GOAL I

IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Type 1 diabetes results from a complex interplay of genetic and environmental factors. To begin to unravel the underlying genetic and environmental causes, the *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of genetics and epidemiologic research consortia and the assembly of appropriate populations of patients for study, which will facilitate investigations by the broad diabetes scientific community.

This Goal of the *Special Statutory Funding Program for Type 1 Diabetes Research* is focused on understanding the interplay of genetic and environmental factors that is at the root of the immune system's attack on the body's insulin-producing cells (beta cells found in clusters called "islets" within the pancreas). Until these factors are completely deciphered, it will not be possible to identify with certainty all those who are at risk for the disease and their specific risk profiles. This knowledge is also urgently needed to develop and tailor the most effective clinical strategies for delaying or completely preventing the disease. It would also facilitate research aimed at reversing the disease as soon as possible after onset—before all the precious insulin-producing beta cells are lost and before patients develop damaging complications of the eyes, kidneys, nerves, heart, and other parts of the body.

It has long been known that the likelihood of a person's developing type 1 diabetes is higher the more closely related he or she is to a person with the disease. However, 80 percent of new type 1 diabetes patients do not have close relatives with the disease.[1] Type 1 diabetes is an extremely complex disease believed to involve many genes, which work in concert and can have both large and small effects. Previous research indicated that one of the implicated genetic regions (the major histocompatibility complex, or "MHC") may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Certain variations of the genes in this region can cause a person to have a predisposition to the disease.

The environmental contributors to type 1 diabetes are also likely to be complex, and a variety of triggers have been suggested. The possible triggers include viruses, diet, environmental toxins, and stress. However, no definitive proof of a causative link with any of these factors has yet been found. When the genetic susceptibility is "triggered" by an environmental agent, the body's immune defense system will then turn against itself. When provoked, the normally protective immune system—which fights against bacteria, viruses, and other foreign invaders—will launch an assault on the body's own insulin-producing beta cells. If the factors that trigger this immune assault were known, genetically-susceptible individuals could avoid certain foods or environmental toxins, or be vaccinated against an infectious agent linked to the disease.

Epidemiological research to adequately investigate the underlying genetic and environmental factors that trigger type 1 diabetes in susceptible individuals requires large-scale, long-term, and well-coordinated research efforts. Long-term investment in the research programs described under this Goal will provide the opportunity to follow at-risk individuals for sufficient lengths of time to observe progression to autoimmunity and type 1 diabetes and to correlate the onset of disease with suspected risk factors. These types of studies may have a dramatic and positive impact on disease prevention and treatment strategies. Such studies could not have been undertaken without the *Special Funds*.

While numerous significant advances have emerged since the beginning of the Special Funding Program, *many of the research efforts to identify the genetic and environmental causes of type 1 diabetes are still in progress, and the full impact of these projects will not be realized for several years. The advances made possible by the* Special Funding Program *thus far are therefore only the beginning of the scientific gains that can be expected in the future.*

Genetic Factors Associated with Susceptibility to Type 1 Diabetes: Numerous studies have investigated genetic susceptibility loci, using both case-control and family study designs. Different versions of two human leukocyte antigen (HLA) genes in the MHC class II region have been shown to represent the primary genetic determinants of risk for type 1 diabetes, although other class II genes, as well as class I and class III genes, may contribute to susceptibility. It has been suggested that genes in the MHC may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Recent studies have also revealed that the *PTPN22* and *CTLA4* genes contribute to several autoimmune diseases, including type 1 diabetes. Studies have also shown that the absence of a protein, called AIRE, which results from a rare mutation in people, promotes autoimmunity in several tissues and increases the incidence of type 1 diabetes and other autoimmune diseases.

Contribution of INS to Type 1 Diabetes Susceptibility: A series of studies has confirmed an association of type 1 diabetes with the insulin gene, INS. Recent reports have suggested that insulin may be the critical initiator of the autoimmune destruction of insulin-producing beta cells. Findings in a mouse model of type 1 diabetes, supported by the Autoimmune Disease Prevention Centers (see Goal II), as well as research in humans, now suggest that the insulin molecule itself is an important, potentially disease-initiating autoantigen in type 1 diabetes.

Identification of Additional Genetic Regions Linked to Type 1 Diabetes Susceptibility: A major barrier to type 1 diabetes gene identification is that previous studies did not include large numbers of sib pair families (families with two or more siblings with type 1 diabetes). The Type 1 Diabetes Genetic Consortium (T1DGC) began collecting data from affected sib pair families and has performed genetic linkage analysis on the subset of the families. Researchers in the T1DGC have demonstrated nine regions in addition to MHC that show some evidence of linkage to type 1 diabetes; three of these regions have a bigger effect on risk than other regions in the chromosome. In addition, the data have clearly excluded other regions. This study represents one of the largest linkage studies ever performed for any common disease.

Genes and Genetic Concepts Discovered in Animal Models of Type 1 Diabetes: Some type 1 diabetes susceptibility genes, such as *CTLA4*, have first been identified in a non-obese diabetic (NOD) mouse model of type 1 diabetes and then found relevant to the disease in humans. Further identification of disease-susceptibility regions is in progress via a NOD mouse genome sequencing initiative (also supported by the *Special Funding Program*), which compares diabetes-susceptible and diabetes-resistant mouse strains. Findings will be pursued in human genetics consortia, such as the T1DGC.

Environmental Triggers of Type 1 Diabetes: Several long-term studies initiated prior to the *Special Funding Program* have suggested that dietary factors, such as timing of introduction of cereal, may affect risk of type 1 diabetes. However, the small size of these studies and variable

findings across studies precluded definite conclusions. In 2004, a carefully designed, long-term international study of sufficient size to test the role of suspected factors and to identify novel triggers was launched. This bold initiative, called The Environmental Determinants of Diabetes in the Young (TEDDY; see Goal II), will follow newborns through age 15 and provide unprecedented data and biosamples for use in identifying the environmental triggers of the disease.

Benefits to Children Participating in Long-term Research Studies: Prior to diagnosis, many patients with undetected type 1 diabetes will develop a condition called diabetic ketoacidosis (DKA) which, if not promptly treated, places them at risk of diabetic coma and death. The severe metabolic disturbance of DKA is not only life-threatening, but also further damages any residual insulin-producing cells. Already, some children who participate in research studies that aim to identify environmental triggers of type 1 diabetes have benefited by avoiding DKA. Researchers can identify those who progress from genetic predisposition to the earliest signs of autoimmunity and educate their families about what to expect in the way of symptoms and how to do blood glucose tests at home. Thus, type 1 diabetes does not blindside their families, and both parents and children are better prepared if and when a child experiences onset of the disease.

Defining the Incidence and Prevalence of Type 1 Diabetes in the United States: Rates of type 1 diabetes are known to be increasing in some European countries. However, reliable data on changes over time in the United States, or even how many children in the United States have diabetes, were lacking. This gap in knowledge is being addressed by the Search for Diabetes in Youth Study (SEARCH). The SEARCH preliminary prevalence data indicate that at least 154,000 children/youth in the U.S. have diabetes. Emerging data from the SEARCH study also suggest that the incidence of type 1 diabetes in American children may be higher than an earlier estimate of 13,000 per year. For example, preliminary results show that incidence exceeds 20 per 100,000 per year for non-Hispanic white youth. Now that this important baseline national data on diabetes in children have been collected by SEARCH, the next phase of this study will determine whether the rates of diabetes are changing over time.

EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO THE IDENTIFICATION OF GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

With the increase in **Special Funds** *that became available in FY 2001, unique, innovative, and collaborative research consortia, clinical trials networks, and resources for the diabetes research community were launched. This section evaluates the progress of these ongoing efforts thus far and describes the impact that the efforts have already had—and have the potential to have—on type 1 diabetes patients.*

Type 1 Diabetes Genetics Consortium (T1DGC)

The T1DGC is organizing and implementing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. Teasing apart the multiple gene combinations that predispose someone to this complex disease requires analysis of a very large dataset covering thousands of patients and closely related family members who may or may not have developed the disease. The monumental first phase of the project, expected to continue through 2007, is to recruit families, particularly those with multiple siblings with type 1 diabetes, to join the study and to collect DNA samples for analysis. A Consortium database containing clinical, genetic, and medical history information has been established to facilitate the search for susceptibility genes. In subsequent project phases, the database and centralized DNA repository will serve as a resource accessible to genetics researchers both within and outside the T1DGC.

Highlights of Progress

The progress that T1DGC has made as of March 1, 2006, includes:

- Recruited over 1,640 families who have two or more siblings with type 1 diabetes, toward the goal of 2,800 families.
- Performed genome scans on over 1,430 families, toward the goal of 2,800 families.
- Performed analyses of four data sets showing that, in addition to genes in the MHC region, nine other genetic regions may be involved in type 1 diabetes.
- Established an MHC fine-mapping project to study genes in this region involved in susceptibility to type 1 diabetes.
- Established a Rapid Response project to study candidate genes that could contribute to type 1 diabetes.

Anticipated Outcomes

The T1DGC is a large-scale, well coordinated effort to identify numerous genes and gene combinations that are important in predicting an individual's risk of developing type 1 diabetes or related autoimmune diseases. The T1DGC is building on the work of the Human Genome Project that spelled out the contents of human genes and the International HapMap Project that is identifying the points at which gene sequences differ from person to person. The T1DGC is resolving which of these genetic differences are significant for type 1 diabetes. Samples stored in NIDDK repositories will be made available to scientists worldwide for application of the latest genetic technology to study DNA from a large and well-characterized set of affected families. As science progresses to the age of personalized medicine, clinicians may soon be able to determine the optimal treatment strategy for an individual based on his or her genetic background. With new insights into the genetic factors that play a role in type 1 diabetes, researchers may be able to identify with great precision those individuals at risk for the disease, and to develop and test prevention-oriented strategies. It is possible, for example, that certain therapies to delay or reverse the development of type 1 diabetes may be more effective in individuals with specific genetic changes that predispose to type 1 diabetes. Such new genetic knowledge
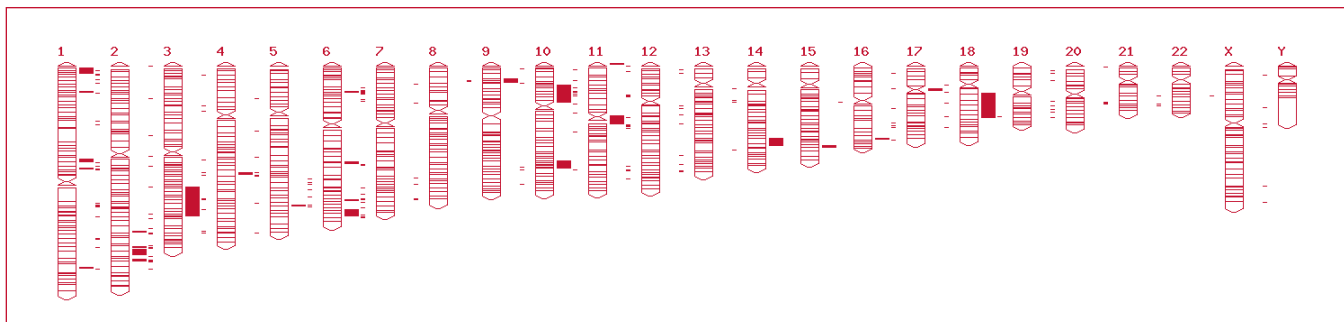
Human genome map. The lines or bars along the sides of each chromosome represent genetic regions that have been linked to type 1 diabetes. The Type 1 Diabetes Genetics Consortium (T1DGC) is pooling data from 2,800 families to tease out disease genes. *(From Smink LJ, et al.* Nucleic Acids Res. *33 (Database Issue): D544-549, 2005.)*

could point the way toward better screening of newborns or to widespread screening of the general population to identify individuals at risk of developing type 1 diabetes. This knowledge would facilitate the design of more specific clinical trials for testing interventions specifically tailored to patients with similar risk profiles. These are just a few examples of the enormously important and predictive and preemptive strides forward that can be envisioned and possibly attained by further understanding the genetic underpinnings of disease development.

External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Advisory Board focused on the T1DGC, leading scientific and lay experts were asked to evaluate the progress of the T1DGC at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

▸ Genes that participate in diabetes susceptibility are apparently very common in the population, yet only certain gene combinations confer disease susceptibility. The way to study these interactions is with extremely large databases; hence, the T1DGC provides the best strategy to identify genetic factors and their interactions.

▸ The Consortium is committed to making its resources available to the research community and has developed the necessary infrastructure to achieve this objective. The External Advisory Board was pleased with the policies developed by the Consortium that weigh the interests of funded Consortium members who have invested years in collecting material with the interests of the research community at large.

▸ Genetic analysis technology is undergoing transition. The Consortium has rapidly and adroitly converted to the more advanced and cost-effective Single Nucleotide Polymorphism (SNP) genotyping approach, and the resulting samples will be available in the NIDDK repository for future technological applications.

Actions Taken in Response to Expert Panel Recommendations

The T1DGC took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Enhance Coordination Among Genetics Consortia Supported by the *Special Funding Program*

▸ In July 2005, T1DGC participated in a coordination meeting with the other human genetics consortia supported by the *Special Funding Program*—Epidemiology of Diabetes Interventions and Complications (EDIC); Family Investigation of Diabetes and Nephropathy (FIND); and Genetics of Kidneys in Diabetes (GoKinD). In response to recommendations from this meeting, new initiatives are being developed to coordinate future research efforts among these studies. A summary of this meeting is available at: www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf

Recommendation: Improve Coordination of Genetics Research in Mice and Humans

▸ The T1DGC is utilizing T1Dbase (http://T1DBase.org) as a web-based tool to coordinate, manage, and interpret human, mouse, and rat genetics data. These data are open access and all software is open source in order to maximize its usage by the broad research community.

Ongoing Evaluation

To ensure continued and ongoing evaluation of the study design and the progress of the T1DGC, the NIDDK established an External Advisory Board (EAB). The EAB is composed of investigators with scientific expertise relevant to research conducted by the T1DGC, but who are not members of the Consortium. The EAB meets annually to:

▸ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical networks, data coordinating center, and core laboratories).

▸ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.

▸ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

Coordination with Other Research Efforts

The T1DGC coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaborative efforts, please see Appendix 2.

Coordinating Patient Recruitment Efforts:

▸ All 14 Type 1 Diabetes TrialNet clinical centers and 4 Search for Diabetes in Youth (SEARCH) study sites are participating as recruitment centers for the T1DGC North American Network.

▸ T1DGC assisted TrialNet in establishing international recruitment sites.

Enhancing Data Comparison Among Studies:

▸ T1DGC, TrialNet, SEARCH, and The Environmental Determinants of Diabetes in the Young (TEDDY) are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparison of genetic data across all four studies, effectively increasing the power of each individual study in learning which genes play a role in disease onset.

▸ T1DGC, TrialNet, and TEDDY share the same North American laboratory for measurement of autoantibodies (markers used to predict an individual's risk for developing type 1 diabetes). This coordination will permit direct comparison of results obtained in each study.

▶ Researchers in the Diabetes Autoantibody Standard-ization Program (DASP) provide tools that T1DGC laboratories use to standardize autoantibody data. Data standardization provides confidence that results are inde-pendent of the laboratory performing the measurements.

Coordinating Studies of Type 1 Diabetes Genetics:

▶ The T1DGC coordinates its research efforts with the other genetics consortia supported by the *Special Funding Program* (EDIC, FIND, and GoKinD) (see "Actions Taken in Response to Expert Panel Recommendations" for a description of coordination efforts).

Sharing Samples, Data, and Resources with the Research Community:

▶ The T1DGC has developed a comprehensive public web-site with information on samples, data, and resources that are available to the scientific research community (www.t1dgc.org).

▶ The T1DGC is repositing samples and data in all three NIDDK Central Repositories (Biosample, Genetics, and Data Repositories). The Repositories were established to expand the usefulness of NIDDK-supported studies by allowing a broader research community to access these materials beyond the end of the study.

T1DGC Administrative History

Date Initiative Started	2002
Date *Special Program* Funding Started	2002
Participating Components	NIDDK, NIAID, NHGRI, and JDRF
Website	www.t1dgc.org

T1DGC consists of a coordinating center and four clinical recruitment net-works in Asia-Pacific, Europe, North America, and the United Kingdom.

The Environmental Determinants of Diabetes in the Young (TEDDY)

Scientists directing six independent studies of environmental triggers of type 1 diabetes in the U.S. and Europe joined forces to create this international consortium. TEDDY is providing a coordinated, multidisciplinary approach to understanding the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. TEDDY investigators will screen newborns in the general population, as well as those who have a first-degree relative with type 1 diabetes. In this large-scale, long-term epidemiological effort, in which patient follow-up is estimated to continue through 2023, high-risk infants will be followed until they are 15 years of age. The TEDDY study is making progress toward amassing the largest data set and samples on newborns at risk for autoimmunity and type 1 diabetes anywhere in the world. To maximize the return on the investment in TEDDY, samples from the study will be made widely available to researchers worldwide.

Highlights of Progress

The progress that TEDDY has made as of March 1, 2006, includes:

- Screened over 62,290 newborns from the general population, toward the goal of 216,000 newborns.
- Recruited over 1,130 newborns from the general population, toward the goal of 5,940 newborns.
- Screened over 1,050 newborns with a first-degree relative with type 1 diabetes, toward the goal of 4,800 newborns.
- Recruited over 120 newborns with a first-degree relative with type 1 diabetes, toward the goal of 1,152 newborns.
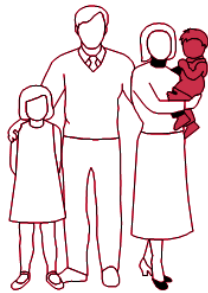
Anticipated Outcomes

Until researchers know what causes type 1 diabetes, it is difficult to develop strategies to prevent it. Previous studies suggested that certain factors, such as early exposure to cereal or cows' milk, might predispose to type 1 diabetes. However, these studies were too small and too short to achieve statistically significant results, and no definitive environmental trigger of the disease has yet been identified. Therefore, TEDDY is a crucially important effort to tease out the environmental factors triggering disease onset. While it is a substantial investment of time and resources to follow individuals for many years, it is only through a long-term, coordinated study such as TEDDY that researchers are likely to answer critically important questions about type 1 diabetes risk and onset. Realization of study goals could have an enormously positive impact on public health efforts regarding disease prevention. For example, if a viral trigger is revealed, a vaccine could possibly be developed to prevent disease onset in genetically susceptible individuals. Alternatively, if a dietary component is found to be causative or protective, individuals at risk could take steps to either eliminate or add it to their diets. By pinpointing the constellation of type 1 diabetes disease genes (as is being done in the T1DGC), environmental triggers (as is being done in TEDDY), and their cascading effects on the immune system (see Goal II), researchers may be able to entirely prevent or reverse disease onset. Combating the disease at the "front-end" is especially beneficial because early steps could preclude or arrest the development of disease complications—including kidney failure, blindness, lower limb amputations, heart attacks, and strokes. Research on the genetic and environmental causes of the disease thus offers the real hope of preventing type 1 diabetes.

Importantly, the studies of environmental factors that play a role in type 1 diabetes may also contribute to understanding the development of celiac disease, which is an autoimmune disease primarily affecting the gastrointestinal tract. In the U.S., the prevalence of celiac disease has been estimated to be

General population cohort	Sibling/offspring cohort
6 centers	6 centers
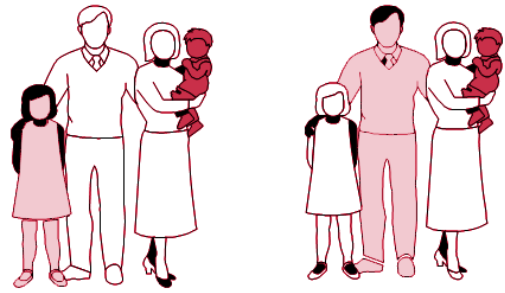
While having a relative with type 1 diabetes greatly increases a child's risk for the disease, most of those newly diagnosed with the disease have no family history. To identify the environmental causes of type 1 diabetes, The Environmental Determinants of Diabetes in the Young (TEDDY) is recruiting newborns at increased genetic risk (red shading) from the general population (left panel) without a family history of the disease. TEDDY is also recruiting newborns with a parent or sibling (pink shading) with type 1 diabetes (right panel). *(Images courtesy of Dr. Marian Rewers and the Diabetes Autoimmunity Study in the Young.)*

approximately one percent of the population.[2] Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Therefore, ongoing studies to identify environmental triggers of type 1 diabetes are also investigating development of celiac disease. These studies may uncover environmental factors initiating both disorders, benefiting not only type 1 diabetes patients, but also persons suffering from celiac disease and other autoimmune diseases.

External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an EAB focused on TEDDY, leading scientific and lay experts were asked to evaluate the progress of the study at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

▸ TEDDY is a major project with an important goal. The design and implementation of TEDDY represent the best research approach to that goal.

▸ The rigorous design of the TEDDY consortium redresses weaknesses in previous newborn diabetes environmental studies with regard to methodological standardization, sample sizes, research biases, study designs, and follow up.

▸ As the consortium began, TEDDY successfully cooperated with on-going newborn studies.

▸ The consortium has made significant progress forming reference laboratories, establishing proficiency tests, and developing a protocol manual.

Actions Taken in Response to Expert Panel Recommendations

TEDDY took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Publicly Publish the Protocols and Solicit Broad Community Support

▶ The TEDDY study group maintains a website that describes the study protocol, manual of operations, and study forms (www.teddystudy.org). This site includes policies, procedures, and other governance documents as well as folders for science and administrative committee support. The site also contains a series of standard reports specific to each geographic region in which the study operates, which can be used by the local sites to enlist broad community support. In addition, the TEDDY study has been presented at various meetings, and the design paper will soon be published.

▶ TEDDY study-related materials have been posted on the NIDDK's public website dedicated to research supported by the *Special Funding Program* (www.T1Diabetes.nih.gov). Furthermore, a website is maintained by each of the clinical programs participating in TEDDY. These websites promote the TEDDY study locally, make the study more visible in the community, and provide links to the TEDDY Study Group website.

▶ TEDDY has organized workshops, in collaboration with NIDDK, JDRF, and NIAID, to solicit broad scientific input. For example, one of the workshops, "Identifying Infectious Causes of Human Disease," helped TEDDY investigators begin their search for potential environmental triggers of diabetes and pre-diabetic autoimmunity. The information provided was valuable for protocol development. Another workshop, "Viral Detection in Type 1 Diabetes," provided a forum for research synergy by bringing together TEDDY researchers and investigators with expertise in proteomics and genomics methodologies, with the aim of promoting identification of viral triggers of type 1 diabetes.

Recommendation: Develop a Mechanism for Grafting New Technologies as They Become Available

▶ A program and explicit guidelines for ancillary studies have been established to facilitate access to TEDDY materials by researchers who seek to expand and embrace new technologies for inclusion into the TEDDY study group. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing research efforts, including TEDDY.

Recommendation: Conduct Hypothesis-Driven Analyses To Help Expedite Translating Laboratory Discoveries into the Clinic

▶ The TEDDY study and its protocol were designed to test scientific hypotheses associated with the initiation and/or promotion of the pathogenic process that results in the development of type 1 diabetes. Specific hypotheses were identified to be confirmed or refuted over the course of the study. The TEDDY study is the clinical, epidemiological study that will provide support for translational science and create new information.

Recommendation: Maintain Active Oversight by an External Advisory Board To Ensure Resources Are Used Most Effectively and That Study Designs Are Appropriate

▶ The TEDDY study group has an active standing EAB. The EAB meets regularly and is provided updates on all aspects of the study, including progress towards meeting study goals. The EAB is comprised of well respected scientists who contribute their highly relevant individual expertise and collective insights to study planning and evaluation.

Recommendation: Bring Investigators from the TEDDY Study and the Trial To Reduce IDDM in the Genetically at Risk (TRIGR) Study Together To Discuss Issues of Coordination and Integration

▸ Representatives from both TEDDY and TRIGR participated in a Type 1 Diabetes Consortia Coordination meeting that the NIDDK convened in May 2005. The purpose of the meeting was to identify opportunities to enhance collaboration among all of the research consortia studying type 1 diabetes. Prior to the larger meeting, representatives from consortia studying newborns (TEDDY, TRIGR, and Type 1 Diabetes TrialNet) met to discuss how to obtain the most useful information when looking at these studies as a group. Participants discussed common data variables across the studies and future analytic strategies.

Ongoing Evaluation

As noted above, to ensure continued and ongoing evaluation of the study design and the progress of TEDDY, the NIDDK established an EAB composed of scientific experts who are not participating in TEDDY. The EAB meets annually, in person or by conference call, to:

▸ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical centers, data coordinating center, and core laboratories).

▸ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.

▸ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

Coordination with Other Research Efforts

TEDDY coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*, particularly those studying newborns. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaborative efforts, please see Appendix 2.

Coordinating Research Studies Involving Newborns:

▸ TEDDY investigators have met with researchers participating in other type 1 diabetes research studies involving newborns (TRIGR and TrialNet) to discuss opportunities for enhancing coordination and collaboration.

▸ TEDDY has shared the following materials with TrialNet investigators who are studying newborns in the Nutritional Intervention to Prevent (NIP) Diabetes Study: genetic-screening procedures, data forms, and parts of the Manual of Operations concerning follow-up of high-risk children.

▸ TEDDY and TRIGR share the same Data Coordinating Center. This coordination has resulted in implementation of similar standards in data collection, entry, management of quality control, and analyses for both studies.

▸ TEDDY, TrialNet, and TRIGR have coordinated patient recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.

▸ TRIGR and TEDDY investigators are considering collaborative efforts on recruitment after TRIGR accrual ends. Both groups are also considering a follow-up intervention protocol.

Enhancing Data Comparison Among Studies:

▸ TEDDY, T1DGC, TrialNet, and the SEARCH for Diabetes in Youth study are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparisons of genetics data across all four studies.

▸ TEDDY, T1DGC, and TrialNet share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison of results obtained in each study.

▸ TRIGR and TEDDY have implemented similar standards in data collection and entry. This coordination is permitting direct comparison between results obtained in each study relevant to nutrition and to diabetes-associated variants of certain immune system genes (HLA genes).

▸ DASP provides tools that TEDDY laboratories use to standardize autoantibody data. Data standardization provides confidence that results are independent of the laboratory performing the measurements.

Sharing Samples, Data, and Resources with the Research Community:

▸ TEDDY is repositing biological samples and data into the NIDDK Central Repositories and will make the material available to the broad scientific community. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing studies, including TEDDY.

TEDDY Administrative History

Date Initiative Started	2002
Date *Special Program* Funding Started	2002
Participating Components	NIDDK, NIAID, NICHD, NIEHS, CDC, and JDRF
Website	www.teddystudy.org/

TEDDY is a consortium of six Clinical Centers and one Data Coordinating Center in the United States, Finland, Sweden, and Germany.

Search for Diabetes in Youth (SEARCH)

Major impediments to diabetes research and efforts to improve public health include lack of uniform national information on the rates of childhood diabetes, whether these are changing over time, and the clinical course and evolution of different forms of diabetes in children and youth. While substantial increases in the incidence of type 1 diabetes have been reported in Europe, reliable data on changes over time in the U.S., or even how many children in the U.S. have diabetes, were lacking. The SEARCH multicenter epidemiological study is identifying cases of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the U.S. The study aims to identify the number of children and youth under age 20 who have diabetes; learn how type 1 diabetes and type 2 diabetes differ, including how they differ by age and race/ethnicity; learn more about the risk for acute and chronic complications of diabetes in children and youth; investigate the different types of care and medical treatment that these children and youth receive; and learn more about how diabetes affects the daily lives of children and youth in the U.S. Now that the first baseline assessment of diabetes rates in children nationwide has been completed, the study is poised to evaluate trends in diabetes incidence and progression of the disease over time.

Highlights of Progress

The progress that SEARCH has made as of March 1, 2006, includes:

- In the year 2001, approximately 3.5 million children less than 20 years of age were under surveillance at the 6 SEARCH centers to estimate how many children/youth had diabetes (prevalent cases).
- Since 2002, approximately 5.5 million children less than 20 years of age (approximately 6 percent of the under 20 years U.S. population) with wide racial/ethnic, socioeconomic, and geographic representation, have been under surveillance at the SEARCH research centers each year to estimate how many children/youth develop diabetes (incidence cases) per year by age, sex, race/ethnicity, and diabetes type.
- Approximately 5,000 children/youth with diabetes, and their families, have participated in SEARCH in-person visits. Nearly 3,000 stored DNA specimens from these participants are being used to extend the genetic component of SEARCH.
- About 8,000 children/youth, and/or their families, have provided basic information on clinical presentation by mailed survey.
- Over 11,200 cases of diabetes in children/youth less than 20 years of age at diagnosis (6,392 prevalent and 4,828 incident) have been identified. Cases identified are highly diverse ethnically (approximately 13 percent Hispanic; 13 percent African American; 3 percent American Indian; 4 percent Asian/Pacific Islander; 68 percent Caucasian). SEARCH provides estimates of 2001 diabetes prevalence (1.8 per 1,000) and based on 2002 and 2003, overall incidence is estimated to be 25.5 per 100,000 per year. Manuscripts reporting final prevalence estimates are in press (*Pediatrics*, 2006), and the initial incidence paper has been submitted.
- Preliminary findings indicate that diabetes incidence varies across U.S. major racial/ethnic groups:
  - In children less than 10 years of age, the incidence of diabetes is highest in non-Hispanic whites and lowest in American Indians. Children less than 10 years of age who are Hispanic, African American, or Asian/Pacific Islander have diabetes incidence rates that are intermediate between those of non-Hispanic white and American Indian children.

- ▸ In older youth (10-19 years), the incidence of diabetes is higher in African American, Hispanic, and American Indian youth than in non-Hispanic whites. In Asian/Pacific Islanders, the incidence is similar to that of non-Hispanic whites.
- The SEARCH prevalence data indicate that at least 154,000 children/youth in the U.S. have diabetes. Diabetes prevalence varies across major racial/ethnic groups:
  - ▸ In children less than 10 years of age, non-Hispanic whites are more affected than children of other racial/ethnic groups.
  - ▸ In older youth (10-19 years), the highest burden of diabetes is observed in non-Hispanic whites and African Americans—about 1 in 300 have diabetes. About 1 in 500 Hispanic and American Indian youth and about 1 in 750 Asian and Pacific Islanders have diabetes.
- Higher Body Mass Index (BMI) was associated with younger age at diagnosis of type 1 diabetes, but only in children with reduced beta cell function. This relationship was independent of the presence of autoantibodies predictive of the disease. These data suggest that, only among individuals with already compromised beta-cell function and/or high rate of beta cell loss, obesity accelerates type 1 diabetes onset.
- Low birth weight may be a factor in accelerating the onset of type 1 diabetes. These data suggest that the intrauterine environment may be an important determinant of age of onset of type 1 diabetes.
- SEARCH has shown that nutritional intake in adolescents with diabetes is poor and does not follow current recommendations. Recommendations for total dietary fat intake are met by only 10 percent of youth with diabetes and recommendations for saturated fat intake by only 7 percent.
- Similarly to the population of youth without diabetes, about 9 percent of adolescents with diabetes have moderate or severely depressed mood. Depressed mood in adolescents with diabetes is associated with poor diabetes control and a higher likelihood of hospitalizations, emergency room visits, and episodes of diabetic ketoacidosis.
- At onset of diabetes, over half of youth are hospitalized, and one in four suffers from diabetic ketoacidosis at onset.
- The prevalence of multiple cardiovascular disease (CVD) risk factors is high in children and adolescents with diabetes. CVD risk factors were present in youth with either type 1 or type 2 diabetes, but were more common in adolescents with type 2 diabetes.
- At similar diabetes duration, youth with type 2 diabetes are more than twice as likely to have microalbuminuria (a sign of deteriorating kidney function) than youth with type 1 diabetes.
- Fully half of youth with diabetes had HbA1c levels greater than recommended by the ADA.
- Although more than 95 percent with diabetes had some form of health insurance coverage, minority youth had poorer glycemic control than non-Hispanic white youth.
- Worse glycemic control is associated with a worse lipid profile, regardless of diabetes type.
- Type 2 diabetes (versus type 1 diabetes) and longer duration of diabetes, but not HbA1c, are independently associated with measures of increased central and peripheral arterial stiffness, suggesting an increased risk of future cardiovascular morbidity.
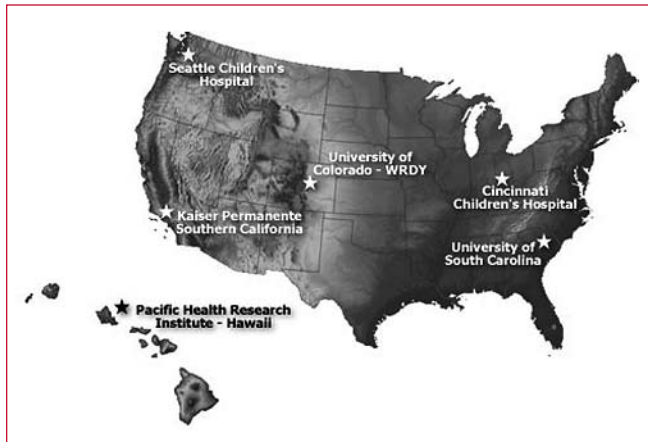
The map shows the location of the six Search for Diabetes in Youth (SEARCH) clinical centers. *(Image courtesy of the SEARCH Study Group.)*

Anticipated Outcomes

Research supported through the SEARCH consortium will enhance understanding of the natural history, complications, and risk factors of diabetes onset in childhood and adolescence. It will also estimate diabetes prevalence and incidence by age, sex, race/ethnicity, and diabetes type, as well as assess the impact of quality of diabetes care in youth on short- and long-term diabetes outcomes, including quality of life. Because the incidence and prevalence of type 1 diabetes in the U.S. have not been precisely known, it has been difficult for researchers to determine with certainly if the number of persons with the disease is increasing or decreasing. Acquiring these data is important in order to ultimately design and implement public health efforts to prevent the disease once prevention strategies are identified. Furthermore, the data that are acquired in the SEARCH study regarding the natural history and risk factors of diabetes can inform the design of new prevention and treatment strategies. Data have already shown that obesity and low birth weight may accelerate onset of type 1 diabetes in some patients (described above). High prevalence of CVD risk factors, including obesity, dyslipidemia,

and hypertension, has been documented in youth with type 1 diabetes, as well as youth with type 2 or hybrid diabetes. The need for identifying effective approaches to improve dietary intake in youth with diabetes has been clearly documented. By building on SEARCH findings, researchers may be able to design interventions that can prevent or delay disease onset in at-risk individuals and, of equal importance, to design interventions to reduce risk for both acute and chronic complications of diabetes.

External Evaluation by Expert Panel

In addition to ongoing evaluation by an External Scientific Advisory Committee, leading scientific and lay experts were asked to evaluate the progress of SEARCH at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

▸ The strength of the SEARCH study is the collection of careful epidemiological data representative of the U.S. population. The preliminary findings have shown a higher incidence of childhood diabetes than was previously believed; however, it will be easier to assess actual progress once the data are published.

▸ Coordinating the genetics of SEARCH with the other genetics consortia supported by the *Special Funds* and linking their repositories would greatly benefit the research community. Samples and data should be available for ancillary studies.

▸ SEARCH could be restructured by more clearly developing its secondary aims and by strengthening the management structure through reorganization. Clearer definitions of protocol extensions and establishment of an external advisory board would strengthen the future of the project.

Actions Taken in Response to Expert Panel Recommendations

SEARCH took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Coordinate the Genetics of SEARCH with the Other Genetics Consortia Supported by the *Special Funding Program* and Link Their Repositories/Databases

▸ There are currently four SEARCH research centers (Cincinnati, Southern California, Seattle, and South Carolina) that are participating as recruitment centers for the T1DGC North American Network. The principal investigator for the T1DGC North American Network provided coordination between TrialNet, SEARCH, and T1DGC through her involvement in all three studies. Procedures across the three studies were standardized to the extent possible. The Colorado site childhood population is participating in TrialNet, among numerous other multicenter, NIH-sponsored research studies.

Recommendation: Make Samples and Data Available to the Scientific Community for Ancillary Studies

▸ SEARCH developed a comprehensive public website with information on samples, data, and resources that are available to the scientific research community (www.searchfordiabetes.org). An updated protocol developed in the first few months of the SEARCH renewal (see below) includes specific statements regarding distribution of data.

Recommendation: Create and Clarify Protocol Extensions

▸ In 2005, the SEARCH study was renewed under a competitive Program Announcement. In response to the Program Announcement, SEARCH (Phase 2 [2005-2009]) has revised the study protocol that will be reviewed by

the SEARCH External Advisory Board. The first aim of SEARCH Phase 2 relates to tracking trends in incidence of diabetes; the remaining three aims reflect expansion of work initiated in SEARCH Phase 1 related to evolution of metabolic and clinical characteristics of incident cases, expanded work related to health care utilization and quality of care, and further work toward approaches to public health surveillance of diabetes. As of March 1, 2006, two ancillary studies to SEARCH have been funded by the NIH after competitive peer review, one other ancillary study has been submitted to the NIH, and three ancillary studies have been submitted to professional societies and research foundations.

Recommendation: Establish an External Advisory Board

▸ An EAB has been established for SEARCH Phase 2, and the initial meeting has been scheduled.

Recommendation: Assess the Standard of Care and Access to Treatment Utilizing the Second Phase of SEARCH

▸ One of the main aims of SEARCH Phase 2 is to assess the impact of quality of diabetes care in youth on short- and long-term outcomes, including quality of life, by: completing analytic work initiated in SEARCH Phase 1 and exploring the interrelationships of patient characteristics with important domains of health care outcomes, such as glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life. A SEARCH paper currently in press evaluates dietary intake of youth age 10 years and older against the ADA's nutrition recommendations for youth with diabetes.

Recommendation: Reconfigure SEARCH To Address the Challenge of Follow-up Rate in Adolescents

▸ A subcommittee of the Protocol Oversight Committee has been formed to regularly review recruitment and retention rates and to develop new approaches to enhance

success in this arena. Site visits are being planned, and targeted discussions of recruitment and retention efforts will be an important component of this effort.

Recommendation: Include Clinicians Who Understand Complications

▸ An investigator at the SEARCH Ohio site is a well recognized expert in risk factors and primary prevention of cardiovascular diseases in children and youth. An investigator at the Southern California SEARCH site is an ophthalmologist and is now preparing a grant proposal for a SEARCH ancillary study focused on diabetic retinopathy and other microvascular complications of diabetes.

Recommendation: Obtain Foundation of Epidemiologic Knowledge About the Development of Complications, Particularly Cardiovascular Disease

▸ The 5,000 children and youth who participated in the in-person visits provided information on behavioral and metabolic risk factors for complications; had a special examination to measure body mass index, blood pressure, and waist circumference; gave blood to measure HbA1c and lipids; and provided urine to measure albumin-to-creatinine ratio. Stored blood specimens from 3,004 participants have been used to measure adiponectin, C-reactive protein, lipoprotein (a), apolipoprotein B, and LDL particle size.

▸ SEARCH has also conducted a pilot study of sub-clinical cardiovascular diseases using measures of arterial stiffness and brachial distensibility. This pilot study involved 700 SEARCH patients from two sites (Colorado and Ohio). Data are being analyzed, preliminary results were presented at the 2006 ADA annual meeting, and manuscripts are being prepared.

Ongoing Evaluation

To ensure continued and ongoing evaluation of the study design and the progress of SEARCH, the CDC and the NIDDK have established an External Scientific Advisory Committee (ESAC). The ESAC is comprised of investigators with scientific expertise relevant to research conducted by SEARCH, but who are not members of the Consortium. The ESAC meets annually to:

▸ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and the performance of research centers, data coordinating center, and central laboratory).

▸ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.

▸ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

Coordination with Other Research Efforts

SEARCH coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaborative efforts, please see Appendix 2.

Coordinating Patient Recruitment Efforts:

▸ Four SEARCH study sites are participating as recruitment centers for the T1DGC North American Network.

▸ The Colorado and South Carolina SEARCH sites are informing participants about TrialNet studies and referring them to the TrialNet coordinator for information on enrollment.

▶ Two SEARCH sites (Colorado and California) are assisting with recruitment for TRIGR by providing brochures and other information about TRIGR to potential study participants.

Enhancing Data Comparison Among Studies:
▶ SEARCH, T1DGC, TrialNet, and TEDDY are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each individual study in learning which genes play a role in disease onset.

Coordinating Research Studies Involving Children:
▶ SEARCH, TrialNet, TEDDY, and T1DGC investigators directly collaborate.

Facilitating Basic Research Studies:
▶ SEARCH investigators receive islets for basic research studies through the Islet Cell Resource Centers (ICRs).

SEARCH Administrative History

Date Initiative Started	2000
Date *Special Program* Funding Started	2001
Participating Components	CDC and NIDDK
Website	www.searchfordiabetes.org

SEARCH consists of a coordinating center, a central laboratory, and six research centers in California, Colorado, Hawaii, Ohio, South Carolina, and Washington state.

Type 1 Diabetes Mouse Repository (T1DR)

This research resource, located at The Jackson Laboratory in Maine, has been established to collect, preserve, and disseminate approximately 150 mouse strains that are important to research in type 1 diabetes. Mouse models, such as the NOD mouse, are an essential resource for researchers studying the genetic and pathophysiologic bases of the disease. It is important that the broad scientific community have ready access to these mouse models to facilitate their research efforts. The repository is enhancing access and ensuring the continued availability of these mouse models to the entire research community.

Highlights of Progress

The progress that T1DR has made as of March 1, 2006, includes:
- Collected and preserved over 126 mouse models, toward the goal of 150 models.
- Distributed mouse models to over 100 investigators per year in the scientific community.

Anticipated Outcomes

Animal models of type 1 diabetes can significantly facilitate the translation of laboratory research findings to clinical research. For example, techniques for gene discovery in small model organisms are much more powerful than in humans. Discovery of diabetes-causing genes in animal models will foster research on corresponding genes in human tissue samples and will thus help to uncover the pathways in which the genes function. Furthermore, animal models of the disease are important for testing promising therapeutic agents identified in the laboratory prior to testing in human clinical trials. Therefore, animal models are a crucial resource for translating laboratory results from the bench to the bedside.

Ongoing Evaluation

Activities and progress of the T1DR are monitored by an EAB comprised of experts in mouse genetics, mouse husbandry, and rodent models of type 1 diabetes. Members of the EAB are not affiliated with the T1DR or with The Jackson Laboratory. The EAB meets annually to:
- Review status of importation and distribution of stocks, identify and make recommendations for new strains to be solicited, and advise on procedures to advertise repository holdings.
- Review quality control of genetics data on repository strains, including genome scans, chromosome-of-interest studies, and incidence studies.

Potential new therapies are often tested first in mouse models of a disease. The non-obese diabetic (NOD) mouse is an important research resource for the study of type 1 diabetes and its complications. The Type 1 Diabetes Mouse Resource is collecting, preserving, and disseminating mouse models for use by the scientific community. *(Image courtesy of The Jackson Laboratory.)*

Coordination with Other Research Efforts

In coordination with other NIH-sponsored mouse reposito-ries, the T1DR serves as an archive for mouse models gener-ated by all scientists engaged in research relevant to type 1 diabetes. The T1DR also services many basic science consortia engaged in type 1 diabetes research, including the Beta Cell Biology Consortium (BCBC) and the Animal Models of Dia-betic Complications Consortium (AMDCC). Mouse models distributed from these NIH-supported repositories support translational research relevant to pancreas development, auto-immunity, and transplantation.

T1DR Administrative History

Date Initiative Started	2001
Date *Special Program* Funding Started	2001
Participating Components	NCRR and NIDDK
Website	www.jax.org/t1dr
T1DR is located at The Jackson Laboratory, Bar Harbor, ME.	

Type 1 diabetes is a disease in which the body's immune defense system attacks and destroys the insulin-producing beta cells of the pancreas. It often strikes in infancy, childhood, and young adulthood. Type 2 diabetes is characterized by the body's resistance to insulin action; is more commonly diagnosed in adulthood; is strongly associated with overweight and obesity; and disproportionately affects minority populations. Although the mechanisms underlying development of the two forms of diabetes differ, type 1 and type 2 diabetes have much in common:

▸ They are caused by an interplay of genetic and environmental factors.

▸ Impaired function of the insulin-producing beta cells of the pancreas is central to both forms of diabetes.

▸ Both involve malfunctions in the body's system for maintaining appropriate blood glucose levels due at least in part to defects in insulin production.

▸ They have the same devastating disease complications, such as blindness, kidney failure, nerve damage, lower limb amputations, heart disease, and stroke. The financial burden of treating both forms of diabetes and their complications is tremendous. In 2002, total medical expenditures attributable to diabetes for all Americans were estimated at $132 billion.[3]

▸ The mechanisms of hypoglycemia (dangerous episodes of low blood glucose) are common to both forms of the disease.

▸ Both type 1 and type 2 diabetes are being increasingly diagnosed at a younger age, when the disease is more difficult to control. Earlier onset increases diabetes' toll in lost health and productivity.

▸ Researchers are increasingly recognizing that patients have "hybrid" forms of diabetes. Careful characterization of patients considered to have type 2 diabetes reveals that a subset also has markers of type 1 diabetes called autoantibodies. Some patients with type 1 diabetes have "insulin resistance" that was previously considered a hallmark of type 2 diabetes.

These similarities underscore how research progress on one form of the disease can have enormous benefits for people with the other form as well.

The interdependence and synergism of research on type 1 and type 2 diabetes have been clearly demonstrated, and NIH-supported type 1 diabetes research has already contributed greatly to improved management of both forms of the disease. For example, a landmark clinical trial in type 1 diabetes, called the Diabetes Control and Complications Trial (DCCT), proved that intensive glucose control can prevent or delay damage to the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). The findings of this trial paved the way to studies that replicated these impressive results in type 2 diabetes patients. Most recently, the DCCT findings were extended to show that intensive control reduces heart attacks and strokes (macrovascular complications). Because of pioneering research in type 1 diabetes, close control of blood glucose levels is now a keystone to the medical management of both forms of the disease. Moreover, this landmark trial in type 1 diabetes also established the value of hemoglobin A1c (HbA1c) levels—a measurement of blood glucose levels over time—as a measure of disease management and an outcome measure for future clinical trials in both type 1 and type 2 diabetes, dramatically shortening the cost and time required for trials of new therapies and encouraging development of new therapies of diabetes. The use of HbA1c as an outcome measure was the basis for FDA approval of improved forms of injected insulin, inhaled insulin, and several new classes of oral drugs for type 2 diabetes which, used in combination, can delay the need for insulin therapy.

Through support from the *Special Statutory Funding Program for Type 1 Diabetes Research*, the NIH has spearheaded numerous initiatives to increase understanding of type 1 diabetes and its complications. The following examples are highlights of efforts that are advancing both type 1 and type 2 diabetes research.

‣ *Beta Cell Biology Consortium:* This Consortium is facilitating interdisciplinary approaches to advance understanding of beta cell development and function. The knowledge gained through these studies is essential for providing clues to increase the beta cell mass in people with type 1 and type 2 diabetes.

‣ *Imaging the Beta Cell:* Techniques for imaging the beta cell will be tested in both forms of diabetes and may prove useful for following the disease development and response to therapy for both disorders.

‣ *Hypoglycemia Research:* Although intensive insulin therapy is known to reduce the risk of long-term diabetes complications, its use has been limited because of the potential for episodes of hypoglycemia. Researchers are studying how the brain and other critical tissues sense and respond to hypoglycemia, as well as the effects of hypoglycemia on brain function. They are also developing more effective methodologies to prevent hypoglycemia, such as the recently approved continuous glucose monitors, which could help patients achieve close control and reduce episodes of hypoglycemia.

‣ *Diabetic Retinopathy Clinical Research Network:* Both forms of diabetes cause damage to the eyes and may lead to blindness. This network is conducting multicenter clinical research studies to test promising therapeutic agents for the treatment of diabetic eye disease. Both type 1 and type 2 diabetes patients are enrolled in the studies.

‣ *Genetics of Diabetes Complications:* Several research consortia are studying the underlying genetics of diabetes complications. Increased knowledge about genetics could help researchers predict who will develop complications, as well as inform the development of new targets for prevention and treatment.

‣ *Angiogenesis Research:* Angiogenesis is a process in which new blood vessels grow from existing ones. Research has shown that angiogenesis plays a key role in the development of some diabetes complications. Angiogenesis research, which has historically focused on cancer, is now being applied to research on diabetes complications. In turn, new insights could inform the understanding of other diseases in which angiogenesis plays a role.

‣ *Animal Models of Diabetic Complications Consortium:* This consortium is developing animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The animal models developed by this group are also critically important for testing promising therapeutic agents prior to testing in type 1 or type 2 diabetes patients.

‣ *Pediatric Endocrinology Training Program:* This program is designed to prepare pediatricians for careers in pediatric endocrinology research related to diabetes. Because type 2 diabetes is now increasingly being observed in children, these specialists could contribute their expertise to children with both forms of the disease.

What It's Like When Two of Your Children Have Type 1 Diabetes

Aiden Berg was a 14-month-old toddler when he was diagnosed with type 1 diabetes. Two years later his older sister, Heather, was diagnosed with the disease at age 10.

If you ask their parents, Toni and Rob Berg, what is the most difficult thing about raising a family when more than one child has diabetes, without hesitation, the answer comes back: scheduling!

"I think of myself as a pretty organized person," says 38-year-old Toni, who works as an airline customer service agent, "but with this disease, we have to stay on top of things all the time." Even then, things can go wrong.

About a month after Heather was diagnosed, the Bergs inadvertently mixed up Heather's and Aiden's doses of insulin, which resulted in a "mini crisis," says Rob. "Heather's dosage was way too much for Aiden, so we were up the entire night monitoring him. Now we always double check everything," adds the 39-year-old accountant. The Bergs have a third child, Dillon, age 8, who so far does not show any signs of the disease. "We check Dillon's blood sugar at least once a month," says Toni, "and keep our fingers crossed."

Understanding the Genetic Link

About 1 out of 5 people with type 1 diabetes has a close family member with the disease. To help scientists better understand the genetics of diabetes, the Bergs are currently taking part in a study called the Type 1 Diabetes Genetics Consortium (T1DGC). This consortium is designed to gather valuable information from 2,800 families like the Bergs, with at least two siblings who have type 1 diabetes. The study, sponsored by the NIDDK and the JDRF, involves researchers from around the world—Europe, North America, Asia-Pacific, and the United Kingdom.

The Berg children.

The T1DGC is different from many other clinical studies in that it does not test a medical intervention, but rather is designed to gather valuable information. Ultimately, information about the genetic basis of the disease may not only help identify new therapies, but also predict which therapy might be best for a particular person. Finding the genes predisposing to type 1 diabetes will also enable those at risk to be identified early so they can benefit from future research. The study is closely aligned with the Type 1 Diabetes TrialNet, which is investigating the development, prevention, and early treatment of type 1 diabetes. Both the T1DGC and TrialNet are supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*.

Dealing with the News

Toni and Rob were familiar with diabetes long before Aiden and Heather were diagnosed. Toni's mother died at age 56 from complications of type 2 diabetes, which she developed after having been diagnosed with gestational diabetes during her last pregnancy. Rob's mother also has type 2 diabetes, but she has avoided its complications so far.

According to the Bergs, before Aiden's diagnosis, he was manifesting many of the symptoms of diabetes. "At 12 months he had lost weight and was drinking

lots of water," says Toni. "I said to our family doctor, 'My God, he has diabetes.'" Toni was told that the weight loss was probably because Aiden had started to walk and thus was using more energy. As for drinking lots of liquids, it was summertime and the temperature was very hot. Aiden's symptoms persisted, however, including: lethargy, constant irritability, and extreme thirst. "We were told over and over that children Aiden's age don't get diabetes," say the Bergs. Recent reports from physicians at diabetes centers suggest that type 1 diabetes may be occurring in younger children than was previously recognized. This is a problem, because it is much harder to control the disease in infants and young children who cannot recognize or respond to episodes of dangerously low blood sugar (hypoglycemia).

Finally, Aiden was given a blood test and was diagnosed with type 1 diabetes. By that time, he was so sick he had to be taken immediately to the hospital where he spent 2 days in the intensive care unit. "It just sank in that this was going to be life-long," says Toni. She adds that she was overcome by it all, especially knowing the history of what her mother and others in her family had gone through because of the disease. However, things didn't end there.

Two years later, Aiden's sister, Heather, was diagnosed with the disease. According to the Bergs, Heather's blood sugar was always a bit higher than the levels of the rest of the family. One day, while at a diabetes health exposition in Seattle, where the family resides, Heather used a blood sugar tester and her reading came out well above the healthy range. The vendor for the product told the Bergs to make sure to have Heather's blood sugar checked by a doctor. Toni hesitated. "I was in denial that two of my children could have diabetes," she says. Heather insisted on having the test because she would feel more comfortable knowing one way or the other. Sure enough, Heather's blood sugar number came out high again. "I still didn't want to believe it—until we got the [hemoglobin] A1c test results—which confirmed for me Heather's diagnosis," says Toni.

"I felt overwhelmed," Toni recalls, "but Heather was brave and never shed a tear."

"I can handle it," the precocious Heather told her parents. And handle it, she has.

One year after Heather was diagnosed, she went on an insulin pump. "She wanted to go on the pump the day she was diagnosed, but we decided we should wait a while," says Rob. Heather has taken to the pump well, and it has helped a lot in terms of family scheduling. "Heather is an extremely competent child and pretty much takes care of herself," says Rob.

"It's not as bad as I thought it would be," says Heather, who is now 11. "The shots don't hurt much, and because I'm on the pump, I don't have to have so many pokes. Also, Aiden had diabetes before me, so I kind of knew what to expect." Besides, she adds, "the pump is cool because people think it's a cell phone."

No Typical Day

The Bergs say that no day is "typical" for their family, but they certainly keep diabetes-related procedures well under control.

Each morning the Bergs check Aiden's and Heather's blood sugar levels and administer insulin according to need. Then, the family goes over what they're going to have for breakfast so they know how many carbohydrates will be taken in; the same for when lunches are made. "There's no such thing as buying lunch at school anymore," says Toni. Most days, the Bergs check in with the school or day-care center to see how the kids are doing. After school, blood sugar levels are checked again, and Aiden and Heather have a snack—either with or without carbohydrates, depending on what their sugar levels turn out to be.

The Bergs also are big on sports. "There is always one sporting event or another that the kids play in," says Toni. Rob adds that, "We try to keep them active all year round. Whether it's baseball, swimming, soccer, cheerleading, gymnastics, riding their bikes, or playing in the backyard pool, it makes a big difference in their [blood sugar] numbers." In the winter months, those numbers are a bit higher because they are not quite as active as in the summer, which, according to Rob, means more of an insulin adjustment.

In the evening, the family has dinner, and blood sugar levels are checked just before bedtime. Depending on how much Aiden's and Heather's blood sugars fluctuate on any given day, "either Rob or I will get up in the middle of the night and check them again," says Toni.

Taking Part in Research Studies

Like many families with a high incidence of diabetes, the Bergs are seeking as much information as possible about the disease. They became involved with the T1DGC study when they stopped by the Benaroya Research Institute's booth at the Diabetes Expo in Seattle and were asked if they would like to participate in diabetes research. They jumped at the opportunity.

Such studies give hope to families like the Bergs. The T1DGC is expected to provide a better understanding of the genetics of diabetes, which may suggest valuable new avenues for treating the disease. Furthermore, genetic testing may one day permit very early diagnoses, thereby enabling earlier management of the disease. Early intervention could reduce or delay onset of diabetes complications and prevent some emergency hospital admissions, such as was necessary for Aiden when he was first diagnosed. Indeed, ongoing research studies are using genetic tests to identify some newborns at high risk for developing diabetes. The studies are indicating that, with careful monitoring of such children, it may be possible to dramatically reduce the likelihood of such hospitalizations.

The hope extends beyond early diagnosis. "Knowing the amount of research going on, we're hopeful that a cure for diabetes will be found by the time our children reach adulthood," says Toni. "We hope and pray other families will participate in this research. The larger the pool of people they have to study, the more they can learn about combating this disease," she adds.

More information on participating in the T1DGC and TrialNet can be found at: www.t1dgc.org and www.diabetestrialnet.org

Genetics and computer science are the proud parents of the burgeoning new field of bioinformatics—the application of information technology and computational methods to manage a deluge of biological data. Although, as a discipline, bioinformatics may be in its infancy, it has already hit its growth spurt by propelling the development of novel tools for studying the genomes of entire organisms (genomics) and the protein expression from entire cells and tissues (proteomics). The *Special Funding Program* has fostered bioinformatics research in its quest to comprehend and cure type 1 diabetes. The Endocrine Pancreas Consortium—an early *Special Funding Program* project initially funded in 1999—developed tools to more fully characterize the genes involved in the hormone-secreting function of the pancreas.

A complementary project, the Beta Cell Biology Consortium (BCBC), which subsumed the Endocrine Pancreas Consortium in 2002, has a mission to facilitate interdisciplinary approaches that will advance understanding of the development and function of the pancreatic islet. These research teams and their collaborators have developed a microarray specifically tailored to the endocrine pancreas—the "PancChip"—that can be used to study gene expression in this tissue and may provide insights into diabetes. The story behind the creation of the PancChip illustrates how targeted research funding—like that provided by the *Special Funding Program*—can catalyze the adaptation of cutting-edge technology into valuable tools targeted toward diabetes.

What Is a Microarray?

With only a few exceptions, every cell of the body contains a full set of chromosomes and identical genes. Only a fraction of these genes is turned on in any given cell at any given time, however, and it is the subset that is "expressed" that confers unique properties to each cell type. "Gene expression" is the term used to describe the multi-step process whereby information contained within the DNA is first transcribed into an intermediary molecule, messenger RNA (mRNA), and subsequently translated into the proteins that carry out important cellular tasks. Scientists study the kinds and amounts of mRNA in a cell to learn which genes are expressed—and how that expression might change—under certain conditions or at certain times. Gene expression is a highly complex and tightly regulated process that allows a cell to respond dynamically both to environmental stimuli and to its own changing needs. Importantly, gene expression is not just a simple "on/off" switch, but may also be thought of as a "volume control," increasing or decreasing levels of expression as necessary.

A microarray is a tool for analyzing gene expression that consists of a small membrane or glass slide containing small samples of many genes. A microarray works by exploiting the ability of a given mRNA molecule to bind specifically to the DNA template from which it was transcribed. By using an array containing many DNA samples, scientists can determine—in a single experiment—the expression levels of hundreds or thousands of genes within a cell by measuring the amount of genetic material bound to each site on the array. With the aid of a computer, the amount of labeled genetic material bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the cell. Microarrays are therefore useful when one wants to survey a large number of genes quickly or when the sample to be studied is small. Microarrays may be used to assay gene expression within a single tissue or cell type as a function of some treatment or developmental change, to compare gene expression in two different cell types or tissue samples, or to monitor changes in gene expression that coincide with the onset of disease.

Over the past decade, microarrays have greatly facilitated large-scale analysis of gene expression in a wide range of tissues. Although commercially available arrays have not been specifically geared to represent the cells and organs known to be affected by diabetes, they have nevertheless been used in studies of both type 1 and type 2 diabetes. Perhaps not surprisingly, given their relative lack of specificity, many of these studies have shown few differences in gene expression in the disease state. It was this relative dearth of genomics tools geared specifically to diabetes that spurred the NIH to act to develop a more powerful tool to advance the science of diabetes genomics.

Building the PancChip

Before the PancChip could be created, it was first necessary to generate a pancreas-specific "library" of genes expressed in this tissue. How does one go about defining which genes are specifically expressed in a particular tissue?

To do this, researchers used a combination of gene expression analysis and database mining. Using a variety of pancreatic tissues, including whole pancreas from adult and fetal mice, mouse insulinoma cells (a tumor of pancreatic islet cells), and human islets, the researchers identified genes that were highly expressed in these cells. Second, they identified additional genes by examining previously prepared libraries generated from human islets and human or mouse whole pancreas. The scientists in the Consortium used this information to assemble the first version of the PancChip, a microarray that contained 3,400 genes. Of these, 3,139 represented genes whose expression is enriched in the pancreas, 231 represented genes expressed in cell signaling pathways important in diabetes, and 30 represented so-called "housekeeping" genes that are responsible for general cellular function and metabolism. Of the pancreas-specific genes, 2,369 had been previously identified while 310 represented novel, theretofore undescribed genes.

In a report published in the July 2002 issue of the journal *Diabetes*, the researchers describe the generation of the
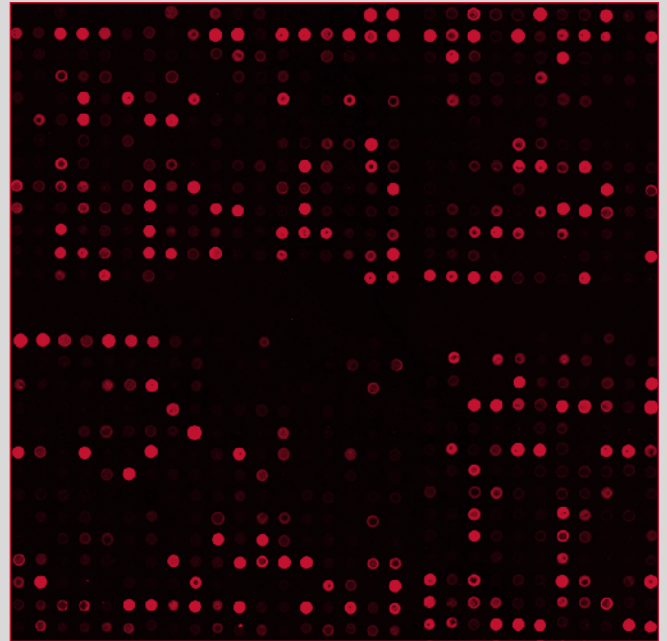
An image of a PancChip. *(Image courtesy of Dr. Klaus Kaestner.)*

PancChip and its use in the characterization of changes in gene expression patterns in the mouse pancreas from mid-embryonic development through adulthood. They reported that the profile of gene expression in the pancreas—as measured using the PancChip—changed markedly from the embryonic stage through adulthood, with proteins involved in binding DNA and RNA highly expressed during embryonic development and enzymes highly expressed in adulthood. The ability to generate a profile of gene expression in this tissue at various time points during development demonstrates the value and utility of the PancChip as a research tool.

Growing Family of PancChips

The efforts of the Consortium to identify and characterize the genes expressed in the pancreas have allowed these researchers to identify over 160,000 individual sequence fragments. Analysis of these sequence fragments has identified close to 14,000 unique human gene sequences and over 9,400 mouse gene sequences. Furthermore, the researchers have identified roughly 4,300 sequences in both human and mouse tissue that have never been previously

described. These discoveries have allowed the members of the Consortium to expand and improve the PancChip. The current mouse PancChip (Version 6) contains over 13,000 unique elements that can be used to measure gene expression levels in a single assay. In 2004, the Consortium offered investigators the first version of a Human PancChip with over 12,000 genetic elements from the pancreas.

Of the vast amounts of genetic material in the body, only 1.5 percent of the DNA codes for proteins. Some of the non-protein-coding DNA helps to regulate whether or not a particular gene is expressed, and to what extent. New bioinformatics technologies allow researchers to probe beyond the coding DNA into the regulatory DNA, once thought of as "junk DNA." In 2005, the Consortium produced two new microarrays of non-coding DNA, called promoter chips, that allow researchers to screen over 35,000 regulatory regions on the mouse DNA.

The promoter chips employ a new technology called the ChIP-on-Chip assay, so named because it combines DNA microarray chips with DNA/protein binding experiments called chromatin immunoprecipitation (ChIP). Every cell type has a unique set of proteins, called transcription factors, that bind to specific regulatory regions of the non-coding DNA, thereby controlling the pattern of gene expression. Researchers can use transcription factors from pancreatic islets as fishing bait to isolate the regulatory regions of DNA that are important in these cells. By matching this isolated DNA to the DNA embedded on the promoter chips, researchers can quickly identify the specific DNA hot spots that give beta cells their unique properties. As of April 2006, the Consortium had distributed over 400 of these promoter chips to labs all over the world.

Future of Diabetes Bioinformatics Research

The generation and availability of the PancChip represent a major success of an initiative funded through the *Special Funding Program for Type 1 Diabetes Research*. The BCBC prints PancChip microarrays for all its members and distributes them at low cost to researchers around the globe. Data, protocols, resources, a searchable database, scientific highlights, and references are easily accessed on their website (www.betacell.org). The availability of these tools will be of great assistance as other researchers pursue new avenues of investigation. Areas in which the PancChips may provide important insights include:

▶ *Islet cell transplants:* Does increased (or decreased) expression of a particular gene or set of genes correlate with success of the transplant? If so, is it possible to manipulate gene expression in the islets prior to transplant in order to improve outcomes?

▶ *Stem cell therapy:* What genes give islet or pancreatic cells their unique nature? Is it possible to influence the differentiation of stem cells so that they can be efficiently coaxed into islets?

▶ *Profiles of gene expression:* Using the PancChip, it may be possible to generate "snapshots" of gene expression within the pancreas under various physiologic conditions. How might gene expression differ in people predisposed to developing diabetes? How does it change early in disease progression? Is it possible to influence pancreas gene expression—either through drugs or gene therapy—and alter the course of disease development?

▶ *Target discovery:* More comprehensive knowledge of gene expression patterns in the pancreas may identify novel genes important in normal function of the organ. What new targets for therapy might there be? Such research could increase treatment options for people with diabetes and those at risk.

- *Beyond diabetes:* The PancChip provides an important resource for other diseases of the pancreas. Researchers studying pancreatic cancer are using this tool to explore patterns of gene expression in pancreatic tumors. Thus, the benefits of the *Special Funding Program* extend beyond diabetes and may help to characterize pancreatic cancers and identify new targets for their therapy.

Overall, it is anticipated that a more complete understanding of the mechanisms involved in the development of the endocrine pancreas may allow researchers to better coax human stem cells into pancreatic endocrine cells for treatment of type 1 diabetes. Insights from these efforts may also provide new approaches to improve insulin secretion in people with type 2 diabetes.

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH*

T**he** Special Funding Program *has fueled the emergence of a wide range of research opportunities. Opportunities that have largely been made possible by the* Special Funding Program *have been excerpted below from the Type 1 Diabetes Research Strategic Plan (see Appendix 6).*

Genetic Causes

Create Resources for the Study of Type 1 Diabetes Genetics:

▸ Complete the T1DGC—an unlimited source of DNA for type 1 diabetes gene discovery from informative families representing various ethnic groups.

▸ Establish a resource of biological materials that will facilitate research on the genetic basis of type 1 diabetes in those who develop the disease later in life.

Identify Human Genes Causing Type 1 Diabetes:

▸ Identify the mechanisms by which the genes within the human MHC contribute to the major genetic susceptibility in type 1 diabetes, and estimate the influence of HLA on other genes with respect to type 1 diabetes risk.

▸ Identify and elucidate the mechanism of non-MHC type 1 diabetes susceptibility loci, and develop, test, and validate appropriate statistical methods for characterizing genome-wide gene-gene interactions.

▸ Utilize newly developed genomic resources to facilitate testing and cataloging of genomic architecture (SNPs and haplotype blocks) to discover all genes and gene variants affecting susceptibility to type 1 diabetes through a genome-wide association study.

▸ Test in prospective clinical studies which genetic factors affect the development of islet autoimmunity, progression to type 1 diabetes, or both.

Use Knowledge About the Genetic Underpinnings of Type 1 Diabetes To Prevent and Treat the Disease:

▸ Integrate knowledge of genetic susceptibility into risk assessment targeted at prevention and treatment of type 1 diabetes.

▸ Develop scientifically based methods of communicating risk information.

▸ Use genetic information to guide the selection of immunomodulatory treatment in new onset patients and islet transplant recipients.

Environmental Causes

Monitor Rates of Type 1 Diabetes:

▸ Monitor the incidence of type 1 diabetes in a representative sample of the U.S. population, as well as in informative populations around the world, to further define the course, and possibly the causes, of the recent rise in type 1 diabetes.

Assess Environmental Causes of Type 1 Diabetes:

▸ Complete enrollment into the TEDDY study, and begin well powered and nested case-control studies of children enrolled in TEDDY who have developed persistent autoantibodies to GAD65, IA-2, or insulin, in order to systematically evaluate candidate environmental causes of islet autoimmunity.

▸ Define the effects of intrauterine environmental exposures (e.g., nutrition, stress, infections) on islet development and islet (beta cell) gene expression and function.

▸ Identify molecular genetic mechanisms by which specific environmental agents may trigger islet autoimmunity and promote progression to type 1 diabetes *in utero*, in early postnatal life, and later in development.

▸ Explore the possible role of emerging infectious agents, orphan viruses, and intestinal bacteria in the etiology of type 1 diabetes.