# XII.
# National Institute of Diabetes and Digestive and Kidney Diseases

## INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports both fundamental and clinical research and research training focused on several diseases characterized by chronicity and long-term disabling effects. NIDDK provides leadership for a National program in diabetes and in diseases resulting from inherited errors of metabolism, including cystic fibrosis; endocrine disorders; diseases of the gastrointestinal tract (e.g., liver and gallbladder); diseases of the blood and bone; and kidney and urologic diseases. The Institute also conducts and supports research in nutrition and nutrition-related disorders. The major objective of this National program is to identify and pursue scientific opportunities yielding fundamental, innovative, and valuable contributions to human health.

NIDDK acquires new biomedical knowledge through grant-supported research, field studies, centrally directed collaborative research contracts, and research at NIDDK facilities in Bethesda, Maryland, and Phoenix, Arizona. The Institute's extramural programs support fundamental and clinical research conducted at universities, medical schools, and other research centers throughout the United States and abroad.

## HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Fifteen research groups from Europe and the United States are participating in a consortium supported by the Division of Diabetes, Endocrinology, and Metabolic Diseases to combine the data for all the genetic markers on chromosome 20. Subcontracts have been issued to groups in France, Sweden, and the United Kingdom. There are 24 data sets, including 2 on African Americans; 13 on whites (6 on residents of Europe and 7 on U.S. residents); 2 on Japanese; 6 on Mexican Americans; and 1 on Native Americans. This is the largest number of data sets ever analyzed for a single disease, and it will be used to map genes for diabetes.

The Clinical Diabetes and Nutrition Section is in the process of establishing a collaborative effort on proteomic approaches to investigate insulin resistance with the University of Auckland, Australia. The Section also established a consortium that includes the Imperial College School of Medicine Hospital, London, England, and Institut Pasteur, Lille, France, to exchange information on markers and technological strategies for the investigation of chromosome 1. In addition, the Section continues to collaborate with the University of Göteborg, Sweden, to study insulin resistance. One research group in the Section is studying gene expression by using profiling for insulin resistance and obesity as a predictor of non–insulin-dependent (type 2) diabetes mellitus in Pima Indians in Arizona and in some families in Sweden.

Prevention of diabetic kidney disease is an important issue for NIDDK. Blockade of the renin–angiotensin system with converting enzyme inhibitors has emerged as the best strategy to slow the progression of diabetic kidney disease, but it is not clear whether early intervention would actually prevent the disease. The Division of Kidney, Urologic, and Hematologic Diseases and the Medical Research Council, Canada, are cofunding the Diabetic Nephropathy Clinical Trial: Renin–Angiotensin System Blockage, which is investigating the efficacy of blockading the renin–angiotensin system to prevent the progression of diabetic nephropathy. Research is being performed at the University of Minnesota, Minneapolis; McGill University, Montreal, Quebec; and the University of Toronto, Ontario.

Another NIDDK-supported initiative is the Chronic Prostatitis Collaborative Research Network, which includes a site at Queen's University, Kingston, Ontario.

A clinical trial, entitled Relative Effects of Diet and Exercise on Body Composition, is based at Tufts University, Boston, Massachusetts, and has two foreign sites—the Chinese Academy of Preventive Medicine, Beijing and Shanghai. In this is a cross-sectional study of 112 healthy men and women, aged 37–47 years, the investigators are studying the relative effects of diet and exercise on body composition. Two hypotheses will be tested: (1) Physical activity but not dietary fat intake is a significant predictor of individual variability in total body fat. (2) The proportion of body fat located centrally is negatively associated with physical activity and not significantly associated with dietary fat intake.

The Division of Kidney, Urologic, and Hematologic Diseases supports a number of initiatives with foreign components. There is a sizable portfolio of work on the therapy for iron overload, a problem of particular importance in thalassemia. One study, on Modeling of Mixed Ligand Therapy for Iron Overload, is being performed at King's College, London, England. The other study, Non–Transferrin-Bound Plasma Iron and Deferoxamine Therapy, is being conducted at University College, London.

NIDDK has major European collaborations on the development of genomic resources for the zebrafish. The Institute, together with the National Institute of Child Health and Human Development, National Institutes of Health (NIH), oversees a large program to develop tools for understanding development of organ formation in the zebrafish. In FY 00, NIDDK participated in a meeting at the Sanger Center, Cambridge, England, on planning for the complete sequencing of the zebrafish genome. Sequencing of this genome will be an important resource for study of organ development, particularly the pancreatic beta cell, the gastrointestinal tract, and the kidney. Other important scientific tools for study of

the zebrafish are being developed in work funded by NIDDK in Germany.

The Division of Digestive Diseases and Nutrition continues to support several international activities. A clinical trial entitled Iron and Vitamin A Deficiency in Children Due to *H. (Helicobacter) pylori* supports a joint effort between the University of Alabama, Birmingham, and the B. C. Memorial Children's Hospital, Calcutta, India. The study is a prospective, randomized, placebo-controlled trial to test the hypothesis that *H. pylori*–induced hypochlorohydria and achlorohydria in the stomach are important factors in the luminal absorption of nonheme iron and provitamin A in food and may be responsible for iron and vitamin A deficiency in children from developing countries. The intervention in this trial is iron and vitamin A therapy combined with the administration of antibiotics to eliminate *H. pylori* infection.

In fiscal year 2000 (FY 00), the Joint U.S.-Japan Nutrition and Metabolism Panel increased collaboration and productive efforts in research in three priority areas: obesity, diabetes, and related metabolic disorders; metabolic bone disease; and nutrition and host defense. In each of these areas, emphasis continues to be on problems of common concern to the United States, Japan, and other countries in Asia. To advance goals in these areas, the joint panel continues to promote studies of molecular genetics, nutritional epidemiology, cellular biology, and clinical research.

In FY 00, the Phoenix Epidemiology and Clinical Research Branch and the Nutrition Division, Centro de Investigación en Alimentación y Desarrollo, Hermosillo, Mexico, completed a 5-year follow-up of Pima Indians residing in Mexico who had impaired glucose tolerance. Glucose tolerance tests were performed on patients who had impaired glucose tolerance in the original survey and on an age- and sex-matched control group with normal glucose tolerance. The purpose of this follow-up study was to determine the initial incidence of diabetes in this group.

## SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

### Country-to-Country Activities and Bilateral Agreements

#### Japan

The Joint U.S.-Japan Nutrition and Metabolism Panel has established a number of cooperative efforts among its members, and these activities continue to be fostered by the annual meetings and conferences. In 1999, the joint panel started discussions with representatives of the International Life Sciences Institute (ILSI) on the possibility of synchronizing the U.S.-Japan Nutrition and Metabolism meetings with the meetings of the ILSI organizations in Japan and the United States. Subsequently, the U.S.-Japan Nutrition and Metabolism Panel cosponsored a meeting entitled Nutrition and Aging, with ILSI, in Tokyo, on September 21–22, 1999. Because the panels were being restructured, no meeting was held in 2000. The next meeting is scheduled for March 22–23, 2001, at the National Institute of Nutrition and Health, in Tokyo. The subject of the conference will be Significance of the Risk Factors of Atherogenesis: Are There Any Differences in Japanese and American Populations? Participating scientists will examine the lifestyle factors, including nutrition and activity, that influence the development of obesity, diabetes, and cardiovascular disease and whether these conditions are predictive of atherogenesis. Interactions of the U.S. national health initiative, Healthy People 2010, with the Japanese Ministry of Health and Welfare's national health initiative, Healthy Japan 21, will also be highlighted.

### Activities With International and Multinational Organizations

#### World Health Organization

##### *Phoenix Epidemiology and Clinical Research Branch*

The Phoenix Epidemiology and Clinical Research Branch serves as a World Health Organization (WHO) Collaborating Center for the Design, Methodology, and Analysis of Epidemiological and Clinical Investigations in Diabetes. During FY 00, the Branch Chief served as a member of the WHO consultation group charged with making recommendations for the definition and diagnosis of diabetes and its complications. He also served as chairperson of the meeting of WHO Diabetes Collaborating Center Directors, in Mexico City, Mexico. In addition, several reports presenting the long-term follow-up results of the WHO Multinational Study of Vascular Disease in Diabetes, in which the Branch is a participating center, were edited, revised, and will soon be published in *Diabetologia*.

The Chief of the Branch was invited to speak at the Chinese Academy of Engineering Life Sciences 2000 meeting, in Beijing, China, on April 18–21, 2000. He was awarded the title of Honorary Professor of Endocrinology, at the China-Japan Friendship Hospital, Ministry of Public Health, Beijing, in recognition of the long-standing collaboration between the Phoenix Epidemiology and Clinical Research Branch and the Division of Endocrinology at that institution.

In addition, the Chief of the Branch participated in planning meetings for the 2nd Asia Pacific Diabetes and Epidemiology Training Course, to be held in Hong Kong, China, in October 2001. He delivered invited lectures at the British Diabetic Association meeting, in Brighton, England, on March 15–17, 2000; the meeting of the Japan Diabetes Society, in Nagoya, on May 24–27, 2000; and the East Meets West meeting, in Hong Kong, China, on September 30–October 1, 2000.

During FY 00, the Branch had one Postdoctoral Fellow (Special Volunteer) from Sierra Leone, who carried out investigations of the long-term significance of body mass index in relation to mortality among the Pima Indian population of Arizona. In this study, small increases above normal body mass index were associated with marked increases in mortality, and only a portion of the excess mortality could be attributed to the development of diabetes per se.

##### *Division of Diabetes, Endocrinology, and Metabolic Diseases*

The Division of Diabetes, Endocrinology, and Metabolic Diseases, an extramural research program, is a WHO Collaborating Center for Diabetes Research, Information, and Education. The center conducts research on diabetes in representative samples of adults in the U.S. population. Data from the U.S. studies are included in analyses of diabetes developed by WHO.

A registry of patients who have had pan-

creas and islet cell transplantation is being supported by an NIDDK contract at the University of Minnesota, Minneapolis. This information, which contains data collected worldwide, addresses the capability of transplantation to prevent, improve, or stabilize the complications of diabetes.

The National Hormone and Pituitary Program, NIDDK, supports preparation and distribution of highly purified hormones and antisera against these hormones. The hormones and antisera are provided for use to qualified investigators in the United States and abroad.

### *Clinical Diabetes and Nutrition Section*

The Clinical Diabetes and Nutrition Section continues to advance new collaborative approaches to investigate insulin resistance. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

One Staff Scientist from the Clinical Diabetes and Nutrition Section and one from the Diabetes and Arthritis Epidemiology Section worked with a research team at the University of Heidelberg, Mannheim, Germany, that had identified a locus for diabetic nephropathy on chromosome 18q in Turkish pedigrees. Genetic markers demonstrating the strongest linkage in the Turkish families were also genotyped in Pima Indian families. Results from the analyses in the Pima Indians confirmed the region of linkage on chromosome 18q. Reports of this international collaboration for diabetic nephropathy genes have been submitted for publication in *Nature Genetics*.

During FY 00, the Clinical Diabetes and Nutrition Section had one Visiting Fellow from China, one from Germany, two from India, one from Korea, and two from Slovakia, as well as one Research Fellow from Italy.

### *Diabetes and Arthritis Epidemiology Section*

The Chief of the Diabetes and Arthritis Epidemiology Section is a member of the executive committee and director of analysis for the Workgroup on Outcomes of Hyperglycemia, American Diabetes Association. This work group is analyzing data submitted from about 15 countries on the prognostic importance of plasma glucose concentrations measured during fasting and during an oral glucose tolerance test. The American Diabetes Association and WHO will use these results to revise screening policies and diagnostic criteria for diabetes mellitus.

A Staff Scientist from this Section is a member of the analysis committee of the International Type 2 Diabetes Linkage Consortium. He has a leading role in comparative analyses of diabetes-susceptibility genes across 26 populations in eight countries.

The Diabetes and Arthritis Epidemiology Section hosted two Visiting Associates from the United Kingdom during FY 00. Both scientists have contributed to studies of the epidemiology and genetics of type 2 diabetes mellitus in the Pima Indians. They have studied the effects of parental diabetes on birth weight and risk for diabetes in children, dietary risk factors for diabetes, diabetic retinopathy, and weight loss in diabetes.

## Extramural Programs

### Division of Diabetes, Endocrinology, and Metabolic Diseases

### *Australia*

Investigators at the Royal Melbourne Hospital, Victoria, are using a preclinical model for preventing diabetes in persons who are at risk for this disease. They are developing a transgenic, nonobese, diabetic mouse in which the gene for proinsulin, the precursor of insulin, will be placed in bone marrow cells. These cells will act as a vehicle for gene expression, which may prevent diabetes.

### *Canada*

The University of Toronto and the University of Western Ontario, London, are participating in the Epidemiology of Diabetes Interventions and Complications Study, which is a multicenter, longitudinal, epidemiologic study of 1,441 patients who participated in the Diabetes Control and Complications Trial. This 10-year follow-up study is focusing on the development of microvascular and macrovascular disease. In addition, a major initiative is being conducted in this study to explore the genetics of diabetic complications. The genetic expertise that is supporting the study design, as well as the genotyping for this project, is provided by the Hospital for Sick Children, Toronto.

Several Canadian institutions are involved in the Diabetes Prevention Trial for Type 1 Diabetes. The participating institutions are the University of Calgary, Alberta; the University of Alberta, Edmonton; British Columbia Children's Hospital, Vancouver; the University of Manitoba, Winnipeg; Grace Health Center, Halifax, Nova Scotia; Kingston General Hospital, the University of Western Ontario, London, and the Hospital for Sick Children, Toronto, Ontario; and Montreal Children's Hospital, Quebec. The major objective of the trial is to determine whether antigen-based therapies (parenteral or oral insulin) in nondiabetic relatives of persons with insulin-dependent (type 1) diabetes mellitus can prevent or delay the onset of clinical diabetes. The investigators have recruited the 340 volunteers needed for the trial of parenteral insulin and approximately 65% of the goal of 490 volunteers for the trial of oral insulin. They will perform follow-up on participants for 2–8 years, depending on when a volunteer is recruited to the study.

Researchers at the University of Toronto are examining insulin secretion from the insulin-secreting cells (beta cells) of the pancreas, in efforts to elucidate the mechanism by which exocytotic proteins interact with ion channels in the plasma membrane. They will use novel techniques for gene transfer to explore these interactions.

A novel protocol for steroid-free immunosuppression has resulted in unprecedented success after islet cell transplantation by a group of investigators at the University of Alberta, Edmonton. However, this protocol requires the isolation of islets from at least two pancreases. These researchers are trying to protect the islets during the isolation and transplantation procedures, so that the islets from a single pancreas can establish control of blood glucose levels in persons with diabetes.

The NIDDK-supported Cystic Fibrosis Research Center, Hospital for Sick Children, Toronto, has made major strides (a) in correlating clinical phenotype with genetic mutations underlying cystic fibrosis and (b) in identifying a broad array of testicular defects that cause infertility in persons with this disorder. In addition, the scientists are studying the role of mutations of the gene for cystic fibrosis transmembrane regulation (CFTR) in the development of idiopathic pancreatitis. These studies have greatly expanded understanding of the biological importance of the CFTR protein encoded by

the CFTR gene. Roles of the CFTR protein that have been demonstrated by this study may suggest avenues for future treatment of cystic fibrosis, male infertility, and pancreatitis.

Under an NIDDK research grant, investigators at McGill University, Montreal, are exploring the role of phosphorylation in regulation of the CFTR protein. This project addresses practical aspects of the function of the protein that would be used to improve the effectiveness of new therapies for cystic fibrosis.

*China*

Researchers at Joslin Diabetes Center, Boston, Massachusetts, are collaborating with researchers at the People's Hospital, Beijing Medical University, to identify susceptibility genes involved in the development of type 2 diabetes. The results suggest that allelic variation at a particular gene locus contributes to the development of type 2 diabetes in a significant subset of families.

*Denmark*

Scientists at the Hagedorn Research Institute, Copenhagen, are studying the role of specific genes that code for proteins in the Notch signaling system. They are investigating how these genes contribute to regulation of endocrinogenesis of the pancreas. The purpose of the study is to determine whether in vitro modulation of the Notch system can lead to indefinite propagation of precursor pancreatic cells and whether these cells can be converted to beta cells.

Another group of scientists at the Hagedorn Research Institute are investigating the role of growth hormone and prolactin in the stimulation of beta cell proliferation and insulin production. The team will examine the pathways involved in the beta cell response to these hormones, with the goal of identifying and determining the function of growth hormone–regulated and prolactin-regulated beta cell genes.

*France*

A researcher at the University of Kansas is collaborating with clinicians in Paris to evaluate a minimally invasive glucose sensor. Together they will determine why the sensor measurement of glucose in the skin lags behind changes in blood glucose levels and whether the tissue around the sensor can cause inaccuracy in the sensor.

*Germany*

Researchers at the University of Geisen, Germany, are trying to perform islet cell transplantation to cure patients with diabetes without the need for permanent immunosuppression. They will use several methods to enable islets to survive in the absence of immunosuppression, which can cause severe side effects such as cancer, as well as the impairment of islet function and insulin action.

*Israel*

Investigators at the Barbara Davis Center, Denver, Colorado, are seeking to characterize the immunogenetics of type 1 diabetes and are exploring methods to determine the ability to predict its development. The focus of their studies is one large consanguineous Bedouin Arab population in Israel, a relatively homogenous population that makes it easier to detect genes for diabetes. Through Tel Aviv University, clinical and genealogical data are being collected on more than 250 persons, including 20 affected with type 1 diabetes. The investigators have used genetic linkage studies in this family to map a diabetes-susceptibility locus (IDDM17) on chromosome 10.

*Sweden*

Researchers at Karolinska Institute, Stockholm, are using transgenic methods to produce "imagable" beta cells. Production of these cells will allow monitoring of engraftment and apoptosis after islet cell transplantation into a nontransgenic host mouse.

**Division of Digestive Diseases and Nutrition**

*Australia*

The Liver and Biliary Diseases Program, Division of Digestive Diseases and Nutrition, supports several clinical trials and research projects in the basic sciences. A joint project at the University of California, Davis, and the Walter and Eliza Hall Institute of Medical Research, Melbourne, is aimed at elucidation of antigen receptors in the autoimmune pathogenesis of primary biliary cirrhosis. A project at the University of Sydney, New South Wales, promises to have a major scientific impact on understanding of the interaction between hepatitis C virus and the liver. The project is expected to provide (a) prognostic indicators for predicting disease outcome in individual patients and (b) a noninvasive test of hepatic fibrosis and function.

A project at the University of Adelaide is aimed at revealing the mechanism for hepatic uptake, hepatocellular transport, and transmembrane transfer of small molecules in the endoplasmic reticulum.

A 5-year project, entitled Neural Mechanisms of Motility and Motility-Related Pain, is being performed at the Flinders Medical Centre, Adelaide, South Australia. Scientists there are identifying the neurons in the enteric nervous system that are responsible for inducing motility in the small intestines. The elucidation of the fundamental mechanisms of intestinal motility and pathways related to peripheral nerve pain is expected to point the way to new preventive strategies and potential targets for the development of drugs to treat intestinal motility disorders.

A study at the Queensland Institute of Medical Research is aimed at gaining a greater understanding of the biology of iron absorption, uptake, and transfer. A major aspect of this study is determination of the three-dimensional structure of the divalent metal transporter protein, DMT1, and of the protein hephaestin, which is important for the passage of iron from cells into the circulation. The three-dimensional structures of these proteins will be used in structure-based studies to design and develop novel therapeutic agents that inhibit intestinal iron absorption.

*Brazil*

A clinical investigator at the University of Iowa, Iowa City, is collaborating with investigators at Universidade Federal do Rio Grande do Norte, Natal, to determine the presence of liver-related immunosuppressive factors in lymphocytes in patients with or without *Leishmania*.

*Canada*

The North American Study for the Treatment of Refractory Ascites, based at the Medical College of Virginia, Richmond, has one foreign site—Toronto Hospital. This study is a multicenter, prospective, randomized, clinical trial designed to test whether transjugular intrahepatic shunt of the portal

system is more effective for refractory ascites than a standard therapy—total paracentesis, sodium restriction, or diuretic agents. Refractory ascites is a serious complication of cirrhotic portal hypertension and is associated with considerable morbidity, increasing health care costs, decreasing quality of life, and eventually, death or increased risk of death after orthotopic liver transplantation.

A clinical trial on functional bowel disorders is based at the University of North Carolina, Chapel Hill, and has one foreign component at the Clarke Institute of Psychiatry, Toronto Hospital. It is hoped that this study will enroll at least 300 female patients with functional bowel disorders (irritable bowel syndrome, painful constipation, or functional abdominal pain) to gain further information on this complicated syndrome. Functional bowel disorders lower quality of life and reduce individual productivity.

### *Chile*

A clinical researcher at the University of Maryland Medical Center, Baltimore, in collaboration with the Center for Vaccine Development, Baltimore, is the principal investigator for a project that will determine the age-specific seroprevalence and seroincidence of hepatitis A infection in Santiago. In addition, the age-specific incidence of fulminant hepatic failure will be determined, to detail the incidence of fulminant hepatic failure secondary to hepatitis A infection.

### *Mexico*

NIDDK is supporting a grant to study the natural history of *Helicobacter* infection in infants of low-income families living on the border of Mexico and the United States. The scientists will study a group of infants from the day-care centers operated by Instituto Mexicano del Seguro Social, Juárez. This study will improve understanding of the epidemiology of *Helicobacter* infection by determining the incidence of *H. pylori* infection in this population compared with a U.S. population in San Elizario, El Paso County, Texas. In addition, the scientists will determine the frequency with which *H. pylori* infections spontaneously clear during the 1st 3 years of life. The studies will also examine the impact of socioeconomic indicators, hygiene, and diet on the incidence, recurrence, and persistence of *H. pylori* among this population.

### *Nigeria*

NIDDK is supporting a collaborative agreement between Loyola University Medical Center, Maywood, Illinois, and the University of Ibadan. This joint effort is expected to develop a substantial resource of pedigrees from the African-American population of Maywood and a second resource from Nigeria. The researchers will investigate candidate genes for obesity and the interactions of these genes with environmental factors.

### *Multinational Studies*

A clinical trial, entitled Prevention of Esophageal Varices by Beta-Adrenergic Blockers, is based at Yale University, New Haven, Connecticut, and has two foreign sites—Royal Free Hospital, London, England, and the University of Barcelona, Spain. This clinical trial is a prospective, randomized, double-blind, placebo-controlled study designed to investigate whether early therapy with a nonselective β-adrenergic blocker can prevent or delay the development of gastroesophageal varices in patients with cirrhosis and portal hypertension.

## Division of Kidney, Urologic, and Hematologic Diseases

The Hematology Program of the Division of Kidney, Urologic, and Hematologic Diseases supports a number of grants with foreign components. There is a sizable portfolio of work on the therapy for iron overload, a problem of particular importance in thalassemia, a disease that is not common in the United States but poses a large health burden in a number of developing countries. Much of the scientific expertise in this research area is in England, where two grantees are developing new approaches to the treatment of iron overload in this disorder. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

Radiation hybrid mapping of the zebrafish genome, a critical step in preparation for complete genome sequencing, is being performed in the laboratory of a Nobel prize–winning geneticist at Max Planck Institute, Tübingen, Germany. Radiation hybrid mapping is a procedure for the stable insertion of chromosomal fragments into another cell nucleus.

The U.S. Renal Data System, a national registry of patients with end-stage renal disease, has been working with other major renal registries through the European Institute of Oncology, Milan, Italy, in the analysis of data to investigate the risk of cancer patients who are having dialysis because of renal failure.

The U.S. Renal Data System is also participating with other members of the International Federation of Renal Registries in an ongoing comparative study of incidence and prevalence of end-stage renal disease, treatment modalities, and outcomes throughout the world. Data are shared and discussed at annual conferences.

The NIDDK research program on acquired immunodeficiency syndrome (AIDS) includes a researcher who is examining the factors that influence transmission of human immunodeficiency virus (HIV) in sperm. The work, which is cofunded by NIDDK and international organizations including the U.S. Agency for International Development, is performed in the United States, but is made possible by the researcher's visits to and collaboration with African agencies.

In addition, NIDDK is funding a Chronic Prostatitis Collaborative Research Network that includes a site at Queen's University, Kingston, Ontario.

The study of developmental biology in the Division of Kidney, Urologic, and Hematologic Diseases is broadening the Division's scope of research by bringing in international investigators with expertise in that field. The following projects are representative of this research:

- Podocyte Cell Lineage in Genitourinary Development—Research Institute, Toronto, Ontario;
- Regulation of TDT (terminal deoxynucleotidyl transferase) Expression During Lymphopoiesis—University of California, Los Angeles, School of Medicine, subcontracted to the Medical Research Council, London, England;
- Genetics and Development of Erythroid Heme Enzymes—Rockefeller University, New York City, New York, subcontracted to Tohoku University, Japan; and

■ First Hematopoietic Stem Cells During Mouse Ontogeny—Erasmus University, Rotterdam, the Netherlands.

## International Meetings

### Division of Digestive Diseases and Nutrition

The Division of Digestive Diseases and Nutrition sponsored a workshop on Management of Hepatitis B, in Bethesda, Maryland, on September 8–10, 2000. The purpose of this meeting was to convene a panel of international scientists from various disciplines with a research interest in hepatitis B virus, to provide an open forum for the exchange of up-to-date knowledge on the management and treatment of infection with hepatitis B virus in several clinical situations.

In response to the increasingly important role of living donors in liver transplantation, the Division of Digestive Diseases and Nutrition and the National Institute of Allergy and Infectious Diseases (NIH), the American Association for the Study of Liver Diseases, and the American Society of Transplant Surgeons organized a research workshop. The goals of the meeting were to assess the current status of liver transplantation from living donors in the United States, to review its history and surgical background, to summarize outcomes and complications, and to discuss the many ethical, medical, and surgical issues that surround this procedure as performed both in children and in adults. Participants from Europe and Japan contributed their experiences.

### Division of Kidney, Urologic, and Hematologic Diseases

The Division of Kidney, Urologic, and Hematologic Diseases is planning a meeting on daily kidney dialysis, to be held in Bethesda, Maryland, in April 2001. The aim of this conference is to explore the feasibility of studies to evaluate the effect of intensified dialysis regimens, daily dialysis, or nocturnal dialysis on the well-being and survival of patients. Some of the experience with these programs comes from investigators in Canada, and an investigator from Toronto is serving on the advisory panel for this conference.

The Division will soon hold two workshops on important urologic conditions. The Interstitial Cystitis Association is cosponsoring the International Research Symposium on Interstitial Cystitis and Bladder Research, to be held in Minneapolis, Minnesota, in October 2000, and the Hyperoxalosis Foundation is cosponsoring a meeting on oxalate stones and hyperoxalosis, in Columbia, Maryland, in November 2000. Both meetings have substantial international participation. Speakers will include investigators from Victoria, Australia; University College, London, England; Hôpital Edouard, Lyon, France; University Children's Hospital, Cologne, Germany; Jivraj Mehia Hospital, India; and Bernhoven Hospital, Oss, the Netherlands.

## Intramural Programs and Activities

### Clinical Endocrinology Branch

#### *Molecular and Cellular Physiology Section*

The Molecular and Cellular Physiology Section, Clinical Endocrinology Branch, has two international studies. One joint study involves scientists from Santiago, Chile, who are examining the role of insulin-like growth factors on the cardiomyocyte. The other study, with Weizmann Institute of Science, Rehovot, Israel, is focusing on the signaling pathways of insulin-like growth factor I and the insulin receptor. Five Visiting Fellows are working in this Section's laboratory: one from China, two from France, one from Israel, and one from Spain. The Section also has two foreign investigators who are students, one from Chile and one from Colombia.

#### *Molecular Regulation and Neuroendocrinology Section*

The Molecular Regulation and Neuroendocrinology Section is beginning several pilot studies to explore the feasibility of future joint research. Expression of Thyroid Hormone and Retinoid Receptors in Bone, will be a joint project with General Hospital, Southampton, England. The researchers will study the expression of these receptors in various bone diseases, by using antibodies previously generated. In another collaborative effort, an investigator from Ecole Normales Supérieure, Lyon, France, will conduct cDNA Microarray Studies of Thyroid Hormone Receptor Knockout Mice. These studies will focus on thyroid hormone receptor (TR) isoform regulation of gene expression in specific tissues of TR knockout mice. The Section will also work with the University of Haifa, Israel, in Studies on the Role of Thyrotropin-Stimulating Hormone (TSH) in Thyroid Development and Migration in Humans. The scientists will investigate thyroid function, structure, and location in patients with TSH receptor mutations.

One Visiting Associate from Israel and one Visiting Fellow from Japan are also working in the Section.

#### *Growth and Development Section*

Three Visiting Fellows (two from China and one from France) are working in the laboratory of the Growth and Development Section.

### Diabetes Branch

#### *Clinical and Cellular Biology Section*

The Clinical and Cellular Biology Section, Diabetes Branch, collaborates with a researcher at the Institute of Histology and Embryology, University of Geneva School of Medicine, Switzerland. In a long-standing joint research effort between NIDDK and researchers in Geneva, morphological techniques have been used to investigate receptor-mediated endocytosis of insulin and related peptides. One Clinical Fellow from Turkey is involved in a collaborative project related to the biology of leptin action.

#### *Experimental Diabetes, Metabolism, and Nutrition Section*

The Experimental Diabetes, Metabolism, and Nutrition Section is continuing to work with institutions in two countries (England and Japan) and has initiated studies in two additional countries (Germany and Sweden). In an ongoing project with the University of Bath, researchers are investigating the development of insulin resistance in adipose cells in culture. A study with a scientist at Yokohama City University is examining the effects of steroid hormones on insulin action. In a joint project with the University of Cologne and the University of Göteborg, investigators are studying components of the insulin receptor signaling pathway that regulate the subcellular trafficking of glucose transporters in isolated adipose cells.

Three Visiting Fellows are working in this Section, two from Canada and one from China.

*Molecular Biology and Gene Regulation Section*

The Molecular Biology and Gene Regulation Section works with investigators at Kyoto University, Japan, to study the role of leptin in insulin resistance in mice. A number of investigators from Canada and Russia have requested the Section's Ucp3 knockout mice, and joint studies may result from their initial research.

Visiting Fellows from the Czech Republic and Italy work in this Section.

**Genetics and Biochemistry Branch**

The Genetics and Biochemistry Branch is host to 12 visiting scientists from nine countries. There are nine Visiting Fellows from the nine countries (Canada, China, the Czech Republic, France, Japan, Russia, Slovakia, the United Kingdom, and Yugoslavia) and three Visiting Scientists who are Research Fellows, one from China and two from Russia. Their studies focus on research in the following areas:

- a novel transcription factor found predominantly in testis;
- the mechanism(s) by which the transcription factor NURR1 regulates expression of tyrosine hydroxylase;
- structural, biochemical, and mechanistic studies of DNA mismatch repair;
- the role of chromatin structure in regulating the late steps of homologous recombination involving DNA branch migration and Holliday junction resolution;
- crystallization and characterization of several proteins associated with recombination and DNA repair;
- the role of specific amino acid residues in the hydrolysis of nucleotide triphosphates;
- identification, purification, and characterization of proteins comprising a ribonucleotide particle essential for processing of pre-rRNA (preribosomal RNA) in *Xenopus;*
- gene expression in bacteria and yeast as a function of DNA damage;
- mechanisms by which proteins are secreted from cells; and
- mechanisms by which proteins are transported into cell membranes.

**Genetics of Development and Disease Branch**

The Genetics of Development and Disease Branch collaborated with scientists at the University of Oxford, England, on therapy for Tay-Sachs disease and Sandhoff's disease and with investigators at the Kekulé Institut für Organische Chemie und Biochemie der Universität Bonn, Germany, in studies on the functions of glycosphingolipids.

During FY 00, the Branch hosted investigators from five countries: Argentina (two), China (four), France (one), Japan (six), and Korea (one). Five of the investigators were Visiting Fellows, five were Visiting Associates, two were Special Volunteers, and two were Courtesy Associates.

**Mathematical Research Branch**

Scientists in the Mathematical Research Branch maintain joint research efforts with groups in Canada and Germany. In FY 00, Branch scientists collaborated with researchers at the University of Alberta, Edmonton, on models of electrical activity in pancreatic beta cells and with researchers at the University of Hannover Medical School, Germany, on the theory of protein folding.

During FY 00, the Branch hosted two Visiting Fellows and one Visiting Associate. A Visiting Fellow from China worked on models of actin–myosin binding in skeletal muscle, and a Visiting Fellow from New Zealand worked on mathematical models of electrical activity and hormone secretion in hypothalamic neurons. A Visiting Associate from Russia worked on mathematical models for neurotransmitter secretion.

**Metabolic Diseases Branch**

*Cell Regulation Section*

The Cell Regulation Section, Metabolic Diseases Branch, has six collaborative projects with laboratories in Italy and Japan. Investigators in the Section and at UniversitB degli Studi "G. D. Annunzio" Faculty of Medicine and Surgery, Palazzina Scuole di Specializzazione, Chieti, Italy, are collaborating to study the role of a 90-kilodalton immunomodulator as a protective factor in autoimmunity, cancer, and AIDS.

In FY 00, the Chief of the Section was invited to speak at Università degli Studi G. D. Annunzio Faculty of Medicine and Surgery, Chieti. He also delivered three presentations at the University of Chiba, Japan.

The Section has five Visiting Fellows, two from Italy and three from Japan, and two Special Volunteers from Japan.

*Genetics and Endocrinology Section*

The Genetics and Endocrinology Section conducts studies on genetic disorders, emphasizing overfunction in parathyroid and other endocrine tissues. Scientists from the Section continued their active involvement in an international consortium to clone the gene for hyperparathyroidism–jaw tumor syndrome. Other participants in this project are from the Netherlands, Sweden, the United Kingdom, and the United States.

An investigator from the Calcium Research Laboratory, McGill University, Montreal, was made an Associate Investigator on two active Branch protocols, because of his collaborations on studies of familial hyperparathyroidism.

The Acting Chief of the Section will be an invited speaker at the International Congress of Endocrinology, in Sydney, Australia, on October 29–November 2, 2000, and at the meeting of the Australian and New Zealand Bone and Mineral Society, at Hamilton Island, Australia, on November 4–7, 2000.

In FY 00, the Section had one Postdoctoral Fellow and one summer student from Italy and one Visiting Scientist from Kenya.

*Molecular Pathophysiology Section*

The Cellular Signaling Unit, Molecular Pathophysiology Section, has an ongoing collaboration with a Turkish scientist who previously worked as a Visiting Fellow in the Unit's laboratory. This work is supported in part by a grant from the Turkish Scientific and Technical Research Council.

In FY 00, the Molecular Pathophysiology Section hosted one Visiting Associate from China.

**Molecular and Clinical Hematology Branch**

The Molecular and Clinical Hematology Branch is working with scientists in China and Thailand in a clinical trial on the effects of hydroxyurea on the level of effective erythropoiesis, transfusion requirements, and the red blood cell production rate in β-thalassemia intermedia. This investigation is being conducted at Shanghai Institute of Medical Genetics, China, and Mahidol

Hospital, Bangkok, Thailand. The preliminary data indicate that hydroxyurea may improve the effectiveness of erythropoiesis in a substantial proportion of patients with β-thalassemia intermedia.

On the basis of these encouraging results, this investigation was expanded to determine whether genotypes that account for diminished synthesis of specific β chains of hemoglobin in β-thalassemia predict response to hydroxyurea. To accomplish this goal, the Branch will organize a working group of investigators from Greece, Israel, Italy, Sardinia, Sicily, and Thailand to begin this trial, using an NIH protocol. Initial review board approval at European and Middle Eastern sites is anticipated in the first quarter of 2001, and accrual of patients is expected to begin by May 2001.

**Transplantation and Autoimmunity Branch**

In FY 00, the Transplantation and Autoimmunity Branch hosted eight scientists from five countries. These scientists included one Visiting Scientist (from Germany), one tenure-track Clinical Investigator (from Germany), two Visiting Fellows (from India), one Special Volunteer (from Israel), two Endocrinology Fellows (one from Israel and one from Switzerland), and one Research Fellow (from Turkey).

*Autoimmunity Section*

In the Autoimmunity Section, Transplantation and Autoimmunity Branch, an Endocrinology Fellow from Israel is assisting with an aggressive clinical trial to test whether transplantation of pancreatic islet cells can be developed into a therapy for type 1 diabetes mellitus. This investigator has assisted in all aspects of the protocol from patient evaluation and enrollment, to the development of the islet isolation procedure to the actual and islet transplantation, through follow-up. In addition, the investigator has started a project to test whether islets can be "grown" in vitro and has spearheaded an ambitious effort to test various approaches to improve islet transplantation in a nonhuman primate model. An Endocrinology Fellow from Switzerland performs studies to better characterize how the pancreatic beta cell regulates insulin production and secretion and studies to more quickly and accurately assess the quality of isolated islets being considered for transplantation. The Visiting Scientist from Germany conducts experiments on mice to better characterize the immune response that leads to the destruction of islet cells that underlies type 1 diabetes. The tenure-track Clinical Investigator is conducting clinical trials to test whether various reagents that modify immune cell function can block the destruction of beta cells after onset of type 1 diabetes and thereby ameliorate disease severity. This investigator will also assist in follow-up after islet transplantation. The Special Volunteer is a scientist on the faculty at Yale University, New Haven, Connecticut, where he is employed as an interventional radiologist. He contributes to the islet transplantation experiments in the nonhuman primate model that NIDDK scientists are using to determine the best site for infusion of the isolated islets.

The Autoimmunity Section also collaborates with researchers from several countries. Researchers in the Section work with researchers at the University of Alberta, Edmonton, to improve the techniques used for islet isolation and transplantation. Other Section scientists work with scientists at the University of Ulm and the University of Thbingen, Germany, to identify the specific beta cell antigens and derived peptide epitopes that are recognized by the immune system during the process that destroys the islets. The goal of this research is to develop specific and nontoxic therapies to abrogate the autoimmune process leading to the destruction of beta cells that underlies type 1 diabetes. In addition, investigators in this Section are participating in the International Immune Tolerance Network protocol to test whether islet cell transplantation can render patients with type 1 diabetes independent of insulin. The protocol was developed at the University of Alberta, Edmonton.

*T Cell Function Section*

To support the design of novel therapies to regulate the immune response, researchers in the T Cell Function Section are working to better define T-lymphocyte function in autoimmune illness and after transplantation of allogeneic organs. The biochemical signaling mechanisms used by various co-stimulatory T-cell molecules (e.g., CD28, CD152, and CD154) are not well defined. Collaborations with scientists at the Universities of Bath and Birmingham, England, have provided expertise and reagents to help elucidate the signaling pathways used by these receptors. During FY 00, this research resulted in the publication of reports describing (1) the characteristics of CD152 and its inhibitory properties (*Journal of Experimental Medicine,* February 2000) and (2) the effects of CD28 signaling on the production of chemokines (*Immunology,* September 2000.)

*Transplant Surgery Section*

An Indian national working as a Postdoctoral Fellow in the Transplant Surgery Section is performing bone marrow transplantation studies to refine the tolerance-induction regimen developed in rodents in preparation for preclinical adaptation. A Turkish national working as a Postdoctoral Fellow in the Section's laboratory is focusing on identification of the donor bone marrow cells that are thought to facilitate the induction of tolerance when administered in conjunction with an organ allograft.

**Laboratory of Biochemistry and Genetics**

*Genetics of Simple Eukaryotes Section*

Genetics of Simple Eukaryotes Section, Laboratory of Biochemistry and Genetics, is studying prions of *Saccharomyces cerevisiae*. In FY 00, the Section hosted Visiting Fellows from France, Korea, and the United Kingdom, who investigated aspects of the genetics of the [PSI] prion and mechanisms of its propagation and generation.

*Physical Biochemistry Section*

The Physical Biochemistry Section is cooperating with scientists in the School of Biochemistry, University of Melbourne, Australia, in a study of the effect of macromolecular crowding on the kinetics of amyloid formation.

In FY 00, the Section hosted a Visiting Fellow from Australia. The investigator was engaged in research on the effect of macromolecular crowding on the formation of microtubules and on specific and nonspecific DNA–protein interactions.

Also in FY 00, the Section, working with scientists at the Biological Research Center, Spanish Council for Higher Research, Madrid, completed a study of the effect of macromolecular crowding on fiber formation by the bacterial septation protein FtsZ. Collaboration with this Spanish research

group continues in a project to develop new methods for the quantitative characterization of macromolecular associations in crowded and heterogeneous media.

**Laboratory of Bioorganic Chemistry**

The Laboratory of Bioorganic Chemistry consists of five Sections: Drug–Receptor Interactions, Molecular Recognition, Molecular Signaling, Oxidation Mechanisms, and Pharmacodynamics. In addition, the Laboratory has four Work Groups: Mass Spectrometry, Natural Products, Neuroscience, and Nuclear Magnetic Resonance Spectroscopy. Scientists receiving postdoctoral training in the Laboratory are from Canada, China, the Czech Republic, France, Germany, India, Israel, Italy, Japan, Korea, New Zealand, and Vietnam. In addition, doctoral-level students sponsored by the Royal Golden Jubilee Program of Thailand are receiving training in the Laboratory.

Numerous scientific advances stem from the international activities of the Laboratory of Bioorganic Chemistry. Cooperative efforts with foreign countries in FY 00 include the following:

■ Argentina—with the University of Buenos Aires on studies of biologically active alkaloids from Argentinean toads and dietary arthropods.

■ Australia—with Southern Cross University, New South Wales, on novel nicotinic agonists from endemic plants; with the University of Adelaide on dietary origin of alkaloids from myobatrachid frogs; and with the University of Sydney on studies of metabolism and tumorigenicity of benzacridines and the mechanism of action of human epoxide hydrolase.

■ Brazil—with Universidade Federal Rio de Janeiro on discovery and investigation of biologically active products and with Fundaço Oswaldo Cruz, Rio de Janiero, on exploration of new approaches to synthesizing fluorinated bioimidazoles.

■ Canada—with the University of Western Ontario, London, Ontario, on development of xanthines for improvement of tolerance to cold; with the Montreal Research Institute on evaluation of analogues of opioid peptides in the central nervous system; with the University of British Columbia, Vancouver, on xanthines as inhibitors of mitosis and as adjuncts for cancer chemotherapy; with the University of Calgary, Alberta, on involvement of excitotoxic mechanisms in neuronal death caused by neurovirulent strains of HIV macrophages; and with the University of Alberta, Edmonton, on novel inhibitors of nucleoside transport.

■ Chile—with the University of Chile, Santiago, on the effects of pumiliotoxin on ryanodine receptors.

■ Denmark—with Bispebjerg Hospital, Copenhagen, on the roles of muscarinic receptors in drug-seeking behavior, using acetylcholine receptor knockout mice.

■ Germany—with the Free University of Berlin on genetic analysis of G protein–coupled receptors; with the University of Freiburg on the study of presynaptic muscarinic receptors, using acetylcholine receptor knockout mice; with the University of Mainz on mechanisms of polycyclic aromatic hydrocarbon–elicited carcinogens; with the University of Münster on reactivites of fluorovinyl imidazoles in cycloaddition reactions and on fluorocyclopropyl amines as substrates for monoamine oxidase enzymes; with the University of Frankfurt on inhibition of ectonucleotidases; with the University of Leipzig on safety of drugs, including biopolymeric drugs; and with the University of Bonn on adenosine receptor antagonists.

■ Israel—with Haifa University, on thio analogues of ultimate carcinogens from polycyclic aromatic hydrocarbons; with the Institute for Biological Research, Nes Ziyyona, on molecular probes for cholinergic receptors; and with Bar Ilan University, Ramat Gan, on the development of novel systems for drug delivery and the action of adenosine agonists and antagonists on cardiac myocytes.

■ Italy—with the University of Bari on renal effects of adenosine receptor agonists and antagonists; with the University of Ferrara on the design of selective adenosine agonists; with the University of Milan on second-messenger systems associated with purinoceptors and on mechanisms of apoptosis induced by adenosine; with the University of Parma on the biological activity of histamine analogues; and with Università degli Studi, Verona, on fluorinated analogues of dihydroxyphenylserine as substrates for decarboxylase enzymes.

■ Japan—with Osaka City University on isolation and elucidation of the structure of alkaloids from amphibians and on the mechanism of human DNA polymerase η; with Kumamoto University on the development of affinity labels for receptors and ion channels; with RIKEN Laboratory of Cell Culture Development, Saitama, on the study of the physiological roles of central muscarinic receptors, using acetylcholine receptor knockout mice; with Tohoku University and the University of Osaka on structural and biological activity of marine toxins; with the National Research Institute, Nagoya, on perfluoroalkylation of aromatic and heterocyclic rings; with Nagoya City University on metabolism of polycyclic aromatic hydrocarbons; with Toyama Medical and Pharmaceutical University on enantio-selective electrophilic fluorination; with Gifu University on the use of cytokine knockout mice in research on dementia secondary to AIDS; with Kyoto University on the mechanism of human DNA polymerase κ; and with Tokushima Bunri University on the synthesis of fluorinated chalcones as potential inhibitors of 5-lipoxygenase and cyclooxygenase.

■ Korea—with the Korea Advanced Institute of Science and Technology, Taejon, on the structure of tetrodotoxin analogues from amphibians, and with Ehwa Women's University on synthesis of P2 receptor antagonists.

■ Madagascar—with Université d'Antananarivo on biologically active alkaloids from amphibians and arthropods.

■ Mexico—with Universidad de Mexico, Mexico City, on centrally active alkaloids from birds.

■ the Netherlands—with the Academic Medical Center, Amsterdam, on pathogenesis of hepatic encephalopathy, and with the Center for Biopharmaceutical Sciences, Leiden, on molecular modeling and site-directed mutagenesis of purinergic receptors and on pharmacokinetics of adenosine receptor ligands.

■ New Zealand—with the University of Canterbury on identification of biologically active compounds from natural products.

■ Northern Ireland—with Queens University, Belfast, on synthesis of optically active arene oxides, and with the University of Ulster on study of biologically active peptides from amphibians.

■ Panama—with the Smithsonian Tropical Research Institute and Universidad de Panama, Panama, on insect origins for bio-

logically active alkaloids in skin of neotropical frogs.

■ Portugal—with the Gulbenkian Institute, Lisbon, on biological activity of xanthines in neuromuscular preparations.

■ Spain—with Universidad Autonoma on the mechanisms of action of human DNA polymerase λ and μ.

■ Sweden—with Karolinska Institute, Stockholm, on evaluation of purine nucleosides and nucleotides, the biological activity of caffeine and related xanthines, and the biological activity of adenosine analogues, and with Uppsala University on synthetic incorporation of fluorinated purines and pyrimidines into polynucleotides and on studies of the biological activities of these analogues.

■ Thailand—with Kasetsart University, Bangkok, on identification, structure, and biological activity of natural products.

■ Turkey—with the University of Ankara on involvement of oleic amide in manifestations of hepatic encephalopathy.

■ United Kingdom—with University College, London, England, on evaluation of adenosine triphosphate analogues and purine antagonists; with the University of Manchester, England, on evaluation of neuropeptide hormone analogues in the cardiovascular system and the central nervous system; with the University of Nottingham, England, on electrophysiological effects of antibodies to the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor elaborated during the course of HIV infection; with Kings College, London, and Victoria Hospital, Newcastle upon Tyne, England, on mechanisms of pathogenesis of hepatic encephalopathy; and with the University of Dundee, Scotland, on immunohistochemical localization of protein kinase C isozymes in transfected cells.

■ Venezuela—with Internacional Instituto de Estudios Advancados on effects of toxins on ion channel function.

### Laboratory of Cell Biochemistry and Biology

The Laboratory of Cell Biochemistry and Biology is hosting four investigators from three countries: two Visiting Fellows (one from Germany and one from Italy); and two Special Volunteers (one from China and one from Italy). The Laboratory is involved in eight studies with investigators in nine countries: Canada, China, Denmark, France, Germany, Hungary, Italy, Japan, and the United Kingdom.

#### *Cell Biochemistry Section*

The Cell Biochemistry Section, Laboratory of Cell Biochemistry and Biology, is collaborating with an investigator at the Medical Research Center, Cambridge, England, on studies of the structural characteristics of nuclear proteins. Other projects on nuclear proteins involve investigators in Denmark and at the Max Planck Institute, Tübingen, Germany.

#### *Lipid Cell Biology Section*

The Lipid Cell Biology Section supports four international research activities. Work with a Canadian investigator at the Royal Victoria Hospital, Montreal, focuses on lipoprotein metabolism. Genetic diseases of cholesterol metabolism are the subject of the joint work with a scientist at Faculté de Médecine, Lyon, France. Two Japanese collaborative efforts, one with Ehime University and one with the Nippon Medical School, Tokyo, involve imaging studies of adipocytes and cultured blood cells.

### Laboratory of Cellular and Developmental Biology

In FY 00, the Laboratory of Cellular and Developmental Biology was host to 21 international researchers.

#### *Developmental Biochemistry Section*

In the Developmental Biochemistry Section, Laboratory of Cellular and Developmental Biology, three Visiting Fellows (two from China and one from Poland) investigated the developmental genetics of germline sex determination in *Drosophila melanogaster.* A tenure-track Senior Staff Scientist (from the United Kingdom) leads a research group with two Visiting Fellows (one from Korea and one from Taiwan) who are using minichromosomes in *Saccharomyces cerevisiae* to study the activation of gene expression. One Visiting Fellow from Slovakia is studying sequence-directed protein folding, by using site-directed mutagenesis in bacteria.

#### *Mammalian Developmental Biology Section*

In the Mammalian Developmental Biology Section, four Visiting Fellows (one each from Australia, Canada, China, and Japan) and one Research Fellow (from Italy) are continuing an investigation of the molecular basis of female gonadogenesis, mechanisms of oocyte-specific gene expression, and the structural basis of species-specific fertilization.

#### *Membrane Regulation Section*

In the Membrane Regulation Section, two Visiting Fellows (one from China and one from Japan) and a Research Fellow (from France) are continuing a study of the role of intrinsic lipid proteins in the formation and hydrolysis of neutral lipid-storage droplets. In addition, three Visiting Fellows (two from China and one from Korea) are studying enhancer-dependent expression of globin genes in K562 cells.

#### *Molecular Mechanisms of Development Section*

In the Molecular Mechanisms of Development Section, two Visiting Fellows (one from China and one from Korea) continue to investigate the role of signal transduction in controlling pattern formation and cell fate in *Dictyostelium discoideum.*

#### *Biotechnology Unit*

In the Biotechnology Unit, one Visiting Fellow (from Korea) is investigating the optimization of large-scale expression systems for clinically relevant proteins.

### Laboratory of Chemical Biology

In FY 00, the Laboratory of Chemical Biology hosted 10 foreign Visiting Fellows from the following countries: Argentina (1), China (2), France (1), Jamaica (1), Poland (1), Russia (1), Serbia (2), and Turkey (1). Primarily, the Fogarty Visiting Fellow Program and the Intramural Research Training Award Program support these scientists. Two of these scientists are conducting research on the control of globin gene expression; 3 are investigating human erythroid cell genomics; 2 are performing studies on the culture of human erythroid, neural, and muscle cells; and several are investigating the cell biology of nitric oxide and the interactions of nitric oxide with hemoglobin.

The Laboratory is collaborating with investigators from several countries, including Macedonia, Serbia, and the United Kingdom. In addition, the Laboratory helped to

initiate the Parisian Prospective Study of Sickle Cell Disease, which is monitoring the progression of symptoms in virtually all newborn babies with sickle cell disease in the area of Paris, France, and continues to participate in international investigations in this field.

In 1998, the Laboratory started a formal research collaboration in the U.S.-Macedonian Scientific Exchange Program, with investigators at the Macedonian Academy of Science and Arts, Skopje, on aspects of the genetic hemoglobin diseases.

**Laboratory of Genetics and Physiology**

The Laboratory of Genetics and Physiology has one ongoing joint study with a research group at the French National Institutes of Health and Research (INSERM), Paris, France, to provide information on the role of the prolactin receptor in mammary gland development and tumorigenesis. In addition, the Laboratory is conducting two joint studies in Germany, one to provide information on the role of the Janus tyrosine kinase 2 (JAK2) gene in mammary gland development, in Göttingen, and one with the Max Planck Institute to monitor gene expression in different tissues.

In FY 00, the Laboratory hosted Visiting Fellows from Canada (one), China (two), England (one), France (one), Japan (one), and Spain (one).

**Laboratory of Medicinal Chemistry**

In FY 00, the Laboratory of Medicinal Chemistry hosted 11 scientists from six countries and Taiwan. These scientists consisted of 7 Visiting Fellows (1 from Austria, 1 from Brazil, 2 from China, 1 from France, and 2 from Taiwan); 1 Research Fellow (from China); 2 Visiting Scientists (from Russia); and 1 Special Volunteer (from Japan).

*Section on Carbohydrates*

The Section on Carbohydrates, Laboratory of Medicinal Chemistry, has one Visiting Fellow from China and one from France and one Visiting Scientist from Russia. These investigators are involved in design, synthesis, and characterization of conjugate vaccines against cholera. The evaluation of immunogenicity of experimental vaccines is conducted in collaboration with the National Institute of Child Health and Human Development, NIH, and with Dartmouth Medical School, Lebanon, New Hampshire.

The Section is also engaged in joint work with researchers at the Massachusetts Institute of Technology, Cambridge, on development of solid-phase synthesis of the carbohydrate antigen of *Vibrio cholerae* 0:1.

In addition, the Section has been working with scientists at the Institute of Chemistry, Slovak Academy of Sciences, on new strategies in oligosaccharide synthesis and their application in syntheses of oligosaccharides of biological and industrial importance.

*Drug Design and Synthesis Section*

In the Drug Design and Synthesis Section, a Visiting Fellow from Austria has synthesized agents that act on serotonin type 2a receptors, to develop agents for positron emission tomography imaging of the human brain in various disease states. He is synthesizing compounds that act on the δ opioid receptors as potential agents for the treatment and prevention of heroin abuse. A Research Fellow and a Visiting Fellow from China have synthesized agents that act on the dopamine, serotonin, and norepinephrine transporter, to develop potential medications for the prevention and treatment of cocaine and methamphetamine abuse. A Special Volunteer from Japan synthesized a number of enantiomeric *N*-substituted phenylmorphans to examine the effect of the *N*-substitution on pharmacological properties. This work was a direct result of the unexpected discovery that a (–)-enantiomer of a phenylmorphan with an *N*-phenylethyl substitution was a relatively pure narcotic antagonist, an effect that markedly contrasts with the effect that is known to occur with other μ receptor–selective opioids. A Visiting Fellow from Taiwan synthesized iodo and fluoro derivatives of a corticotropin-releasing hormone antagonist, as potential imaging agents for single photon emission computed tomography studies and positron emission tomography scans, respectively.

The Section is also involved in work with investigators from the Polish Academy of Sciences in a program designed to gain further insight into the mechanism of action of cocaine and other stimulant drugs in the central nervous system. A Visiting Fellow from Brazil synthesized new drugs for study as potential analgesics.

In addition, the Unit of Receptor Biochemistry and Pharmacology, Drug Design and Synthesis Section, continues to work with a research group at the Institute for Pharmaceutical Chemistry, University of Vienna, Austria, on studies of the structure and activity of σ ligands. This project is aimed at determining the effect of various azole and aminoazole systems on σ receptor binding affinity. The research will involve quantitative molecular modeling techniques to devise a pharmacophoric model predictive of ligand affinity at σ receptors. The Unit also has a Visiting Scientist from Russia who is studying σ receptor mechanisms with scientists at Hadassah Medical School, Hebrew University, Jerusalem, Israel. This project is aimed at determining the role of σ receptors in regulation of intracellular calcium and examining the possibility that σ receptors use calcium as a second messenger. Furthermore, the scientists are investigating the role of σ receptors in regulation of cell growth and induction of apoptosis.

Collaborative work continues with researchers at Centre Hospitalier, Universitaire de Bicetre, Assistance Publique Hôpitaux de Paris, France. The purpose is to investigate the role of a novel, haloperidol-insensitive binding site in modulation of non–*N*-methyl-D-aspartate receptors by σ ligands. The Section continues to work with researchers at the Laboratory of Endocrinology and Cellular Communication, INSERM. The researchers are investigating the relationship of anti-estrogen binding sites and σ receptors, with respect to cytotoxicity of various compounds, particularly those related to tamoxifen.

**Laboratory of Molecular Biology**

The Laboratory of Molecular Biology continued extensive collaboration with eight institutions in each of eight countries: Canada, the Czech Republic, Germany, Italy, Japan, Mexico, Spain, and the United Kingdom.

In FY 00, 23 investigators from 12 countries and Taiwan worked with scientists in the Laboratory. These investigators were from Bulgaria (1), Canada (4), China (4), the Czech Republic (1), France (1), Ireland (1), Japan (3), Malta (1), Singapore (1), Spain (1), Sri Lanka (1), the United Kingdom (3), and Taiwan (1).

## Laboratory of Molecular and Cellular Biology

### *Section on Genomic Structure and Function*

The Section on Genomic Structure and Function, Laboratory of Molecular and Cellular Biology, is working with a scientist at Pontificia Universidad Javeriana, Bogotá, Colombia, to investigate the use of polymorphic LINE-1 (L1) inserts for studying the population genetics in South America. In addition, the Section is providing a Fogarty Fellowship for a French scientist, who is participating in the Section's studies on the evolutionary dynamics and the biological properties and effects of the L1 family of mammalian retrotransposons, which are intragenomic, autonomously replicating DNA elements. These studies include the use of L1 DNA as a genetic marker.

The Section hosted two Visiting Fellows from India. One investigator is studying the regulation of FMR1, a gene involved in brain development that is affected in fragile X syndrome—one of the group of diseases characterized by expansion of repeated DNA sequences. The second investigator is working on the molecular basis of chromosome fragility in this disorder and on a mouse model for this group of diseases. This research team is also collaborating with an investigator at the Chiba Radiological Institute, Japan, to examine the role of the XPG endonuclease as a cause of these diseases.

### *Molecular Biology Section*

The Molecular Biology Section is hosting two Visiting Fellows, one from Greece and one from India. Both scientists are part of a group that studies cell-cycle regulation in budding yeast. The Visiting Fellow from Greece is undertaking an analysis of the structure and function of the anaphase inhibitor—a key regulator in cell-cycle progression in mitosis. The function of this regulator is conserved throughout evolution, but almost nothing is known about its mode of action. The Visiting Fellow from India is using a biochemical approach to study the pathway to the checkpoint for DNA damage. This pathway is defective in many types of cancer, and the research is directed toward elucidation of key steps in the process of DNA damage.

A member of the Molecular Biology Section attended the VIIIth Parvovirus Workshop, in Mont Tremblant, Quebec, on June 28–July 2, 2000.

### *Nucleic Acids Biochemistry Section*

The Nucleic Acids Biochemistry Section hosted two Visiting Fellows and one Visiting Scientist from India. One Visiting Fellow and the Visiting Scientist have been studying protein–protein interactions among the transcriptional activator MotA for the bacteriophage T4, the coactivator AsiA, and the sigma-70 subunit of host RNA polymerase. The other Visiting Fellow is studying how the single-stranded binding protein for T4 replication and the polymerase clamp alter the nuclease activity of RNase (ribonuclease) H.

### *Steroid Hormones Section*

The Steroid Hormones Section hosted two Visiting Associates (one from Belgium and one from India) and three Visiting Fellows (two from China and one from Korea). The Visiting Associate from Belgium has been studying the modulation of glucocorticoid receptor (GR)–regulated gene expression by transcriptional cofactors. One Chinese Visiting Fellow has been characterizing a new cofactor that the Section found to modulate properties of GR induction by an apparently different mechanism. The other Visiting Fellow from China is examining the role of coregulators in causing different responses of GR and progesterone receptors from the same reporter construct. These studies have also involved a collaboration with the University of Fribourg, Switzerland. The Visiting Associate from India has been working to identify the molecular determinants of the GR that are involved in the binding of the heat shock protein, hsp90, to produce a functional GR. The Visiting Fellow from Korea is looking at possible ligand-induced differences in cofactor binding to GRs.