Appendix 3

SCIENTIFIC SCOPE AND OBJECTIVES OF MAJOR SPECIAL STATUTORY FUNDING PROGRAM INITIATIVES

Synopses of research goals and examples of scientific advances of initiatives launched through the Special Statutory Funding Program for Type 1 Diabetes Research are available in the main text. Additional information on detailed scientific plans and infrastructure development are provided in this appendix.

International Type 1 Diabetes Genetics Consortium

In order to identify genes that increase (or decrease) an individual's risk for type 1 diabetes, a large collection of patient samples will be required. To maximize efficiency and to coordinate this effort, the NIH has established the International Type 1 Diabetes Genetics Consortium. The goal of the consortium is to develop uniform protocols for collecting DNA samples from families and for genotyping and storage of these samples in a common repository. The consortium plans to ascertain, study, and establish a renewable source of DNA on 2,500 families with at least two type 1 diabetic children, one non-diabetic child, and two parents for studies, and 5,000 families with one type 1 diabetic child, one non-diabetic child, and two parents to map genes that increase susceptibility to type 1 diabetes. In addition, the consortium intends to create a database for the scientific community with clinical, genetic, and medical history information that would facilitate the search for type 1 diabetes susceptibility genes, and to provide a centralized DNA repository to allow targeted studies of genetic structure and function for type 1 diabetes.

With the special statutory funds, a supplement was issued to establish a Consortium Coordinating Center. This Center is developing infrastructure, including identification of key personnel and production of a computing environment, to allow rapid start-up and management of the data collection. Available genome screen data from more than 1,000 diabetic sibling pairs from the U.S. and Europe have been combined and analyzed; consortium members can access the results of this analysis through a website at http://www.t1dgc.org/.

The consortium has begun generating cell lines on 77 multiplex families collected by the Human Biological Data Interchange. A budgetary supplement given to the consortium has allowed expansion of genetic studies on the existing family collections so that all families have the same data collected and entered into a database. An extension of this study for 5 years was approved in FY 2002. This research effort will lead to the development of methods of risk prediction, prevention, and therapy for type 1 diabetes.

International Histocompatibility Working Group (IHWG)

The 13th International Histocompatibilty Working Group (http://www.ihwg.org) works to identify single nucleotide polymorphisms (SNPs) in type 1 diabetes candidate genes. Type 1 diabetes is a polygenic disease caused by differences in multiple genes. Identifying genes and polymorphisms associated with type 1 diabetes will enable accurate prediction, diagnosis, and, ultimately, treatment of this disease. One approach for finding disease-associated genes is to screen affected and unaffected individuals for genetic polymorphisms in candidate genes. The preferred genetic markers for candidate gene association studies are SNPs, single base pair differences that are present in the genome at one per 1,000-10,000 base pairs. To ensure discovery of the common SNPs and determination of their frequency in a population, high-density SNP maps for 100-200 candidate genes will be developed by DNA sequencing from 10 healthy individuals in each of two ethnic groups. Although European Americans are at a greater risk for type 1 diabetes than African Americans, the longer genetic histories of African populations can provide information on mutation patterns that will facilitate data interpretation in linkage studies.

Special statutory funds supplemented an ongoing SNP discovery project, which provided the investigator an opportunity to apply current knowledge and techniques in SNP discovery to type 1 diabetes. When this project began in 2001, a prioritized list of 222 candidate genes was developed based on an understanding of the immune

processes in type 1 diabetes. SNPs identified in these genes are deposited in dbSNP (http://www.ncbi.nlm.nih.gov/SNP/index.html), allowing all researchers to access the data for use in their own studies.

Population-Based Registries for Children with Type 1 Diabetes (SEARCH)

The SEARCH study will develop a uniform, population-based approach to case ascertainment, typology, surveillance, and research on childhood diabetes in the U.S. Through a cooperative agreement, the CDC and NIH funded six centers that will identify prevalent and incident cases of diabetes in youth less than 20 years of age in defined populations. Four SEARCH centers will use a geographically defined population of children and the others will use members of participating health plans. The SEARCH centers will provide access to a population of approximately five million children aged less than 20 years, with an excellent representation of minority groups. The six SEARCH centers are expected to have access to about 7,000 prevalent cases and about 800 incident cases of diabetes per year. The SEARCH study will document the burden of disease associated with type 1, type 2, and other types of diabetes in children and will provide a unique opportunity to define algorithms to classify the different types of diabetes, which will facilitate the identification and management of diabetes in children. The SEARCH study will also describe risk factors for selected micro- and macrovascular complications of diabetes, and describe health care utilization, processes of care, and quality-of-life in children with diabetes.

SEARCH is being conducted over a 5-year period from October 2000 to December 2005. Activities under this cooperative agreement are conducted in two phases. Phase 1, which includes the planning and development of consensus protocols and obtaining IRB clearances, was initiated in November 2000. The study protocol, manual of operations, and forms for SEARCH have been developed and finalized. A comprehensive and detailed typology algorithm has been developed as part of the national protocol and, following successful application in the SEARCH study, may form the framework for a nationally accepted algorithm for clinical classification of children with diabetes. Methods for case finding and ascertainment have been agreed upon, and the study centers are finalizing partnerships with other regions, clinics, and centers for case notification. The SEARCH Executive Committee established a Coordinating Center to facilitate data management and coordination activities and a central laboratory to standardize study procedures. In addition, a website was developed to improve communication between the study centers. A tracking database provides assistance with case ascertainment and tracking of participants at the different study centers, and a web-based data management system has been created for centralized data management coordination. In Phase 2, launched in June 2002, the six SEARCH centers will implement standardized data collection methods, conduct data analyses, and report the study results.

Epidemiology of Diabetes Interventions and Complications (EDIC) Genetics Study

This genetics study was designed to identify DNA sequence differences that influence susceptibility to diabetic complications in the type 1 diabetic cohort of the Epidemiology of Diabetes Interventions and Complications (EDIC) study. EDIC is the long-term follow-up study of the Diabetes Control and Complications Trial (DCCT). The 1991-1993 DCCT/EDIC family study demonstrated significant familial clustering of severe retinopathy and nephropathy. At that time, DNA and cell lines were collected from all DCCT/EDIC participants and most of their diabetic relatives. Since then, many advances in genetics have allowed for testing of whether DNA variation in a number of candidate genes is related to diabetic complications. In 1999 and again in 2000, the NIDDK convened meetings of experts in genetics and diabetic complications to advise the NIDDK and the EDIC study group on the most appropriate use of the cohort for additional genetic studies.

EDIC is identifying all family members of the 1,410 DCCT/EDIC subjects who have had diabetes diagnosed since 1991-1993 and obtaining measures of diabetic complications on all diabetic siblings. DNA is being collected from all available parents as well as one additional non-diabetic sibling. When it is not available from both parents, DNA is being obtained from all available siblings of the proband. It is anticipated that approximately 4,000-4,500 first-degree relatives will be studied. Repeat assessment of familial aggregation will be performed, similar to that in the 1991-1993 family study. Association analyses will be conducted with DNA markers at selected functional candidate genes using transmission disequilibrium testing. If association is found, attempts will be made to identify additional polymorphisms in association tests. Genotype-phenotype correlations will be analyzed to provide insight into the progression of complications and, potentially, the function of gene products. Immortalized cell lines will be established so that sufficient DNA is available for future research.

The study protocol is being conducted at all 28 clinical centers of the DCCT/EDIC. Data collection should be completed within 2 years and family-based association analysis will begin in earnest thereafter. The identification of disease susceptibility genes will provide insight into the mechanisms underlying diabetic complications, which, in turn, will direct future studies to understand, diagnose, and treat diabetic complications.

TrialNet Epidemiology Study

TrialNet (*see also Goal II*) will conduct epidemiologic studies of individuals identified through the Type 1 Diabetes TrialNet and the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) to support the assessment of environmental triggers, genetic interactions, and the natural history of the immunopathogenesis of type 1 diabetes.

The DPT-1 has screened approximately 100,000 non-diabetic relatives of individuals with type 1 diabetes in the process of conducting clinical trials to determine whether parenteral (injected) or oral insulin may delay the onset of diabetes. Approximately 3.5 percent of these relatives test positive for islet cell antibodies and are staged to determine eligibility based on other autoimmune, metabolic, and genetic markers for the clinical trials. The remaining approximately 95,000 individuals have no autoantibodies, yet are at increased risk for diabetes because of their family history. In spring 2002, a follow-up questionnaire was sent to all individuals who were screened in the DPT-1 to ascertain whether they have been diagnosed with diabetes since screening and whether they would like to be involved in further studies. Non-diabetic subjects interested in participation could be followed to determine risk factors until the onset of autoimmunity. Those individuals becoming antibody positive would be compared to those remaining negative to evaluate genetic factors and potential environmental triggers (e.g., dietary, infectious, and psychosocial factors) during the preceding interval. Individuals would be followed until the onset of clinical diabetes, with oral glucose tolerance testing every 6 months and, potentially, continued assessment of environmental exposures. Collecting DNA samples from participants and their complete families, especially parents, would enhance this approach. The ongoing screening of pre-diabetic subjects in TrialNet, which has taken over the oral insulin trial of the DPT-1, will contribute to ascertainment of individuals for epidemiologic studies.

The enormous screening effort necessary for the conduct of DPT-1 and TrialNet to identify non-diabetic relatives of individuals with type 1 diabetes offers an excellent opportunity to conduct parallel epidemiologic studies. These epidemiologic studies will complement the studies of the Triggers and Environmental Determinants of Diabetes in Youth (TEDDY) consortium and the International Type 1 Diabetes Genetics Consortium and will lay a strong foundation for disentangling the genetic and environmental causes of diabetes.

Triggers and Environmental Determinants of Diabetes in Youth (TEDDY)

The NIH and CDC, in collaboration with the JDRF and ADA, established an international consortium of collaborating investigators to participate in the

development and implementation of studies to identify infectious agents, dietary factors, or other environmental factors that trigger type 1 diabetes in genetically susceptible individuals. Creation of the consortium will lead to a coordinated, multidisciplinary approach to this complex problem, collection of information and samples in a standardized manner, and greater statistical power than can be achieved in smaller, independent studies.

TEDDY is funded through seven cooperative agreements, which were awarded in September 2002. A single data coordinating center (DCC) will be responsible for the development of the study protocol and manual of operations, for communication and coordination among the clinical centers, and for management of the collection and analysis of genetic, immunologic, pathogen, and clinical data. Clinical centers (CCs) will recruit and enroll subjects, obtain genetic and other samples from neonates and parents, and prospectively follow selected neonates throughout childhood or until development of diabetes. The cooperative group is sufficiently large to allow for analyses of gene-environment interactions using both diabetes and islet autoimmunity as endpoints and to include appropriate representation of the major racial/ethnic groups. The consortium will also create a central repository of data and biologic samples for subsequent hypothesis-based research.

Type 1 Diabetes Mouse Repository

The Type 1 Diabetes (T1D) Repository at The Jackson Laboratory (JAX) will serve as a central repository and distribution resource for at least 150 mouse strains important to research on type 1 diabetes. These include strains of non-obese diabetic (NOD) mice carrying transgenes or targeted mutations, as well as other strains required for the genetic and pathophysiologic analysis of type 1 diabetes and the development of new therapies. Major goals of this repository include the importation of model strains into a high health status barrier facility and cryopreservation of their embryos. This will ensure that these mouse models continue to be available for future research from a central, stable repository.

Funding for the T1D Repository was provided by a supplement to the NCRR-funded Induced Mutant Resource (IMR) grant submitted in response to RFA RR01-006 "Competitive Supplements for Type 1 Diabetes Murine Model Resource." The T1D Repository is managed as an independent component of the IMR and, hence, utilizes its existing operational systems, including The Total Mouse Database (TTMD) that provides the international scientific community with information on mouse strain characteristics and uses (http://www.jax.org/t1dr/). This website has an on-line form for external investigators to propose mouse strains for inclusion in the T1D Repository.

An external scientific advisory committee has been established to provide advice regarding inclusion of models in the T1D repository. JAX has supplied the repository with a newly renovated high barrier vivarium with 400 breeding pens. This space will be used for genetic quality control of mice recovered from cryopreservation and will serve as the site for distributing live mice. Cryopreservation of 15 T1D strains already present at JAX is in progress. These in-demand strains include NOD cytokine knockout strains, such as IL-4, IL-10, IL-4/10, IFNalpha, IFNalpha receptor beta chain gene knockouts, as well as C57BL/6 strains that carry mono- or bi-congenic *"Idd"* chromosomal segments of NOD origin.

Bioinformatics Integration Support Contract (RFP NIH-NIAID-DAIT-02-16)

Advanced technologies are profoundly altering the study of immunology and infectious diseases; offering new approaches to understanding immune activation and regulation; uncovering the genetic causes of disease susceptibility; and developing new diagnostic, treatment, and intervention strategies. These technologies are also generating large amounts of data to be captured, analyzed, and stored. To take full advantage of technological advances, researchers must be able to extract meaningful information from the vast amounts of data that these technologies now generate. Computers and networked computer systems are critical to this task.

This project provides advanced support in the production, analysis, archiving, and exchange of scientific data for a diverse community of immunology researchers, and access to best practices in the management of scientific information for as many as 150 researchers engaged in allergy, immunology, and transplantation research around the world. In FY 2002, the NIAID awarded two contracts with the special funds to implement the bioinformatics support contract.

Mammalian Gene Collection

The Mammalian Gene Collection (MGC) is a large, trans-NIH program to compile a complete set of full-length (open reading frame) sequences and cDNA clones of expressed genes for human and mouse. The MGC supports the production of cDNA libraries, clones, and sequences. All resources generated by the MGC are publicly accessible to the biomedical research community (http://mgc.nci.nih.gov/). As of fall 2002, more than 10,200 human and 6,800 mouse clones representing distinct genes have been entered into the collection, which continues to grow. These clones provide a high quality resource for studies of protein structure, function, and gene expression for the community at large. Genes that are large, highly specific to certain tissues, or expressed in very low abundance are absent or underrepresented in this collection to date.

Special statutory funds support the incorporation of new pancreatic islet genes into the Mammalian Gene Collection. Novel genes from the Endocrine Pancreas Consortium (*see Goal III*) are being added to the full-length clone collection to aid in the assignment of function to these genes and in determination of their potential role in type 1 diabetes. In addition, this project supports the inclusion of known genes that are only, or preferentially, expressed in the endocrine pancreas in the full-length clone collection. This resource will accelerate progress in understanding beta cell function in both healthy and disease states.

Sequencing the NOD Mouse for Immune System Genes for Type 1 Diabetes

The NOD (non-obese diabetic) mouse model of spontaneous autoimmune diabetes is central to research on the genetics and pathogenesis of type 1 diabetes. A supplement to the Immune Tolerance Network (*see also Goals II and III*) was awarded through NIAID in FY 2001 for the sequencing of eight *Idd* regions of the NOD genome that are implicated in susceptibility to diabetes. Because genes in the mouse often have strong sequence similarity to human genes, NOD sequence data should aid in the identification of human genes involved in type 1 diabetes.

Biotechnology Resource Centers (RFA DK00-002)

This initiative established core expertise in microarray performance and analysis at research centers around the U.S. Regularly appropriated funds were provided for nine centers in FY 2000 to support a wide range of research within the NIDDK mission. An additional center of relevance to type 1 diabetes was awarded using special type 1 diabetes research funds.

The Biotechnology Center supported with the special statutory funds has been one of the most successful centers to date. The principal investigator has played an instrumental role in developing standards for microarray analysis and has developed the use of oligomers—very short pieces of DNA—in place of cDNAs. In September 2001, supplemental funds were provided to use oligomers to identify surrogate markers of diabetes progression. This center continues to support studies to identify surrogate markers for diabetes progression and the development of complications. In addition, the investigator participates in a study designed to identify markers for improved islet viability using microarray analysis of transplant tissue.

Public Health Pilot Programs in Newborn Screening

Prevention and intervention trials for type 1 diabetes are costly, long-term studies that are most valuable if large cohorts are followed from the youngest age at which they can be selected. General population studies are needed to expand the scope of clinical trials, since

familial type 1 diabetes represents less than 20 percent of all cases. Recent advances in laboratory tests for genetic markers provide a cost-effective means of identifying children with familial-level risk in the general population.

The public health infrastructure for newborn screening (NBS) provides an existing framework for the systematic, unbiased selection of children for general population studies. NBS programs are operated under individual state laws and state public health laboratory policies. Coordination and centralized laboratory support from the CDC make it easier to harness the resources of these programs for type 1 diabetes prevention research. The CDC continues to foster, initiate, and support pilot programs between type 1 diabetes research centers and state public health newborn screening laboratories.

The CDC National Diabetes Laboratory (NDL) has used the special statutory funds for several projects to enhance screening and identification of newborns at risk for type 1 diabetes. The CDC provided additional support from regularly appropriated funds. The Diabetes Evaluation in Washington State (DEWIT) study, with support from the NDL, has established a cohort of children for pathogenesis studies, by testing newborn blood spots from about 32,000 children at higher genetic risk for type 1 diabetes. In addition, the CDC has established proficiency testing (PT) programs in the Newborn Screening Quality Assurance Program (NSQAP) for type 1 diabetes genetic markers and autoantibody testing on dried blood spots. This initiative will help to ensure the validity of these tests and reduce variability among laboratories.

Proficiency Testing for Laboratory Assays to Measure Markers of Innate and Acquired Risk for Type 1 Diabetes in Dried Blood Spots

Various analytical approaches are used to test for genetic and serologic markers that identify higher-risk individuals in long-term, multi-center studies of type 1 diabetes. Genetic tests conducted on newborns usually make use of dried blood spots (DBS) as the sample matrix. DBS also allow home collection of samples from children enrolled in these studies for surveillance for the appearance of autoantibodies. The CDC Newborn Screening Quality Assurance Program (NSQAP) conducts a proficiency testing (PT) program in newborn screening laboratories around the world, ensuring the validity of laboratory data over time and among centers. The CDC has conducted pilot multi-center studies for genetic risk markers of type 1 diabetes and for autoantibodies measured in DBS. These pilot studies form the basis for two PT programs that will be administered under NSQAP. For each program, five DBS samples with reference values previously obtained in multi-center studies will be sent three times each year to participating laboratories. The first PT challenge for type 1 diabetes genetic risk assessment is being conducted in January 2003.

High-Throughput, High-Sensitivity Methods for Measuring Markers of Type 1 Diabetes in Humans

Emerging "nanoscale" and "multiplexing" measurement technologies with extremely high throughput promise cost-effective laboratory methods for measuring soluble and cellular markers of type 1 diabetes from dried blood spots and other microvolume samples. Tests for these markers are used in long-term, multi-center studies based on type 1 diabetes risk, pathogenesis, progression, and response to intervention. The validity of results from emerging technologies is usually unclear, and the translation of this technology to clinical and public health laboratories requires a coordinated effort in quality assessment.

CDC is engaged in method development and quality assessment of emerging technologies for population-based screening. The CDC proficiency testing program in newborn screening ensures the validity and comparability of laboratory data over time and among centers. CDC conducts an ongoing certified proficiency testing program for genetic risk markers of type 1 diabetes and for autoantibodies measured in dried blood spots. Through this program, the CDC has contributed to the development and standardization of laboratory measurements of type 1 diabetes markers that are critical to large-scale, epidemiological research on the initiation and progression of type 1 diabetes.

Type 1 Diabetes TrialNet (RFA DK01-003 and DK01-004)

Through a network of clinical centers, investigators, and core support facilities in the U.S. and Canada, the Type 1 Diabetes TrialNet will develop and implement clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent type 1 diabetes in those at risk of the disease. TrialNet will also perform studies on the natural history, genetics, and immunopathogenesis of type 1 diabetes and will complete the ongoing Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) examining whether oral insulin can delay the onset of type 1 diabetes.

The TrialNet initiatives respond to recommendations of the Diabetes Research Working Group (DRWG) that identified additional clinical trials of immunoprevention of type 1 diabetes as an extraordinary research opportunity. The DRWG also recommended the establishment of a national diabetes trial network of cooperative clinical research groups that would create a stable, high-quality infrastructure for the conduct of effective and efficient clinical trials in diabetes. TrialNet, which was initiated in September 2001, comprises 14 clinical centers, a coordinating center, and laboratory facilities. The clinical centers will direct the efforts of approximately 350 recruitment sites located throughout the U.S. and Canada; many of these sites actively recruited patients to the DPT-1 and are expected to participate in new trials. Central laboratories will be established depending on the needs of specific clinical trials. In addition, TrialNet will collaborate with the laboratories of the Immune Tolerance Network, which provide state-of-the-art methods for the measurement of immune parameters and broad immunology expertise extending to multiple autoimmune disorders.

TrialNet, which is sponsored by the NIDDK, NIAID, NICHD, JDRF, and ADA, will facilitate rapid, preliminary testing of emerging therapeutic strategies. A number of potential protocols of new agents being considered are in varying stages of development. Examples of potential agents include antigen-based therapies such as recombinant human GAD65 and the heat shock protein hsp60 p277 peptide, monoclonal antibodies such as anti-CD3 and anti-CD25, and cytokine-based therapies. Those agents that prove most promising in small studies aimed at preserving beta cell function in patients with new-onset diabetes can then be moved quickly into larger scale prevention trials within the network. TrialNet will also be a valuable tool for efforts to find genes and other factors that predispose people to type 1 diabetes (*see Goal I*) and for studies of the development of type 1 diabetes in those at risk. To gain maximum benefit from the resources supported by TrialNet, researchers may place genetic and other biological samples and data from participating patients into repositories for use by many investigators. Thus, TrialNet will be an extremely valuable resource for the entire diabetes research community.

Immune Tolerance Network: Immunomodulation for New-Onset Type 1 Diabetes (RFP NIH-NIAID-DAIT-99-30)

The Immune Tolerance Network (ITN) is an international, cross-disciplinary consortium of more than 70 basic scientists and clinical investigators. The ITN evaluates promising tolerogenic treatment regimens in four clinical areas, including islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergy diseases. Protocol proposals are accepted from investigators three times each year and, in the area of autoimmunity, type 1 diabetes accounts for about one-third of the proposals for new studies. (*See also Goal III*)

The ITN has established core laboratories for the development of diagnostic assays to measure the induction, maintenance, and loss of immune tolerance in humans. Such laboratories include facilities for genomic and

tetramer analysis, cytokine measurement, T cell receptor profiling, and autoantibody analysis. These resources are being made available to TrialNet investigators and to other large research networks sponsored by the NIH, as opportunities arise.

Special statutory funds have been utilized by the ITN to develop therapeutic approaches for the prevention and reversal of type 1 diabetes. A two-arm, phase 2 trial of 81 subjects was launched in May 2002 to evaluate hOKT3Igamma1 (Ala-Ala), a humanized monoclonal anti-CD3 antibody recombinantly engineered to lack activating effects on target T cells. In a small pilot study, treatment with this agent maintained or improved insulin production in nine of 12 subjects for up to 1 year after the onset of type 1 diabetes; only two of 12 control patients showed a similar response. In addition, a phase 1 study will test the safety of vaccination of newly diagnosed type 1 diabetics with human insulin B-chain in incomplete Freunds adjuvant. This study will collect data on the function of beta cells in 12 subjects randomized to either treatment or control.

Autoimmune Disease Prevention Centers (RFA AI00-016)

This program supports a closely interactive and collaborative network of investigators in a unique study group to focus on autoimmune disease prevention. This group will: 1) advance the understanding of immune homeostasis in autoimmune disease states as well as non-disease states, including the pediatric immune response, and 2) build the knowledge base needed to develop interventions for the prevention of human autoimmune diseases, with special emphasis on type 1 diabetes. The Prevention Centers will engage in collaborative and individual projects focused on understanding the immune mechanisms that underlie autoimmunity and autoimmune diseases, mechanisms and consequences of manipulation of the immune response in autoimmunity, and application of this information to the prevention of autoimmune disease in humans. Importantly, prevention is defined as halting the development of an autoimmune disease prior to clinical onset by mechanisms other than global immunosuppression.

The Prevention Centers were launched in Fall 2001 with major support from the special funding program, so the network has a strong emphasis on type 1 diabetes. A network steering committee, composed of the centers' principal investigators and an NIH representative, reviews pilot project applications for funding through network resources awarded for the support of pilot projects, core resources, and clinical studies. As of Summer 2002, five of 13 funded pilot projects focus specifically on type 1 diabetes.

Prevention Center research studies of relevance to the prevention of type 1 diabetes include: novel methods to enhance the ability of antigens (e.g., insulin) to induce tolerance when given orally; the role of the phosphatidylserine receptor in regulating the immune response and in autoimmune diseases, including type 1 diabetes; the role of Notch signaling in the development of tolerance and autoimmune diabetes; transfer of regulatory genes into dendritic cells to modulate autoimmune diabetes; and the use of genetic immunization with DNA vectors expressing antigens and co-stimulatory molecules to interrupt autoimmune diabetes.

Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically-At-Risk (TRIGR)

TRIGR, a multi-center, randomized, controlled clinical trial, will ascertain if weaning infants onto a hydrolysate of cow's milk formula *versus* standard cow's milk formula will reduce the incidence of the development of autoantibodies to beta cell antigens. Cow's milk has been hypothesized to be an environmental trigger of type 1 diabetes; the hydrolyzed milk used in this study will be treated to break down its proteins into subcomponents in the hope that this will reduce the milk's ability to stimulate an immune response. Approximately 8,000 infants with first-degree relatives who have type 1 diabetes will be screened for diabetogenic HLA alleles. Only those with high-risk alleles, and none with protective HLA alleles, will be enrolled in the study. Anticipated enrollment is 2,370 infants at high risk for type 1 diabetes. The infants will be followed periodically to assess the development of autoantibodies to beta cell

antigens, glucose intolerance, and clinical type 1 diabetes. In addition to testing whether modifying cow's milk will reduce the development of diabetes, TRIGR will provide an opportunity for careful study of newborns at high risk for type 1 diabetes. The trial may generate important information about other factors that influence the development of diabetes with implications for novel strategies to prevent this disease.

The TRIGR study, which is led by the NICHD, was initially funded in September 2001. Steering committee meetings and training sessions for trial coordinators have been held and a data management unit has been established. A Manual of Operations details the inclusion and exclusion criteria for entry into the trial, method of randomization to formula, as well as issues of laboratory measurements of autoantibodies, clinical endpoints, data collection, adherence to assigned formula, and data management. A major accomplishment has been the smooth coordination of trial operations in multiple clinics and laboratories in 14 countries involved in the study, including: the U.S. and Puerto Rico, Canada, Australia, Finland, Germany, Estonia, Sweden, Poland, France, Italy, Spain, Switzerland, Hungary, and the Netherlands.

Diabetes Autoantibody Standardization Program

Autoantibodies are currently the best way to predict the onset of type 1 diabetes before the appearance of clinical symptoms, such as impaired glucose tolerance. These assays, which help to define risk in most type 1 diabetes natural history studies and prevention trials throughout the world, are complex and vary from laboratory to laboratory. The Diabetes Autoantibody Standardization Program (DASP) seeks to improve the measurement of the autoantibodies predictive of type 1 diabetes and to decrease laboratory-to-laboratory variability. Major goals include helping laboratories improve methods by providing technical support, training, and information about the best methods to use, supporting the development of highly sensitive and specific measurement technologies, and developing reference materials and CDC reference assays as an accuracy base for performance evaluation and new assay development. In addition to support from the special funding program, DASP also receives funds from regular appropriations to the CDC.

Following a planning period beginning in 1998, DASP was formed as a collaboration of the CDC with the Immunology of Diabetes Society (IDS). In 2000, sets of aliquots from 50 patients with newly diagnosed type 1 diabetes, 50 healthy control subjects, the World Health Organization (WHO) standard positive for GAD and IA-2 autoantibodies, and a negative serum diluent were distributed to participating laboratories. Evaluation results were received from 46 laboratories in 13 countries. The results of extensive data analysis for the major autoantibody assays (i.e., autoantibodies to glutamic acid decarboxylase, GAD, tyrosine phosphatase, IA-2, and insulin) were distributed to participants to aid them in improving their assays.

Designated DASP laboratories, chosen on the basis of performance in the DASP 2000 evaluation, are being identified to provide training in the best techniques for autoantibody assay methods and to provide reference values for sets of DASP materials. Laboratories with the highest sensitivity and best assay characteristics met the criteria for this designation. The CDC has developed GAD and IA-2 methods that meet these criteria and is producing an IAA method that is based on the best methodology from the DASP 2000 evaluation to serve as CDC reference methods. The DASP Evaluation was repeated in 2002, using sets of aliquots from 50 patients with newly diagnosed type 1 diabetes, 100 healthy control subjects, the WHO standard, an insulin autoantibody reference standard, and a negative diluent.

C-Peptide Standardization

C-peptide is a small protein fragment that is cut out of insulin and released into the bloodstream when this protein hormone is produced in the pancreatic islets. Because C-peptide is not present in purified insulin preparations that diabetic patients inject to control their blood sugar, C-peptide levels serve as a surrogate measure of the amount of insulin being produced within the pancreas. Clinical trials of agents to preserve beta cell

function in new-onset type 1 diabetes will use C-peptide as an outcome measure of insulin production. In 2001, the ADA convened an international C-peptide workshop at which participants agreed on the need for C-peptide standardization across laboratories to facilitate the conduct of clinical trials.

This initiative will: 1) evaluate the variability between laboratories that analyze C-peptide; and 2) examine the possibility of harmonizing C-peptide assays to allow comparison of results across laboratories. In addition to laboratories currently analyzing C-peptide for DPT-1 and TrialNet, other national and international laboratories will be invited to participate in this study. Laboratories will be surveyed to obtain general assay information (i.e., type of methods, source of calibration, detection limits, test ranges, known interference, sample stability) and available laboratory quality control (QC) data. A sample exchange will be performed (including WHO standards) among all participating laboratories to assess the variability in C-peptide measurement. Future topics—such as the use of plasma or serum, sample stability at different temperatures, linearity, sensitivity, specificity, accuracy, recovery, and reproducibility—will be discussed after completion of the initial program.

Data and Biosample Repository (RFP NIH-NIDDK-02-04)

In FY 2003, the NIDDK is establishing a central repository for data and biologic samples, such as blood, DNA, and cell lines, collected in the course of large, multi-site clinical studies. The repository will expand the usefulness of these studies by increasing access to trial-related biosamples and data. When appropriate, researchers seeking to re-analyze samples or data will be able to obtain these materials quickly and efficiently.

The repository will serve several functions: 1) gather, store, and distribute samples from completed clinical studies; 2) gather, store, distribute, and facilitate analysis of finished datasets of completed studies; 3) process, analyze, and store samples that are being gathered in ongoing and new studies; and 4) provide support services for genetics studies, including cell line immortalization and DNA extraction. This resource will benefit multiple type 1 diabetes research consortia and trial networks, including TrialNet, Triggers and Environmental Determinants of Type 1 Diabetes in Youth (TEDDY), and the Type 1 Diabetes Genetics Consortium.

Gene Therapy Approaches to Diabetes and Its Complications (RFA DK01-006)

Over the last decade, gene transfer techniques have been developed for introducing genes into the body's cells to correct a defect or alter the properties of those cells. Many approaches to blocking the development of type 1 diabetes and treating diabetic complications appear to be amenable to gene transfer technology. This program facilitates preliminary studies on the appropriate use and feasibility of this new technology.

The NIDDK, NHLBI, and NIAID awarded seven pilot and feasibility grants of 2-years duration in September 2001; the NIDDK funded an additional six grants through its regular appropriation. Research topics being explored through this initiative include:

- New gene therapy methods are being studied that could help to prevent or delay the onset of type 1 diabetes. Techniques are under development to modulate the immune system in ways that promote tolerance to diabetes-associated autoantigens, such as GAD65 and insulin. In addition, different approaches are being explored to block the activation of T cells that mediate the autoimmune process leading to diabetes.

- Scientists are studying ways to alter islets by gene therapy before transplantation into a diabetic patient. Such modified islets might resist immune-mediated rejection and allow transplant recipients to avoid taking harsh immunosuppressive drugs for the rest of their lives.

- Therapeutic angiogenesis—the stimulation of new blood vessel growth—is a procedure with great promise for the treatment of poor blood flow in the limbs and heart. Though such conditions, known as ischemia, may affect more than 50 percent of diabetic patients, current gene-based treatments carry a high risk of side effects for such individuals. New gene delivery techniques are being developed to improve angiogenesis therapy and minimize the risk of side effects to the diabetic population. Other gene therapy approaches are being investigated for the treatment of bladder dysfunction, a serious neurological complication of diabetes.

Innovative Grants in Immune Tolerance (RFA AI00-006)

We are growing closer to the day when autoimmune diseases and transplant rejection will be treated by the induction of immune tolerance—the selective and long-term inactivation of harmful immune responses without global suppression of the body's protective immune system. This initiative supports innovative, high impact research on the mechanisms and applications of antigen-specific immune tolerance to promote the development of tolerogenic protocols applicable to immune-mediated diseases, including type 1 diabetes, and transplant rejection.

In September 2001, the special funds enabled the award of 11 investigator-initiated grants for research on the mechanisms and applications of immune tolerance in addition to 21 grants funded from other sources within the NIH. These 3-year pilot grants for innovative research are sponsored by the NIAID, NIDDK, and NHLBI. Research topics of these investigator-initiated projects include:

- Scientists are using new methods to identify "self-" or autoantigens that can activate T cells in genetically-susceptible mouse models of autoimmune disease. Hematopoietic stem cell gene transfer techniques are being explored as a means of inducing immune tolerance to diabetes-associated autoantigens, such as GAD65.

- Studies are under way to characterize antigen-presenting cells (APCs) and to better understand the parameters influencing how APCs interact with T cells to confer either tolerance or an immune reaction against autoantigens.

- Researchers are developing novel techniques to study molecular interactions on the cell surface that are involved in the induction of T cell tolerance and to inhibit signaling pathways within the cell that lead to T cell activation. The role of apoptosis—programmed cell death—is under study in the NOD mouse model of type 1 diabetes. Innovative treatments are being designed to physically eliminate T cells involved in autoimmunity or islet transplant rejection by inducing apoptosis in this cell population.

- Several methods are being developed to prevent immune destruction of transplanted organs, including islets. Mechanisms used by viruses to evade the immune system are being harnessed to promote immune acceptance of xenografts—tissue transplanted from a different species. New therapies are being designed around the principles of "reverse chemotaxis," which would result in the exclusion of destructive T cells from the site of transplantation, and "suppression by linked recognition," which specifically suppresses the immune response against a foreign tissue graft without impairment of the entire immune system.

Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013)

Insulin therapy, though life-sustaining for individuals with type 1 diabetes, is not a cure and does not prevent the devastating complications that affect nearly every organ system. In FY 1999-2000, the NIDDK, NEI, NHLBI, and NIAID supported 23 pilot and feasibility grants to explore new therapies for type 1 diabetes and its complications: eight awards proposed studies relevant to preventing or reversing type 1 diabetes (*Goal II*); six grants supported research on cell replacement therapy (*Goal III*); one grant was focused on the prevention of

hypoglycemia (*Goal IV*); and eight grants were related to the prevention or treatment of diabetic complications (*Goal V*). Two additional grants were supported by regularly appropriated NIH funds. Examples of scientific advances and research publications that have emerged from these grants are located in the main text and Appendix 4.

Immunopathogenesis of Type 1 Diabetes (RFA DK98-010)

Type 1 diabetes is an autoimmune disease in which toxic T cells of the immune system destroy the insulin-producing beta cells of the pancreas. Seventeen pilot and feasibility grants and research projects of 2-3 years were awarded by the NIDDK, NIAID, and NICHD in FY 1998. An additional two grants were awarded with regularly appropriated NIH funds. These grants supported investigator-initiated studies related to the development of improved methods for risk prediction, prevention, and therapy for type 1 diabetes. Examples of scientific advances and research publications supported by these grants are located in the main text and Appendix 4.

Autoantibodies in Type 1 Diabetes

IA-2 is a major autoantigen in type 1 diabetes with nearly 70 percent of newly diagnosed patients displaying autoantibodies to this protein. A similar percentage of patients with type 1 diabetes, but not always the same individuals, also have autoantibodies to a second major autoantigen, glutamic acid decarboxylase (GAD). Together, nearly 90 percent of newly diagnosed patients have autoantibodies to either IA-2 or GAD. Thus, autoantibodies to these two proteins have become diagnostic markers to identify individuals with autoimmune type 1 diabetes.

This NIDCR intramural research project focuses on: 1) the autoimmune response to IA-2 and GAD in different populations; 2) identification of the immuno-dominant regions of IA-2; 3) the genomic organization of IA-2, showing that the IA-2 gene has 23 exons; 4) the evolutionary history of IA-2 (i.e., identification of homologs in worms, flies, and fish suggests that IA-2 is a highly conserved molecule); and 5) the autoantibody response and molecular biology of an IA-2-related protein, IA-2beta, which was discovered in this laboratory. IA-2 and IA-2beta-deficient ("knockout") mice have been generated to examine the role of these autoantigens in triggering an autoimmune response. Studies with the IA-2 knockout animals have shown that these mice have statistically significant alterations in glucose tolerance tests and insulin secretion. Thus, IA-2 appears to be involved in glucose-stimulated insulin secretion.

Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) Supplements

The Diabetes Prevention Trial for Type 1 Diabetes (DPT-1), sponsored by the NIDDK, NIAID, and NICHD, undertook two major clinical trials to determine whether parenteral (injected) or oral insulin can delay or prevent diabetes in non-diabetic relatives of individuals with type 1 diabetes. Clinical symptoms of type 1 diabetes occur in genetically predisposed individuals after a long period of immune-mediated destruction of the insulin-secreting beta cells. The risk of diabetes during this pre-diabetic period may be predicted using immunologic markers and tests of insulin secretion. The DPT-1 screened non-diabetic relatives, 3-45 years of age, for islet cell antibodies. Those screening positive were staged to measure insulin autoantibodies, insulin response to an intravenous glucose tolerance test, and the presence of a protective genetic marker.

Approximately 100,000 relatives of type 1 diabetes patients have been screened at more than 350 sites across the U.S. and Canada. Individuals found to be at over 50 percent risk were offered enrollment in the now-complete parenteral insulin trial. The DPT-1 showed no effect of injected insulin on the development of type 1 diabetes despite previous data from animal studies and a small pilot trial in humans suggesting that this could be an effective prevention strategy. Because some physicians, relying on the preliminary studies, had already been treating at-risk patients with insulin injections, the disappointing, yet definitive, results of this trial show the importance of conducting large-scale, randomized, controlled clinical trials to thoroughly validate potential therapies.

The injected insulin arm of the DPT-1 has laid the groundwork for future prevention trials for type 1 diabetes by demonstrating that high-risk subjects could be accurately identified. The DPT-1 has also provided important new information that will be invaluable for planning future prevention studies. Individuals at 26-50 percent risk for developing type 1 diabetes were eligible for the oral insulin trial, which is ongoing within the TrialNet infrastructure. Because these participants are recruited to the trial earlier in the pre-diabetic course of the disease and the mechanism of action is different from that of parenteral insulin, scientists are hopeful that oral insulin may delay or prevent the onset of type 1 diabetes.

The enormous number of relatives who must be screened to find eligible subjects for DPT-1 across a continent-wide group of investigators, working cooperatively with standardized procedures, has made this an exceedingly difficult study to conduct. The special statutory funds augmented regular NIH support and allowed for increased efforts to identify and enroll high-risk subjects. In addition, these supplements enhanced the screening of samples collected in DPT-1 and helped to determine the most appropriate assays for identifying individuals at risk of type 1 diabetes.

Beta Cell Biology Consortium (RFA DK01-014)

The Beta Cell Biology Consortium (BCBC) consists of five cooperative agreements, which support a diverse group of more than 30 laboratories in the U.S. and Europe. The BCBC focuses on basic developmental and cell biological research on the pancreatic islet, including studies on islet cell lineage and beta cell regeneration, the isolation and characterization of putative pancreatic progenitor/stem cells, and the establishment of clonogenic assays. Basic research in developmental biology of the endocrine pancreas combined with cutting edge technologies in stem cell biology should enable the development of cellular replacement therapies for type 1 diabetes. The BCBC works collaboratively to create and distribute necessary reagents such as antibodies, vectors, relevant mouse transgenic lines, and beta cell lines that serve the diabetes research community. Importantly, the BCBC is capturing the wealth of this information in an annotated public database that will be a logical extension of the Functional Genomics of the Developing Endocrine Pancreas, (http://www.cbil.upenn.edu/EPConDB/).

At its first meeting in December 2001, the BCBC steering committee laid out common objectives for the consortium, made recommendations for the expansion of three scientific cores that would benefit the entire consortium, and established four subcommittees to help coordinate research efforts in the areas of transgenic mouse generation, antibody generation, stem cell biology, and bioinformatics. A website (http://www.betacell.org/) has been created to provide information about the BCBC laboratories, research objectives, and upcoming activities. In 2002, the NIDDK funded seven pilot and feasibility studies that are complementary to ongoing BCBC research projects. Consistent with NIH policy regarding the use of human embryonic pluripotent stem cells, the BCBC is poised to support groundbreaking basic research on manipulating embryonic stem cells into becoming pancreatic islets.

The Functional Genomics of the Developing Endocrine Pancreas project is nearing completion of its library construction, sequencing, and assembly phase. This project has identified a large number of novel genes expressed in both the developing and adult pancreas. Now being integrated into the BCBC, this group will provide access to cell-based functional assays and protein expression and interaction assays for novel pancreatic genes.

Comprehensive Programs in Beta Cell Biology (RFA DK02-014)

Increased understanding of beta cell biology may help researchers to improve the viability of islets used for transplantation, lead to the development of new treatments for diabetes (e.g., beta cell replacement), and prevent beta cell destruction through the development of novel therapeutics. This program bolsters investigator-initiated collaborative research aimed at understanding the signaling pathways in the adult pancreatic beta cell, and studying the integration of these signaling networks among the different cell types of the pancreatic islet.

The NIDDK funded seven grants in September 2002 for research on the biology of the beta cell and pancreatic islets. Unlike typical R01 applications headed by single investigators, these grants are awarded to teams of investigators with complementary expertise that have come together to tackle important research problems of the beta cell. One additional grant was awarded with regularly appropriated NIDDK funds. Research topics being addressed by these grants include:

- Studies will be performed to examine how specific gene expression patterns are established in the beta cell. Researchers will determine the role of the transcriptional co-activators, CBP and p300, in regulating beta cell growth and function. In addition, an innovative genomics approach will combine

experimental techniques with bioinformatics and computational analyses to identify beta cell-specific gene control elements.

- To fulfill the early promise of experimental islet transplantation techniques, new strategies are needed for expanding islets in culture or stimulating new beta cell growth in diabetic patients. Researchers are studying the role of growth factors—including betacellulin and GABA—in beta cell growth and differentiation and in glucose-stimulated insulin secretion. In addition, investigators are examining the role of specific types of "connexins"—proteins that form channels between neighboring cells—in distinct stages of pancreatic cell growth and development. Identifying the unique signaling functions of different connexins may help scientists use these proteins as molecular tools to promote beta cell development or differentiation.

- Research is under way to investigate intracellular signaling mechanisms that regulate beta cell function. Scientists will define the function of the JNK kinase pathway in beta cells—a component of this signaling cascade is mutated in some diabetic patients. Another group will analyze the molecular mechanisms that mediate the interaction between insulin granules and the interior architecture of the beta cell during granule docking and fusion.

Non-Human Primate Immune Tolerance Cooperative Study Group (RFA AI01-006)

This Cooperative Study Group will develop and evaluate novel, donor-specific tolerance induction regimens for allogeneic kidney and islet transplantation. Recent attention has focused on the potential for donor-specific immune tolerance to achieve long-term graft survival without nonspecific, lifelong immunosuppressive therapies that have deleterious and often life-threatening side effects. The Study Group evaluates tolerogenic approaches in preclinical models to obtain safety and efficacy data before clinical trials are launched.

In FY 2001, the special statutory funds were used to supplement individual investigator cooperative agreements. These projects include the evaluation of two novel, steroid-free immunosuppressive tolerance protocols in kidney and islet transplantation. Preliminary data suggest that withdrawal of immunosuppression in one of the protocols may facilitate tolerance. However, careful studies on the mechanism and duration of graft survival are necessary before clinical trials are designed. In FY 2002, the NIAID and NIDDK renewed the Non-Human Primate Cooperative Study Group, which was originally established in FY 1999. The special funding program supports three meritorious cooperative agreements for islet and kidney transplantation research.

Immune Tolerance Network: Islet Transplantation (RFP NIH-NIAID-DAIT-99-30)

The Immune Tolerance Network (ITN) is an international consortium of more than 70 basic scientists and clinical investigators. The ITN evaluates promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergy diseases. Core ITN laboratories have been established for the development of diagnostic assays to measure the induction, maintenance, and loss of tolerance in humans. (*See also Goal II*)

Special statutory funds are utilized by the ITN to develop cell replacement therapies for the treatment of type 1 diabetes. One of the initial clinical trials conducted by the ITN is the "Edmonton protocol," an experimental islet transplantation protocol for brittle type 1 diabetics. The initial study, conducted by the

University of Alberta, resulted in insulin independence for seven patients, at least during follow-up periods of 4.4 to 14.9 months. The ITN trial will further assess the safety and efficacy of this treatment regimen in 40 patients and expand the capacity for islet preparation and clinical transplantation at nine sites in the U.S., Canada, and Europe.

Two additional trials of islet transplantation that build upon the success of the Edmonton protocol have been approved for implementation. Researchers are testing potentially tolerizing regimens using monoclonal antibodies, anti-CD3 or anti-CD52, in combination with withdrawal of sirolimus, a component of the Edmonton immunosuppression protocol. Additional measures to enhance islet engraftment, survival, and function include: 1) ex vivo culture of harvested islets prior to transplantation, allowing for future modifications such as exposure to islet growth factors and genetic manipulations to enhance islet acceptance; and 2) pre-transplant induction with a non-T cell activating humanized monoclonal anti-CD3.

NIDDK Intramural Program

Type 1 diabetes results from specifically targeted, immune-mediated killing of the insulin-producing beta cells by mechanisms that are not well understood. Nevertheless, it is known that blunting the immune system can delay disease onset for those at risk and that replacing lost beta cells, through transplanting a pancreas or isolated islets, can return those with type 1 diabetes to insulin independence. In 1999, the NIDDK Division of Intramural Research, in collaboration with the Department of Defense, the NIH Clinical Center, and the Diabetes Research Institute of the University of Miami, established the Transplantation and Autoimmunity Branch (TAB). This intramural clinical research program studies new approaches to both kidney transplantation and islet transplantation for the treatment of diabetes. The special funding program partially supported the establishment of the TAB through the purchase of equipment and the installation of a facility in the NIH Clinical Center to harvest pancreatic islets for study and for human transplantation.

Since its establishment, the TAB has maintained a diverse and successful research program to understand and treat type 1 diabetes. The first U.S. islet transplantation procedures for type 1 diabetes were performed at the TAB using the Edmonton protocol. The TAB continues research on islet transplantation in cooperation with the Immune Tolerance Network. This branch supports basic research on beta cell biology and preclinical studies in animal models of type 1 diabetes, including nonhuman primates.

In FY 2001, the special type 1 diabetes research funds augmented Division of Intramural Research (DIR) funds to establish a new section within the Diabetes Branch, DIR, NIDDK; the majority of funding for this initiative came from the DIR budget. Renovation of old laboratories and construction of a new laboratory accounted for the majority share of the budget obligations; the remainder was used to purchase instrumentation for these laboratories. The Diabetes Branch focuses on the development and differentiation of the endocrine pancreas. These researchers study human cells (including adult and embryonic stem cells, consistent with NIH policy) in vitro and in animal models, and examine endocrine pancreas development in mice. These efforts will help to define the process by which progenitor cells differentiate into mature pancreatic islet cells, and will allow researchers to apply this knowledge to the treatment of patients with type 1 diabetes. The investigators of the Diabetes Branch and the TAB, along with the Clinical Endocrinology Branch of the DIR/NIDDK, constitute a cohort of diabetes investigators whose interactions and collaborations will synergistically enhance research in this area.

Islet Cell Resource Centers (RFA RR01-002)

Some type 1 diabetics suffer severe complications, such as blindness, gangrene, kidney failure, and hypoglycemic coma, even though they monitor their blood glucose level and employ multiple injections of insulin throughout the day. Recent advances in islet transplantation provide hope of a cure and prevention of complications. While the Immune Tolerance Network plans to replicate the results of the Edmonton protocol, other experienced islet transplantation programs are in the process of optimizing clinical parameters and islet isolation techniques to ensure that this methodology will be readily available to a large number of individuals with type 1 diabetes. A major problem in implementing these studies is the need for isolation laboratories that meet the very strict sterility and procedural requirements that assure the quality of isolated islets and the subsequent safety of the islet recipients.

Ten Islet Cell Resource Centers (ICRs) were established in FY 2001 as a consortium of academic laboratories. The first major goal of the ICRs is to provide pancreatic islets to eligible investigators for use in FDA- and IRB-approved clinical protocols through which isolated human islets are transplanted into patients afflicted with type 1 diabetes. These geographically dispersed ICRs are now poised to supply clinical-grade islets to centers throughout the country that have expertise in organ transplantation, but do not have islet isolation facilities. The second goal is to optimize the harvest, purification, function, storage, and shipment of islets, while developing tests that characterize the quality and predict the effectiveness of the transplants in curing diabetes. The centers will pool their collective experience in a central database to correlate laboratory data and clinical outcomes. The special statutory funds have supported the infrastructure costs of developing the ICRs and the substantial costs of procuring sufficient numbers of pancreata in organ-donor settings.

Islet/Beta Cell Transplant Registry (RFP DK00-002)

The Collaborative Islet Transplant Registry (CITR) (http://www.citregistry.org/) will expedite progress and promote safety in islet/beta cell transplantation in North America. After a contract for the CITR was awarded by the NIDDK in FY 2001, an Executive Committee to oversee day-to-day activities and a six-member Scientific Advisory Committee (SAC) to provide overall direction to the registry were formed. Organizations with an interest in the activities of CITR have designated representatives to become ex officio members of the SAC; these organizations include the NIAID, NCRR, JDRF, FDA, Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), United Network for Organ Sharing (UNOS), and Canadian Organ Replacement Registry (CORR). In particular, the CITR will collaborate with CORR and UNOS to facilitate data exchange with these organ procurement agencies. The CITR coordination efforts will enhance the identification of both risk factors and determinants of success for islet transplantation.

Islet Encapsulation Research

The development of pancreatic islet transplantation holds great promise as a treatment for type 1 diabetes. However, to prevent rejection of donated islets, patients must rely on long-term immunosuppression, which presents the risk of multiple adverse effects. An alternative to immunosuppression is to coat or "encapsulate" the islets with a material that would prevent the islets from being recognized as foreign by the patient's immune system, yet allow necessary nutrients to reach the islets.

Four pilot and feasibility awards made with the special funds in FY 2002 will promote encapsulation research. Novel approaches to islet encapsulation being pursued include: a method to decrease the dead space within the

capsule to allow better delivery of nutrients and oxygen; the development of polyethylene glycol as a potential encapsulating material; the use of a three-dimensional collagen matrix containing endothelial cells to help blood vessel development and increase oxygen delivery to transplanted islets; and the development of a vascularized, implantable device containing islets that would improve their oxygenation.

Gene Transfer Approaches to Enhance Islet Transplantation (RFA DK02-020)

Many scientific and medical issues remain before transplantation can become a routine treatment for type 1 diabetes. A major barrier to widespread use of this technology is the limited supply of transplantable islets. Gene transfer approaches to engineer new beta cells or to enhance islet viability could improve the efficiency and availability of islet transplantation.

In September 2002, the NIDDK and NIAID funded 12 pilot and feasibility grants of 2-years duration for innovative, high-impact projects on the application of gene transfer technology to islet transplantation. Research projects being pursued through these grants include:

- Transplanted islets in type 1 diabetic patients are vulnerable to attack by two immune-mediated pathways—rejection of the foreign tissue and recurrence of the underlying autoimmune process. To improve islet survival and function, investigators are testing a variety of genes to find ones that can be successfully transferred into islets before transplantation and which will subsequently protect those islets from immune destruction. Candidate genes include the anti-apoptotic protein "A20," a serine proteinase inhibitor "elafin," interleukin-10, NF-kB inhibitory proteins, and a membrane glycoprotein "CD200." In a related approach, scientists will transfer a protein called "galectin-1" into dendritic cells of the immune system to determine whether this factor will interfere with the immune reaction against transplanted tissue.

- Pancreatic islets are heavily vascularized or embedded with an extensive network of blood vessels that carry needed nutrients and oxygen. Islet isolation procedures necessarily sever the connection of the islets to larger blood vessels, so revascularization is critical to the survival and function of islets after transplantation. Researchers have devised a strategy to transplant human islets into a diabetic mouse model. This approach will enable them to study the molecular events of human islet vascularization in a highly manipulable system. Another group will investigate the potential of transferring genes to blood vessel cell precursors to enhance their ability to revascularize and promote the survival of transplanted islets.

- Gene therapy depends on the ability to introduce new genes into cells in ways that are both safe and efficient, and that lead to reliable expression of the inserted gene. Novel viral and peptide-mediated vectors are being designed to optimize the delivery and expression of foreign genes in beta cells or their progenitors.

- Widespread use of promising islet transplantation protocols to treat a significant number of type 1 diabetic patients will require a much larger, and preferably renewable, source of beta cells than is currently available. Scientists are studying whether transfer of beta cell transcription factor genes into hematopoietic (blood-forming) stem cells can induce these cells to transform into fully-differentiated, insulin-producing beta cells.

Imaging Pancreatic Beta Cell Mass, Function, Engraftment, or Inflammation (RFA DK02-002)

In type 1 diabetes, insulin-producing beta cells are destroyed in an autoimmune process that involves infiltration, and subsequent inflammation of the pancreatic islets by immune system T cells. Methods to non-invasively image beta cell mass, function, and inflammation and the engraftment of transplanted islets would enhance

the ability to monitor disease progression and response to therapy in individuals who have or are at risk of developing type 1 diabetes. The technologies required to meet these goals are in their infancy, and much work remains before pancreatic beta cells will be routinely imaged in the clinic or in clinical research. The success of this effort will depend on the identification of specific cell surface molecules that can be targeted with contrast agents that discriminate beta cells from the surrounding tissues.

Six individual-investigator grants were awarded by the NIDDK in September 2002 for 2-4 year projects on the development of new techniques or reagents for imaging beta cells in vivo. Research topics being addressed through these grants include:

- Researchers will explore new methods to apply Magnetic Resonance Imaging (MRI) technology to the non-invasive monitoring of beta cells and transplanted islets. These studies focus on the identification of beta cell surface markers that can be used as targets for antibody-linked MRI contrast agents, the development of agents that selectively identify inflammatory T cells invading the pancreas, and the use of novel contrast agents to label beta cells and track their location and mass after transplantation.

- Fluorescence and luminescence-based technologies are being examined for use in real-time, non-invasive imaging of beta cells and islets. Scientists are developing fluorescent-tagged beta cells to study tolerance induction to transplantation in mice, luciferase-labeled beta cells to track cellular viability and function after islet transplantation, and fluorescent calcium sensors to characterize molecular signaling pathways in intact islets.

New Strategies for Treatment of Type 1 Diabetes Mellitus (RFA DK00-001)

Patients with type 1 diabetes are at increased risk for severe complications due to long-term elevations in blood glucose. Although the Diabetes Complications and Control Trial (DCCT) showed that close glucose control could reduce the incidence of complications, such control is difficult to achieve and creates a high risk of acute, life-threatening hypoglycemia. This initiative supports the development of new, clinical strategies for the prevention, treatment, or cure of type 1 diabetes in human patients. In FY 2000, the NIDDK awarded three grants of 2-3 years duration for clinical trials to improve islet transplantation or to maintain residual beta cell function in new-onset patients.

Functional Genomics of the Developing Endocrine Pancreas (RFA DK99-007)

This initiative sought to identify all genes expressed in the developing endocrine pancreas and to generate both microarray and bioinformatics tools, which could be used to study development, function, and disease progression in type 1 diabetes. A supplemental objective was added in FY 2001 to screen cDNA libraries for clones that might be useful as markers for beta cell precursors. The NIDDK and JDRF awarded two resource-related grants in FY 1999 to establish an Endocrine Pancreas Consortium. One project provided the consortium with expertise in diabetes and high throughput sequencing capacity through the Washington University Genome Sequencing Center. The other project brought expertise in mouse genetics and bioinformatics through the University of Pennsylvania Center for Bioinformatics. A third investigator offered expertise in pancreatic development through subcontracts to both sites.

A database and tools to query sequence and expression data generated by the consortium have been created (http://www.cbil.upenn.edu/EPConDB/).
The Consortium has deposited more than 160,000 sequences into dbEST, the expressed sequence tag (EST) database (http://www.ncbi.nlm.nih.gov/dbEST/). At the conclusion of this project, it is anticipated that over 200,000 clones will have been sequenced and deposited in dbEST. Examples of scientific advances and research publications supported by this initiative are located in the main text and Appendix 4.

Cellular and Molecular Approaches for Achieving Euglycemia (RFA DK98-007)

This program encouraged the development of therapies to achieve normal glucose levels in patients with type 1 diabetes. Grants were awarded on a range of relevant topics, including islet and beta cell transplantation, engineering of regulated insulin secretion in non-beta cell surrogates, hematopoietic stem cell therapy for the induction of tolerance, and development of technologies to preserve beta cell function and stimulate beta cell regeneration. Particular emphasis was placed on the development of clinically applicable technologies.
The NIDDK, NIAID, and NICHD awarded 20 grants in FY 1998 for 2-3 year periods; two additional grants were supported with regularly appropriated funds. Examples of scientific advances and research publications supported by this initiative are located in the main text and Appendix 4.

Beta Cell Proteomics (PAR-00-101)

The NIDDK supported one application received in response to this NHGRI announcement that encouraged development of innovative tools and technology for functional annotation of the human genome.
The NIDDK funded this project for 1 year to introduce novel pancreatic cDNAs into a recombinable vector system, to express these proteins in quantity for collaborative investigation, and to perform pilot investigations on the function of these proteins in collaboration with investigators in the Beta Cell Biology Consortium.

Glucagon-like Peptide as a Differentiation Factor for Pancreatic Beta Cells

Transplantation of a cadaveric pancreas or isolated islet tissue is currently the only effective means of restoring functional beta cells to type 1 diabetes patients. These protocols could be advanced by the development of techniques to isolate and propagate potential beta cell precursors from a patient's own pancreas and, then, to differentiate these precursors into functional beta cells for transplantation back into the patient.

Several lines of evidence suggest the existence of a malleable population of precursor beta cells in the adult mammalian pancreas. The adult pancreas can respond to increasing demands (from obesity, pregnancy, partial pancreatectomy, or toxic injury to the pancreas) for insulin synthesis and secretion by hypertrophy of existing beta cells, mitosis of existing beta cells, and neogenesis from a pool of beta cell precursors. Neogenesis—the formation of new beta cells from undifferentiated precursors—occurs through islet budding from the larger pancreatic ducts during pancreatitis and after partial pancreatectomy. Formation of new beta cells may also be possible from a population of nestin-positive cells in the islets. Moreover, the formation of small clusters (fewer than 10 cells) of insulin-positive cells in the centroacinar parts of the pancreas is observed following treatment with glucagon-like peptide-1 (GLP-1). This NIA intramural project studies methods to propagate centroacinar cells of the pancreas in culture and, subsequently, to convert them into endocrine cells.

DirecNet: A Network to Test Glucose Sensors in Children with Type 1 Diabetes (RFA HD01-009)

Hypoglycemia had been the major limitation to implementation of intensive glycemic control, which has been shown to prevent or delay microvascular complications in adolescents and adults with type 1 diabetes. Intensive therapy has not been systematically evaluated in children younger than 13 years of age with type 1 diabetes. Younger children may be at increased risk for hypoglycemia in the setting of intensive therapy and the risk/benefit ratio of intensive glycemic control achieved with current therapeutic tools may be less favorable in this population.

This initiative was designed with two main objectives: 1) to assess glycemic control and the incidence, magnitude, and duration of hypoglycemia in children with type 1 diabetes, and 2) to measure glucose levels of children without diabetes for the purpose of defining the normal range of glycemia in this population. Further, this study will examine continuous glucose sensing technology, which has not yet been tested in children, to determine its value in improving metabolic control and reducing the risk of hypoglycemia in young children.

In August 2001, five clinical centers and a coordinating center were awarded and the resulting research consortium was named "The Diabetes Research in Children Network (DirecNet)." At an organizational meeting in November 2001, the Network initiated the development of a protocol for a clinical trial to establish the accuracy of the two continuous glucose monitors that are currently available. While the accuracy level of the glucose sensors is under evaluation, the Network is designing additional protocols. Future plans entail a study to determine glucose levels in non-diabetic children as well as an outpatient study to address the feasibility of sensor use in diabetic children and to collect data on the glucose profiles of these patients.

Standardization Program to Improve the Measurement of Blood Glucose by Portable Monitoring Systems

People with diabetes and their health care providers rely on the results reported by portable blood glucose monitoring systems to make treatment decisions. Improper treatment can result if performance is not comparable among the many different systems that are available. This project was launched by the CDC to evaluate the variability among blood glucose monitoring systems and to develop a standardization program to normalize results among these systems.

The CDC has established a laboratory devoted to developing a mass spectrometry-based reference method for measuring glucose in whole blood. Researchers have optimized and validated a published isotope dilution gas chromatography mass spectrometry method for use as a potential reference method for measuring glucose in whole blood. In addition, the laboratory initiated research on secondary reference materials for whole blood glucose, and developed an extensive study protocol, with input from manufacturers, the FDA, and clinical chemistry experts, to examine variability among popular handheld blood glucose monitoring systems.

Effects of Hypoglycemia on Neuronal and Glial Cell Function (RFA NS02-008)

Recent therapeutic strategies aimed at closely controlling elevated glucose levels in diabetic individuals put them at risk for experiencing multiple episodes of hypoglycemia. Acute episodes of hypoglycemia can result in alteration of brain function, confusion, abnormal behavior, seizures, or coma. Likewise, recurrent hypoglycemia can potentially harm the cells of the central nervous system or impose long-lasting damage on the brain. This initiative focuses on

elucidating the effects of acute and recurrent episodes of hypoglycemia on glial and neuronal cells of the developing and mature central nervous system.

The six grants funded in September 2002 by the NINDS, NIDDK, and JDRF should enhance understanding of the effects of hypoglycemia on brain function, and could lead to new targets for therapeutic intervention of this serious complication. Research projects in progress through these grants include:

- Various approaches will be taken to study the effect of hypoglycemia on glial-neuronal interaction. The ability of astrocytes, a type of glial cell, to maintain neuron survival during hypoglycemic episodes by supplying energy substrates, growth factors, and/or neurotransmitters to neurons will be examined. Scientists are researching metabolic interactions between neuronal and glial cells during hypoglycemia and as a function of age. Results from these studies may help to determine how glial-neuronal signaling is impacted by acute and/or recurrent episodes of hypoglycemia.

- Several studies will examine the molecular mechanisms of hypoglycemia-induced nerve cell injury and/or death. Research on the damaging effects of adenosine and, conversely, the potentially protective role of ketones during episodes of hypoglycemia may, in the long term, lead to new strategies for the clinical management of hypoglycemia to reduce brain injury.

- Researchers are investigating the cellular mechanisms by which glucose is sensed in the brain, how glucose signaling is affected by hypoglycemia, and how those signals are integrated to initiate the counter-regulatory response to hypoglycemia.

Sensor Development and Validation (RFA EB02-002)

Management of type 1 diabetes has been improved by the availability of continuous, non-invasive glucose monitoring systems and insulin pumps. Nonetheless, this advanced technology does not fully replicate the body's natural ability to link insulin secretion directly and continuously to blood glucose levels. The NIDDK participated in this broad NIBIB solicitation to support research on novel glucose sensing methods and "closed-loop" insulin delivery systems. In particular, applications related to technologies leading to a closed-loop, indwelling, artificial pancreas that can sense blood glucose and deliver insulin in a manner that reproduces normal physiology were considered.

In September 2002, NIBIB and NIDDK awarded four individual investigator research grants of 3-5 years duration. Research projects supported through this program include:

- New algorithms are being developed to link the output of an implantable glucose sensor to an insulin pump in a way that closely mimics the physiological release of insulin from the beta cells in response to changes in glucose levels. Such a closed-loop system would enable diabetic individuals to control their glucose levels without the need for constant intervention.

- Scientists are engineering cells from the pituitary—a gland in the brain—to express insulin and other proteins that are needed to sense glucose and translate this signal into insulin release. In preliminary animal studies, these bioengineered cells were capable of evading attack from the immune system, an important consideration for treatment of type 1 diabetes. Studies are in progress to optimize the viability and insulin-delivery function of the cells.

- A team of 11 researchers with expertise in subjects ranging from chemical sensors to wireless communications is developing a novel sensor that will use a miniature near infrared spectrometer to detect and measure glucose levels. Another group is designing an implantable glucose sensor for long-term use

in humans. This research could provide critical new tools for the management of glucose levels and the detection of hypoglycemia before the onset of life-threatening complications.

Understanding Hypoglycemia Unawareness in Patients with Type 1 Diabetes (RFA DK01-031)

Many individuals with diabetes experience a progressive decay in the counter-regulatory response to hypoglycemia over time. Falling blood glucose levels fail to trigger epinephrine secretion and, therefore, no neurogenic symptoms occur to warn the patient of a problem. Such "hypoglycemia unawareness" can cause prolonged exposure to hypoglycemia and result in potential brain injury, seizure, or loss of consciousness. The development of hypoglycemia unawareness makes the implementation of intensified blood glucose control more difficult and puts patients at risk for severe hypoglycemia-related complications. This initiative fosters basic and clinical research on molecular mechanisms underlying hypoglycemia unawareness and novel approaches to prevent or reverse this condition in diabetic patients.

The NIDDK, NINDS, and JDRF awarded eight research grants relevant to hypoglycemia unawareness in September 2002 for funding periods of 2-5 years. Research topics being pursued through these grants include:

- Structures in the brain, such as the hypothalamus, act as critical sites of physiological response to hypoglycemia. Researchers will use both animal models and human patients to explore how the brain reacts to hypoglycemia, and to determine how these response mechanisms change under conditions of repeated hypoglycemic episodes.

- In addition to the brain, the peripheral nervous system is involved in sensing and responding to hypoglycemia. Investigators will study how the rapid production of glucose in the liver in response to falling glucose levels is impaired in type 1 diabetes patients. Further, the role of portal vein glucosensors in the body's response to hypoglycemia will be explored.

- Secretion of glucocorticoids—hormones produced in the adrenal glands—may contribute to the condition of hypoglycemia unawareness. Researchers are developing a mouse model of chronic hypoglycemia and hypoglycemia unawareness that will enable them to more closely examine the role of glucocorticoids in the body's defense against repeated hypoglycemia.

Glucose Sensors in the Treatment of Diabetes (RFA DK98-008)

Accurate, non-invasive glucose sensors hold great promise for improving glucose control and quality-of-life for individuals with type 1 diabetes. This initiative supported research on the development of novel glucose sensors or the creation of a closed-loop system for regulating blood glucose, incorporating advances in chemistry, engineering, cell biology, biochemistry, and endocrinology. In FY 1998, the NIDDK and NCRR awarded 17 grants of 2-3 years duration for research on novel glucose-sensing technologies. Examples of scientific advances and research publications supported by this initiative are located in the main text and Appendix 4.

Developing New Tools for Detecting and Monitoring Low Blood Glucose for People with Diabetes

Hypoglycemia is the most common problem limiting diabetes management. This program focuses on the development of innovative and minimally-invasive technology to alert people with diabetes of an impending hypoglycemic episode, to minimize the morbidity and mortality associated with hypoglycemia, and to aid glycemic control, thus reducing the risk for microvascular complications of diabetes. The CDC funded three research grants in response to program announcement #99151, "Innovative Technology Development Grant for the Detection and Monitoring of Diabetic Hypoglycemia by Non- or Minimally-Invasive Techniques." Regularly appropriated CDC funds were also used to support this program. Examples of scientific advances supported by this initiative are located in the main text and Appendix 4.

Genetics of Kidneys in Diabetes (GoKinD) Study

Kidney disease, which is a major complication of type 1 diabetes and contributes to much of the illness and death associated with the disease, is thought to have a significant genetic component. However, large sample sets for the study of the genetics of kidney disease in diabetes are not currently available. The CDC is collaborating with the Juvenile Diabetes Research Foundation (JDRF), the Joslin Diabetes Center, and George Washington University (GWU) on the Genetics of Kidneys in Diabetes (GoKinD) Study, which will develop a set of DNA samples for the study of the genetics of kidney disease in type 1 diabetes. This study complements a similar collection in the U.K., as well as the NIH Family Investigation of Nephropathy in Diabetes (FIND) Study for determining genetic risk factors for kidney disease associated with different predisposing conditions.

Major study goals include recruiting 600 people with type 1 diabetes and kidney disease together with their parents, and 500 people with type 1 diabetes and kidney disease whose parents are not available (cases). As controls, 500 people with type 1 diabetes who do not have kidney disease and their parents, and 500 people with type 1 diabetes and no kidney disease whose parents are not available will be recruited. The total number of participants is expected to be 4,300.

The CDC is: 1) genotyping the major type 1 diabetes genetic risk factors; 2) isolating DNA from stabilized cell lysates or transformed cells; 3) providing quality control for the DNA collection; 4) providing a repository for the DNA, transformed cells, serum, plasma, and urine; 5) aliquoting the DNA and distributing it to approved researchers; 6) providing oversight of studies of genetic risk factors for kidney disease; and 7) serving on the Executive and Steering committees.

Planning for the study, including staffing, training, protocol development, and IRB approval, occurred in 1998-2000. The study launch and patient recruitment began in 2001. Enrollment is ongoing at both study sites and the CDC is genotyping samples for sequence-based typing of: 1) the HLA class II genes, DRB1, DQA1, and DQB1; 2) the B23 insulin gene SNP; and 3) a set of markers for sample verification. Samples have also been received at the CDC for potential participants that did not meet the criteria for case subjects and will be held for follow-up in a year to determine whether their kidney disease has progressed such that they qualify as case subjects at that time. DNA sample sets are being prepared for distribution to investigators interested in performing genome-wide or other proposed genetic analyses.

Epidemiology of Diabetes Interventions and Complications (EDIC) Study

The prevalence, incidence, and determinants of cardiovascular disease and uropathic and other complications of autonomic neuropathy are being investigated in the type 1 diabetic cohort of the Epidemiology of Diabetes Interventions and Complications (EDIC) study. EDIC —the long-term follow-up of the Diabetes Control and Complications Trial (DCCT)—offers a unique opportunity to study the prevalence and determinants of complications because of the depth and breadth of clinical data on glucose control, other risk factors for diabetic complications, co-morbid conditions, genetic factors, and family history that have been collected in this cohort for nearly 20 years. Participation rates for these faithful and enthusiastic study volunteers remain near 95 percent.

- **Cardiovascular Disease:** Carotid ultrasounds were obtained to assess carotid artery atherosclerosis—"hardening of the arteries"—in 1994-1995 at EDIC baseline through regular NIDDK funding and, using special statutory funds, in 1998-2000. At EDIC baseline, carotid artery intima-medial thickness (IMT)—an indirect measure of artery blockage—was similar to that in controls. However, after 6 years, IMT was significantly greater in the EDIC diabetic cohort than in the non-diabetic controls. Progression of IMT was significantly less in the former DCCT intensive than in the conventional treatment group, after adjusting for other risk factors.

  These results demonstrate that atherosclerosis develops more slowly with age in type 1 diabetic individuals whose blood sugar has been kept near normal by intensive treatment of their diabetes. Moreover, the risk of atherosclerosis in type 1 diabetes was shown to be increased by higher blood pressure and cholesterol and by smoking, just as it is in non-diabetic individuals. Thus, the complications resulting from premature atherosclerosis, such as heart attacks and strokes, may be prevented by intensive treatment to keep blood sugar, blood pressure, and cholesterol levels as low as is safely possible.

  A third carotid ultrasound and a coronary calcification study are planned through the special funding program. These will allow a more precise measure of the change in atherosclerosis over time. Such changes can be correlated cross-sectionally with atherosclerotic cardiovascular events and other co-morbidity such as nephropathy, and prospectively with future incidence of events, which are expected to accelerate as this cohort ages. The rate of change in atherosclerosis will be correlated with risk factors measured earlier in DCCT/EDIC. The change in carotid IMT will be correlated with the presence, magnitude, and change in coronary atherosclerosis measured by CT scanning. The extent to which carotid IMT and coronary calcification correlate when measured close in time will help other investigators who wish to relate surrogate measures of cardiovascular events in other studies.

- **Uropathy and Autonomic Neuropathy:** Although it has been suggested that bladder dysfunction, sexual and erectile dysfunction, and urinary tract infections are more common in individuals with diabetes, only limited data on these conditions is available among adults with type 1 diabetes. In addition, little data exists on other neuropathic complications of diabetes, including gastroparesis, diabetic diarrhea/constipation, gall bladder dysfunction, orthostatic hypotension, cardiac sudden death, sweating dysfunction, and hypoglycemia unawareness.

  In 2001, NIDDK convened a meeting of scientific experts in sexual function, urinary incontinence, and urinary tract infections. The meeting included discussions of the current state of knowledge, gaps in knowledge, and future directions for research in urologic complications in individuals with diabetes. Researchers have developed a self-administered questionnaire, brochure, and informed consents for the EDIC cohort, which will provide information on the prevalence of these conditions in this patient population. Plans are under way to obtain identical information on a cohort of individuals without diabetes. In May 2002, a meeting of experts in autonomic neuropathy helped to define and rank the clinical importance of various forms of autonomic neuropathy. This panel advised on optimal methods for measuring and quantifying these syndromes and on the costs of such methods in terms of time, money, and imposition on study participants.

Studies to Identify Genetic Associations in Patients with Microvascular Complications

The special statutory funds have been used to add a diabetic retinopathy genetics component to the ongoing diabetic nephropathy genetics study known as FIND—Family Investigation of Nephropathy in Diabetes. This consortium seeks to identify genes or genomic regions that are associated with risk for the development and progression of diabetic nephropathy and retinopathy. Evidence suggests that genetic factors may contribute to the initiation and/or rate of progression of both diabetic retinopathy and nephropathy, although it is not known whether those factors are distinct for the two conditions. The projected number of patients for the retinopathy study is 1,350 and the total projected enrollment is approximately 3,375. Six participating investigative centers will recruit these individuals over a period of 3.5 years.

In 2002, a contract was signed with an extramural Fundus Photograph Reading Center to train and certify fundus photographers at the clinical centers, and to coordinate the acquisition, transfer, storage, and analysis of the ophthalmologic data. The study protocol has been finalized and the six study centers are actively recruiting subjects.

Diabetic Macular Edema Clinical Trials Network (RFA EY01-001)

Macular edema secondary to diabetic retinopathy—eye disease—is a major cause of visual loss in patients with diabetes. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy suggest that the incidence of developing diabetic macular edema (DME) is 20 percent in patients with type 1 diabetes. Current treatments for diabetic macular edema reduce the risk of vision loss by only 50 percent. A number of compounds for the treatment of DME have entered development programs, and new treatment concepts have emerged.

The DME Clinical Trials Network will develop the infrastructure needed to accelerate the development and conduct of multi-center clinical trials of new, potential treatments for diabetic macular edema. This approach provides a framework for rapid initiation of important studies, efficient use of pooled clinical expertise in idea generation and protocol development, and efficient use of central resources for data management, quality control, and endpoint evaluation. Clinical trials, targeting different stages of DME, will be designed to evaluate strategies to prevent clinically significant macular edema (CSME) in patients at risk, treatments for newly diagnosed CSME, and treatments for persistent CSME. A Network Protocol Review and Oversight Committee will make the final selection of studies that will be performed.

In FY 2002, NEI awarded cooperative agreements that support three core centers to plan, implement, and conduct clinical trials of the treatment of diabetic macular edema. These will include a Network Study Chair, a Coordinating Center (CC), and a Fundus Photograph Reading Center. The coordinating center is supported through the special funding program. Clinical centers will be added to the network during the first year of operation as subcontracts to the Coordinating Center. One clinical center will be established in the NEI Intramural Program and supported by NEI intramural funds.

Animal Models of Diabetic Complications Consortium (RFA DK01-009 and HL01-010)

The cross-disciplinary Animal Models of Diabetic Complications Consortium (AMDCC) (http://www.amdcc.org) will promote the development of innovative mouse and large animal models that closely mimic human complications of diabetes. Complications to be examined include diabetic kidney disease, retinopathy, neuropathy, micro- and macrovascular disease, peripheral vascular disease, hypertension,

impaired wound healing, diabetic cardiomyopathy, abnormalities of the coagulation system, urinary tract infection, oral diseases, and altered gastrointestinal and bladder function. The primary goal of the AMDCC is to generate animal models that will be useful for studying disease pathogenesis, prevention, and treatment. The AMDCC will also test the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, particularly diabetic kidney disease and accelerated cardiovascular diseases.

The special funding program supports six of the nine principal investigators of the AMDCC, which was established in September 2001 by the NIDDK and NHLBI. A steering committee, subcommittees to address the topics of cardiovascular disease, animal husbandry, nephropathy, bioinformatics, and ontogeny, and an external advisory panel have been organized.

Improving the Clinical Measurement of Hemoglobin A1C

Measurement of hemoglobin A1C (HbA1C) reflects the average degree of blood glucose control achieved over the preceding 3 months. The correlation between HbA1C and risk-associated outcomes demonstrated in the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) underscores the need to measure HbA1C with sufficient reliability such that clinical laboratory results can be directly related to these studies and, therefore, to the risk for development or progression of diabetes-related chronic complications. A lack of comparability of HbA1C test results among methods and laboratories is a major obstacle to the effective implementation of a national strategy to reduce the complications associated with diabetes through proper glycemic control.

The CDC provides continuous technical support and assistance to the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry (IFCC) programs to improve and standardize HbA1C laboratory measurements. Moreover, technical assistance is offered to public health groups involved in diabetes translation to enhance diabetes management using HbA1C measurement. This ongoing CDC program, which has also received support from regular CDC appropriations, was launched in FY 1998.

Pilot Trials to Prevent or Slow Progression of Diabetic Nephropathy (RFA DK02-025)

Patients with type 1 diabetes have a 20-40 percent lifetime risk of kidney failure. Because many of these patients develop progressive kidney disease despite adequate management of risk factors, new strategies to prevent disease and slow its progression are needed. This initiative supports clinical research on new therapies to prevent or treat diabetic kidney disease that might potentially be taken to large, phase 3 interventional trials. Support from this program should ensure that sufficient preliminary data will be available to plan such trials. Unless contraindicated, proteinuric subjects in the control and trial groups will be treated with a renin-angiotensin system blockade as the current standard of care, and the studies will examine either addition of alternate agents or incremental effects of this blockade. Enrollment strategies will emphasize a patient population in young- to mid-adulthood and strong representation of patients with type 1 diabetes.

The NIDDK awarded three grants in September 2002 for 2-year pilot studies of novel therapeutic agents for the treatment of diabetic nephropathy. An additional grant is supported with regular NIDDK appropriations. Strategies being explored through these grants include:

- Blockade of the renin-angiotensin system with angiotensin converting enzyme inhibitors (ACEIs) can help slow, but often does not stop, the progression of diabetic kidney disease. Pilot trials are being performed on the effectiveness of combining ACEI treatment with: perfenidone, an inhibitor of transforming growth factor beta production; angiotensin receptor blockers; spironolactone, a mineralocorticoid receptor antagonist; or a diuretic.

Surrogate Endpoints for Diabetic Microvascular Complications (RFA DK02-016)

Prevention and treatment of long-term micro- and macrovascular complications remain critical problems in the management of type 1 diabetes. Early identification and intervention of patients at risk for the development of diabetic complications are essential. By the time disease symptoms are recognized, irreversible organ damage may have already occurred. This program supports research on the development of surrogate endpoints, which are biological markers that can be used to gauge a person's health without having to wait for full-blown disease to develop. Ideally, these biomarkers will predict patients who are at high risk for developing complications and who may benefit from aggressive intervention, aid in early diagnosis of complications, or correlate with disease progression. Such endpoints could be used as diagnostic tools for the individual patient, or as outcome measures for clinical trials of new therapeutic agents.

The NIDDK, NEI, and NINDS awarded 10 grants for basic and clinical projects of 2-5 years, starting in September 2002. These grants support several promising lines of research on surrogate endpoints, including:

- Due to limitations of tissue access in the eye, as well as other organs affected by diabetes, surrogate biomarkers or non-invasive assays are needed for the assessment of early tissue damage. Researchers are using a laser Doppler imaging method to determine whether reduction in blood flow to the retina can serve as an early marker of retinopathy. Other studies are exploring the hypothesis that circulating proteins or cells in the blood may act as biomarkers by displaying measurable changes that reflect damage to the vasculature of the retina due to diabetes.

- Investigators are developing tests for diabetic nerve disease that could assess both the extent of disease and the response to therapy. Strategies include a test for corneal nerve fiber degeneration; the measurement of blood levels of p75NTR, a protein that is shed into the blood upon small nerve fiber stress or damage; and a statistical analysis to detect qualitative differences in the spatial pattern of nerves in diabetic and non-diabetic individuals.

- Researchers will examine the relationship between the development of kidney disease or other complications and blood and/or urine levels of proteins that may contribute to vascular damage in diabetes. Potential biomarkers include matrix metalloproteinases and their inhibitors; factors that affect the production or detoxification of advanced glycation endproducts (AGEs); and the complement regulatory protein CD59. In addition, scientists will test the hypothesis that elevated glucose can lead to clonal selection of mesangial cells in the kidney microvasculature that carry a genetic marker of susceptibility to nephropathy. This research could lead to new paradigms for identifying and treating patients at risk of diabetic kidney disease and other complications.

Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissues (RFA DK02-001)

Impaired perfusion—the ability of oxygen to reach tissues—may be an early event in the development of microvascular complications of diabetes. This program will provide the diabetes clinical community with reliable, inexpensive imaging tools to measure perfusion and tissue oxygenation at the level of the microvasculature, or to identify inflammation associated with diabetic

complications. Such tools will help define the mechanisms leading to microvascular complications of diabetes in peripheral tissues. Moreover, this research may result in the development of new techniques to detect the early stages of these complications, identify patients likely to benefit from therapeutic interventions, and monitor disease progression and response to therapy.

In September 2002, the NIDDK approved six grants of 2-4 years duration that will pursue research on the development of new, clinically useful imaging tools for the study of microvascular disease in the diabetic population. Specific research topics include:

- Diabetes often leads to significant loss of blood flow, perfusion, and oxygenation in the limbs, which impairs wound healing and increases an individual's risk for amputation. Several studies will use novel imaging technologies to assess defects in the skeletal muscle blood supply of diabetic individuals. These non-invasive techniques, which include new methods for magnetic resonance imaging (MRI), contrast-enhanced ultrasound, and dynamic near-infrared optical tomography (DYNOT), make use of systems that are readily available or easily adaptable. If successful, research findings from these projects could be rapidly adopted for the clinical management of diabetes.

- Diabetic retinal disease and peripheral nerve damage frequently occur together in diabetic patients and exhibit similar pathologies. It is much easier to visualize the microvasculature in the retina than in the skin or nerves. Therefore, researchers will evaluate whether retinal imaging tests can also be used to diagnose early damage to peripheral nerves or microvasculature.

- Osteomyelitis—inflammation of the bone—and deep infection in the diabetic foot are relatively common complications. Early diagnosis of these conditions can reduce the need for amputation in these patients. Scientists will determine whether a non-invasive imaging technology—[18F] fluorine deoxyglucose Positron Emission Tomography (FDG-PET)—can reveal sites of inflammation in the foot with high sensitivity and accuracy.

Oral Microbiology and Immunology of Type 1 Diabetes (RFA DE01-001)

Diabetes is a significant factor for severe and extensive periodontal (gum) disease. Recent studies indicate that diabetes alters the immune system and connective tissue, making the patient more susceptible to oral tissue destruction and inflammation. This initiative supports exploratory research that will broaden the understanding of the microbiology and immunology of oral complications associated with type 1 diabetes. A primary objective is to stimulate collaborative projects between principal investigators (PIs) with expertise in a variety of scientific disciplines, and especially from women, underrepresented minorities, or disabled scientists.

The NIDCR awarded five grants of 2-years duration in FY 2001 for innovative, collaborative research on the oral complications of diabetes. An additional grant was awarded with regular NIDCR appropriated funds. Research topics being addressed include:

- Research is under way on the efficacy of treating diabetic patients with low dose doxycycline (LDD) to reduce periodontitis (gum disease). LDD appears to block the action of enzymes that destroy the tissues that support the teeth.

- Oral bacteria, antibody, and cytokine levels will be measured in adult type 1 diabetes patients with disease duration of 10 years. These studies will provide fundamental information about the microbiological and immunological characteristics of type 1 diabetes.

- The neutrophil response to oral pathogenic bacteria and associated bacterial virulence products will be examined in type 1 diabetic patients with periodontal diseases. This study will test the hypothesis that these patients have an unusually high inflammatory response that contributes to the onset and progression of periodontal diseases.

- Researchers will assess the prevalence, incidence, and progression of periodontal diseases of type 1 diabetic and non-diabetic control subjects. The microbial content of oral plaque and antibody levels to oral bacteria will also be determined.

- Scientists are studying the symptoms, bacteria, and resolution of tooth pulp infections in diabetic patients, about which very little is currently known.

Neurobiology of Diabetic Complications (RFA NS00-002)

Chronically high blood glucose levels result in significant nerve damage in more than half of all diabetic individuals. Diabetic peripheral neuropathy—affecting the hands, arms, feet, and legs—is associated with vascular disease and impaired wound healing, and often results in chronic skin ulcers and limb amputation. The nervous system also controls the body's counter-regulatory response to hypoglycemia. This program supports research on the mechanisms by which diabetes results in painful, disabling peripheral neuropathy, autonomic neuropathy, impaired counter-regulation and hypoglycemia unawareness, and other neurological complications.

Diabetic neuropathy is a very difficult and underfunded area of research. Because of two initiatives (RFA NS99-005 and RFA NS00-002) supported by the special statutory funds, the number of funded research projects in diabetic neuropathy is far greater than it would have been otherwise. The NINDS, NIDDK, and JDRF awarded 18 grants of 2-4 years in FY 2000 for research on diabetic neuropathy. One additional grant was supported with regularly appropriated NIDDK funds. Though some of these grants are active through FY 2003, examples of scientific advances and research publications supported by this initiative are located in the main text and Appendix 4.

Neurological Complications of Diabetes (RFA NS99-005)

Neurological complications are significant problems for diabetic individuals. In many patients, symptoms such as pain, numbness, weakness, or even paralysis are serious enough to interfere with daily activities. Other symptoms of diabetic neuropathy may include heart rate abnormalities, high blood pressure, dizziness, digestive disturbances, and impotence. Autonomic neuropathy can cause sudden cardiac death in persons with diabetes. Prevention and treatment are often ineffective, so new approaches are needed. This program supports research on the mechanisms by which diabetes results in painful and disabling neuropathies and other neurological complications, and on the development of interventions to prevent, limit, or reverse these conditions.

In FY 1999, the NINDS and NIDDK funded 10 grants for 2-4 years to individual investigators for the support of research on neurological complications of diabetes. Examples of scientific advances and research publications that have emerged from these grants are located in the main text and Appendix 4.

Pathogenesis and Therapy of Complications of Diabetes (RFA DK98-009)

Prevention and treatment of chronic complications are central medical issues for patients with type 1 diabetes. In the U.S., diabetes is the leading cause of new blindness in working-age adults, of new cases of end stage renal disease, and of non-traumatic lower leg amputations. In addition, macrovascular complications are a major cause of morbidity and mortality in diabetic individuals. This program encouraged research on the mechanisms by which hyperglycemia causes vascular complications, and the application of this information to the development of interventions to prevent or treat diabetic complications. In FY 1998, the NEI, NHLBI, NICHD, NIDDK, and NINDS awarded 30 grants of 2-5 years duration. An additional six grants were supported with regularly appropriated funds. Examples of scientific advances and research publications attributable to these grants are located in the main text and Appendix 4.

Development of Clinical Markers for Kidney Disease

This initiative ensures access by the research community to all needed genomic and bioinformatics tools for the study of diabetic renal injury and bladder dysfunction in human disease. The program aims to develop a detailed website-based inventory of resources, databases, and other scientific tools of utility for investigation of the mechanisms of diabetic nephropathy and bladder disease, and, simultaneously, to provide funding that will remedy major gaps in existing resources. The activities of this program are closely integrated with the NIDDK Biotechnology Resource Centers (*see Goal I*) and the Animal Models of Diabetic Complications Consortium.

Advanced Glycation Endproducts

Advanced glycation endproducts (AGEs) may serve as potential biomarkers for diabetic complications. However, the lack of comparability of assay results from different laboratories and the lack of appropriately characterized reference materials have prevented the appropriate testing of these promising biomarkers. These issues have also impaired the transfer of research findings into relevant information for public health application. This CDC project helps to clarify the role of AGEs in diabetes management by improving laboratory measurements and translating research findings into information suitable for appropriate public health activities through technical assistance to research laboratories. The AGE standardization effort was launched in FY 2001. After consultation with a team of seven extramural scientific experts to start the program, the CDC has established the laboratory infrastructure to research measurement issues and develop reference methods and materials.

Training Programs in Diabetes Research for Pediatric Endocrinologists (RFA DK02-024)

To foster development of a diverse and highly trained workforce of pediatric endocrinologists to assume leadership roles related to research efforts in the area of pediatric diabetes, this initiative establishes joint programs for the research training and career development of pediatric endocrinologists. Complementary institutional research training (T32) and clinical scientist career development program (K12) grants provide integrated programs to prepare pediatricians for careers in pediatric endocrinology research related to diabetes. By creating multi-level (postdoctoral fellow and junior physician scientist) training and career development programs, the T32 and K12 programs provide a pathway for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator. Moreover, the institutions receiving these awards are encouraged to interact with one another and to facilitate career development pathways involving multiple institutions.

These new training and career development programs for pediatric endocrinologists, in combination with the NIH-wide loan repayment program, offer a means for pediatric endocrinologists to pursue careers in academic medicine related to diabetes research. This joint program of the NIDDK, ADA, and JDRF awarded seven combined T32/K12 training program grants in FY 2002 and 2003.

Innovative Partnerships in Type 1 Diabetes Research (RFA DK02-023)

This program fosters collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and researchers from other scientific areas who have relevant expertise. This initiative will attract new research talent, strengthen the efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research, and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. Type 1 diabetes researchers are encouraged to act as "talent scouts" by actively recruiting leading scientists with needed expertise to the field.

In September 2002, the NIDDK, NEI, and NIAID awarded 16 pilot and feasibility grants of 2-years duration for research on innovative approaches for the detection, prevention, and treatment of type 1 diabetes and its complications. Specific research topics of these grants include:

- Several studies are in progress to define the genetic and environmental causes of type 1 diabetes. Zebrafish genetics, which is much less complex than human or mouse genetics, will be exploited to identify new genes that predispose to aberrant T cell activity and the development of autoimmunity. New, high-throughput technologies are being applied to identify the potential roles of specific viral pathogens as triggers of autoimmunity and type 1 diabetes. Researchers are investigating the underlying pathology of a new rat model of autoimmune diabetes; this work will help to validate the LEW.1AR1/Ztm-iddm strain, which arose from a spontaneous mutation, as a useful animal model of type 1 diabetes.

- Developing new methods to prevent or reverse type 1 diabetes will require a complete understanding of the autoimmune disease process. Investigators are studying the molecular signaling pathways of two types of molecules that may contribute to the underlying pathogenesis of type 1 diabetes: "cathepsins,"

which are a class of protein-degrading enzymes involved in antigen processing, and the "toll-like receptor," which is known to participate in the immune response to infections. Another study will focus on how T cells that recognize "self" molecules are able to escape negative regulatory mechanisms that would normally kill these cells, and then establish an autoimmune disease process. Scientists will also determine the feasibility of using a virus carrying diabetes-related autoantigens to promote immune tolerance and suppress the development of type 1 diabetes in at-risk individuals.

- Understanding the development and function of the insulin-producing beta cells, which are lost in type 1 diabetes, is key to preventing or treating this disease. Scientists will investigate the cellular signaling mechanisms of GLP-1, a hormone originating in the intestine that regulates beta cell function, proliferation, and survival. Another group will test the hypothesis that inserting the insulin gene into the "G" cells of the stomach can produce surrogate beta cells. If the proper signaling environment is present, such genetically engineered cells could release insulin in response to food intake and, thereby, help to regulate blood sugar levels. Similarly, researchers are exploring the use of embryonic stem cells to produce replacement beta cells. A bioassay in development will screen a 15,000 compound library for small molecules that can activate the "*pdx-1*" gene, an early marker of beta cell differentiation, in the stem cell population.

- A team of investigators has proposed a novel, multidisciplinary approach to study the growth of blood vessel networks within islets during normal development and after transplantation. These studies should enhance efforts to proliferate and expand islets in culture, and to support the survival and function of transplanted islets. Other investigators are testing ways to inhibit chemical signals that instruct T cells to migrate to and destroy transplanted islets. Inhibition of "Fas"—a protein that promotes programmed cell death—is being explored as a mechanism for promoting the survival of transplanted islets.

- Diabetes affects nearly every organ system in the body and research on these complications can benefit from expertise in a wide variety of biomedical subjects and cutting-edge technologies. Researchers will develop new model systems and technologies to study glucose regulation of genes expressed in neurons, about which very little is known. These studies will identify critical genomic mechanisms responsible for diabetic nerve disease. Another team will study the chemical signals that recruit endothelial precursor cells to the surface of the retina where they participate in new blood vessel formation—the process underlying the development of diabetic eye disease and blindness.

Bench to Bedside Research on Type 1 Diabetes and its Complications (RFA DK02-022 and DK03-001)

Recent advances in fundamental science and in understanding the pathophysiology underlying type 1 diabetes and its complications offer tremendous promise for the development of new therapies. This initiative promotes partnerships between clinical and basic biomedical researchers with the goal of translating scientific discoveries into new strategies for the prevention, treatment, and cure of type 1 diabetes and its complications. In these "bench to bedside" research partnerships, a team of clinical and basic scientists will conduct collaborative research that, if successful, will bring basic research

advances from the laboratory to a point where a potential new therapy can be tested in patients or in preclinical studies in animal models.

Due to the high number of scientifically meritorious applications received in response to RFA DK02-022, this solicitation was reissued as RFA DK03-001. The program co-sponsors, NIDDK, NIAID, NEI, and NHLBI, anticipate awarding four to eight grants in FY 2003, dependent on the receipt of meritorious applications. The NIDDK and NIAID awarded 11 pilot and feasibility grants in September 2002. Research collaborations initiated in FY 2002 through these 2-5 year grants include:

- Type 1 diabetes originates from dysregulation of the immune system, so agents that can modulate the aberrant immune recognition, infiltration, or inflammation of islets hold promise for preventing this disease. Researchers are pursuing numerous strategies for the development of immune modulating agents for type 1 diabetes therapy. Candidate agents include altered peptide ligands for T cell recognition of the diabetes-associated autoantigen, GAD65; long-lasting, orally bioavailable analogs of an anti-inflammatory agent, Lisofylline; and a matrix-metalloproteinase inhibitor to prevent T cell infiltration of islets.

- Dendritic cells (DCs), a component of the immune system, help to define "self" molecules and establish immune tolerance. Previous research has shown that injection of DCs can effectively prevent type 1 diabetes in the NOD mouse model of this disease. Moreover, injection of DCs into non-diabetic human volunteers appears to be safe. Proof-of-principle studies are under way in both mouse models and diabetic humans to gather more data on the therapeutic potential of DCs for blocking autoimmunity and preventing type 1 diabetes.

- Current islet transplantation protocols, while extremely promising as a cure for type 1 diabetes, rely on lifelong immunosuppression to avoid graft rejection and recurrence of the autoimmune process. These protocols also require large numbers of islets to ensure sufficient viability and function after transplantation. Researchers are developing a strategy to cure type 1 diabetes by combining transplantation of blood-forming stem cells with islet transplantation. This approach, which will be tested in the NOD mouse model of type 1 diabetes, may enable the establishment of a mixed host/donor immune system capable of suppressing autoimmune destruction of the islets. Another team of scientists is constructing "islet kidneys" for the simultaneous treatment of both type 1 diabetes and end-stage renal disease. In this protocol, islets will be harvested from a living donor and transplanted under the membrane surrounding one of the donor's kidneys. This "islet kidney" will remain in the donor for a period of time before the entire organ is transplanted into a type 1 diabetic patient, so that full blood circulation can be restored to the islets. This strategy could potentially improve islet graft viability, while also restoring kidney function.

- Scientists are generating a "humanized" mouse model of type 1 diabetes in which T cells express a human insulin-specific T cell receptor. This animal model will aid in the design of clinical immunoprevention agents for type 1 diabetes that could be more effective in human trials than previous agents that were first tested in the context of the mouse immune system. Another team of investigators is developing a high-throughput system for quantitating T cells that are reactive to islet antigens. Having an accurate measure of such T cells, which represent only a fraction of the entire repertoire, will enable clinicians to evaluate an individual's risk of type 1 diabetes, monitor disease progression, and evaluate the efficacy of novel therapies.

- Researchers are designing a fast, cost-effective, and flexible technique for quantifying podocyturia—the loss of cells from a section of the kidney and their excretion in the urine. This assay could be useful as both a surrogate marker for assessing the risk of progression of diabetic kidney disease and a means to non-invasively monitor patients' response to treatment.

Phased Innovation Supplements to Diabetes Research Centers

This initiative invited applications from NIDDK-funded Diabetes Research Centers to promote two different types of research projects. Projects were awarded to translate fundamental discoveries into improved health care, by bringing a body of fundamental science from the laboratory to a point where hypotheses could be tested in humans. Each proposed project had at least two co-investigators, one from a basic science and one from a clinical science department. A second set of awards supported collaborations between at least two co-investigators—one scientist currently working on type 1 diabetes or its complications and another scientist, not currently working in diabetes, with a special skill or technology that could enhance diabetes research.

The NIDDK made 25 supplemental awards in FY 2001. Applications from the following scientific disciplines were funded: immunology, transplantation, islet stem cells and islet cell biology, glucose sensors and metabolism, and neurobiology. As of spring 2002, seven awardees had generated enough preliminary data to apply for new research funding through other NIDDK initiatives.