University of Texas, Austin, continues to study the increase in the use of cesarean delivery and surgical sterilization in Brazil. The data are still being collected through interviews with obstetricians and pregnant women. Preliminary findings indicate a strong link between cesarean delivery and subsequent choice of sterilization. This study examines the determinants of that link, focusing on issues important to individual women and those important to the medical service delivery system where they deliver their children. The researcher expects that findings from this study will increase understanding about the choice of contraception during a period of rapid decline in fertility.

Scientists at RAND, Santa Monica, California, continue to study the consequences of rapid urbanization and environmental degradation on infant mortality in the state of São Paulo during the past 25 years. The results of this research are expected to suggest effective policies for mitigating the negative health effects of rapid urbanization currently experienced at unprecedented rates around the globe. Data continue to be collected.

Bulgaria

A researcher from the University of South Carolina, Columbia, is investigating the demographic effect of family planning in Bulgaria. Changes in the Bulgarian health care delivery system have provided a natural experiment to study how women and health care providers respond to the increasing availability of family-planning services in a system that earlier had relied on abortion for fertility control. This research will compare trends in births, abortions, and family-planning knowledge, attitudes, and behavior over time in the regions with clinics and those without clinics.

Canada

One of the fundamental puzzles of life is the origin of germ cells, which eventually develop into sperm and eggs. In some organisms, special molecules, which are necessary to establish the germ cell line, are localized in a certain section of unfertilized eggs. At McGill University, Montreal, Quebec, a scientist is conducting a study to determine how these molecules control the development of certain cells in the embryo into germ cells. If the processes by which germ cells originate do not occur normally, then the offspring may be infertile. In this study of the establishment of germ life in *Drosophila melanogaster,* the scientist is using genetic approaches to characterize these molecules and the proteins with which they interact. Because these compounds are present in both the fruit fly and human reproductive systems, the work may lead to a better understanding of the basic mechanism of germline development in humans. One of the key genes under study is known to be involved in mammalian germline development, whereas another is homologous to a gene in the human genome sequence and is also expressed in mouse oocytes.

McGill University participates in a multisite study on locomotor therapy for spinal cord injury. The other sites are in the United States and include Ohio State University, Columbus; Rancho Los Amigos Medical Center, Downey, California; Shepherd Rehabilitation Center, Atlanta, Georgia; Thomas Jefferson University and Magee Rehabilitation Hospital, Philadelphia, Pennsylvania; and the University of Southern California, Los Angeles. Safe, effective, and independent ambulation is one of the most important rehabilitation goals for patients after an acute spinal cord injury. This ongoing, randomized, clinical trial is comparing conventional therapy for mobility with conventional therapies plus body weight–supported treadmill training (BWSTT) after acute spinal cord injury. Results of this study will help to determine the effect of BWSTT on recovering the ability to walk or, in those who can walk, increasing walking speed so that individuals can function independently. Preliminary findings suggest that intervention through physical therapy in the acute phase after injury results in greater improvements than treatment offered later, during the long-term phase of recovery. In addition, BWSTT appears to be a useful adjunct to a task-oriented approach to physical therapies.

In addition, McGill University serves as the data and coordinating center for a network of seven pediatric study centers established at major medical institutions in the United States for the purpose of using modern neuroimaging technology to study normal brain development in infants, children, and adolescents. The centers will enroll approximately 500 children who will be studied longitudinally over 5 years. The investigators will examine their brain, behavior, and cognitive development. The project will provide a reliable source of control data for studies of childhood neurobehavioral disorders, including autism. This project is jointly supported by NICHD, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke,

NIH, which have formed the Pediatric Neuroimaging Network to foster collaboration within the broader pediatric neuroimaging community. This network sponsored a seminar at the International Human Brain Imaging Conference in June 2000.

Scientists at Arkansas Children's Hospital, Little Rock, and McGill University are collaborating in a study of the nutritional and genetic aspects of folate-related effects that may interact in the etiology of neural tube and heart defects. Strong epidemiologic evidence has accumulated in recent years to suggest that periconceptual folic acid is an effective agent in reducing the occurrence and recurrence of several common congenital malformations. However, the metabolic and molecular basis for this preventive effect is unknown. The scientists hypothesize that common polymorphisms in genes coding for critical enzymes in the folic pathway will interact with inadequate maternal micronutrition status to influence negatively the fetal microenvironment and to promote alterations in homeobox gene expression and tissue-specific developmental malformations. This project has the potential to advance the knowledge of factors involved in maternal and infant risk, to aid in the design of nutritional intervention strategies, and to provide a basis for future mechanistic studies of human malformations.

At McMaster University, Hamilton, Ontario, researchers are undertaking a longitudinal study of children aged 5–13 years with physical disabilities, to determine the factors that enhance participation in formal and informal activities of childhood. Innovative methods will be used to evaluate the relative contribution of child, family, and environmental factors in determining participation of children with long-term, nonprogressive physical conditions associated with physical functional limitations in day-to-day activities. Knowledge of such factors will inform the planning of interventions to enhance such participation.

Through an NICHD-funded contract, McMaster University has established the Neonatal Collaborative Review Group, within the International Cochrane Collaboration, to develop and maintain a neonatal trials database. This database provides current reviews and meta-analyses of the clinical trials in newborn medicine and serves as a resource for institutes and investigators.

At Mt. Sinai Hospital, Toronto, Ontario, newly funded research aims to define the contribution of the mechanical stretch of the myometrium to the initiation of labor. Studies will be conducted in healthy pregnant rats and in cultured myometrial cells that are stretched; molecular biology techniques are being used to determine expression of specific genes.

Scientists at the Texas Women's University, Denton, are studying the influence of skeletal loading and calcium supplementation with dairy products on bone mineral accretion in the prepubescent skeleton, in a group of Canadian children in elementary school. The skeletal-loading intervention program includes a variety of skipping and box-jumping activities designed to stimulate bone formation. The dietary groups are instructed to supplement their diets with dairy products to attain a calcium intake of 1,200 mg/day. The primary objective is to investigate the effect of the program on bone accrual at the lumbar spine and the proximal femur and for the total body, in a group of prepubertal boys and girls. Data were collected at baseline and at 8 months from the start of the study; the final data will be obtained at 20 months.

A Canadian investigator at Université Laval, Quebec, is studying the spatial expression and function of a class of developmental regulators in vertebrates, the Hox genes. Different Hox genes are expressed in each region of the early embryo and determine which structures will develop in that region. However, it is not known how Hox gene expression is restricted to specific regions. The experiments in this project are designed to reveal how the regulatory elements controlling the expression of HoxA5 determine the spatial pattern of its expression. This is one of the major questions of developmental biology. These studies are made possible by the investigator's development of a unique line of HoxA5 mutant mice and the identification of HoxA5 regulatory elements. The function of the identified regulatory sequences and *trans*-acting factors will be tested in vivo through mutational analyses. These studies will help to elucidate the control of the Hox gene expression and are expected to lead to a more detailed understanding of regional patterning during development and of the formation of birth defects.

Chile

Scientists at the University of Michigan, Ann Arbor, in collaboration with the Institute of Nutrition and Food Technology, Santiago, are testing the hypothesis that hypomyelination causes the changes in neuromaturation observed in infants with iron deficiency anemia. They also are testing a model of mechanisms explaining why this condition in infancy is associated with poorer developmental outcome. Impaired myelination is a promising explanation for evidence of immature neuromaturation in 6-month-old infants with iron deficiency anemia. The most important result to date has been the finding of delayed nerve conduction in the auditory pathway among 90, 6-month-old infants with iron deficiency anemia in Chile. Preliminary analyses also indicate altered visual evoked potentials in the formerly anemic children. Early iron deficiency anemia affects an estimated 25% of the world's infants, including many poor or minority infants in the United States. This study provides a unique opportunity to examine biological and environmental effects on developmental outcome among poor children in a developing country.

China

A collaborative longitudinal study by Chinese University, Hong Kong, and Emory University, Atlanta, Georgia, is investigating the relationship between fetal brain and behavioral profiles and emotional responsivity before and after birth in African Americans, Chinese in Hong Kong, and whites in the United States. The investigators found that the velocity of fetal cerebral blood flow changed significantly as a function of fetal age. The findings suggest that this velocity could be used to predict postnatal neurobehavioral organization. This work is advancing knowledge in the important area of prenatal brain characteristics and behavior.

Researchers from the University of North Carolina, Chapel Hill, collected and disseminated data sets from the longitudinal China Health and Nutrition Survey, which was designed to study the effects of the sweeping social and economic changes that were introduced in China over a short period of time. The data under analysis cover 1989–1997 and provide a unique opportunity to monitor changes in economic and social behavior, health, nutrition, and de-

mographic factors, including occupation, income, marriage, pregnancy, and household size. This survey was designed as the sister survey of the Russian Longitudinal Monitoring Survey. Both surveys will make available basic information needed for planning economic and health programs and policies. A particularly striking result is that between 1989 and 1997, the percentage of overweight females doubled (from 10.4% to 20.8%) and the percentage of overweight males almost tripled (from 5.0% to 14.1%). The shift in the structure of work was the major baseline predictor of these changes. Adults with reduced physical activity in their occupations were most likely to experience heavy weight gain.

An investigator from Queens College, New York, New York, is examining different forms of migration (interprovincial, intraprovincial, temporary, permanent, and rural to urban) within China between 1982 and 1995. This project looks at how structural-level factors have influenced migration during this period of rapid social and economic transformation in China. These factors include variables such as the national economy, transportation systems, and the ability to obtain permission to live in a city. Findings show that, during the years studied, China's migrant population was the largest in migration history. There were increases in the numbers of temporary migrants, long-distance migrants, and migrants to coastal and city areas. There also have been changes in the selectivity of emigration from Fujian by socioeconomic status from 1990 to 1995. Specifically, these changes are characterized by a significant shift from urbanites to rural peasants. In addition, results suggest that there is still a large potential for migration from China.

The National Opinion Research Center, Chicago, Illinois, is conducting the first nationally representative survey of Chinese sexual health and family behavior. The researcher will describe the social organization of human sexuality in China and test whether social networks explain the pattern of spread of sexually transmitted diseases. This study is timely because China is experiencing sharp annual increases in the incidence of AIDS and other sexually transmitted diseases.

Researchers at the University of Michigan, Ann Arbor, are collaborating with psychologists at the Chinese University, Hong Kong, and the Chinese Academy of Sciences on a series of cross-linguistic studies of noun-phrase usage by preschoolers and their parents who speak Chinese compared with preschoolers and their parents who speak English. In earlier studies, the researchers found that children first use generic noun phrases in spontaneous speech by 2½ years of age. The researchers are examining the use of such constructions in the speech of the parents of these children. They also found that children understood subtle linguistic differences between generic noun phrases and indefinites (e.g., some) and universals (e.g., all). This research has demonstrated emergence of early links between conceptual distinctions and language in the first few years of life. Additional studies will be conducted, including use of generic noun phrases in India, from both urban and rural samples, to gather a comparable database on parent–child talk about social categories and to examine generic gestures in deaf children who have their own communication system.

An investigator at Brown University, Providence, Rhode Island, is investigating the consequences of population policy in China for child well-being. The project seeks (1) to describe the children's well-being by using multiple outcomes for children aged 1–6 years and to investigate its relationship to variation in the implementation of the one-child policy; (2) to examine the link between local characteristics of the one-child policy and individual fertility behavior and use of contraceptive methods; and (3) to evaluate the effects of a population policy directed toward women, on fertility behavior, contraceptive use, and child well-being. Early findings indicate that the risk of sterilization is highest in communities where birth-planning policy is least strong and that the one-child policy leads to greater involvement by parents in child care. In addition, boys and girls receive similar care regardless of the one-child policy in their communities. However, mothers living in communities where couples are permitted another child if their first is a girl are more likely to receive prenatal care than mothers in other communities.

A researcher at Harvard University, Boston, Massachusetts, is undertaking a prospective cohort study of 1,150 women who work in textile mills in Shanghai, to assess the effects of rotating shift work on adverse reproductive outcomes, including menstrual disturbances, time to conception, spontaneous abortion, preterm delivery, and low birth weight.

Costa Rica

Investigators at the University of Michigan, Ann Arbor, continue to examine the late functional and developmental effects of iron deficiency in infancy by performing follow-up on a longitudinal cohort of 200 young adults in Costa Rica. To explore the emotional and behavioral deficits related to iron deficiency in early infancy, the investigators studied iron status and cerebral development in this cohort, during infancy and at 5, 10, and 19 years of age. These studies have demonstrated the impact of iron deficiency on cognitive, motor, and affective development in childhood. When these subjects were 10–13 years old, they had major deficits in school achievement and problems in internalizing behavior that varied directly with the level of iron deficiency. This cohort will provide information about whether the behavioral and neurobehavioral effects of infant anemia persist into young adulthood.

The investigators completed analyses of the initial prolactin results at 11–14 years. The results demonstrate that iron deficiency in infancy is associated with altered prolactin response years later. This observation implies that iron deficiency in infancy can exert deleterious effects on cerebral neuroendocrine function that may persist for decades. These results remained statistically significant after adjustment for age, gender, and pubertal development.

Ecuador

Researchers at Tufts University School of Medicine, Boston, Massachusetts, are conducting a major clinical trial in Quito to evaluate the use of low doses of vitamin A, zinc, or combined vitamin A and zinc supplementation in underweight, malnourished children. The study is aimed at the prevention of acute respiratory infection, acute lower respiratory infection, and incidence of diarrheal disease. Thus far, 680 children, 4–34 months of age, from three impoverished neighborhoods have been enrolled in the trial. All have some degree of malnutrition and have been stratified by weight for

age into three groups by using WHO criteria. During the 1st 8 weeks of active enrollment, 180 cases of mild diarrhea, 48 cases of severe diarrhea, 186 cases of acute upper respiratory infection, and 18 cases of pneumonia had been recorded. Final results on the primary end point have not yet been obtained.

Investigators from the University of North Carolina, Chapel Hill, are studying the demographic, socioeconomic, and biophysical factors affecting the intensity of land use by migrant colonists and indigenous populations in the Ecuadorian Amazon. By integrating demographic, anthropological, and cross-cultural approaches, this project is expected to develop a comprehensive understanding of the factors affecting land use in the region and provide the knowledge base for policies aimed at ensuring sustainable development. In FY 00, the study was in the beginning stages of data collection.

Egypt

At the University of Maryland, Baltimore, researchers are collaborating with Egyptian investigators from three institutions to determine the incidence and prevalence of hepatitis E virus (HEV) infection. Household and environmental risk factors for acquiring HEV will be studied, as well as the role of HEV infection in acute viral hepatitis. This project is part of the NICHD collaboration with the NIAID ICIDR Program.

France

An investigator at Institut Pasteur, Paris, is conducting a study to establish and define the role of Notch signaling in the regulation of skeletal myogenesis in the mouse embryo. To test the hypothesis that the Notch signaling pathway represses myogenesis, a dominant Notch 1 allele, comprised of the Notch intracellular domain, will be "knocked into" the locus of the myf5 gene. Under the direction of the regulatory elements of this gene, the misexpression of the Notch 1 allele in the earliest muscle precursor cells is designed to perturb normal signaling in the myogenic lineage, potentially resulting in anomalies in cell fate, cell differentiation, and morphogenesis. These studies offer insights into the role of Notch signaling throughout myogenesis in vivo and in understanding certain pathological conditions.

Ghana

A team of researchers from the Population Council, New York, New York, and the State University of New York, Stony Brook, is conducting a study in Ghana to examine how the diffusion of family-planning information and the pace and timing of fertility changes are influenced by social dynamics. Scientists are studying a wide range of factors, including child mortality, education, the political economy, the properties and perceptions of contraceptive methods, and understanding of the risks of sexually transmitted diseases. The team has documented the role of family-planning services in fostering change in reproductive preferences, contraceptive knowledge, and fertility. A simulation model has been developed to assess whether social network structures have implications for contraceptive use, and a supplement has been added to model HIV/AIDS knowledge and practices as a function of social network characteristics. In FY 00, multiple rounds of data from panel surveys were in the final stages of collection. Intensive data analysis will follow.

Guatemala

Scientists at Emory University, Atlanta, Georgia, continue to study the effects of improved nutrition in early childhood on later functional performance in adolescents and adults. This research links two data sets originating from a landmark longitudinal study of growth and development, which was conducted in 1969–1977 in four Guatemalan villages. The scientists have collected additional data on reproductive history and have assessed long-term effects of a nutritional intervention that was shown to improve growth and development in the preschool period. This follow-up analysis indicates that nutritional interventions during the pregnancy of the mother and during early childhood culminate in improved body size and intellectual performance for the child.

These Emory University scientists are conducting another follow-up project in Guatemala that evaluates the generational effects of malnutrition. These efforts link mothers and children of the original study, who are now grandmothers and mothers, with the current generation of children. The research focuses on the hypothesis that malnutrition and developmental impairment in early childhood constrain the future capacity of women to bear healthy newborns and their ability to care for them and, thus, constrain the growth and development of the next generation. This study promises to be the most comprehensive current evaluation of the repercussions of malnutrition in early childhood across generations and the first such investigation in a developing country. Findings to date demonstrate that dietary supplementation in early childhood improves the cognitive and educational ability of young women. The women who had received supplementation in childhood scored better in reading comprehension and arithmetic than did women who had not received supplementation.

India

A researcher from the University of Pennsylvania, Philadelphia, is conducting a longitudinal study of 4,000 households in 250 villages in rural India, on the basis of data for 1968–1982. This study examines the effect of economic growth and population size on environmental changes. The goal of the project is to provide information on interventions that could alter the environmental impact of population growth on forest degradation. Results have shown that changes in agricultural technology resulted in higher incomes of residents in the region but also increased deforestation, whereas rural industrialization did not increase deforestation.

This researcher also is implementing a survey of 7,000 households in rural India and linking the data from that survey with the data from the previous survey. The second study will assess the effect of economic development and program interventions on demographic and social change in India. An analysis using the 1968–1982 data indicated that members of households are more willing to engage in risk-sharing arrangements (e.g., borrowing or lending money) with nuclear family members than with other households. Improved methods for modeling were used to show that if economic growth had been diffused widely across India, 40% of the differential in mortality rates between girls and boys would have been eradicated.

Investigators at Johns Hopkins University, Baltimore, Maryland, continue to evaluate the role of zinc in childhood growth and development and the effects of zinc defi-

ciency on childhood morbidity. They are developing new methods to analyze longitudinal data from randomized, controlled field trials of dietary supplementation that involve variables of childhood growth and development. This research builds on the recent discovery that zinc replacement lessens the effects of childhood diarrhea, as established in a field trial in India.

These investigators also are analyzing data from two large studies in India on zinc supplementation. The studies target outcomes such as incidence of infectious diseases, morbidity, and changes in copper status, growth, and development. New and traditional methods are being compared to determine the better approach for studying hypotheses on the potential effect of zinc supplementation. These studies will increase understanding of the role of zinc deficiency in childhood illness, which is particularly important to specific high-risk groups. The investigators expect to establish nutritional guidelines for zinc fortification of foods in developing countries. Findings indicate that zinc supplementation reduces the incidence of pneumonia and augments cellular immunity. These results are important for much of the developing world, where pneumonia is a major killer in children younger than 5 years of age. The findings suggest that improving zinc intake will improve the health and survival of children in developing countries. This research is also relevant to the United States, because studies have shown that approximately 30% of U.S. children are not obtaining sufficient zinc from their diet.

A project on zinc and iron supplementation conducted by researchers from the University of Maryland, Baltimore, builds on an existing trial of the effect of micronutrient supplementation on children's growth, immune functioning, and morbidity. The supplements were administered from birth through 9 months of age to term infants born small for gestational age in a low-income community in India. The children now range in age from 34 to 52 months. The study provides a unique opportunity to examine the effects of early micronutrient supplementation on behavior and development during the 3rd and 4th years of life in children who are consuming diets consisting of indigenous foods. The researchers documented that zinc supplementation for the 1st 9 months of life led to better motor development at 10 months of life among children born weighing less than 2,500 g. Children with birth weight higher than 2,500 g did not have better motor development after receiving zinc supplementation. The results have important public health implications for the timing of micronutrient supplementation and the relationship between micronutrient deficiency and children's behavior and development.

NICHD is collaborating with investigators in southern India in the development of a project site for operational research on prevention of mother-to-child transmission of HIV in a rural setting. This work will be complementary to the ongoing and planned activities of the National AIDS Control Organization of India. The pilot project will include antenatal assessments of acceptance by clinic attendees of both voluntary counseling and HIV testing and of antiretroviral prophylaxis to prevent mother-to-child transmission. Evaluations of breast-feeding patterns and of the safety and tolerability of antiretroviral prophylaxis for perinatal transmission are also planned. Extension of the pilot project activities to other rural settings within India is envisioned. The pilot project and later extensions of this project will provide experience to investigators at other clinical sites who have little or no experience with clinical trials. This experience will include data collection, completion of forms, and activities related to other clinical trials. The ultimate goal is to have such clinical sites participate in future trials of HIV prevention and treatment.

Indonesia

Researchers at RAND, Santa Monica, California, are implementing the third wave of data collection of the Indonesian Family Life Survey of Mothers and Children. This major new panel of data supports research on the health and well-being of women and children in a low-income setting. Results from a follow-up survey in 1998 on the 1997 financial crisis in Southeast Asia suggest that the effects of the crisis in Indonesia have been heterogeneous and that households have responded to the crisis in different ways. They also suggest that targeted interventions are needed to reach the most vulnerable members of the population and that children in poor households are especially at risk. Between 1997 and 1998, the poverty rates in Indonesia rose by 25%, while the percentage of household budget spent on food increased, the percentage of income spent on health and education decreased, and the school enrollment decreased. Health status for a number of dimensions improved. Previous results also indicated that the role of a woman's empowerment within the household is related to reproductive health outcomes. Measures of a woman's empowerment, such as her share of assets within the household and her resources relative to those of her spouse, were related to whether she received prenatal care.

Italy

Ongoing research by a scientist at the University of Colorado Health Sciences Center, Denver, addresses issues in pregnancies complicated by fetal growth restriction. The clinical studies are being conducted at the University of Milan. Preliminary findings suggest that there is a subset of infants with intrauterine growth retardation in pregnancies with a reduced umbilical blood flow, even after the results are adjusted for fetal weight.

Japan

Investigators at Duke University, Durham, North Carolina, are working to isolate genes involved in autistic disorder. The gene search will focus on chromosome 15q11–q13, because of recent evidence that links this region to this condition. The primary aim of the project is to produce a detailed genetic map of the region in families with members who have autistic disorder, to determine the most likely locus of the gene for this condition. DNA from families in Finland and Japan will also be examined for methylation abnormalities and chromosomal duplications, insertions, deletions, or inversions.

Kenya

Researchers at the Population Council, New York, New York, continue to examine the quality of schooling for adolescents in Kenya and its effect on educational attainment and reproductive behavior. Using data from approximately 800 adolescents, their parents, principals, and teachers, the research has shown that although there is variation in the quality of primary schools, girls have lower achievement test scores than boys

have at all schools. Teachers tend to have lower expectations for girls, traditional assumptions about gender roles, and a double standard about sexual activity. Families largely determine whether girls remain in school, but dropout rates are higher among girls whose teachers and schools discriminate against them. Other research in Kenya studies how schooling affects young girls' attitudes toward and adoption of reproductive health practices.

As part of a larger study of the factors that influence the quality of and returns to schooling, an economist at the Massachusetts Institute of Technology, Cambridge, is examining an experimental program to improve early childhood education in locally organized preschools in Kenya. Findings after the 1st 2 years show some positive impact on grade progression. Children who attend the preschools in the experimental program progress to first grade sooner than the comparison group. However, impact on test scores for the children in the experimental schools was not detected.

Kuwait

An investigator at Mt. Sinai School of Medicine, New York, New York, is endeavoring to clone the gene for the autosomal-recessive skeletal dysplasia, the Kenny-Caffey syndrome (KCS), a rare condition that is found primarily in Middle Eastern countries. The investigator plans to include a number of consanguineous Kuwaiti pedigrees in this study. Persons with KCS have short stature and hypocalcemia, and they may exhibit additional manifestations including eye abnormalities, developmental delay, and immune deficits. In addition to narrowing the KCS critical region on the chromosome before the positional cloning of the gene, this project will also better define the natural history and phenotypic spectrum of KCS and provide additional insights into the disease pathogenesis and the function of the KCS gene.

Malawi

Researchers at Washington University, St. Louis, Missouri, are studying the role of infection in human nutrition. The vicious cycle of malnutrition, infection, lack of immune competence, and growth failure in children has been a well-recognized phenomenon for many years. It is regarded by many as one of the most important sources of morbidity and developmental compromise in the developing countries and has received substantial attention in the epidemiologic and public health literature. However, there have been very few quantitative studies of this problem and virtually none in which stable isotopic techniques have been applied under carefully controlled circumstances. In Malawi, where primary malnutrition is prevalent, the researchers will study children with marasmus, with or without concurrent infection, and compare them with a group of infected, well-nourished children. Whole-body and splanchnic-bed protein response and pro-inflammatory cytokine response will be measured. In a second study, nitrogen conservation and the acute-phase response of infected, malnourished children will be studied while they receive diets that differ in tryptophan content. These studies may also be useful in developing rational dietary recommendations for chronically ill children with protein–energy malnutrition in the United States.

Mexico

Investigators at Eastern Virginia Medical School, Norfolk, are performing follow-up on a cohort of Mexican mothers and their children to ascertain whether human milk prevents disease in breast-fed babies. The cohort study was initiated in March 1988, at the study site at San Pedro Martir, Mexico City, and was continued through FY 00, with 283 postpartum mother–infant pairs enrolled. The study protocol includes weekly collection of infant stool samples, maternal milk collection every week in the 1st month after birth of the infant and every month thereafter until breast-feeding ends, and collection of infant blood samples immediately after birth and every 3 months thereafter. In FY 00, the investigators began to compare outcomes by analyzing data from the previous (1988–1991) and current (1998–present) cohort studies. In the current cohort, mothers receive counseling about breast-feeding during pregnancy and immediately after birth. As a result, the percentage of mothers who breast-feed exclusively at 4 months after birth is significantly higher (70% versus 3%), and the median duration of breast-feeding is significantly longer (17 versus 6 months). Consistent with this change in breast-feeding, the incidence of all cases of diarrhea is significantly lower in the current cohort than in the previous cohort, among infants younger than 6 months of age. The same reduction is not observed through the 1st 2 years after birth.

In the largest field study of Mexican migration, a researcher from the University of Pennsylvania, Philadelphia, continues to collect and analyze survey and ethnographic data on more than 60 Mexican communities paired with corresponding destination communities in the United States. These data from the Mexican Migration Project are a critical source of information on demographic change. Analyses of these data have helped to determine the factors that stimulate legal and illegal immigration, the impact of U.S. policies on migration streams, and the effects of migration on sending and receiving communities.

Another researcher at the University of Pennsylvania is examining how the industrialization and expansion of employment during the past 30 years in Tijuana have affected the probability of migration to the United States. Data from that project are being analyzed.

At the University of Wisconsin, Madison, a scientist is assessing the cultural assimilation and health of Mexican immigrants by using a new approach that considers related women and children on both sides of the border, rather than comparing immigrants and U.S.-born or non-Hispanic women in the United States. By addressing the problem in this manner, the scientist is able to deal directly with the issue of migrant selectivity. This project aims to (1) carry out health-related interviews in two samples of Mexican women living in neighborhoods in Chicago, Illinois, and Milwaukee, Wisconsin; (2) identify, trace, and interview selected siblings and sisters-in-law who live in sending areas of Mexico; and (3) assess response rates and quality of responses to the most sensitive items included in a questionnaire on maternal and child health.

Nepal

An investigator from the University of Michigan, Ann Arbor, is expanding an ongoing project in Nepal. This research provides an opportunity to observe how population, institutional, and environmental changes interrelate in a relatively pristine environment in a country that is just be-

ginning economic development. A related study continues to examine the influence of changing social contexts on marriage, childbearing, and contraceptive use in a sample of 150 neighborhoods in Nepal's Chitwan Valley. Data continue to be collected.

Researchers at Johns Hopkins University, Baltimore, have started a project to assess the impact of zinc supplementation on morbidity, growth, and mortality in children 3–36 months of age in Nepal who are already receiving routine vitamin A supplementation. Previous studies conducted by the researchers in Nepal have demonstrated large reductions in preschool child and maternal mortality with vitamin A supplementation. The study is designed as a randomized, placebo-controlled, community-based, clinical trial to be conducted in a well-defined study area of southern Nepal. Approximately 36,000 children will be recruited over a 2-year period and randomly assigned to receive either daily supplementation of zinc sulfate or placebo. The analysis will focus on comparison of rates of mortality and morbidity between treatment groups, and additional analyses of subgroups will be performed to look for interaction by age, gender, or baseline nutritional status. This study has important implications for child survival programs in developing countries. It will determine the life-saving potential of zinc supplementation in young children in these high-risk settings where the vast majority of child deaths occur. Zinc supplementation has the possibility of being one of the most cost-effective interventions for the prevention of child mortality.

The Netherlands

A scientist at Utrecht University Medical School is working to perfect the isolation, cell culture, and establishment of immortalized cell lines of spermatogonia; to identify factors important for their growth and differentiation; and to improve the procedure for transplanting these cells into germ cell–depleted testes. Success in these studies will have important implications for future research in the areas of sperm cell development, stem cell development, transgenic production of different genomes through alteration of male germ cells, male fertility and infertility, and novel approaches to male contraception.

Investigators at the University of Amsterdam and the University of Connecticut, Storrs, are collaborating on a study that aims to expand knowledge of the early development of arousal, attentional, and affective behaviors, especially as they are shaped by culturally specific interactions and caretaking practices of parents with their children. This cross-cultural project will follow two groups of infants in parallel communities in the Netherlands and the United States from shortly after birth until 2 years of age. It is anticipated that the study results will increase understanding of the biological, behavioral, and environmental causes of poor arousal regulation, attentional difficulty, and sleep deprivation, as well as their consequences for social, cognitive, and self-regulatory functioning in the preschool years.

New Zealand

Scientists at the University of Auckland and Yale University, New Haven, Connecticut, are collaborating on a recently funded, retrospective cohort study of pregnancy outcomes, especially the outcomes for preterm labor after treatment of cervical dysplasia. They will analyze data from two high-quality, comprehensive databases. A preliminary data set for linkage has been established and shows good matching of several predictors for outcome between cohorts.

Investigators at the University of Auckland continue to study the molecular basis for the biological activities of human lactoferrin. They are addressing wider questions of iron homeostasis by extending these structure–function studies to serum transferrin; evaluating the structural basis of specificity in these proteins; and studying the ability of lactoferrin to inhibit *Haemophilus influenzae* colonization by inactivating IgA (immunoglobulin A) protease, the bacterium's major virulence factor. This project is an extension of previous crystallographic studies of lactoferrin and new structural studies of transferrin. In FY 00, the investigators crystallized four site-specific mutants of human lactoferrin and determined their crystal structures. Other mutant proteins are being expressed in an animal model to assess their ability to bind iron and anions.

Another investigator at the University of Auckland is studying the key mechanisms that underlie the susceptibility of the premature brain to hypoxic–ischemic injury. A series of studies conducted with premature sheep in utero have demonstrated a paradoxical relationship between vulnerability of the fetus to asphyxia and neural injury. The greater anaerobic reserve of premature fetuses in comparison to the near-term fetus demonstrated that they were able to tolerate much longer periods of total asphyxia (up to 30 minutes versus just 10–12 minutes).

Researchers at Pennsylvania State University, University Park, and the University of Otago are collaborating on a study that examines whether childhood experiences of child-rearing practices are predictive of parenting practices during adulthood and whether a supportive marital experience disrupts the intergenerational transmission of problematic parenting. They analyzed archival data on more than 900 New Zealanders who had follow-up from age 3 years and who are now parents. The researchers are continuing to collect new data on the assessment of their parenting during adulthood. Insight into these issues will help to prevent problematic parenting and promote competent parenting.

Philippines

An investigator at Georgia State University, Atlanta, is studying language factors in early reading in 81 bilingual (English and Filipino) boys in two schools in the Philippines. Increasing evidence suggests that characteristics of the written alphabet of the particular language being used will affect the processes in learning to read. This study attempts to increase understanding of how linguistic characteristics of a bilingual child's learning environment and the child's facility with either language influence reading acquisition. Factors such as language dominance, language of reading instruction, and differences in the orthographic depth of English and Filipino are expected to be critical predictors of the development of early reading. Findings are expected to further theoretical development regarding bilingual reading processes and ultimately to inform bilingual education.

Russia

The Russian Longitudinal Monitoring Survey was designed as a household-based survey to monitor the effects of Russian reforms on the well-being of households and individuals. The survey monitors changes in eco-

nomic and social behavior, health, nutrition, and demographic factors, including occupation, income, marriage, pregnancy, and household size. Analyses of the data from 1989 to 1997 by scientists from the University of North Carolina, Chapel Hill, indicate that Russia's older adults have not experienced a major decline in economic or nutritional well-being during the reform period. This survey was designed as the sister survey of the China Health and Nutrition Survey. Both surveys will make available basic information needed for planning economic and health programs and policies.

In collaboration with a researcher at St. Petersburg State University, Russia, investigators at the University of Pittsburgh, Pennsylvania, are conducting an intervention in a St. Petersburg baby home with children from birth to age 4 years. The study will examine the effects of improved caregiving on the early mental, social, and emotional development and physical health of the children. Efforts to improve staff training, stability, and consistency will also be assessed in terms of their influence on the behavior and personal well-being of the caregiving staff. Data on the development of children in the baby home will be compared with baseline data, information on the results of a training-only condition in another baby home, and information from a baby home in which the intervention is not provided. Long-term adjustment, mental health, and progress of children who are adopted into the United States will be compared with those of untreated children from the same baby homes, adopted children from other baby homes, home-reared U.S. children, and children in Minnesota who also were adopted from a foreign country.

Saudi Arabia

Investigators at Baylor College of Medicine, Houston, Texas, have previously mapped the locus of the gene GLC3A for primary congenital glaucoma (PCG) to chromosome 2p21. Mutations in a cytochrome gene for drug metabolism (CYP1) localizing to the GLC3 locus were found in five Turkish families with PCG. Investigators screened the coding regions for the CYP1 gene, which produces the CYP1B1 enzyme, in 25 Saudi Arabian families with PCG and identified three missense mutations in 24 of these families. All three mutated amino acid residues are highly conserved among different species and across the entire superfamily of P-450 cytochromes. The investigators also confirmed their initial finding of variable expression of the phenotype by performing sequencing in all the clinically unaffected individuals who had haplotypes identical to those of their affected siblings and by demonstrating either homozygous or compound heterozygous mutations in the CYP1B1 enzyme in all these individuals. Sequence analysis of the coding region for the CYP1B1 enzyme in 50 randomly sampled Saudi control subjects with no known inherited eye disease is in progress. Detailed clinical and molecular examinations of the mildly affected patients and their environmental exposures are expected to identify additional factors that influence the expression of the PCG phenotype. Such knowledge will suggest pharmacological targets for the antenatal moderation or postnatal treatment of PCG and possibly other forms of glaucoma. Future study of the CYP1B1 enzyme and the identification of its ligands and their roles in ocular development will increase understanding of the embryology of ocular development and the roles of other drug-metabolizing enzymes in organogenesis.

South Africa

In Durban and Johannesburg, scientists from Columbia University, New York, New York, are conducting studies of HIV-specific responses of helper T cells in pregnant women. They are using perinatal transmission as an instructive model, because it may offer valuable insight into immunologic responses to HIV, so that vaccine development may be rationally guided toward successful strategies.

The explosive nature of the South African AIDS epidemic calls for urgent measures for HIV prevention in the country. A multidisciplinary group of researchers from South Africa, the United Kingdom, and the United States is undertaking a series of innovative studies to determine the acceptability of microbicides. The project, which was started in FY 00, is in its beginning stages.

In a study of HIV-infected children in South Africa, investigators from the University of Massachusetts, Amherst, are examining the role of cytotoxic T lymphocytes in the control of viremia and protection against disease progression.

Researchers from the New England Medical Center, Boston, Massachusetts, in collaboration with the University of Natal School of Medicine, are studying the role of micronutrients in reducing the morbidity and mortality associated with enteric infections. They will work to identify the organisms involved in enteric infections in HIV-infected children in South Africa and then carry out a randomized trial of zinc supplementation to reduce the morbidity and mortality associated with these infections.

Switzerland

At the University of Geneva, scientists are studying the function of the homeodomain Hox proteins by using mutagenesis screening in mice. They will generate and identify point mutations in the posterior HoxD genes that either remove or alter the function of the proteins coded by these genes. Deletions will be created in the genes in the posterior HoxD complex by using targeted meiotic recombination. Females homozygous for deletions of these genes will be mated with males carrying point mutations induced by the mutagen ENU. When this technique is used, the only copies of the genes being studied will come from males in which gene mutations occur. If the mutations generated affect HoxD protein function, the phenotype will be identified by malformed digits or limbs. The immediate goal of this research is to identify amino acid residues that are critical for Hox protein function. Ultimately, these studies will lead to a better understanding of how Hox proteins control developmental decisions.

Tanzania

An investigator from Harvard University, Boston, Massachusetts, is examining demographic change in an area around Kilimanjaro. In a study of 605 multigenerational families, the investigator has access to high-quality records on fertility, migration, and mortality trends starting in 1897 and continuing through achievement of Tanzanian independence in 1961. Infant and child mortality rates over time have been analyzed, and a database is being constructed, verified, and assessed.

Another Harvard University researcher in Tanzania demonstrated that relatively inex-

pensive vitamin A supplementation to HIV-infected women during and after pregnancy significantly reduced low birth weight, preterm delivery, and the birth rate for babies who are small for gestational age. In FY 00, this project was expanded to study the effects of multivitamin supplementation on pregnancy outcome in Tanzania. The investigators are now enrolling 6,000 pregnant women who have tested negative for HIV infection. The intervention group will receive dietary supplements of thiamine, riboflavin, niacin, pyridoxine, and vitamins B12, C, and E. The control group will receive placebo pills. Both the intervention and the control groups will receive dietary supplements of folate, iron, and vitamin A. The outcome measures of interest are rates of low birth weight, preterm birth, and infant mortality. Also in FY 00, the same investigators showed striking improvements in the rate of infant mortality in babies born to HIV-infected women in Tanzania who received similar micronutrient supplementation.

Thailand

An investigator at the University of Chicago, Illinois, is working with investigators in Thailand to study the role of the family and other social networks in managing economic risk. This ongoing study has collected data on economic activity and exchanges in Thai villages and relevant institutions such as village-level funds and national banks. The study will examine whether the importance of informal mechanisms for risk-sharing among kin and neighbors declines with the rise of formal institutions that provide credit and insurance. The impact of the local, regional, and national context on the role played by networks will also be examined.

Scientists at the University of North Carolina, Chapel Hill, have conducted a large survey in Nang Rong, Thailand, to examine the interrelatedness among population dynamics, land use patterns, and social and economic change over the last two decades. Data collected in 1984, 1988, 1994, and 2000 have been compiled into a comprehensive, longitudinal, integrated, multilevel data set. Analyses of data on the relationship between land use and migration suggest that migration is both a cause and a consequence of land use and that, in Nang Rong, household formation is more important to land use patterns than is household size. Data on social networks will be used to explore the relationships between choice to use contraceptives and migration in Nang Rong. Data newly collected in 2000 will be used to examine the impact of Thailand's economic downturn in 1997 on migration; the influence of return migration on the local economy; and the relationships among family, family structure, social networks, and migration.

Researchers from Harvard University, Boston, are conducting a study in Thailand to determine whether adding nevirapine to the short-course regimen of AZT used in Thailand will further reduce the transmission of HIV from mother to infant. The study will also examine the timing of transmission and cofactors for transmission, including viral load, phenotype, and coreceptor use; host genetics and the cellular immune response; and mutations related to resistance to AZT and nevirapine.

Turkey

An investigator at Rutgers University, New Brunswick, New Jersey, is using data from spontaneous speech and from research on comprehension, imitation, and judgment to study the acquisition of Turkish as a first language by children between 1½ and 6 years of age. These data will be used to increase understanding of the fundamentals of language acquisition. End points include the following: when and how well children begin to use functional category morphemes; how children learn to map words onto grammatical functions (e.g., subject and object) and to map these functions onto thematic roles; and the extent to which children are predisposed to assume that language has a fixed word order.

Uganda

At Pennsylvania State University, University Park, a researcher is using epidemiologic network modeling and social network data in Uganda to examine the issues related to concurrent and sequential partnering and the impact of sexual networks on transmission of HIV infection. The data obtained from field studies on the sexual network in Uganda will be compared with data from similar studies in Thailand. Results show that traditional core groups play a weaker role in the HIV transmission system than expected. Mobile populations, often thought to play a key role in the geographic spread of HIV, may play a more important role in spreading safer sex practices. In addition, condom use with nonspousal partners is three times higher among travelers than nontravelers, and travel remains a significant determinant of condom use, after adjustment for respondents' age, education, residence, occupation, and multiple partners. Although travelers are somewhat more likely to have higher levels of sexual risk behavior and HIV prevalence than nontravelers, the risk differential is explained by occupational exposure, higher socioeconomic status and, for women, being in higher-risk age groups.

Investigators from Johns Hopkins University, Baltimore, continue to work in Uganda to study the hypothesis that the genotype and glycosylation pattern in the V3 region of glycoprotein 120 (gp120) are important determinants of vertical transmission of HIV-1. These studies will characterize the genotypic features of the V3 region in HIV-1 variants in Ugandan mothers and their infants. In addition to elucidating the determinants of mother-to-child HIV transmission in a high-prevalence area of the world, this research also may aid in the development and testing of vaccine candidates.

United Kingdom

Researchers at the University of London, England, continue to study the relationships among children's social and moral understanding, family and peer relationships, and school adjustment during middle childhood. A sample of children of African-Caribbean descent in England has had follow-up since age 4 years and will be monitored until age 9 or 10 years. The group includes children identified as "hard to manage" and at risk for later problems with conduct and peer relationships. Early findings have highlighted the significance of maternal education as a contributor to these individual differences, the importance of social understanding to the quality of children's friendships, and the significance of understanding inner states for moral sensibility. Other findings indicate that children who are hard to manage engage in violent fantasy and antisocial behavior. These characteristics predict later differences in moral sensitivity. Such results are relevant to better understanding of the development of vio-

lent behavior in middle childhood and adolescence. Longitudinal analyses will focus on adjustment to school and its relevance to early measures of social understanding and children's family and peer relationships.

A multisite NICHD Collaborative Program of Excellence in Autism is part of the International Autism Genetics Consortium. The international team includes NICHD-funded scientists from Oxford University and the University of London, England, and universities in Denmark, France, Germany, Greece, the Netherlands, and the United States. The team has completed a genome scan based on 97 sibling pairs with autism who were uniformly characterized.

An investigator at the National Institute for Medical Research, London, England, is defining global regulatory mechanisms that influence the expression of genes in the HoxB complex during development, in a highly coordinated, temporal and spatial pattern. Using transgenic analyses and targeted mutagenesis in mice, this investigator aims (1) to identify regulatory regions that function as initiating elements, enhancers, and polycomb response elements; (2) to determine which HoxB genes are controlled by such elements; and (3) to demonstrate the functions of these elements in vivo. Use of a transposon-enhancer trap has helped to identify previously unknown regulatory elements located 3' to HoxB-1 that may be regulators of an unidentified gene. This research is expected to provide important insights elucidating the control of HoxB gene expression in ordered, anterior-to-posterior patterns, and it has important implications for understanding of pattern formation, development of vertebrates, and formation of birth defects.

A scientist at the University of Newcastle, Newcastle upon Tyne, England, is conducting a pilot study to generate three-dimensional (3-D) reconstructions of electronically digitized, high-resolution patterns of gene expression in the developing brain. In this pilot study, the scientist will prepare an anatomic map from sectioned material and then examine the expression of several marker genes, including PAX6, DLX1, WNT3, and WNT7B. These patterns, as well as previously generated data on gene expression from nine other markers, will be painted onto the 3-D reconstruction of the fetal brain at selected stages. This procedure will test the feasibility and reproducibility of mapping expression domains onto the reference 3-D images of human fetal brains. The scientist also plans to create a prototype database on gene expression in the human fetal brain. This interactive, image-based database will be publicly available, permitting remote input of data from many laboratories, thus facilitating the integration of additional data. Creation of this database will provide an important resource to the international developmental biology community.

Uruguay

The worldwide dramatic decline in infant mortality is perhaps the most widespread and significant social change of the past century. How this transformation has taken place remains a question of great importance. Despite the relevance of longitudinal analyses of population dynamics to developing countries, there have been no detailed studies of pre-1940 mortality declines outside North America. A project by an investigator at the New School for Social Research, New York, New York, is examining infant mortality patterns in Uruguay in 1882–1950. Preliminary results suggest the following findings:

1. Declines in mortality in the early 20th century were not universal.
2. Leading causes of infant mortality, especially diarrhea, may have been far more intractable than previously believed, perhaps in part due to exposure to healthy adults who were disease carriers.
3. Uruguayan data may have been more accurate and comprehensive than those of other countries.
4. The country's level of medical progress may have been an extremely important factor in improving infant mortality.
5. The persistence of diarrheal mortality may have been exacerbated by adults who served as healthy carriers of the *Shigella* form of bacillary dysentery.

Zambia

Researchers from the University of Alabama, Birmingham, and the University of Lusaka are using a randomized study to compare contraceptive use and pregnancy incidence among couples in which one or both partners are HIV positive. One group of couples was given information only, another group received education on and access to contraceptives, and a third group received the same education and access and a motivational message. Results show that maternal HIV status is not correlated with starting to use nonbarrier contraceptives, such as Norplant (levonorgestrel), Depo-Provera (medroxyprogesterone acetate), or oral contraceptives. In the group receiving on-site access to contraceptives, more than 80% adopted a modern method, compared with 28% of those who received education only. This result suggests that decisions about pregnancy incorporate multiple factors, of which HIV status is only one. The mistaken belief that all children of HIV-positive mothers will die of AIDS was not associated with an increase in contraceptive use. This finding may indicate that, for some women, fertility has value whether or not the child survives.

An investigator from Harvard University, Cambridge, Massachusetts, is conducting an ICIDR study in two urban health clinics in Lusaka. The study aim is to determine whether exclusive breast-feeding with abrupt weaning at 4 months of age will reduce transmission of HIV from mother to infant more than full or partial breast-feeding with gradual weaning. Children will have follow-up both for HIV infection status and to determine any differences in morbidity or mortality in the two feeding groups. The study is expected to contribute to development of a strategy for breast-feeding in a resource-poor setting that will minimize the risk of HIV infection but allow children to gain the benefits of breast-feeding.

International Meetings

During FY 00, NICHD researchers helped to organize and convene, attended, and made presentations at many international conferences, seminars, and workshops. Selected meetings that involved NICHD participation are as follows:

- Indo-U.S. Workshop on Health and Nutrition in Women, Infants, and Children, in Hyderabad, India, on February 10–12, 2000;
- International Symposium on Stress, Hormones, and Human Parturition, in Udine, Italy, on February 27–29, 2000;
- Research Meeting on Child and Adolescent Health and Congress on Teaching in Pediatrics, in São Paulo, Brazil, on March 22–25, 2000;

■ National Congress of Pediatrics, in Monterrey, Mexico, on May 1–3, 2000;

■ 10th International Conference on Prenatal Diagnosis and Therapy, in Barcelona, Spain, on June 18–22, 2000;

■ XIIIth International AIDS Conference, in Durban, South Africa, on July 9–14, 2000;

■ VIIIth International Congress of Inborn Errors of Metabolism, in Cambridge, England, on September 13–17, 2000; and

■ 1st Workshop on Biological Physics 2000, in Bangkok, Thailand, on September 18–22, 2000.

Intramural Programs and Activities

Many international investigators are given the opportunity to train and work with NICHD scientists on projects conducted in the Institute's laboratories. NICHD intramural scientists also are involved in collaborative efforts with investigators in many countries.

Division of Epidemiology, Statistics, and Prevention Research

In collaboration with investigators from Denmark, the Office of the Director, DESPR, is analyzing data from girls who were born in the 1960s. The investigators have interviewed girls who were small for gestational age or preterm at birth and control girls. Hospital records of their deliveries have been retrieved, and women who were small for gestational age at birth were found to be at doubled risk to develop hypertension during pregnancy.

The Epidemiology Branch participates in the WHO study of Health Behavior in School Children and cosponsors the International Collaborative Effort on Injury Statistics. (See also the section on "Activities With International and Multinational Organizations.")

The Branch continues to study markers for fetal alcohol syndrome with the University of Chile, Santiago. Researchers have identified pregnant women with high alcohol intake, are collecting blood specimens over the course of pregnancy, and will examine the ability of various markers to predict which offspring will have fetal alcohol syndrome. All case patients and control subjects have been identified, and neurological and behavioral evaluations are being conducted.

In joint research efforts with the U.S. Naval Medical Research Unit 3 and the University of Alexandria, Egypt, the Branch continues to evaluate the role of enterotoxigenic *Escherichia coli* (ETEC), *Campylobacter,* adenoviruses, and caliciviruses as causes of diarrhea in a cohort of infants. It has also conducted phase II trials of an inactivated oral ETEC vaccine in differing age strata of this population. Researchers at the field site in Egypt are studying the epidemiology of *Helicobacter pylori* infections in a cohort of newborn infants and are conducting a large-scale, phase III, efficacy trial of the ETEC vaccine.

In collaboration with the Health Research Board of Ireland and Trinity College, Dublin, the Branch continues to study the cause of neural tube defects. This research focuses on genetic errors that result in mutants of the enzymes involved in folate metabolism. Specifically, a gene defect produces a thermolabile variant of the 5,10-methylenetetrahydrofolate reductase enzyme. The original study, which was recently expanded, confirmed that the mutant enzyme is found significantly more frequently in individuals with neural tube defects than in healthy individuals. The findings indicate that, in women who received 200 mg of folic acid per day, folate in red blood cells was raised to levels that are known to protect against most neural tube defects in infants and that 100 mg is also protective in many women. A major focus of current research efforts is to identify other genes for folate enzyme that are related to neural tube defects. In addition, possible relationships between these genes and oral clefts are being examined. Arrangements are being made to recruit families with neural tube defects in England and families with oral cleft in Ireland.

A field site for evaluating vaccines for enteric fever has been established in South Vietnam. A baseline epidemiologic study of enteric fever was conducted in three communes, and safety and immunogenicity studies of enteric vaccines were completed. A phase III trial is under way. In addition, an exploratory surveillance of shigellosis is being conducted in North Vietnam for evaluation of *Shigella* vaccines.

Cell Biology and Metabolism Branch

The Cell Biology and Metabolism Branch conducts research in various areas of molecular cell biology. These areas include the mechanisms of intracellular protein trafficking; the biology of intracellular organelles; the characterization of tumor-suppressor genes and their products; the genetic response to environmental stress; iron metabolism in humans; the regulation of gene expression at the transcriptional and post-transcriptional levels; and the developmental control of the cell cycle. The Branch has collaborative projects with groups in France, Germany, Italy, Japan, and South Korea. Among the scientists working at the Branch are researchers from Argentina, Canada, China, Germany, India, Israel, Japan, Malaysia, the Netherlands, Russia, Spain, Turkey, the United Kingdom, and Taiwan. During FY 00, scientists from the Branch attended meetings in Austria, Canada, Finland, France, Germany, India, Italy, Switzerland, and the United Kingdom.

Developmental Endocrinology Branch

The Developmental Endocrinology Branch conducts basic and clinical investigations of endocrine diseases, with broad emphasis on adult, pediatric, and reproductive endocrinology. Much of the Branch's research aims to discover the molecular causes and cures of reproductive, growth, and developmental disorders. Visiting Fellows and Visiting Scientists from many countries participate in research meetings, clinical conferences, medical rounds, and outpatient clinics. During FY 00, the Branch had 30 visitors from Argentina, Australia, Belgium, Brazil, China, Germany, Greece, Hungary, India, Japan, Lebanon, New Zealand, Nigeria, the Philippines, Poland, Turkey, and the United Kingdom. The Branch has established ongoing joint efforts with the Bulgarian Academy of Sciences; the University of Toronto, Ontario; the Institute of Maternal and Child Research, University of Chile, Santiago; the United Medical and Dental School, University of London, England; Medizinische Universitätsklinik, Würzburg, Germany; the University of Athens Medical School, Greece; and Tel Aviv University, Israel.

Endocrinology and Reproduction Research Branch

The Endocrinology and Reproduction Research Branch investigates basic aspects of hormone action in endocrine and reproductive tissues, with particular emphasis on peptide hormone receptors and their signal

transduction mechanisms. The Branch maintains collaborative research programs with scientists in Germany, Hungary, Italy, and Japan and trains Visiting Fellows and Visiting Scientists from Argentina, Canada, China (including Hong Kong), Croatia, Hungary, Japan, Korea, Mexico, Pakistan, Romania, Russia, Spain, Turkey, and Yugoslavia. During FY 00, Branch investigators attended international conferences and symposia in Australia, the Bahamas, Germany, Hungary, Israel, Japan, and the United Kingdom.

Research Fellows from China, Japan, Korea, and Mexico are studying the structure–function properties and expression of receptors for angiotensin II, gonadotropin-releasing hormone, prolactin, and luteinizing hormone, as well as those for angiotensin II and prolactin receptor subtypes. Investigators from Canada, Croatia, and Serbia are using single-cell imaging and electrophysiological techniques to study the regulation of cytosolic calcium oscillations and secretion in cells of the hypothalamus and the pituitary gland, as well as the nitric oxide/soluble guanyl cyclase signaling pathway. A Research Fellow from Hong Kong, China, is studying the mechanism of P2x channel inactivation. Scientists from Argentina, Spain, and Yugoslavia are using cultured and immortalized hypothalamic neurons for in vitro studies on the control of gonadotropin-releasing hormone secretion by neurotransmitters and other ligands. Postdoctoral Fellows from China, Hungary, and Russia are investigating the role of inositol phospholipids and lipid kinases in cellular regulation and are developing novel molecular probes for fluorescence imaging to analyze inositol lipid dynamics in single living cells.

Branch scientists are continuing a study with the Peking Union Medical College, Beijing, China, to analyze the regulation of a DNA-binding protein by protein kinase C. Branch collaboration is continuing with scientists at the Leibniz Institute for Neurobiology, Magdeburg, Germany, to study changes in neuronal plasticity in neurogranin gene knockout mice. Joint research also continues with the Department of Obstetrics and Gynecology, University of Lübeck, Germany. The current focus is on the role of P2Y2 purinergic receptors in human ovarian and endometrial cells and the role of androgens in the control of pituitary hormone secretion. Research with investigators at the University of Rome (La Sapienza), Italy, is addressing the communication among testicular compartments, the role of leptin and opiates in the modulation of testicular function, and the actions of growth hormone–releasing hormone in the testis and ovary. In addition, studies on the role of endothelin in the intracellular signaling and growth regulation of ovarian tumor cells are in progress with scientists at the Regina Elena Cancer Institute, Rome. Collaborative projects with a research group at the Netherlands Cancer Institute, Amsterdam, and the Hospital for Sick Children, Toronto, involve using pleckstrin homology domain–GFP (green fluorescent protein) chimeras to follow inositol lipid synthesis in various cellular processes.

Heritable Disorders Branch

The Heritable Disorders Branch trains foreign scientists and supports extensive international research efforts. Branch associations include joint studies with scientists from Canada, Germany, India, Israel, Italy, Japan, Korea, the Netherlands, Puerto Rico, Thailand, the United Kingdom, and Taiwan.

Visiting Fellows from Canada and Japan are collaborating on the cloning and expression of the glucose-6-phosphate transporter gene. Visiting Fellows from Germany are using the Brittle mouse model to develop a gene therapy approach to osteogenesis imperfecta and are pursuing mutation analysis of patients with sialic acid storage disorders. Visiting Fellows from India are working to characterize a member of the uteroglobin gene family, lipophilin B; to isolate and characterize putative uteroglobin receptor cDNA (complementary DNA) and the gene and its signal transduction pathway; and to delineate the physiological role(s) of the $sPLA_2Ib$ gene by targeted disruption of the gene in the mouse. Postdoctoral Fellows from India have carried out studies on the custom synthesis of three cDNAs encoding uridine diphosphate (UDP)-glucuronosyltransferase (UGT), as part of an effort to determine the function of the locus of the UGT1 complex. They are also working to define a signaling pathway that controls the activity of UDP-glucuronosyltransferases. A Visiting Fellow from Israel has performed mutation analysis of the gene for cystinosis and, in FY 00, identified a gene responsible for a subtype of Hermansky-Pudlak syndrome, a disorder of intracellular vesicle formation and trafficking. A Visiting Fellow from Italy has shown that adenovirus-mediated gene therapy corrected glucose-6-phosphatase deficiency in a mouse model of glycogen storage disease type 1a. The finding suggests that this disorder in humans can potentially be corrected by gene therapy. An Intramural Research Training Award Fellow from Korea is characterizing another member of the uteroglobin gene family, lymphoglobulin. A Postdoctoral Fellow from the Netherlands has made important discoveries about the cellular and molecular biology of Hermansky-Pudlak syndrome, and a Postdoctoral Fellow from Thailand has identified the promoter region for cystinosis. A Nigerian Clinical Fellow who is a Canadian citizen is involved in the characterization of RSH/Smith-Lemli-Opitz syndrome in both a clinical protocol and in laboratory research. A Taiwanese fellow has established the structural requirements for stability and microsomal glucose-6-phosphate transport function of the glucose-6-phosphate transporter, which is deficient in patients with glycogen storage disease type 1b.

An active collaboration with a Canadian group involves establishing the disease frequencies and population carrier frequencies for RSH/Smith-Lemli-Optiz syndrome in Canada. Other joint research efforts include studies with an English scientist to study mineralization in the Brittle mouse model for osteogenesis perfecta and with Italian scientists to study the matrix of the Brittle mouse. Ongoing work with investigators in Israel is aimed at finding the molecular cause of the gray platelet syndrome, a rare congenital disorder of platelet alpha and delta granules. The natural substrates for human UDP-glucuronosyltransferase have been supplied by a collaborator in Japan. Another collaboration with Japan is aimed at finding the molecular cause of renal dysfunctions in glycogen storage disease types 1a and 1b.

Pediatric and Reproductive Endocrinology Branch

The Pediatric and Reproductive Endocrinology Branch performs biomedical research, training, and clinical activities that focus on the physiology and pathophysiology of growth, development, and metabolic, immune, and reproductive functions. The Branch also studies the major neurohor-

monal systems, including the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamus–pituitary–gonadal (HPG) axis, as well as the autonomic nervous system that subserves these functions. Both developmental and static functions of these systems are studied on the in vivo integrated and reduced cellular, subcellular, and genomic levels. Studies of these systems are performed in normal, human volunteers throughout the life span and in appropriate animal models, whereas the cellular and molecular actions of their key effector molecules, including corticotropin-releasing hormone, arginine–vasopressin, corticotropin (ACTH), glucocorticoids, gonadotropins, estrogens, progestins, androgens, and catecholamines, are performed in appropriate cell systems.

The Branch studies patients with (1) diseases of the HPA axis, such as pituitary tumors, Cushing's syndrome, adrenal insufficiency, resistance to ACTH, congenital adrenal hyperplasia, adrenocortical tumors, and resistance to glucocorticoids; (2) diseases of the HPG axis, such as hypothalamic hypogonadism, disturbances of the menstrual cycle, resistance to ovarian and testicular gonadotropin, endometriosis, and infertility; and (3) diseases of the autonomic nervous system, such as pheochromocytoma and catecholamine deficiency. Studies are also conducted on development, psychiatric, metabolic, and immune disorders related to the functions of the HPA and HPG axes and the autonomic system, such as eating disorders (e.g., anorexia, bulimia nervosa, and adolescent obesity), adolescent conduct disorder, childhood asthma and rheumatoid arthritis, the premenstrual tension syndrome, and postpartum and climacteric depression and autoimmunity.

Additional studies focus on the critical influences of stress in early life on the later development of behavioral disorders (e.g., dysthymia, depression, dissociative and conduct disorders, and substance abuse) and metabolic disorders (e.g., metabolic syndrome X). The Branch sponsors the Pediatric and the Reproductive Endocrinology Fertility Training programs and also participates in the Adult Inter-Institute Endocrinology and Metabolism Program administered by the National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

During FY 00, the Branch had Visiting Scientists from Israel, Japan, and Sweden and Clinical Research Fellows from Eritrea, Nigeria, and Syria. There were 17 Research Fellows from Bulgaria, the Czech Republic, Germany, Greece, Israel, Italy, Japan, and the Netherlands. The Branch has established long-term collaborations with the University of São Paulo, Brazil; the University of London, England; the University of Düsseldorf, Germany; the University of Athens and the University of Crete, Greece; the University of Parma, Italy; Kyoto University, Japan; the Slovak Academy of Sciences, Slovakia; and Karolinska Institute, Sweden. More than 20 visitors from foreign countries visited the Branch in FY 00.

Perinatology Research Branch

The Perinatology Research Branch carries out clinical and basic science studies of maternal, fetal, and neonatal disorders. Studies emphasize frequent, important, and clinically relevant human disorders, such as premature labor, congenital anomalies, intrauterine growth retardation, and pregnancy-induced hypertension. The Branch uses state-of-the-art imaging modalities to study fetal anatomy and hemodynamics, as well as invasive procedures of prenatal diagnosis (amniocentesis and fetal blood sampling) to study fetal physiology and disease. In addition, the Branch continues its efforts to better understand the role of subclinical intrauterine infection as a cause of premature birth and long-term developmental handicap. The Branch pioneered fetal endoscopic surgery for the treatment of disorders of multiple gestation and congenital anomalies. The Perinatology Research Branch has Visiting Scientists and Postdoctoral Fellows from Italy, Korea, and Thailand. Collaborative efforts have been established with Catholic University, Santiago, Chile; Ben Gurion University, Beersheva, Israel; and the University of Seoul, Korea.

Laboratory of Cellular and Molecular Biophysics

The Laboratory of Cellular and Molecular Biophysics studies biological phenomena such as membrane fusion, intracellular interactions, metabolic analysis and mass spectrometry, and macromolecular analysis, to elucidate their physical basis. Physical and organic chemists, membrane biochemists, cell biologists, and physicians interact to extend understanding of physiological and pathophysiological mechanisms, often using the language of mathematics and theoretical physics. This Laboratory develops and uses novel, noninvasive technologies to probe physical parameters of living systems ranging from cells to humans. At the same time, the Laboratory's investigators synthesize and study systems of well-defined molecular composition and structure that exhibit an essential biological function. This approach provides a robust description of the physicochemical basis of molecular and physiological activity. Scientists from Belarus, Canada, China, the Czech Republic, France, India, Israel, Russia, and Spain are trained and work in an extremely interactive laboratory.

The Laboratory has an ongoing collaboration with A. N. Frumkin Institute of Electrochemistry, Russian Academy of Sciences, Moscow, which is facilitated by the U.S. Civilian Research and Development Foundation. Laboratory staff have participated in international meetings in Germany, Israel, and Italy and have received a grant from the U.S.-Israel Binational Foundation to continue the work initiated during one of these meetings. The Laboratory has sponsored sabbatical visits by professors from Israel and Russia.

The Laboratory of Cellular and Molecular Biophysics also collaborates with the Laboratory of Pathogenesis of Lentiviruses, Parc Scientifique de Luminy, Marseille, France; the Institute of Clinical and Molecular Biology, University of Erlangen, Germany; the Russian Academy of Sciences, Moscow; and the Institute of Microbiology, University Vaudois, Switzerland. In the field of HIV pathogenesis, the Laboratory has established joint research efforts, including the training of a Guest Researcher, with the Retrovirology Laboratory, University of Barcelona, Spain.

The Laboratory works with Tel Aviv University, Israel, to study the mechanism of viral membrane fusion, and staff have lectured in Germany at the University of Heidelberg and at Max Planck Institute for Biophysical Chemistry, Göttingen. In the field of electrophoresis, a collaboration with the Research Center for Medical Genetics, Russian Academy of Medical Sciences, Moscow, was supported in part by a Biomedical and Behavioral Sciences Program Award from the Civilian Research and Develop-

ment Foundation. Additional research activities are continuing with the Agricultural Biotechnology Center, Gödöllö, Hungary; the University of Milan, Italy; and the Department of Chemistry, National Taiwan University, Taipei.

Laboratory of Cellular and Molecular Neurophysiology

The Laboratory of Cellular and Molecular Neurophysiology conducts research on signaling mechanisms in the central nervous system. Visiting Fellows from Canada, Germany, and Italy are studying the regulation of hippocampal neuron excitability by voltage-gated potassium channels; the role of NMDA receptor function at subtypes of mossy fiber synapses; and the role of pacemaker currents in the induction of gamma-frequency oscillations in mouse hippocampus. Visiting Fellows from Russia and Ukraine are studying the structure and function of glutamate receptors. Current projects focus on mutational analysis of the pore region and polyamine block of kainate receptors; ion channel block by cytoplasmic polyamines; the mechanism of action of insect venom toxins on mammalian glutamate receptors; allosteric regulation of glutamate receptor desensitization; and assembly of kainate receptors.

Visiting Fellows from Belgium, Canada, China, France, South Korea, and the United Kingdom have worked on projects related to the function of glial cells. These include the transcriptional regulation and function of kainate receptor genes; neurotransmitter receptor control of cell-cycle regulation and the differentiation of oligodendrocytes; the expression and functional properties of glial cell potassium channels in vivo; calcium-channel stores and their function in astrocytes; expression and modulation of voltage-gated potassium channels; and the physiological consequences of selective knockout of channel subunits in hippocampal neurons. Laboratory staff were invited speakers at meetings in the British Grand Cayman Islands, Chile, Denmark, France, Germany, Italy, and Singapore. The Laboratory also collaborates with the Imperial College of Science, Technology, and Medicine, London, England.

Laboratory of Comparative Ethology

The Laboratory of Comparative Ethology collaborates on several long-term studies with research teams from 15 countries in Africa, Asia, the Caribbean, Central and South America, and Europe. One collaborative study examines the relationship between patterns of mother–infant interaction and the emergence of language and cognitive competence over the 1st 4 years of life in children in Argentina, Belgium, Brazil, France, Israel, Italy, Japan, Kenya, and the United Kingdom. A follow-up study of the same children at 10 years of age continued in FY 00. A second series of collaborative studies focuses on the effects of various day-care arrangements on the social, emotional, and cognitive development of infants, toddlers, and grade-school children in Germany and Sweden. A third major collaborative project, involving researchers from England, Israel, and Sweden, has been investigating factors that influence children's eyewitness testimony and recall memory for specific events. Collaborating scientists from Canada, the Central African Republic, Colombia, and Germany are assessing the values and practices of parents in diverse cultures. Finally, several foreign investigators are collaborating with scientists in the Laboratory of Comparative Ethology in the study of various aspects of biobehavioral development in two nonhuman primate species living in natural habitats in Puerto Rico and on nature preserves in the Alsace region of France and in southern Germany.

Laboratory of Developmental and Molecular Immunity

The Laboratory of Developmental and Molecular Immunity conducts clinical studies ranging from phase I evaluations to efficacy trials of the Laboratory's investigational vaccines. These include acellular pertussis vaccines and their derivatives; vaccines for enteric bacterial diseases, including typhoid fever, and diseases caused by *Salmonella, Shigella,* and *E. coli 0157;* and vaccines for anthrax. Studies are ongoing in Israel, the United States, and Vietnam and are being considered for Angola, Bangladesh, and Pakistan.

The Laboratory has hosted Visiting Scientists and Guest Researchers from China, the Czech Republic, Ghana, Israel, Mexico, Poland, Slovakia, and Vietnam. The investigators are working to characterize bacterial pathogenesis and immunity, examining the structural and functional roles of surface polysaccharides and toxins, and investigating the mechanisms regulating immune response at the cellular level. In addition, the Laboratory is planning to conduct trials of a radically new synthetic vaccine. These activities have led to presentations of data at international meetings in Chile, China, Denmark, France, Italy, Japan, the Netherlands, Spain, Sweden, the United Kingdom, and Vietnam. The findings have also been published in several foreign-language research reports.

Active involvement of the Laboratory staff in vaccine development and field trials has led to several international studies. For example, the Laboratory collaborates with the Israeli Armed Forces and Provincial Health Centers in China and Vietnam in testing the efficacy of conjugate vaccines for two types of *Shigella (S. flexneri* and *S. sonnei)* in adult volunteers. The University of Chile, Santiago, and the Laboratory are studying the *S. flexneri* conjugate and the *S. sonnei* conjugate in infants and school-age children. An informal collaboration continues with an industrial manufacturer of a new vaccine for *Staphylococcus aureus*.

Laboratory of Developmental Neurobiology

The Laboratory of Developmental Neurobiology studies the regulation of gene expression at the cellular and molecular levels and the physiological processes important for development of the nervous system. Of particular importance are the mechanisms that couple stimuli from the environment to the neurodevelopmental program. Action potentials in neurons, the actions of neurotransmitters, and a variety of cell biological coupling mechanisms are under study as being important for environmental determination of brain development. Detailed structural and functional studies of the evolutionary development of the important pineal molecule, *N*-acetyl transferase, are being pursued, and the cell biology of selective protein secretion is under investigation.

A member of the Laboratory serves as a Co-director of the Laboratory of Molecular Neurobiology at the Chinese Academy of Sciences, Shanghai, and has been instrumental in establishing the Chinese Institute

of Neuroscience. Collaborative work is under way with scientists from France, Germany, India, Italy, Japan, New Zealand, Norway, and Spain. Postdoctoral Fellows from China, Ethiopia, Germany, Guatemala, Korea, Russia, and Venezuela are active in the different Sections and Units of the Laboratory. Members of the Laboratory have helped to organize a number of international meetings, including one on peptide hormone processing. A Cooperative Research and Development Agreement (CRADA) is in place between the Laboratory and the Servier Corporation in France.

Laboratory of Eukaryotic Gene Regulation

The Laboratory of Eukaryotic Gene Regulation uses a combination of genetics, molecular biology, and biochemistry to study the mechanisms of translational and transcriptional control of gene expression and the structure and function of the general factors involved in the initiation steps of both processes in the yeast *Saccharomyces cerevisiae*. In addition, the mechanism of transposition by retrotransposon elements is being analyzed in the yeast *Schizosaccharomyces pombe*. Among the scientists working on these projects are Visiting Fellows and Guest Researchers from China, Germany, India, Japan, Korea, Spain, the United Kingdom, and Vietnam. In addition, joint research is conducted with laboratories in Japan and Spain.

Laboratory of Integrative and Medical Biophysics

The Laboratory of Integrative and Medical Biophysics is dedicated to understanding the basic biophysical mechanisms underlying cell and tissue function. Many of the Laboratory's research activities involve applying physical and engineering sciences to the development of novel methods for determining cell and tissue status. During FY 00, the Laboratory sponsored and organized three international workshops on this subject that were held on the NIH campus, in Bethesda, Maryland. One of the workshops dealt with the use of laser capture microdissection for isolating subpopulations of cells from complex tissues and analyzing their gene expression; another addressed in vivo optical imaging for clinical diagnosis; the third focused on the state of the art in biological and clinical applications of diffusion-tensor magnetic resonance imaging to characterize tissue microstructure and monitor its changes in diseases. Each workshop attracted several hundred participants.

Together with researchers from Naples, Italy, the Laboratory has developed robust techniques for laser capture microdissection, which is used to isolate specific mouse embryo cells that yield exceptionally high-quality RNA recovery. This team also is developing new protocols for the construction of libraries of full-length cDNA from such laser capture microdissection microsamples. In addition, Laboratory personnel have active, ongoing collaborations with scientists in France, Germany, Israel, Italy, and the United Kingdom on problems relating to the use of light for quantitative analysis of tissue. Other joint research projects, with Canadian, French, German, Israeli, and Italian scientists, aim to develop new techniques, such as magnetic resonance imaging and small-angle neutron scattering, to characterize tissue microstructure.

A number of foreign visitors presented seminars to members of the Laboratory. Members of the Laboratory and Israeli colleagues were awarded grants from the U.S.-Israel Binational Science Foundation to study diffusive transport of water in nerve tissue by magnetic resonance imaging techniques and to develop optical methods for noninvasive assessment of lymphocyte invasion of salivary glands in patients with Sjögren's syndrome. The Laboratory also hosted 1-month visits of scientists from Israel, Italy, and Russia. Laboratory staff presented symposia talks and research seminars in Canada, as well as in various European and Middle Eastern countries.

Laboratory of Mammalian Genes and Development

The Laboratory of Mammalian Genes and Development uses advanced gene targeting and transgenic technologies to study genes that control specific events of mouse development. Of particular interest to the Laboratory are the development of the central nervous system and the thymus and mechanisms of genetic imprinting.

Among the scientists working in the Laboratory are many researchers from foreign countries, including Canada, China, India, Japan, Korea, Russia, and the United Kingdom. During FY 00, members of the Laboratory visited research institutions and attended conferences in China, France, and Germany. Current international collaborative projects involve scientists in Germany, Israel, and Sweden. The College de France honored the Chief of the Laboratory with a special invitation to serve as a guest professor in Marseille, Paris, and Strasbourg, France, during June 2000.

Laboratory of Molecular Embryology

The Laboratory of Molecular Embryology researches the molecular mechanisms that establish and maintain stable states of gene activity during development. Particular interests include the significance of nucleic acid packaging for the function of the molecular machines that use DNA or RNA as a template.

Within the Laboratory, a British scientist supported by the Wellcome Trust investigates the role of DNA methylation in regulating transcription of the promoter for gene 1 for human fragile X syndrome, a type of mental retardation. The International Human Frontiers Research Program supports the research of German and Greek scientists on how the post-translational modification of chromosomal proteins influences gene expression. Japanese scientists supported by the Japanese Society for the Promotion of Science study the remodeling of somatic nuclei after transplantation into eggs. Elucidation of this process is important to understanding the molecular basis of recent successful cloning experiments. The Netherlands Natural Sciences Research Council supports a Dutch scientist in his studies of the role of DNA methylation in vertebrate development. Two Spanish scientists supported by the Natural Sciences and Engineering Research Council of Canada and the Spanish Ministry of Education are investigating the role of CCG triplet repeats in chromosomal structure and human disease.

The Laboratory of Molecular Embryology works with laboratories in China, France, Germany, Japan, Russia, Switzerland, and the United Kingdom. Principal investigators in the Laboratory have organized international meetings in Canada, China, Spain, and the United Kingdom. Within the Laboratory, scientists from Bulgaria, Canada, China, France, Germany, Greece, Japan, the Netherlands, Russia, South Africa, Spain, and

the United Kingdom, together with colleagues from the United States, conduct independent research on gene expression.

Laboratory of Molecular Genetics

The Laboratory of Molecular Genetics is broadly concerned with gene structure, expression, and transmission, especially as concomitants of development. Disciplines represented and techniques used in the laboratory include enzymology, molecular biology, genetics, transgenic models, histochemistry and cytochemistry, and embryological manipulations. Many organisms are under study, including viruses, bacteria, flies, zebra fish, frogs, and mice. During FY 00, the Laboratory included among its staff many researchers at the postdoctoral and senior levels, from China, France, Germany, Hungary, India, Ireland, Israel, Italy, Japan, Korea, Poland, Russia, and the United Kingdom. The Laboratory has ongoing collaborations with scientists in Germany, France, Israel, and Japan on a variety of projects. Members of the Laboratory participated in international conferences and visited institutes in various countries, including Austria, Canada, France, Germany, Israel, Japan, and the United Kingdom. Laboratory scientists act as members of advisory committees to institutions such as the National Science Foundation of Austria, the National Center for Scientific Research of France, and the Riken Institute in Japan.

Laboratory of Molecular Growth Regulation

The Laboratory of Molecular Growth Regulation conducts research in several complementary areas. One area of strong interest is molecular mechanisms underlying the control of mammalian cell proliferation. Scientists from Bulgaria, China, and Korea have contributed to studies on cellular protooncogenesis, tumor-suppressor genes, and chromatin-modifying genes, which are at the core of this part of the research program. A second major research focus in the Laboratory is regulation of gene expression, which is divided into three groups. One group, including scientists from China and Japan, investigates transcriptional initiation and termination of the gene for RNA polymerase III, as well as RNA processing and RNA–protein interactions. A second group, comprising scientists from France, India, Italy, and Japan, examines molecular mechanisms regulating the immune response. An additional independent group, with internationally recognized expertise in eukaryotic DNA replication, benefits from the contributions of scientists from Bulgaria, China, Germany, and Japan.

Laboratory of Physical and Structural Biology

The Laboratory of Physical and Structural Biology focuses on the organizing powers of intermolecular and intramolecular forces of large molecules. It collaborates with laboratories in several countries, most extensively Armenia, Brazil, Canada, China, France, Germany, Israel, Italy, Russia, Slovenia, Spain, Switzerland, the United Kingdom, and Uzbekistan. During FY 00, members of the Laboratory lectured in Canada and several European countries, including France, Germany, Russia, Spain, Switzerland, and the United Kingdom.

In collaboration with German scientists, a Laboratory investigator developed a theory of interactions among various types of helical biomolecules. This theory explained the mechanisms of such phenomena as DNA overwinding from 10.6 base pairs per turn in solution to 10.0 base pairs per turn in fibers; spontaneous aggregation of DNA in the presence of certain ions; and B-to-A and packing transitions in dense DNA fibers. This work is building theoretical foundations for design of future experiments and for understanding forces that have already been directly measured among DNA double helices, four-stranded guanosine helices, collagen, and some polysaccharides.

A Visiting Fellow from Russia has conducted experiments that clarify the role of dielectric reorganization of surface water in catalytic activity of enzymes. The measurements revealed that the reorganization energy is strongly reduced by solutes capable of disrupting the hydrogen-bond network structure. This reduction correlates with the change in the activation energies of hydrolysis by chymotrypsin and trypsin in the same mixed solvents. These findings explain how cosolvents may accelerate enzyme catalysis without directly interacting with the protein.

Research in interaction, stability, and phase transitions in lipid systems involved studies with scientists from Canada and Israel. In collaboration with the KFA Research Center, Juelich, Germany, the Laboratory continues to investigate intermolecular interactions. Work with a Spanish scientist from the University of Castellón involved studies of mobile charge distribution in the vicinity of lipid planar bilayer, by using a small cation–selective gramicidin A channel and alamethicin. To understand the influence of membrane surface charge on ion channel function, scientists examined channel conductance when the surface charge density was varied, by using two techniques: titration of the lipid charge through bulk solution pH and dilution of a charged lipid by a neutral lipid. The technique of dividing surface construction for the countercharged layer describes the data well and can be a useful analytic tool in membrane biophysics.

The Laboratory is also working with scientists from Canada and France on phase transitions in lipid systems. In joint research with a French Atomic Energy Commission laboratory, scientists in the Laboratory of Physical and Structural Biology are determining the properties of lipids. In addition, Visiting Scientists from Germany and Slovenia performed several studies on the arrangement of DNA and other long molecules at the high concentrations seen in viruses. In FY 00, members of the Laboratory participated in international conferences in France, Italy, Poland, Sweden, Switzerland, and the United Kingdom.

Laboratories of the Scientific Director

The Section on DNA Replication, Repair, and Mutagenesis focuses on elucidation of (1) the mechanisms for repair of exogenous damage to DNA, such as that caused by prolonged exposure to sunlight, and (2) the consequences of the damage if it is left unrepaired. These studies use the bacterium *E. coli* and the lower eukaryote *Saccharomyces cerevisiae* as model systems. The goal is to elucidate similar processes in mammalian cells in mice and humans. The Section is led by a British senior investigator and includes a Visiting Fellow from France and two Visiting Fellows from Spain. These studies also involve collaborations with scientists from Japan and the United Kingdom.