

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 that 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 participated in the HIVNET (HIV Network) 012 Prevention Trials of nevirapine, which demonstrated in clinical trials that a two-dose, oral regimen of the agent, given once to HIV-infected pregnant women at the onset of labor and once to the infants at 48 hours of life, resulted in a remarkable 47% reduction in the risk of perinatal HIV transmission. The interpretation and application of these study results may produce a safe, cost-effective, feasible regimen for reduction of vertical transmission of HIV in some developing countries.

NICHD has supported a study of mother-to-child transmission of HIV in Kenya for more than one decade. Investigators recently reported data from their Nairobi-based study of breast-feeding in HIV-infected women. This randomized clinical trial examined the impact of formula feeding compared with exclusive breast-feeding on the transmission of HIV from infected mothers to their offspring. The investigators found that 37% of breast-fed infants were infected with HIV, compared with only 21% of formula-fed infants. The study report emphasized the prominent role of breast-feeding in vertical HIV transmission. Investigators from this

team also have demonstrated a relationship between the presence of genital human immunodeficiency virus type 1 (HIV-1) DNA and vertical transmission. This association is independent of plasma levels of viral HIV-1 RNA. With continuing NICHD support, this group of investigators will determine the effect of cytotoxic T lymphocytes in breast milk on transmission of HIV-1 from infected mothers to their breast-fed infants in Nairobi. NICHD's uninterrupted, long-term support of this international team has resulted in substantial contributions to the understanding of HIV transmission, the training of Kenyan scientists, and the strengthening of in-country research capacity.

In an international study that brought together investigators from Canada, Europe, and the United States, there was a significant reduction in the rate of HIV transmission from mother to infant for women who delivered via cesarean section before the onset of labor and rupture of membranes. These findings have formed the basis of recommendations by the American College of Obstetricians and Gynecologists on the utility of elective cesarean section in the reduction of vertical HIV transmission.

Using knowledge of how insulin works at the cellular level, a NICHD-supported team of investigators developed an experimental treatment for polycystic ovary syndrome (PCOS) that is based on a naturally occurring component of the cells' signaling system. With funding from a Small Business Innovation Research grant, the team studied 44 women in Venezuela with PCOS. The research team tested the hypothesis that, because the insulin resistance in PCOS seems to be due to a deficiency of inositol, the syndrome could be overcome by administering inositol as a drug. The researchers found that *D-chiro*-inositol lowered plasma levels of insulin and testosterone. Significantly, 86% of treated women ovulated, compared with 27% of those who received placebo. It is ex-

citing that the idea for this treatment came from understanding the cell biology of insulin's action in promoting ovarian steroid production. This promising result from research by a small business is being expanded as a multicenter clinical trial.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

NICHHD convened a working group on Opportunities for Scientific Progress: Global Research on Women's and Children's Health, Population, and Human Development, at the National Institutes of Health (NIH), in Bethesda, Maryland, in September 1999, for the purpose of advising the Institute on the expansion of its international research activities. Participants included program staff from the NIH and other Federal agencies; extramural and intramural scientists involved in international research; and representatives from the World Health Organization (WHO), the World Bank, the Global Forum for Health Research, the March of Dimes Birth Defects Foundation, and other organizations interested in improving the health of women and children worldwide.

As a follow-up to this meeting, NICHHD, in cosponsorship with the Fogarty International Center (FIC), the National Institute of Allergy and Infectious Diseases (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, and in partnership with the Bill and Melinda Gates Foundation, planned a solicitation for fiscal year 2000 (FY 00), to establish an innovative and flexible Global Network for Women's and Children's Health Research. The Gates foundation has donated \$15 million over a 3-year period to NICHHD to help support the Global Network. Cooperative agreement grants will support collaborating teams of investigators from the United States and developing countries, to conduct research related to the most critical and emerging health problems of women and children in developing countries. Initial efforts will focus on safe pregnancy and birth outcomes. The Global Network also is intended to strengthen and expand the infrastructure for research on women's and children's

health in developing countries. The efforts of FIC's International Maternal and Child Health Research and Training program to build training and research capacity are designed to complement and facilitate the research on maternal and child health to be undertaken by the Global Network grantees.

As part of its interest in expanding global research related to health problems in developing countries, NICHHD provided support for the development of two reports by the National Academy of Sciences and its Institute of Medicine. Prepared by the Institute of Medicine's Board on Global Health, one report will focus on nervous system disorders in developing countries; the other report is related to improving birth outcomes in developing countries. The reports are scheduled to be published in 2000.

NICHHD 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.

NICHHD is supporting investigators from Northwestern University, Evanston, Illinois, in Argentina, Belgium, Italy, and Sweden, who are conducting cross-linguistic studies of children acquiring different languages, including English, French, Italian, Spanish, and Swedish. The aim of the study 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, and Spanish that confirms predictions made from adult studies. They are extending their findings from previous work to studies of noun and adjective usage in Italian.

The NICHHD HIV Perinatal AIDS Clinical Trials Network has worked for more than one decade with the NIAID-sponsored Pediatric AIDS Clinical Trials Group on an agenda for research on prevention and therapy for HIV and AIDS (acquired immunodeficiency syndrome) in mothers, newborns, infants, children, and adolescents. NICHHD is

expanding its plans and support for the conduct of clinical trials internationally, with special emphasis on the implementation of appropriate trials in midlevel developing countries. With NICHHD sponsorship, technical assistance, and support, patients are being enrolled in clinical trials in Nassau, the Bahamas. Enrollment into trials at two sites in Rio de Janeiro, Brazil, also is anticipated. Additional expansion will include sites in several nations in the Caribbean.

NICHHD is supporting a researcher at Johns Hopkins University, Baltimore, Maryland, to conduct 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 husband and wife agreement or disagreement 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.

The Institute continues to participate in a major research project involving Canada, Mexico, and the United States. A series of planning meetings were held at the NIH and in Mexico to develop and refine the details of the observational study of preeclampsia, an important factor in maternal morbidity and mortality and a major determinant of preterm birth. The aim is to enroll 20,000 pregnant, nulliparous women in each of the three nations. A major goal is the assessment of the quality of care received by these women. It is anticipated that enrollment will begin in FY 01, after completion of a detailed observational study of 2,000 pregnant women that is being conducted by the NICHHD-sponsored Maternal-Fetal Medicine Units Network.

NICHHD hosted the 2nd meeting of the Joint Working Group of the Indo-U.S. Joint Program on Contraception and Reproductive Health Research, in Bethesda, Maryland, on April 13-14, 1999. This program is based on a bilateral agreement between the Indian Department of Biotechnology and NICHHD. Other participating agencies include the Indian Council of Medical Research, the Ministry of Health and Family Welfare, the U.S. Agency for International Development (USAID), and the Contraceptive Research

and Development Program. The agenda of the meeting included a discussion of current contraceptive methods and future approaches to conception and reproductive health. The Joint Working Group reviewed 36 grant proposals received in response to a solicitation for proposals and made funding suggestions. After peer review, it was jointly decided that six cooperative projects would be funded beginning in 1999. NICHD sponsored a workshop in India on clinical trials methods. The next meeting of the Joint Working Group was scheduled to take place in New Delhi, India, in February 2000, and a workshop on spermicides and microbicides also was planned for 2000.

The Institute, in partnership with FIC, the NIH Office of Dietary Supplements, the Centers for Disease Control and Prevention, USAID, and the Indian Council for Medical Research, helped to plan and coordinate the Indo-U.S. Workshop on Health and Nutrition in Women, Infants, and Children, to be held in Hyderabad, India, on February 10–12, 2000. This meeting aims (a) to facilitate exchange of scientific information and development of shared research priorities for nutrition research and public health programs, including the role of micronutrients, and (b) to develop strategies for implementation of a cooperative research program and approaches for translation of that research into effective program and policy initiatives.

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. A study of condom usage has found that condom promotion programs, which target travelers and their partners, may be an efficient method for spreading behavioral change into rural areas.

NICHD, through the Division of Epidemiology, Statistics, and Prevention Research (DESPR), continues to collaborate with the Vietnamese National Institute of Hygiene and Epidemiology, of the Ministry of Health, on a large-scale trial of the effectiveness of a locally produced, inactivated cholera vaccine. NICHD's medical team of DESPR and the Laboratory of Developmental and Molecular Immunity, in cooperation with the Vietnamese Ministry of Health, Pasteur Institute, Ho Chi Minh City, and Dong Thap Provincial Health Services, has established a field site in Dong Thap Province for the evaluation of enteric vaccines developed by scientists in 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. It is now conducting a phase III efficacy trial of the vaccines in children.

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 disorders of skeletal dysplasia. Funded as part of a program project at Cedars-Sinai Medical Center, Los Angeles, California, the registry's computerized database contains more than 8,985 documented cases of skeletal dysplasias. It also includes photographs and radiographs of patients, chondroosseous tissue fixed for morphological and ultrastructural studies, frozen bone and cartilage, cultured cells (fibroblasts, chondrocytes, and lymphoblastoid cell lines), and DNA. The registry staff collects materials on patients with skeletal dysplasias, distributes samples to appropriate investigators, performs clinical research by using the registry's computer system and database, and provides diagnostic assistance to investigators throughout the world. During FY 99, staff conducted bimonthly teleconferences with the Genetics Group at the Hôpital Necker-Enfants Malades, Paris, France, which is the

other major skeletal dysplasia group in the world. The registry staff continues to collaborate with other registries worldwide and has seen patients in Argentina, Italy, and Uruguay. The registry is now on the World Wide Web (www.csmc.edu/genetics/skeldys), making instructions on specimen collection available internationally.

Reproductive Sciences of the Americas Network

Initiated in 1995, the Reproductive Sciences of the Americas Network (RSANET) 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. Through its electronic newsletter and bulletin board, RSANET provides information on career and training opportunities, relevant scientific meetings, and availability of reagents. NICHD and RSANET sponsor the Americas Fellows Program, which supports three Latin American postdoctoral investigators for training with reproductive scientists in Canada and the United States.

The RSANET research training course on Frontiers in Reproduction: Cellular and Molecular Concepts and Technologies, designed with NICHD guidance, receives multiyear funding from public-private partnerships involving U.S. foundations, NICHD, and international funding agencies. In 1998 and again in 1999, an extramural review panel of senior scientists selected 16 participants from among advanced postdoctoral fellows who were early-career or midcareer independent investigators, to attend the course at the Marine Biological Laboratories in Woods Hole, Massachusetts. To date, participants from Argentina, Brazil, Chile, and Mexico have taken the course, which has significantly changed the direction of their research. The intensively mentored, 6-week, hands-on laboratory and lecture series course will be offered at the Marine Biological Laboratories, on May 21–July 1, 2000. Internationally acknowledged scientists will provide comprehensive and sophisticated training in research strategies and state-of-the-art methods for use in cellular, immunologic, and molecular biological research for exploration of emerging issues in the reproductive sciences.

United Nations

Since 1994, NICHD staff have served on the Informal Working Group on Prevention of Mother-to-Child Transmission of HIV, sponsored by the Joint United Nations Program on HIV/AIDS. The group meets two or three times yearly and functions to update information on strategies to prevent the mother-to-child transmission of HIV. In 1999, international representatives from developed and developing countries met to review progress on implementation of short-course zidovudine (AZT) regimens and formula feeding. Later in the year, the group met to review the results of a highly cost-effective trial of a two-dose, oral course of nevirapine to reduce the mother-to-child transmission of HIV. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

NICHD worked with the United Nations Foundation (UNF) in planning a joint UNF-WHO international research initiative on the development of interventions to improve the health of mothers, children, and adolescent girls in developing countries. NICHD staff participated in the review of proposals, and grants were awarded by UNF in the fall of 1999.

World Health Organization

NICHD's collaboration with WHO in a 4-year clinical trial of a new prenatal care model was completed in 1999. The model is based on scientifically proven interventions for conditions that are known to affect the health of both the mother and her child. In this model, prenatal care takes place over 4 visits during the pregnancy of low-risk mothers, rather than the traditional 12–14 visits. The emphasis in the revised model is (a) to recognize and diagnose conditions and complications of pregnancy that are known to affect the health of the mother, the fetus, or both and (b) to intervene and treat conditions and complications that are identified. The randomized trial was conducted with about 25,000 pregnant women in four countries: Argentina, Cuba, Saudi Arabia, and Thailand. Results are being analyzed.

In further joint efforts with WHO and USAID, NICHD also supports a population-based, case-control study of vasectomy and prostate cancer in New Zealand. The goal of this research is to determine whether vasc-

tomy affects the risk of prostate cancer, overall and taking into account age at vasectomy, age at interview or diagnosis, time since vasectomy, ethnicity, and other demographic factors. The study design allows pooling of these data with data from a WHO multinational study on vasectomy and prostate cancer.

Working with the WHO Regional Office for Europe and various coordinating centers, NICHD's DESPR sponsors U.S. research as part of a WHO project on Health Behavior in School Children in 30 countries. The study 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 evaluates the causes of adolescent injury and violence and related behaviors. NICHD completed the first of the quadrennial surveys in 1998, and final data from all countries are expected to be released to participants in November 1999. DESPR scientists are collaborating with other selected countries to analyze factors related to prevalence of overweight or to injury and violence. An international report on comparative health factors among all countries is ready for release early in 2000.

DESPR also cosponsors the WHO International Collaborative Effort on Injury Statistics, which is coordinated by the National Center for Health Statistics. A working group of representatives from 15 countries is seeking to improve the comparability and quality of international statistics on injury, to provide the data needed to better understand the causes of injury and the most effective means of injury prevention. U.S. and Canadian investigators in this WHO study are using survey results to enhance the *International Classification of Diseases, 10th Revision*, for classification of injury by activity, mechanism, and location. An advance report, based on data from 11 countries, gave preliminary results on international differences in mortality rates related to injury and the effects of classification on determination of causes, intent, and age-specific mortality. U.S. mortality rates from injury were comparable to those in New Zealand and Norway; lower than those in Denmark and France; and higher than those in Israel, the Netherlands, and the United Kingdom.

Under the Cochrane Collaboration on Reproductive Health, NICHD cosponsored a

WHO symposium on Mechanisms of Endometrial Bleeding as Affected by Steroidal Contraceptives, at Monash University, Melbourne, Australia, on May 27, 1999. The meeting reviewed current research on mechanisms of endometrial bleeding in normal women not using contraceptives and in those using progestin-only contraceptives; clinical treatments of menstrual disturbances in women using progestin-only contraceptives; and animal models for research on endometrial bleeding. The proceedings of the meeting will be published as a supplement to the journal *Human Reproduction*.

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 are described here, beginning with brief summaries of several multi-country studies in Africa, Asia, and Latin America.

Africa

In a couple-based study of family planning in four sub-Saharan countries with recent declines in fertility, a researcher at Johns Hopkins University, Baltimore, expects that information obtained from husbands will significantly contribute to the prediction of contraceptive use.

In Kenya and Malawi, an investigator is conducting a related 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.

Through an interagency agreement with NIAID, NICHD supports an epidemiologic study on the influence of oral and injectable contraceptives on the spread of HIV infection. The research is being conducted through the HIVNET. In this case-control study, HIV-negative women are being monitored for HIV seroconversion at sites with a high incidence of HIV infection in Thailand, Uganda, and Zimbabwe.

Asia

Investigators from the University of Pennsylvania, Philadelphia, continue to examine how cultural, economic, and familial conditions relate to the empowerment and autonomy of married women in five countries in Asia. Results show that in the more traditional South Asian countries of India and Pakistan, living as the wife of the head of the household and having a marriage of longer duration enhances a woman's economic decision-making power in the family and increases her freedom of movement outside the home. In contrast, in Malaysia, the Philippines, and Thailand, a woman's age and education are far more important than family characteristics in determining her autonomy. Bearing a large number of children does not enhance a woman's decision-making power in any of the countries.

Latin America

Researchers at the University of Pennsylvania, Philadelphia, 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 through a Web site already established by the Mexican Migration Project, which will be renamed the Latin American Migration Project.

Argentina

In Buenos Aires, investigators at Maternidad Sarda continue to conduct a clinical trial similar to the Management of Hyperbilirubinemia study in Greece. The trial will determine whether administration of a heme oxygenase inhibitor (tin mesoporphyrin) to term breast-fed infants will reduce or eliminate the need for phototherapy and exchange transfusion. Enrollment of infants in the study is proceeding on schedule, and preliminary results have shown that the inhibitor prevented increased bilirubin levels, whereas 21% of infants in the standard

therapy group required phototherapy. The treatment appears to be efficacious, and follow-up examinations reveal no adverse outcomes.

Australia

At the Institute of Reproduction and Development, Clayton, Victoria, a scientist is using several approaches to improve the technology for cryopreserving mouse sperm and to reconstitute cryopreserved mouse sperm, so they are capable of fertilizing eggs that will develop into healthy offspring. This project will lead to improvement in the technology for obtaining mouse sperm and to study of the long-term outcomes of cryopreserving mouse sperm, by using microchip arrays, chromosomal analysis, pathology assessments, and several analyses of mouse behavior. This project is part of a four-site international consortium related to the Trans-NIH Mouse Genome Project, which will collaborate in producing tens of thousands of new strains of mice and in developing rapid, safe, reliable, easy, and inexpensive methods to preserve these valuable strains.

Brazil

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 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.

Investigators at the University of Michigan, Ann Arbor, are analyzing long- and short-term changes related to household economic conditions in Brazil and their effects on children's repetition of a grade in school and on child employment. Results demonstrate that in Brazil (a) children of poorly educated parents are far less likely to become educated than are children of educated parents and (b) children with low ed-

ucation have higher levels of economic activity. The investigators also found that the slowdown in the rate of growth in schooling in Brazil is most evident for boys and is also related to high levels of work activity.

Scientists at Rand Corporation, 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.

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

At McGill University, Montreal, Quebec, a scientist is conducting a project to determine the mechanisms by which germ cells that eventually develop into sperm or eggs are designated as separate from somatic cells that form the rest of the body. In many species (e.g., *Drosophila melanogaster*), this designation occurs during development of the egg. Using the power of genetic approaches, the gene product Vas protein, which is involved in mammalian germ line development, was found to be involved in germ cell specification, as well as patterning of early *Drosophila* embryos. The scientist discovered that Vas carries out its functions through regulation of the production of other gene products by binding to an intermediary compound, which is conserved from bacteria through humans. The striking presence of these compounds in fruit fly and human reproductive systems may lead to a better understanding of human reproductive processes, as well as new approaches

to alleviating infertility and discovering novel means of regulating fertility.

An investigator from McMaster University, Hamilton, Ontario, is conducting a longitudinal study of motor function in children with cerebral palsy. The goal of the research is to create motor growth curves for cerebral palsy that are similar to those on the growth charts used to follow the height and weight of children as they mature.

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.

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.

Researchers at the University of Colorado Health Sciences Center, Denver, are continuing their studies of glutaric acidemia in a population of Island Lake Canadian Indians. This condition results from an inborn error of lysine and tryptophan oxidation, which causes degeneration of the basal ganglia and a progressive movement disorder in childhood.

An investigator at the University of Western Ontario, London, is working to develop completely defined yet safe and effective techniques for the culture of bovine embryos *in vitro*. These methods include derivation of embryos from ova that were matured and fertilized *in vitro* and derivation of cloned embryos through transfer of

the nucleus from a somatic cell. Results of these studies also will include improvement in technology for *in vitro* maturation of bovine oocytes in completely defined culture medium, which is expected to be achieved in FY 00, the last year of this award. The beneficial effects of culture media on gene expression have been studied. Overall, this project is expected to result in the development of bovine blastocysts of high quality that can be evaluated before embryo transfer to the uterus. Consequently, these blastocysts should yield healthy offspring.

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. In view of the importance of iron in myelin formation and maintenance, 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 poorer developmental outcome among poor children in a developing country. Because 86% of all children are born in developing countries, there is an urgent need to introduce the perspective of a developing country into models based on industrial societies.

China

A collaborative longitudinal study by Emory University, Atlanta, Georgia, and Chinese University, Hong Kong, is investigating the relationship between fetal brain and behavioral profiles and emotional responsivity before and after birth in African Americans,

whites in the United States, and Chinese in Hong Kong. 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 unique 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 an opportunity to monitor changes in economic and social behavior, health, nutrition, and demographic 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 project at the State University of New York, Albany, is investigating the changing intergenerational relationships in Chinese families, including living arrangements, frequency of contact, exchanges of financial assistance, and mutual help. Evidence from a study of populations in two large cities in China shows persistence of a pattern of adult children residing with their parents, despite many changes in society. Reasons for this persistence include a deeply rooted history of co-residence and a scarcity of housing. Results also indicate that ties between parents and children who do not live together are strong, with little gender-specific difference in frequency of contact or in the exchange of help.

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. In addition, results suggest that there is still a large potential for migration from China. The investigator also plans to examine the relationship between migration and education.

NICHD is supporting the National Opinion Research Center, Chicago, Illinois, to conduct 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 is a timely study because China is experiencing sharp annual increases in the incidence of AIDS and other sexually transmitted diseases.

Investigators 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 cross-linguistic study 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 investigators found that children first use generic noun phrases in spontaneous speech by 2½ years of age, and they 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 ("some") and universals ("all"). This research has demonstrated emergence of early links between conceptual distinctions and language in the first few years of life.

In another study, scientists at Harvard University, Boston, Massachusetts, continue to assess the effects of rotating shift work on adverse reproductive outcomes in China. This prospective cohort study will enroll 1,150 women working in Chinese textile mills—700 workers on rotating shifts and 450 workers on a regular day shift. These women are married nonsmokers between the ages of 20 and 34 years who have permission to have a child and are attempting to become pregnant.

Costa Rica

Researchers at the University of North Carolina, Chapel Hill, are analyzing the effects on age-specific mortality of a large expansion in government health insurance coverage in Costa Rica that occurred in the 1970s. Although it is commonly believed that lower health care costs increase demand for health care, little is known about how these changes influence cause-specific mortality rates. The regional variations in the timing of introduction of the health insurance and the extensive collection of death certificates in Costa Rica enable the researchers to study these issues in depth.

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 15 years of age. These studies have demonstrated the impact of iron deficiency on cognitive, motor, and affective development in childhood. Investigators observed that lower test scores persisted at 5 years of age, despite correction of anemia with iron therapy during infancy. This unique research has documented much of what is known about the long-term behavioral consequences of iron deficiency.

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. Detailed tests of attention were included because problems in this area were reported at age 5 years for children who had anemia as infants. Behavioral measures also were used to evaluate the problems of hesitation, wariness, and internalizing observed in these children at age 5 years.

A critical component of this study is assessing the children's cognitive and motor development at transition to adolescence. To interpret the cognitive, motor, and behavioral results, it is important to assess intervening and masking variables. The family's situation (e.g., household composition and type of employment) is being updated in the follow-up project. The investigators also are collecting sequential samples of

serum prolactin and salivary and plasma cortisol, to assess neuroendocrine responses to stress. The results are scientifically and clinically of major importance to determining the effects of iron deficiency and the limited impact of iron supplementation in eradicating this problem. These findings have implications for influencing national and international public policy and for indicating a direction for future treatment.

Denmark

NICHD-funded researchers at Case Western Reserve University, Cleveland, Ohio, are using cytogenetic, molecular, and epidemiologic tools to investigate the hypothesis generated by their previous work on Down syndrome (trisomy 21). The primary goals of this program are to study the cause of trisomy 21, including the mechanisms of disjunction and the factors that influence its frequency, and to investigate the phenotypic consequences of the extra chromosome 21.

France

An NICHD-supported investigator at the Pasteur Institute, Paris, is conducting a project focused on the regulation of murine cell fate and myogenic differentiation by the morphogen Notch I. Specifically, the study aims to define the role of Notch signaling in the regulation of myf5-dependent functions during embryonic development, by engineering a dominant negative allele of Notch I under the control of myf5 regulatory elements and by using "knock-in" technology to restrict its expression to muscle. Myf5, the earliest known myogenic-determining factor in embryogenesis, is restricted to cells with myogenic potential in the somites. The evolutionarily conserved Notch signaling pathway is involved with regulating cell fate and subsequent differentiation. In transgenic mice with aberrant phenotypes, the involvement of Notch in the complex developmental process is expected to be evident at different stages of commitment to the myogenic lineage and muscle differentiation. This research has important implications for understanding normal development and certain pathological conditions.

Germany

A U.S. postdoctoral fellow at the European Molecular Biology Organization, Heidelberg, who is supported by an NICHD National

Research Service Award, is studying the role of the Mad gene during retinal development in *Drosophila*. The purposes of the research are to determine the effects of the constitutively activated Mad gene on retinal development; to explain genetically the relationship between the Mad gene and “early eye genes”; and to use genetic-screening techniques to identify genes that interact with the Mad gene in retinal development. The researcher has nearly completed analysis of the role of Dpp/Mad signaling in controlling the function and expression of the early-acting, eye-specific genes. Molecular analysis of factors that interact with the Mad gene and analysis of other genes involved in the establishment of the early eye field will continue. A genetic screen to identify novel genes involved in the establishment of the eye field has been completed. This research should add substantially to understanding of transforming growth factor β signaling in mediation of eye development.

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.

Greece

Since 1989, researchers from Rockefeller University, New York, New York, have carried out a clinical trial in Athens, to determine whether the administration of a heme oxygenase inhibitor (tin mesoporphyrin) to preterm infants would reduce or eliminate the need for phototherapy and exchange

transfusion to treat hyperbilirubinemia. In a study of 844 preterm infants, the use of the inhibitor proved to be safe and efficacious. Additional studies were conducted in two groups of neonates: those who had ABO-incompatible blood types and those who were deficient in glucose-6-phosphate dehydrogenase. Results were positive, and no adverse effects were found on follow-up.

Guatemala

Investigators at Emory University, Atlanta, are studying the causal relationships among malnutrition, infection, and diet in preschool children living in impoverished communities. The major goal is to determine the direction and quantify the relative importance of these relationships. The study tests several hypotheses. One hypothesis is that diet modifies the effect of infectious diseases on nutritional status, for example, that diarrhea has a negative influence on the nutritional status of children with poor diets but little impact on the nutritional status of those with adequate diets. To test these hypotheses, scientists are comparing the results of standard epidemiologic approaches with those of alternative approaches, particularly structured equation modeling. Although such modeling is frequently used in the social sciences, its use in the biomedical field is rare. Comparing structured equation modeling with standard epidemiologic techniques will ascertain the usefulness of the modeling method in other areas of health research that involve multi-level determinants of reciprocal causal relationships. Findings to date indicate that acute diarrhea has an impact on nutritional status on a daily basis but that persistent diarrhea has a greater impact on nutritional status throughout childhood. Each year, approximately 14 million children die, most from the synergistic effects of infection and malnutrition. In addition to the Guatemalan databases, large databases obtained in collaboration with the Save the Children organization are being used to examine the causes of child mortality. This research will enable policy makers to design effective interventions to improve global child health and survival.

Other investigators at Emory University 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. 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 researchers recently initiated another follow-up project in Guatemala that evaluates the generational effects of malnutrition. Scientists are studying the effects of nutritional insults during growth and development on the subsequent reproductive behavior of women and the growth of their offspring. 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. Data are being collected on maternal body composition, lactational performance, birth weight and newborn status, physical growth and maturation, child health and nutrition, cognitive assessments in adults and children, maternal-child behaviors, and aspects of socioeducation. 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. Preliminary findings demonstrate that dietary supplementation in early childhood improves the cognitive and educational ability of young women. The women who had received supplementation 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 new 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, continue to evaluate the role of zinc in childhood growth and development and the effects of zinc deficiency 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 on zinc supplementation targeting outcomes such as incidence of infectious diseases, morbidity, changes in copper status, growth, and development. A comparison of new and traditional methods is being used 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. 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 also is 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 conducted by investigators 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 trial has four cells: a mixture of micronutrients (riboflavin, calcium, phosphorus, folate, and iron); the mixture with zinc; riboflavin with zinc; and riboflavin alone. The children now range in age from 22 to 40 months. The study provides a unique opportunity to examine the effects of early micronutrient supplementation on behavior and development during the 2nd and 3rd years of life in children who are consuming diets consisting of indigenous foods.

The researchers are performing follow-up on 600 children who participated in the micronutrient supplementation trial and a comparison group of 225 children, born at term with birth weight appropriate for gestational age. Children will be studied at 24, 30, and 36 months of age to determine whether differences in behavior and development are related to (1) the micronutrient supplementation they received as infants and (2) the timing and duration of their micronutrient deficiency as toddlers. The project tests the theory of functional isolation, which is based on the hypothesis that the lethargy and social isolation that accompany nutritional deficiency interfere with reciprocal, stimulating interactions with caregivers, thereby leading to developmental and behavioral delays. The design and analysis are based on an ecological model in which birth weight, supplementation his-

tory, growth, temperament, parent–child interaction, and family environment contribute to children's behavior and development. Analyses will be conducted by longitudinal strategies, including multiple regression and hierarchical linear modeling. 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.

Indonesia

Investigators at Rand Corporation, Santa Monica, are conducting the Indonesian Family Life Survey of Mothers and Children, which is now in the third wave of data collection. This major new panel of data supports research on the health and well-being of women and children in a low-income setting. The investigators implemented a follow-up survey in 1998 to provide data on the 1997 financial crisis in Southeast Asia. Their data suggest that the effects of the crisis in Indonesia have been heterogeneous and that households have responded to the crisis in different ways. They 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. Surprisingly, health status for a number of dimensions improved. Previously, investigators at Rand Corporation used the data to examine the role of a woman's empowerment within the household in outcomes related to reproductive health. 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 the woman received prenatal care.

Other Rand Corporation studies in Indonesia are examining governmental funding of family planning and how it affects both women's fertility and their economic opportunities. Investigators also are examining the effects of the community and the family on child health in Indonesia, by using a data set that contains 16 years of information collected from households,

community facilities, and five censuses of village infrastructure. Preliminary findings indicate that better-educated mothers are more likely to identify specific health problems and to access prenatal care early in pregnancy. Other analyses on the effect of access to health care show that introducing a maternity clinic in a village decreases the odds of infant mortality by almost 16%, whereas an additional physician reduces the odds by only about 1.7%.

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.

Jamaica

At Baylor College of Medicine, Houston, Texas, scientists are testing the hypothesis that reduction in plasma nutrient transport proteins induced by infection in malnourished patients results from the compromised synthesis of these proteins, secondary to a decrease in aromatic amino acids and availability of cysteine. A specific hypothesis is that this shortage of aromatic amino acids is due to an infection-induced stress response, which increases synthesis of other proteins (e.g., acute-phase proteins and glutathione). In baseline studies in 52 severely malnourished Jamaican children, with or without infections, fibrinogen synthesis did not increase in response to the stress of an infection. This finding may explain why recovery from injury and surgery is delayed in malnourished patients.

Infections also play a role in mediating the lower plasma concentrations of transport proteins in malnourished patients. The concentration of plasma apolipoprotein A-1 is partly determined by in utero growth, and this relationship may contribute to the increased risk of coronary heart disease in adults who had low birth weight. This study will enhance understanding of the pathogenesis of reduced plasma nutrient transport proteins and protein metabolism in

malnourished individuals with an infection. The findings are expected to suggest therapeutic approaches to stimulate protein synthesis during early treatment, restore concentrations of nutrient transport proteins, and limit whole-body protein catabolism. Results also indicate that malnourished children have decreased rates of glutathione synthesis. Early cysteine supplementation increases synthesis and plasma concentration of glutathione, thus protecting against oxidant damage.

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 also will be examined for methylation abnormalities and chromosomal duplications, insertions, deletions, or inversions.

Kenya

A study by the Population Council, New York, New York, continues to investigate 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 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 examines how schooling affects young girls' attitudes toward and adoption of reproductive health practices.

Kuwait

NICHD supports a scientist at Mt. Sinai School of Medicine, New York, New York, who has initiated positional cloning studies

of an autosomal-recessive skeletal dysplasia, the Kenny-Caffey syndrome (KCS), by using eight consanguineous Kuwaiti pedigrees. The principal manifestations of the syndrome are short stature and hypocalcemia, but significant additional manifestations include eye abnormalities, developmental delay, and immune deficits. To identify the KCS gene and elucidate its function, further laboratory and clinical investigations are required. These studies will (a) narrow the critical region on the chromosome by development of new polymorphic markers and identification of new families with the syndrome; (b) allow the natural history and phenotypic features of KCS to be further delineated to gain additional insight into the disease pathogenesis and the function of the KCS gene; (c) provide a physical map of the critical region; and (d) identify and evaluate candidate genes in the critical region. Although KCS is a rare disease, its unique manifestations suggest that identification of the disease gene will lead to novel insights into bone metabolism and calcium homeostasis and into the development of other affected organ systems, including the immune system and the central nervous system. One aspect of this work will be to define the phenotypic spectrum and the pathophysiology of KCS, and that effort will involve the identification and analysis of additional families with KCS in Kuwait. No funds will be expended on the identification of additional families in Kuwait until pending assurances from the NIH Office for Protection From Research Risks are in place. However, analysis of existing samples has begun.

Malawi

A researcher in Malawi showed that subclinical mastitis was associated with higher levels of HIV RNA in human milk and an increased risk of HIV transmission through human milk to breast-fed infants of HIV-infected mothers. This study suggests interventions that should be examined to determine their role, if any, in reducing HIV transmission via breast-feeding.

Malaysia

Investigators from Rand Corporation, Santa Monica, continue to examine retrospective data collected in the first and second Malaysia Family Life Survey, to study migration patterns in a poor but rapidly developing

economy. The study focuses on the effect of life-cycle events such as marriage and education in individuals, the extended family, and the community, as well as other characteristics that might explain migration behavior.

Mexico

At Brown University, Providence, Rhode Island, researchers are analyzing the effect of local economic conditions in Mexico on the decision to migrate to the United States and on the decision to return to Mexico. They are using retrospective life histories and cross-sectional data available from the Mexican Migration Project, based at the University of Pennsylvania, Philadelphia. This analysis permits a careful examination of the "life course" of immigration. Results indicate that men are less likely to migrate to the United States if they live in areas with good employment opportunities. Also, temporary migration to the United States is a popular method of acquiring capital for investment in areas of Mexico with widespread opportunities for small-scale investment. There is a significant positive association between migration to the United States and upward occupational moves, although migrants who return to Mexico experience slightly higher rates of temporary downward mobility.

In the largest field study of Mexican migration, an investigator from the University of Pennsylvania, Philadelphia, used a combination of survey and ethnographic techniques to collect 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 investigator 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.

Researchers at Eastern Virginia Medical School and Medical College, Norfolk, are performing follow-up on a cohort of Mexi-

can mothers to ascertain whether human milk prevents disease in breast-fed babies. The study demonstrated a marked increase in exclusive breast-feeding in mothers receiving home visits from a trained peer counselor. Researchers also are assessing the variability of concentrations of antibody, glycoconjugates, and anti-inflammatory components in the milk of lactating women. They are evaluating genetic control as a determinant of the concentrations of protective factors in maternal milk.

These scientists continue to determine the effectiveness of feeding specific purified glycoconjugates identified in human milk, for prevention of diarrhea due to specific enteropathogens. They will evaluate the efficacy of maternal immunization with rotavirus vaccine, which is given to boost concentrations of antibodies in breast milk, for prevention of diarrhea in breast-fed infants. This project will define the relevant antibodies and glycoconjugates that protect infants from rotavirus diarrhea, with the overall goal of preventing infection and illness, despite viral antigenic diversity. The scientists are working to prove that antibodies and nonantibody factors in human milk bind viral pathogens and protect breast-fed infants from disease. They have found that human milk provides antibodies and nonantibody factors that may explain why breast-feeding appears to protect infants from symptomatic shigellosis. New methods for analysis of constituents of human milk that previously could not be measured are likely to lead to significant new information on the protective components of human milk and on the pathobiology, at the molecular level, of many pathogens that commonly infect infants. Diarrheal diseases, particularly dysentery due to *Shigella*, represent a major cause of human morbidity and mortality. The recent rapid worldwide spread of resistance to antibiotics has complicated management of these common infections.

Investigators at Eastern Virginia Medical School and Medical College also are conducting field studies in San Pedro Martir, Mexico City, a predominantly low-income, urban area with a population of 45,000. Community-based studies have been conducted in this area for 18 years. These investigators conducted a blinded, controlled, community-based, clinical study to evaluate the effect of feeding a probiotic mixture

containing *Bifidobacterium infantis*, *Lactobacillus acidophilus*, and *Lactobacillus reuteri* on prevention of community-acquired diarrhea among children 12–36 months of age. After random assignment of the type of feeding, 120 control children received their usual feeding and 123 children received the beverage containing the probiotic mixture for 14 weeks. A significantly higher proportion of children who were fed the probiotic mixture were free of diarrhea (76%), compared with the proportion of children in the control group who were free of diarrhea (64%). Seven cases of rotavirus diarrhea occurred among control children, and two cases occurred among the children receiving the probiotic mixture. Although not statistically significant, this trend suggests that probiotics may protect against rotavirus diarrhea.

Another field project involved the immunization of postpartum women with tetravalent rhesus rotavirus vaccine. Researchers are evaluating the safety and immunogenicity of the vaccine and the effect on concentrations of antibodies and lactadherin in human milk after administration of the vaccine to women in Mexico and Norfolk within 24 hours or at 14 days after delivery. The groundwork for testing for the presence of calicivirus and astrovirus in the cohort also is under way. Evaluation of the association of antibody titers with protection against rotavirus infection and illness will be undertaken. Techniques for identifying calicivirus infections in the new cohort study are being refined.

Milk samples from a second maternal immunization study have been sent for determination of levels of lactadherin, butyrophyllin, and mucin. This testing is needed to complete the study to evaluate the effect of maternal immunization on the levels of these compounds in milk, to determine the effect of time on the concentration of these compounds, and to compare results with different concentrations of immunoglobulin A (IgA) in milk.

Nepal

An investigator from Pennsylvania State University, University Park, 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 beginning economic development.

A project at the University of Michigan, Ann Arbor, 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. The researcher performing that investigation is also involved in a related NICHD-funded project to explore the reciprocal relationship between changes in population processes and the environment, by using a geographic information system.

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 testes. Greatly improved survival of undifferentiated spermatogonia was recently achieved with use of a culture medium (KSOM/AA) that was developed under an NICHD special Culture Club program.

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 also are studying the molecular basis for the biological activities of human lactoferrin; 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 protease, the bacterium's major virulence factor. This research will elucidate the control of levels of iron and other trace elements in bodily fluids, which is related to diseases of iron overload or deficiency and bodily defense mechanisms, especially antibacterial and

antioxidant activity. Aspects of the biology of human milk and infant health and the bioavailability of trace elements also will be explored. This project is an extension of previous crystallographic studies of lactoferrin and new structural studies of transferrin. During the course of the research, the investigators initiated (a) a program of complementary techniques in x-ray crystallographic studies of human transferrin and (b) an investigation of the ability of lactoferrin to bind certain antitumor complexes. In addition, further advances were made in relation to the nature of conformational change in lactoferrin and the versatility of metal and anion binding. The investigators recently 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.

Researchers at Pennsylvania State University, University Park, and the University of Otago are collaborating on a study that examines links between childhood experiences of child-rearing practices and parenting practices during adulthood. By studying 500 subjects from a cohort of approximately 1,000 New Zealanders who have had follow-up since preschool and are now parents themselves, the study will determine whether childhood experiences of child-rearing practices are predictive of parenting during adulthood and whether a supportive marital experience disrupts the intergenerational transmission of problematic parenting. Archival data on research participants have been analyzed, and the researchers are beginning to collect new data on the parenting during adulthood. Insight into these issues will help to prevent problematic parenting and promote competent parenting.

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 economic 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 investigators 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 will make available basic information needed for planning economic and health programs and policies.

NICHD and the National Center for Health Statistics are jointly supporting activities to improve the Russian infrastructure to obtain reliable vital statistics and health indicators. Pilot studies in three regions of Russia involve training in the use of revised birth and death certificates. Also, computer-assisted training in the use of the *International Classification of Diseases, 10th Revision*, will be implemented for Russian states.

Saudi Arabia

The Baylor Child Health Research Center, Baylor College of Medicine, Houston, Texas, was awarded project development funds to support gene-mapping studies and cloning strategies in research on primary congenital glaucoma (PCG). Investigators screened 25 Saudi Arabian families with PCG and identified three missense mutations in 24 of these families. The most common mutation changes a glycine to a glutamic acid in 78% of the PCG chromosomes. The second most common mutation changes an arginine to a tryptophan in 10% of the PCG chromosomes. The third mutation changes an aspartic acid to an asparagine in 6% of the PCG chromosomes. 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 research will increase understanding of the embryology of ocular development and the role of other drug-metabolizing enzymes in organogenesis.

South Africa

In Durban and Johannesburg, NICHD supports studies of HIV-specific responses of helper T cells in the pregnant woman. Scientists from Columbia University, New York City, New York, are using perinatal transmission as an instructive model, because that setting may offer valuable insight into

immunologic responses to HIV, so that vaccine development may be rationally guided toward successful strategies.

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. A database is being constructed, verified, and assessed. Infant and child mortality rates over time already have been analyzed.

Another Harvard University researcher in Tanzania demonstrated that relatively inexpensive vitamin A supplementation to HIV-infected women during and after pregnancy significantly reduces low birth weight, preterm delivery, and the birth rate for babies who are small for gestational age. This project will be expanded to examine the impact of multivitamins in pregnant women who are not infected with HIV. Samples derived from this multivitamin study will be used to determine whether recombinant viruses are better fitted for perinatal transmission than parental genomes. The research will further define viral determinants associated with HIV vertical transmission and will elucidate whether different HIV-1 subtypes have different biological features and characteristics.

Thailand

Investigators at the University of North Carolina, Chapel Hill, developed 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 were collected in 1984, 1988, and 1994, and more data will be collected in 2000. These investigators have compiled a comprehensive, longitudinal, integrated, multilevel data set that is used for varied analyses. Analysis on the relationship between land use and migration suggests that migration is both a cause and a consequence of land use. Results suggest that, in Nang Rong, household formation is more important to land use patterns than is household size. The investigators also are using the study informa-

tion on social networks to explore the relationships between choice to use contraceptives and migration in Nang Rong. The data 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.

NICHD also supports a Harvard University study in Thailand to determine whether shortened courses of AZT given to HIV-infected pregnant women might reduce the rate of mother-to-fetus HIV transmission. Another NICHD study is exploring the epidemiologic, immunologic, and virological characteristics of HIV-infected Thai women and the role of protective immunity in the transmission of HIV infection from mother to infant. The University of Chiang Mai is one of the sites for the NICHD-supported study of HIV infection and use of contraceptive hormones, which is conducted by the HIVNET project in Africa. (See also the section on "Africa.")

An NICHD-funded project, with an investigator from the University of Michigan, Ann Arbor, will provide a comprehensive empirical assessment of problems that AIDS poses for older adults in Thailand. The investigator will determine the magnitude of the problems of older adults who have AIDS and examine the effects on adult children and grandchildren.

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.

NICHD-supported investigators also 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 HIV-1 vertical transmission. 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, these studies may aid in the development and testing of vaccine candidates.

United Kingdom

Investigators at the University of London, England, are examining 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 at least 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. They also have provided important evidence for differentiation of social understanding. The documentation and analysis of early problems of disruptive children in reasoning, relationships, moral sensitivity, and emotional control is of clear social and theoretical significance, especially in view of the current recognition of the importance of behavioral research on violence. The findings that children who are hard to manage engage in violent fantasy and antisocial behavior and that these characteristics predict later differences in moral sensitivity are clearly relevant to better understanding of the development of violent behavior in middle childhood and adolescence.

A multisite NICHD Collaborative Program of Excellence in Autism is part of the International Autism Genetics Consortium. This Program involves scientists from Yale University, New Haven; the University of Chicago, Illinois; and the University of California, Los Angeles. The international team includes NICHD-funded scientists from the United States; Oxford University and the University of London, England; and universities in Denmark, France, Germany, Greece, and the Netherlands. The team has completed a genome scan based on 97 autistic sibling pairs who were uniformly characterized.

Researchers in London, England, are investigating the effect of specific forms of

mother–infant relationships in the first 24 months of life on infant social, emotional, and cognitive development. They are comparing attachment patterns in infants of mothers with borderline personality disorder and infants of mothers with no psychiatric diagnosis. In addition, a 3-year, NICHD-funded project at the University of London will build on earlier molecular genetic analyses related to cognitive ability in children. The researchers are conducting a systematic genome scan for allelic association, by using a new DNA-pooling technique. This work will genotype DNA markers as part of a study of general cognitive ability, one of the most heritable behavioral traits, in a control group and in a group with high intelligence quotient (IQ). The researchers have developed permanent cell lines for 202 subjects, and additional control subjects, 100 with average IQ and 100 with high IQ, will be used as a replication sample. Finding specific genes associated with cognitive ability will ultimately open windows through which to view neurocognitive processes involved in human learning and memory. More immediately, this project is increasing the ability to investigate the interplay between genes and environment in cognitive development. It also represents a significant step toward understanding neurophysiological pathways between genes and cognitive development.

An NICHD-supported scientist is conducting a fellowship project at the National Institute for Medical Research, London, England. The project seeks to elucidate the global regulatory elements that influence the expression of genes in the *Hoxb* cluster in exquisitely coordinated, highly ordered, temporal and spatial patterns during development. Using an experimental approach, the scientists will perform transgenic analysis and targeted mutagenesis in mice. The study will identify regulatory regions that function as initiating elements, enhancers, polycomb response elements, and boundary elements, to determine which *Hoxb* genes are controlled by such elements and to demonstrate their functions *in vivo*. This research should provide important insights toward elucidating the regulatory elements controlling expression of the *Hoxb* gene complex in ordered, anterior-to-posterior patterns. Consequently, this project has great implications for our understanding of pattern formation and development in

vertebrates and in the formation of birth defects.

Zambia

Investigators 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.

Another study focuses on sexual networks as a method to identify effective and efficient intervention strategies for prevention of the spread of HIV and other sexually transmitted diseases. A significant proportion of adults older than age 30 years had at least one concurrent partnership among their last three sexual partnerships. These concurrent partnerships, rather than the actual number of partnerships, may account for the rapid and pervasive spread of HIV in the study population.

International Meetings

During FY 99, NICHD researchers helped to organize and convene, attend, and made presentations at many international conferences, seminars, and workshops. Selected meetings that involved NICHD participation are as follows:

- 14th Annual Conference on Current Issues in Developmental Psychobiology, in St. George's, Grenada, on January 7–11, 1999;
- 12th International Conference on An-

tiviral Research, in Tel Aviv, Israel, on March 21–26, 1999;

- 11th World Congress on In Vitro Fertilization and Human Reproductive Genetics, in Sydney, Australia, on May 9–10, 1999;
- Global Forum for Health Research Conference, in Geneva, Switzerland, on June 8–10, 1999;
- 3rd International AIDS Symposium, in Abha, Eastern Province, Saudi Arabia, on June 20–23, 1999;
- International 3rd Summit Meeting on Male Hormonal Contraception, in Paris, France, on June 24–25, 1999;
- International Perinatal Collegium, in Villars, Switzerland, on July 7–8, 1999;
- 35th Annual Congress of the Japan Neonatal (Perinatal) Society, Takamatsu, Japan, on July 10–13, 1999;
- Annual Meeting of the Infectious Diseases Society for Obstetrics and Gynecology, in Toronto, Ontario, on August 3–7, 1999;
- 2nd Conference on Global Strategies for Prevention of HIV Transmission From Mothers to Children, in Montreal, Quebec, on September 1–5, 1999; and
- 2nd International Congress on New Technologies in Reproductive Medicine, Neonatology, and Gynecology, in Sardinia, Italy, on September 18–21, 1999.

Intramural Programs and Activities

Many international researchers 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 Office of the Division Director also works with researchers at the Aga Khan University, Karachi, Pakistan, on studies of maternal and infant mortality and related

outcomes, such as preterm births and intrauterine growth retardation, which is present in about 24.4% of live births in certain parts of Karachi. Risk factors include low level of maternal education, paternal unemployment, consanguinity, short interval of birth to conception, short maternal stature, and low maternal weight. Interventions emphasizing family planning and programs aimed at improving nutrition and education for women of childbearing age are expected to have a major impact on achieving this goal. An intervention to integrate existing components of prenatal and delivery care is continuing in Baluchistan.

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 are identifying pregnant women with high alcohol intake, collecting blood specimens over the course of pregnancy, and examining the ability of various markers to predict which offspring will have fetal alcohol syndrome.

In joint research efforts with the U.S. Naval Medical Research Unit 3 and the University of Alexandria, Egypt, the Branch continues (a) to evaluate the role of enterotoxigenic *Escherichia coli* (ETEC), rotaviruses, astroviruses, and caliciviruses as causes of diarrhea in a cohort of infants and (b) to conduct 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-methylene tetrahydrofolate 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.

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. 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 carries out research in various areas of molecular cell biology. These areas include mechanisms of intracellular protein trafficking; the biology of intracellular organelles; T-cell activation; the characterization of tumor-suppressor genes and their products; genetic response to environmental stress; iron metabolism in humans; regulation of gene expression at the transcriptional and post-transcriptional levels; and developmental control of the cell cycle. The Branch is involved in an international effort in South Africa, Swaziland, and Zimbabwe to identify the genetics of iron overload in Africans. In addition, the Branch has collaborative projects with groups in Germany, Israel, Italy, Japan, Korea, and the Netherlands. Among the scientists working in the Branch are researchers from Argentina, Canada, China, Germany, India, Israel, Japan, the Netherlands, Singapore, Spain, Turkey, and the United Kingdom. During FY 99, scientists from the Branch attended meetings in Canada, France, Germany, Italy, Japan, 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. International scientists have important roles in this research program, which involves both basic and clinical studies. Visiting Fellows and Visiting Scientists from many countries participate in research meetings, clinical conferences, medical rounds, and outpatient clinics. During FY 99, 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; 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, Bulgaria, Canada, China, Croatia, Hungary, Italy, Japan, Korea, Mexico, Pakistan, Serbia, Spain, and Turkey. During 1999, Branch investigators attended international conferences and symposia in Germany, Hungary, Italy, and Japan.

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 and the properties of 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. Scientists from Argentina and Serbia are using cultured and immortalized hypothalamic neurons for *in vitro* studies on the control of gonadotropin-releasing hormone secretion by neurotransmitters and other ligands. In the Unit on Molecular Signal Transduction, Postdoctoral Fellows from Bulgaria, China, and Hungary 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. The Branch also is continuing to collaborate with scientists at the Leibniz Institute for Neurobiology, Magdeburg, Germany, to study changes in neuronal plasticity in neurogranin gene knockout mice. The Section on Cellular Signaling continues to work with the 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. As part of this project, a German scientist who worked in the Section for 6 months was supported by the University of Lübeck. 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 investigators at the Regina Elena Cancer Institute, Rome.

Heritable Disorders Branch

The Heritable Disorders Branch trains foreign scientists and supports extensive international research efforts. Branch associations include joint studies with scientists from Belgium, Canada, Denmark, France, Germany, India, Israel, Italy, Japan, Sweden, and the United Kingdom.

A Visiting Fellow from Australia is developing a gene therapy approach to correcting osteogenesis imperfecta by using ribosome

technology. Visiting Fellows from Canada and Japan are collaborating on the cloning and expression of the glucose-6-phosphate transporter gene. Visiting Fellows from India are working to characterize human uridine diphosphate (UDP)-glucuronosyltransferases; are isolating the cDNA (complementary DNA) and the gene for pancreatic soluble phospholipase A2 uteroglobin receptor cDNA and performing gene cloning and signal transduction; and are characterizing the gene for acid ceramidase and performing mutation analyses in patients with Farber's lipogranulomatosis. A Visiting Fellow from Israel is studying mutations of the gene for cystinosis and investigating intracellular trafficking of the CTNS gene product. Three Visiting Fellows from Italy are working, respectively, on gene therapy for glycogen storage disease, by using mice deficient in glucose-6-phosphatase; on generating a knock-in nonlethal murine model for osteogenesis imperfecta; and on characterizing genetically defective bilirubin UDP-glucuronosyltransferase from patients with Crigler-Najjar syndrome. Visiting Fellows from the Netherlands and Thailand are collaborating to study gene mutations for cystinosis and Hermansky-Pudlak syndrome and the functions of the gene products. A Visiting Fellow from Turkey is examining expression of steroid regulatory element binding protein in fibroblasts of patients with Smith-Magenis syndrome.

Other joint research efforts include studies with Belgian scientists on gene mutations in sialuria; with Danish researchers on cystinosis gene mutations; with British investigators on UDP-glucuronosyltransferase; and with Israeli researchers on glycogen storage disease. The Branch's bone researchers are working with Canadian scientists who are studying bone morphometrics and Italian scientists engaged in studies of binding between mutant collagen and other proteins. The phospholipid group collaborates with French colleagues on hereditary IgA nephropathy; with German scientists on familial Fn glomerulopathy; and with scientists in India on the uteroglobin receptor.

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. The Perinatology Research 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 Australia, Israel, and Peru. Strong collaborative efforts have been established with Catholic University, Santiago, Chile; Ben Gurion University, 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 Foun-

dation (CRDF). 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, and the Russian Academy of Sciences on apoptosis and with the Institute of Microbiology, University Vaudois, Switzerland. In addition, a Laboratory staff member gave a lecture at the 12th International Conference on Antiviral Research in Jerusalem, Israel. A professor from the Institute of Mutagenesis and Differentiation, Pisa, Italy, has joined the Laboratory to learn its system. In the field of HIV pathogenesis, the Laboratory has established joint research efforts with the Retrovirology Laboratory, University of Barcelona, Spain, which involved the training of a Guest Researcher.

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 the Max Planck Institute for Biophysical Chemistry, in 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 CRDF Biomedical and Behavioral Sciences Program Award. Additional research activities are continuing with the Agricultural Biotechnology Center, Gödöllő, Hungary; the University of Milan, Italy; and the Department of Chemistry, National Taiwan University, Taipei.

Laboratory of Cellular and Molecular Neurophysiology

Scientists in the Laboratory of Cellular and Molecular Neurophysiology study signaling mechanisms in the central nervous system. In the Section on Neurophysiology and Biophysics, Visiting Fellows from China, Russia, and Ukraine are studying glutamate receptor channels, by using the techniques of biophysics and molecular biology. Current pro-

jects 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.

In the Section on Molecular Neurobiology of Glia, Visiting Fellows from China, Italy, Singapore, and the United Kingdom are studying transcriptional regulation of glutamate receptor genes; regulation of glial development by neurotransmitters; signal transduction pathways and gene transcription in glia; and the role of voltage- and ligand-gated channels in the regulation of glial development *in vitro* and *in vivo*. A Postdoctoral Fellow is supported by a Wellcome Foundation Fellowship. In FY 99, a senior scientist from Italy spent his sabbatical year with the group, and collaborative projects were carried out with laboratories in Germany and the United Kingdom. In the Unit on Cellular and Synaptic Physiology, Visiting Fellows from Hungary and Italy are working on the analysis of synaptic transmission and plasticity in inhibitory interneurons in hippocampal brain slices; the expression and modulation of voltage-gated potassium channels; and the physiological consequences of selective knockout of channel subunits in hippocampal neurons.

In the Section on Cell Biology and Signal Transduction, Postdoctoral Fellows from Brazil and Italy work on the cell biology of Ca²⁺ wave propagation in different types of glial cells, by using optical recording techniques, and a Japan Society Fellow has studied pineal cell excitability. The Section also collaborates with laboratories in Denmark and France.

Members of the Laboratory were invited speakers at international meetings in France, Germany, and Greece.

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 joint 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, France, Israel, Italy, Japan, Kenya, and the United Kingdom. A follow-up study of the same children at 10 years of age was started in FY 99. A second series of 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 project involving researchers from England, Israel, and Sweden has been investigating factors that influence children's eyewitness testimony and recall memory for specific events. Scientists from Canada, the Central African Republic, Colombia, and Germany are jointly assessing the values and practices of parents in diverse cultures. Finally, several foreign investigators are working with scientists in the Laboratory of Comparative Ethology in the study of various aspects of biobehavioral development in four non-human primate species living in natural habitats in Brazil, Costa Rica, and Puerto Rico and in a nature preserve 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 and vaccines for enteric bacterial disease. Studies continue in Israel, the United States, and Vietnam and are being considered for Kenya and Myanmar.

The Laboratory has hosted Visiting Scientists and Guest Researchers from China, the Czech Republic, Ghana, Mexico, and Slovakia. The investigators are working to characterize bacterial pathogenesis and immunity, examining the structural and functional roles of the major histocompatibility antigens, and investigating the mechanisms regulating immune response at the cellular level. These activities have led to presentations of data at international meetings in Chile, Denmark, Italy, Japan, the Netherlands, Spain, Sweden, and the United Kingdom. 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 cooperates with the Israeli Armed Forces in testing the efficacy of two types of *Shigella* conjugate vaccines (*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.

The Laboratory and investigators in Iceland are studying non-species-specific protective antigens of pneumococcus that could assist in inducing vaccine immunity to the acute respiratory diseases of infants and children and of adults with compromised immune systems.

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. A Gordon Research Conference, held in Beijing, was organized by a Laboratory staff member. Joint research continues between the Laboratory and scientists in Israel, under a U.S.-Israel Binational Science Foundation Research grant. Collaborative work is under way with scientists from France, Germany, New Zealand, Spain, and Wales. Postdoctoral Fellows from China, Ethiopia, Germany, Guatemala, Malawi, Nigeria, Russia, Spain, and Venezuela are active in the several Sections and Units of the Laboratory. Members of the Laboratory have helped to organize a number of international meetings, including conferences on

Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins and on VIP PACAP and related peptides. A Cooperative Research and Development Agreement (CRADA) is in place between the Laboratory and the Servier Corporation in France. A member of the Laboratory also serves on the advisory board of a university neuroscience group in Puer to Rico.

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 99, the Laboratory sponsored and organized two international workshops on this subject. The meetings 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; the other addressed in vivo optical imaging for clinical diagnosis. 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 em-

bryo cells that yield exceptionally high-quality RNA recovery. 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 French, 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. A member of the Laboratory and a colleague from Tel Aviv University, Israel, were awarded a grant from the U.S.-Israel Binational Science Foundation to study diffusive transport of water in nerve tissue by magnetic resonance imaging techniques. The Laboratory also hosted 1-month visits of scientists from Italy, Korea, and Russia. Laboratory staff presented research seminars in the Czech Republic, France, Germany, Israel, Italy, and the United Kingdom.

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 stages of mouse development. Of particular interest to the Laboratory are the development of the central and peripheral nervous systems; pituitary, gonad, and thymus development; and mechanisms of genomic imprinting. The discovery and characterization of genes that control the development of these various tissues have resulted in the generation of mouse models of a variety of human genetic disorders.

Among the scientists working in the Laboratory are many researchers from foreign countries, including China, Germany, India, Israel, Japan, Korea, and Sweden. During FY 99, members of the Laboratory attended conferences and visited research institutions in Chile, China, Estonia, Finland, Germany, Japan, Spain, and Sweden. Current international collaborative research projects involve scientists at the Institute of Biotechnology, University of Helsinki, Finland; the German Cancer Research Center, Heidelberg, Germany; the Faculty of Medicine, Tel Aviv Uni-

versity, Israel; and the Asahikawa Medical College, Hokkaido, Japan.

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 embryology, molecular biology, genetics, transgenic models, histochemistry and cytochemistry, and embryological manipulations. Many organisms are under study, including viruses, bacteria, flies, zebra fish, and frogs. Numerous scientists from foreign countries are among the Laboratory's researchers at the postdoctoral and senior levels. During FY 99, the Laboratory included among its staff, researchers 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, 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 and the National Center for Scientific Research of France.

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 Bulgaria, China, Japan, and Russia, focuses on interactions between transcription factors and the RNA polymerase II basal transcription apparatus. A third group, including scientists from China, France, India, Italy, Japan, and Korea, examines molecular mechanisms regulating the immune response. An additional inde-

pendent group with internationally recognized expertise in eukaryotic DNA replication benefits from the contributions of scientists from China 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 maintains close working ties 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 99, members of the Laboratory lectured in Canada and several European countries, including France, Germany, Switzerland, and the United Kingdom.

In collaboration with a German scientist, one 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 a series of experiments clarifying 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, Jülich, Germany, the Laboratory continues to investigate intermolecular in-

teractions. 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 channel gramicidin A. 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. A previously unrecognized approach, the technique of dividing surface construction for the countercharged layer, describes the data well and, consequently, can be a useful analytic tool in membrane biophysics.

The Laboratory also is working with scientists from Canada and France on phase transitions in lipid systems. In joint research with a French industrial laboratory (Rhodia), scientists in the Laboratory of Physical and Structural Biology are determining the properties of polysaccharides for both biological function and potential application. 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 99, members of the

Laboratory participated in international conferences in France, Italy, Poland, Sweden, Switzerland, and the United Kingdom. In October 1999, the Laboratory sponsored an international workshop on electrostatics within ionic channels, with participants from Canada, France, Israel, Italy, the Netherlands, Sweden, and Switzerland.

Laboratories of the Scientific Director

In the Laboratories of the Scientific Director, the Section on Growth Factors has been disbanded because of the tragic death of the Deputy Scientific Director, NICHD, and Chief, Section on Growth Factors, Dr. Gordon Guroff, on July 9, 1999.

During FY 99, this Section hosted one scientist from China and three from Japan. These investigators studied various aspects of the action of nerve growth factor and other neurotrophins. One focus of the work involved the kinase that appeared to mediate the cytoplasmic and nuclear actions of the growth factor. The investigators also explored the molecular changes that lead to the various phenotypic alterations induced by the growth factor in its target cells. In joint projects, two senior scientists from Israel studied the role of ganglioside in the actions of nerve growth factor and the

mechanism of the downregulation of mitogen receptors during differentiation induced by nerve growth factor. Collaborative efforts with two former postdoctoral students in Japan focused on the action of ganglioside in receptor function and on the kinase phosphorylating transcription factors that mediate the actions of nerve growth factor. During FY 99, members of the Section were involved in experiments with scientists from Israel and Japan.

The Section on DNA Replication, Repair, and Mutagenesis is focusing on elucidation of (a) the mechanisms for repair of exogenous damage to DNA, such as that caused by prolonged exposure to sunlight, and (b) the consequences of the damage if it is left unrepaired. The primary focus of these studies is the bacterium *E. coli*, but the scientists are also investigating related processes in another bacterium, *Bacillus subtilis*; in a lower eukaryote, *Saccharomyces cerevisiae*; in a vertebrate, *Xenopus laevis*; and in mammalian cells in mice and humans. The Section is led by a British senior investigator and includes three Visiting Fellows from France; one Visiting Fellow from Russia; and one from Spain. These studies also involve scientists from Japan and the United Kingdom.