GOAL V

PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

The *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of large-scale collaborative research groups and clinical trials networks that seek to understand and treat the complications of type 1 diabetes. The *Special Program* has also enabled the valuable long-term follow-up study of a well-studied cohort of type 1 diabetes patients as they begin to develop complications.

Although the discovery of insulin in 1921 has nearly eliminated death from the acute effects of type 1 diabetes, patients can never ignore the looming specter of chronic health complications that affect nearly every organ system in the body. The *Special Funding Program* has created exciting new opportunities to study the basic mechanisms underlying complications and to develop tools and therapies to prevent or reduce them. In diabetes, damage is caused by persistent elevation of blood glucose levels (hyperglycemia) and by cellular stress due to altered metabolism of sugars and fats. Damage to heart tissue and larger blood vessels (macrovascular complications) gives rise to cardiovascular disease and clogged arteries (atherosclerosis), and increases the risk of premature death from heart attacks and strokes. Damage to the networks of small blood vessels embedded in tissues (microvasculature) leads to: eye disease (diabetic retinopathy), the leading cause of new blindness in the U.S.; kidney disease (nephropathy), which can lead to irreversible kidney failure, known as end-stage renal disease (ESRD); and nerve disease (neuropathy), an often painful condition contributing to foot ulcers, which can lead to limb amputation in extreme cases. Diabetes impedes repair pathways necessary for the success of established cardiovascular therapies such as coronary angioplasty and bypass grafting, and lower extremity revascularization. In addition, diabetic individuals are at increased risk of gum disease and other oral complications, pregnancy-related complications, urinary incontinence, nocturnal diarrhea, and erectile dysfunction. Furthermore, type 1 diabetes increases the likelihood of depression and, in some cases, increases family conflict, which may exacerbate problems with metabolic control.

NIH-supported clinical trials dramatically proved that intensive glucose control can reduce the long-term risk for microvascular, cardiac, and neurologic complications of type 1 diabetes. Nonetheless, even with optimal diabetes care, complications constitute a significant burden for people with diabetes and compromise their quality of life. Therefore, uncovering the molecular mechanisms underlying cellular damage and designing novel therapies to reverse this damage remain high research priorities.

Patients with type 1 diabetes vary in their risk of developing specific complications. Risk factors are dependent on duration of disease, control of blood sugar, co-morbid conditions, and genetic background. Large-scale genetic studies supported by the *Special Funding Program* have enabled identification of genes that confer protection from (or susceptibility to) different diabetic complications. The development of new therapies is a long process requiring basic discoveries, reliable animal models, technology development, and extensive clinical trials, particularly for chronic complications that develop years after diagnosis. The *Special Funding Program* has supported efforts in each of these areas, as well as accelerated research progress through various initiatives that: identify and validate biomarkers and surrogate endpoints that facilitate clinical trials; screen libraries of approved drugs for their potential use in diabetes complications; provide drug development resources through the Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) program (see Goal VI); and establish a clinical trial network to test new therapies. Importantly, the scientific and clinical accomplishments that emerge from the complications research supported by the *Special Funds* may benefit individuals affected with any form of diabetes, including both type 1 and type 2 diabetes.

HIGHLIGHTS OF SCIENTIFIC PROGRESS

While numerous significant advances have emerged since the beginning of the **Special Funding Program**, *many of the research efforts to prevent or reduce type 1 diabetes complications 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.*

Sustained Benefit of Intensive Glucose Control on Complications Susceptibility—"Metabolic Memory": The Diabetes Control and Complications Trial (DCCT) revolutionized the management of diabetes. Started in 1983, the multicenter clinical trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of disease complications in over 1,400 people with type 1 diabetes. It proved conclusively that intensive therapy dramatically reduces the occurrence and severity of microvascular (small blood vessel) complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered for the valuable follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, which is supported by the *Special Program*.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all patients were encouraged to use intensive treatment. The post-DCCT glycemic values for both groups have become nearly identical during the approximately 10 years of follow-up in EDIC. Surprisingly, the effects of intensive glucose control during the DCCT on the incidence of retinopathy persisted, and had even become greater over 7 years after the study ended when the glucose control was similar between the two groups. This report by the EDIC investigators in May 2002 was followed by another exciting finding in October 2003 that showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group 8 years after the end of the DCCT. In February 2006, it was reported that the benefits of 6.5 years of intensive therapy also extended to symptoms and signs of neuropathy for at least 8 years beyond the end of the DCCT.

Analysis showed that these long-lasting differences in development of complications could be explained by the difference in control of glucose levels between the two treatment groups during the DCCT. The phenomenon of long-lasting effects of a period of intensive or nonintensive glucose control has been termed metabolic memory, and provides further impetus for early intensive therapy of diabetes.

Delay or Prevention of Large Blood Vessel Complications of Type 1 Diabetes: While the DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye, and nerve problems, controversy remained about the effect of elevated blood glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlated with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven in a rigorous, randomized clinical trial. The *Special Funding Program* made it possible to follow the valuable DCCT/EDIC study patients as they reached the life stage at which CVD begins to take its toll. In June 2003, the EDIC research group reported that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared with the patients in the former conventional therapy group. In December 2005, the EDIC researchers reported that during an average follow-up time of 17 years, the patients who had been intensively treated during the trial had fewer than half the number of CVD events—heart attacks, strokes, or death due to CVD—than those in the conventionally-treated group. These results were the first to prove that

intensive control of blood glucose levels has long-term beneficial effects on CVD risk in diabetes patients. These findings are particularly significant because CVD is the cause of death in two-thirds of patients with diabetes.

Progress in Reducing Diabetic Nephropathy: Recent reports indicate that prevention efforts are beginning to have dramatic effects on the rates of diabetic nephropathy in people with type 1 diabetes. This devastating complication of diabetes has historically been seen in as many as one-third of diabetic individuals after 20 or 30 years of disease. In the most recent population-based study from Finland, however, only 7.8 percent of patients with type 1 diabetes have renal failure after 30 years of diabetes. Declines in the incidence of end-stage renal disease due to diabetes are being noted for the U.S. population as well, in reports from the United States Renal Data System. The rate of end-stage renal disease in Caucasians under age 30 with diabetes (most of whom have type 1 diabetes) is almost half the rate seen in the late 1980s and early 1990s. Since that time, several clinical strategies have been proven to significantly reduce the progression of diabetic nephropathy. These include angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin receptor blockers (ARBs), which lower protein in the urine and are thought to directly prevent injury to the kidneys' blood vessels, and careful control of blood glucose and blood pressure. Credit for the recent gains likely goes to implementation in clinical practice of these strategies to prevent disease. Thus, the investment of *Special Funds* in DCCT/EDIC and the National Glycohemoglobin Standardization Program (see Goal II) is already reaping dividends by helping patients with their blood glucose control, which reduces diabetes complications.

Genetic Influence in Diabetic Nephropathy: Mounting evidence suggests that some people with diabetes are more genetically vulnerable to certain complications than others. To tease out the genetic contributions, DCCT/EDIC geneticists are conducting systematic analyses of candidate genes. For example, angiotensin-converting enzyme (ACE) is key to physiologic pathways regulating blood pressure. Elevated ACE activity can increase pressure in the filtering units of the kidney (glomeruli), which ultimately causes permanent injury. Drugs known as "ACE inhibitors" have been proven to help stave off diabetic kidney damage. In a retrospective study of genetic and other data from 1,365 DCCT/EDIC participants, investigators examined specific genetic variants in the ACE gene for two renal outcomes: incidence of persistent microalbuminuria (leakage of small amounts of protein in the urine) and incidence of severe nephropathy. The standardized methods used in DCCT/EDIC to measure renal function, coupled with comprehensive health data collected for over 17 years, provided a unique opportunity to control for variables other than ACE variants that could affect nephropathy onset and severity, such as age, duration of diabetes, and blood pressure levels, as well as glucose control in the DCCT study. As a result, the group was able to confirm that a specific variant of the ACE gene—"extra" DNA inserted in a non-coding region—is associated with reduced risk of microalbuminuria and severe nephropathy. Furthermore, by analyzing "SNPs"—DNA landmarks for genetic variation—they identified a common variant of the ACE gene that conferred a reduced risk of nephropathy when present in two copies. In the Genetics of Kidneys in Diabetes Study (GoKinD), a variant in another candidate gene, TGF-beta-1, was found to increase the risk of nephropathy. The genetic data that has been collected in EDIC, GoKinD, and the Family Investigation of Nephropathy and Diabetes (FIND) studies will enable further studies of the genetic underpinnings of specific complications in type 1 diabetes. Genome-wide studies currently under way will go beyond looking at candidate genes suspected to predispose to complications, and have the potential to identify new pathways involved in complications and open new avenues of therapy. Identification of genes such as ACE

and TGF-beta-1 that modify risk for nephropathy will help identify patients who can benefit most from intensive control of glucose and blood pressure.

Role of Reactive Oxygen Species (ROS) in Complications Pathogenesis: Over the past 35 years, several molecular mechanisms have been implicated in glucose-mediated vascular damage. Each of these mechanisms has been studied independently of the others, and there has been no apparent common element linking them. Recent discoveries have made clear that all of these seemingly unrelated mechanisms may arise from a single, hyperglycemia-induced process: the overproduction of the reactive free radical molecule, superoxide. It now appears that the energy-generating cellular organelles called mitochondria are required for the initiation of hyperglycemia-induced superoxide production, which can, in turn, activate a number of other superoxide production pathways that may amplify the original damaging effect of hyperglycemia. Increased free fatty acid oxidation in mitochondria produces superoxide as well. In diabetic mice genetically engineered to produce high levels of an enzyme that degrades superoxide (called "superoxide dismutase"), the classic hyperglycemia-induced damaging pathways are not activated, and these mice do not develop diabetic kidney disease. This advance points to the central role of a single pathway involved with complications in multiple organs. Several novel pharmacologic approaches based on this unifying mechanism have already prevented diabetic eye, kidney, and nerve pathology in rodent models of diabetes.

Impaired Blood Vessel Formation from Bone Marrow Progenitor Cells in Diabetes: Diabetic complications result not only from damage to cells and tissues, but also from the inadequacy of the repair process. During the acute response to injury, new blood vessel growth rescues "stunned" areas of the heart or central nervous system, reducing morbidity and mortality. With chronic low perfusion, the development of collateral vessels reduces the size and severity of a subsequent infarction. Circulating progenitor cells from the bone marrow promote the regeneration of blood vessels by acting in concert with the cells and extracellular matrix at the site of injury. A major advance is the observation that these endothelial progenitor cells are depleted and dysfunctional in diabetes, and that injection of normal progenitor cells can improve blood supply to the tissues and nerve function in experimental diabetes. Research focused on the diabetes-induced impairment of this process could lead to novel drug- and cell-based therapies for people with diabetes to restore compensatory vessel formation in CVD, stroke, peripheral vascular disease, and wound healing. In the diabetic retina, however, overly exuberant vascular repair processes can result in excessive proliferation of small vessels. Molecular pathways responsible for the new vessel growth have been identified, and this work suggests new molecular targets for drugs that could protect the retina.

EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO PREVENTING OR REVERSING THE COMPLICATIONS 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.*

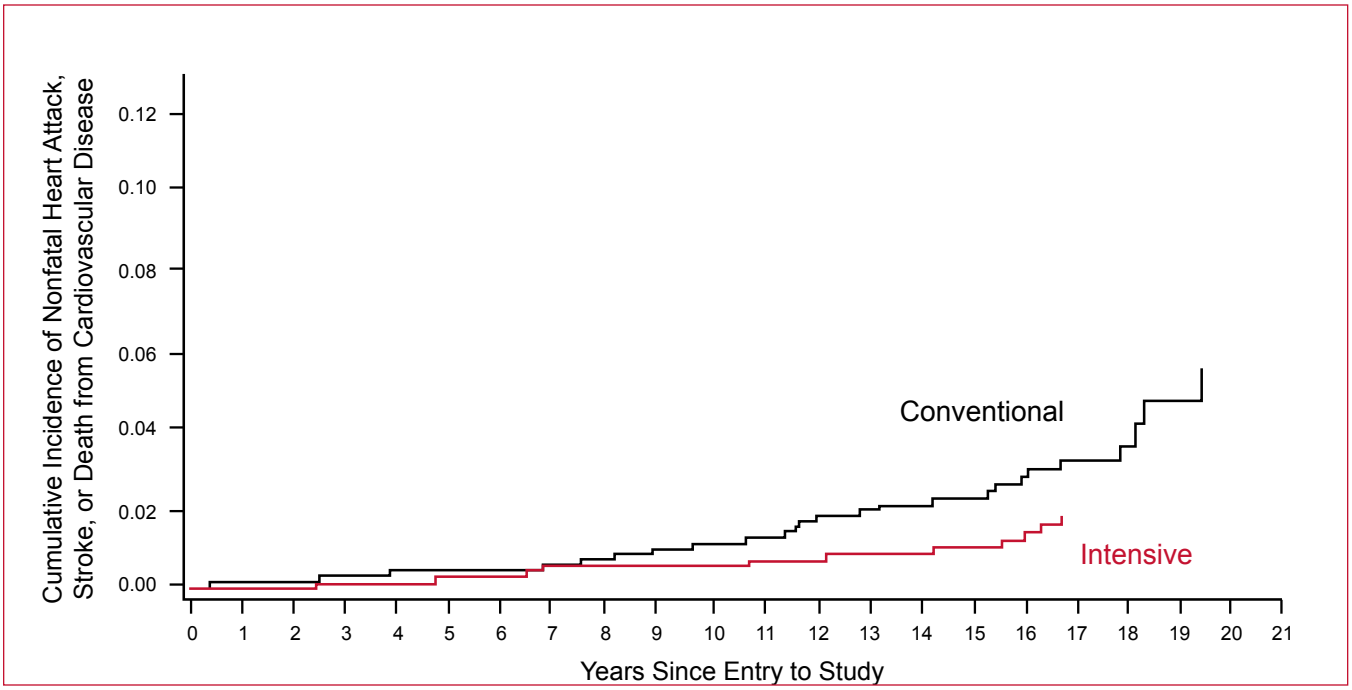
Epidemiology of Diabetes Interventions and Complications (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT). Completed in 1993, the DCCT revolutionized diabetes management by demonstrating the benefit of intensively controlling blood glucose levels with frequent monitoring and insulin injection for preventing or delaying the early complications of the disease. Both the "conventional" and "intensive" treatment groups from the DCCT are being followed observationally, but all participants are now recommended to follow the intensive therapy guidelines. DCCT/EDIC is a prospective study: one of its major strengths is the well-studied cohort of patients in which disease progression has been followed for over 20 years before most complications developed. The *Special Funding Program* support has been pivotal to the success of EDIC. Major findings from the study are described in the Highlights of Research for Goals IV and V. Additional findings below derived from studies to measure the onset and progression of CVD, diseases of the urinary tract (uropathy), and diseases of the nerves that communicate with the internal organs such as the bladder, bowel, and sexual organs (autonomic neuropathy). A separate genetics component is described in the next section entitled "Genetics of Diabetic Complications."

Highlights of Progress

The progress that the EDIC studies have made as of March 1, 2006, includes:

- Results show that intensive control of blood glucose levels cut the number of CVD events (heart attacks, strokes, or death) in half relative to the control group in the DCCT. This is the first demonstration of the long-term beneficial effects of intensive diabetes therapy on macrovascular complications in type 1 diabetes patients.
- Results of carotid ultrasonography show significant thickening in arteries of EDIC diabetes patients relative to non-diabetic controls and significantly less progression in the DCCT intensively-treated group compared to the conventionally-treated group.
- Preliminary results show that the DCCT intensively-treated group is associated with reduced coronary calcification (a subclinical progression of CVD).
- Recent, important, and provocative findings are the persistent, long-term benefits of intensive treatment and reduction in glycemia resulting in substantially reduced risk of retinopathy, nephropathy, neuropathy, and CVD in EDIC, termed "metabolic memory."



Intensive treatment of type 1 diabetes, which includes four or more glucose measurements and three or more insulin injections daily or use of an insulin pump, has previously been shown to dramatically reduce the onset and progression of eye, nerve, and kidney complications. Until recently there was no proof that intensive glucose control reduced cardiovascular disease, the leading cause of premature death in diabetes. Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study have demonstrated that intensive treatment can reduce the risk of heart attack, stroke, or death from cardiovascular disease by 57 percent compared to conventional treatment. *(Image courtesy of Dr. David Nathan and adapted with permission from Nathan DM et al. DCCT/EDIC Study Research Group.* N Engl J Med. *353: 2643-2653, 2005. Copyright © 2005 Massachusetts Medical Society. All rights reserved.)*

Anticipated Outcomes

The dramatic results of the DCCT/EDIC demonstrate the benefits of a long-term prospective study. The DCCT proved conclusively that intensive diabetes therapy reduces the risk and progression of eye disease (retinopathy) by 47 to 76 percent, of kidney disease (nephropathy) by 39 to 54 percent, and of nerve damage (neuropathy) by 60 percent. However, only in the long-term follow-up EDIC study (average 17 years of follow-up) have the benefits for CVD become apparent as well: intensive diabetes therapy reduces non-fatal CVD events by 57 percent. The impact of these findings applies not only to patients with type 1 diabetes, but also is likely to apply to the roughly 19 million people with type 2 diabetes who suffer from the same complications. The research has already been translated from the clinic into practice as close control of blood glucose levels is now a keystone to the medical management of both forms of diabetes. In addition to reducing the burden of complications, these results have implications for improving the life expectancy in a disease in which heart disease is the leading fatal complication.

Heart disease is a chronic condition, developing over decades. It is difficult to prospectively study a population continuously from a young age before the onset of symptoms through CVD events, such as heart attacks and stokes. Yet as shown in EDIC, therapy early in the course of disease has profound consequences decades later. Because pharmaceutical companies and

the biotechnology industry have a limited willingness to develop products that require years of testing before their clinical effects can be realized, it is therefore important to develop and validate subclinical biomarkers that the FDA will accept as a basis for approval of new drugs for diabetes complications. For example, the DCCT demonstrated that the level of HbA1c—a modified form of hemoglobin that circulates in the blood and correlates to the average blood glucose levels over a 3 month period—can be used as a surrogate endpoint for therapies that seek to reduce complications of diabetes. This test has subsequently become an important outcome measure for future clinical trials of both type 1 and type 2 diabetes. The use of HbA1c as an outcome measure was the basis for FDA approval of improved forms of insulin, as well as many other new drugs for type 2 diabetes.

Comprehensive and meticulous data collection in the DCCT/EDIC cohort for more than 20 years, with participation rates about 95 percent, has created an unparalleled resource of individuals with type 1 diabetes that is ideal for future study of the clinical course of diabetes and its complications and for the validation of surrogate endpoints that can facilitate future drug development. These include assessment of subclinical markers such as testing new imaging techniques to measure the clogging, narrowing, and hardening of major arteries (atherosclerosis), heart muscle function, and other signs of CVD. EDIC has pioneered the use of new noninvasive diagnostic tools such as using ultrasound to measure the thickness of the carotid artery, or use of a "heart scan" (electron beam computed tomography) and multi-detector scanning to determine the extent of coronary calcification. By validating new analytical tools for early detection of CVD complications before events occur, the results of EDIC are paving the way for future trials that are smaller, shorter in duration, and less expensive to conduct.

Longitudinal assessment of the cohort allows analysis of rate-of-change of complications over time, including the interactions among complications and co-occurrence of complications, as well as further evaluation of the longer-term effects of original DCCT interventions on advanced complications. This study also could lead to an examination of the longevity of the metabolic memory phenomenon and whether it applies to all diabetic complications. Important insights will be gained regarding the disease-causing mechanisms that underlie the development and progression of diabetic complications.

External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Advisory Committee focused on EDIC, leading scientific and lay experts were asked to evaluate the components of EDIC, such as genetic studies and measures of CVD, supported through the *Special Funding Program* at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- EDIC has been extremely productive over the years with valuable studies, high quality publications, and meaningful bedside applications.
- These cardiovascular studies address a limitation in the original DCCT studies that examined a young group of patients with few cardiac complications.
- The relevant question now is to consider the value of continuing these ancillary observational studies versus designing new prospective studies with the latest technology. Despite the lack of baseline data in cardiovascular studies in the DCCT participants, there are still opportunities to capitalize on the long-term investment in resources in this select cohort of patients.

- The study participants are just beginning to have cardiac events, so this cohort provides a good opportunity to examine subclinical CVD markers (carotid intima-medial thickness, coronary calcification, myocardial function) as predictive of cardiovascular events. The longer-term follow-up just to monitor cardiac events will be less costly than a new prospective study.
- Neurological manifestations of type 1 diabetes have been less extensively studied than eye and kidney disease in DCCT/EDIC, and plans are under way to redress this with support of the *Special Funding Program*.

Actions Taken in Response to Expert Panel Recommendations

EDIC 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: Increase the Study of Neurologic Manifestations of Type 1 Diabetes

- In addition to core EDIC neurologic assessment, a neurology protocol is being implemented to assess metabolic memory of intensive glycemic therapy on peripheral and autonomic neuropathy, the impact of neuropathy on health-related quality of life, and the association of autonomic neuropathy with CVD.
- Preliminary results from an ancillary study have shown that there are no significant differences in neurocognitive function between the two treatment groups, suggesting that the higher rates of hypoglycemia in the intensive-treatment group have not affected cognitive function.

Recommendation: Continue Studies To Verify Surrogates for Cardiovascular Events and Utilize Cardiovascular Data in the Design of Future Prospective Studies

- A third carotid ultrasound is being implemented, and comparative studies of surrogates with clinical outcomes are planned.
- A cardiac magnetic resonance imaging (MRI) study will be funded through the *Special Funding Program*.

Ongoing Evaluation

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

- Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, central laboratories, and reading centers);
- Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results; and
- Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

In addition, *ad hoc* advisory groups have been assembled to review new initiatives being proposed in EDIC and to review progress once initiatives have been implemented. Examples of these groups include an *ad hoc* advisory group for the current genetics study, review groups for proposals to obtain EDIC nonrenewable biologic samples, and groups recommending specific measures to be obtained for assessing CVD and autonomic and peripheral neuropathy.

Coordination with Other Research Efforts

EDIC 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. The coordination of the genetic components of EDIC is described in the subsequent section entitled "Genetics of Diabetes Complications." For a full description of ongoing collaborative efforts, please see Appendix 2.

Capitalizing on Research Investment by Collaborating in Ancillary Studies:

- The EDIC study group has collaborated on studies of CVD, microvascular disease, urology, and neuropathy, thus providing access to this well-characterized patient population and to biosamples derived from the study to talented investigators outside the network.

Enhancing Data Comparison Among Studies:

- The National Glycohemoglobin Standardization Program certifies clinical laboratories to use the standard set by DCCT/EDIC for measurements of HbA1c. Nearly all commercial laboratories providing this clinical test in the U.S. are now certified through this program supported by the *Special Funding Program*. This has allowed the National Diabetes Education Program to promulgate a nationwide public health campaign to achieve target HbA1c values based on the DCCT/EDIC.

EDIC Administrative History

Date Initiative Started	1994
Date *Special Program* Funding Started	1998
CVD and Urology Components Started	2002
Participating Component	NIDDK

EDIC is a long-term follow-up study to the Diabetes Control and Complications Trial (DCCT) of 1,441 patients with type 1 diabetes conducted between 1983-1993.

Genetics of Diabetic Complications

The following three consortia were grouped because they all address genetic factors that predispose diabetes patients to, or protect them from, developing complications in various organs. Each has unique attributes that make it highly valuable for genetic studies: EDIC's strength is the careful characterization of the cohort over 20 years of follow-up; FIND has a very large collection of families in which two or more siblings have diabetes; and GoKinD matches patients with type 1 diabetes with and without kidney complications and collects information from their parents.

Epidemiology of Diabetes Interventions and Complications (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT), which showed that intensive glucose control can prevent or delay microvascular (eye, kidney, and nerve) disease complications. For a detailed description of EDIC, please see the previous section. To capitalize on the long-term investment in the select EDIC cohort, the *Special Funding Program* supports a study on the genetics underlying diabetes complications in these patients. The study is analyzing expanded data regarding the progression of complications in EDIC participants and their affected and non-affected family members to identify DNA sequence differences that influence susceptibility to diabetic complications.

Highlights of Progress

As of March 1, 2006, the progress of the genetics component of EDIC includes:

- Follow-up in over 2,983 relatives of EDIC participants to ascertain presence of diabetes; complications information for 147 diabetic siblings of EDIC participants.
- DNA collection in 1,399 living parents and 1,584 siblings.
- DNA analyzed for association with complications in 1,428 genetic markers (for mapping gene locations on chromosomes).
- Genetic variations in the angiotensin-converting enzyme (ACE) gene are associated with persistent leakage of a small amount of protein in the urine (microalbuminuria) and severe nephropathy in type 1 diabetes.

Family Investigation of Nephropathy and Diabetes (FIND)

The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease (nephropathy) in patients, especially those with diabetes, as well as genetic susceptibility to eye disease (retinopathy) in patients with diabetes. Five to ten percent of the people in FIND have type 1 diabetes. FIND is primarily supported by regularly appropriated NIH funds; however, support from the *Special Funding Program* has permitted expansion of FIND by initiation of a study of the genetic determinants of diabetic retinopathy in persons enrolled in the FIND family study. This component of the study compares the genes in pairs of siblings to identify candidate genes that may influence the development and severity of diabetic eye disease. FIND has also created a resource of genetic samples and data for use by investigators outside the FIND study group, for ancillary or follow-up studies. FIND represents the first large-scale study of the genetic determinants of retinopathy.

Highlights of Progress

The progress that FIND has made in retinopathy research as of March 1, 2006, includes:

- The family study exceeded recruitment goals, collecting genetic information from 2,367 individuals, who form over 2,000 pairs of siblings from 896 families.
- Preliminary results indicate that sibling correlation for retinopathy is 0.2, indicating that about 40 percent of the severity of the disease can be attributed to genetic causes.
- The entire FIND study, including retinopathy, has recruited over 8,000 individuals, and early genome scan results have identified putative places in the chromosomes contributing to various diabetic conditions, including diabetic eye disease.
- Cell lines have been established for all participants to provide a renewable source of DNA to study.

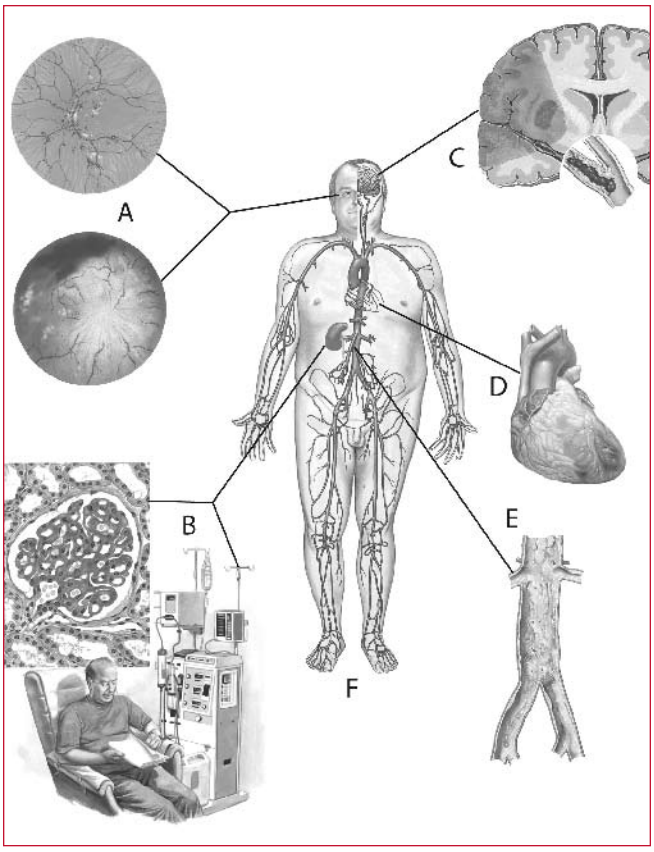
Genetics of Kidneys in Diabetes Study (GoKinD)

Patients with type 1 diabetes have a high risk of developing kidney disease. The fundamental aim of GoKinD is to facilitate investigator-driven research into the genetic basis of diabetic nephropathy by creating a resource of genetic samples from patients who have both type 1 diabetes and renal disease and "control" patients who have type 1 diabetes but no renal disease. With this design, the genes that confer risk for renal disease can be distinguished from those that are primarily risk factors for type 1 diabetes. Any researcher can apply for access to this collection of samples and data to investigate the role of specific genes.

Highlights of Progress

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

- Completed collection includes recruitment of 935 patients with both type 1 diabetes and nephropathy; 271 of these include sample collections from parents of the patients. Collections also include samples from 945 diabetes patients without nephropathy; 322 of these collections include parental samples.
- High-resolution genetic data have been analyzed in the most important chromosomal regions for type 1 diabetes (insulin gene; important immune system components known as HLA genes). Because of the design of the collection, very specific information on the genetic risk in a closely inherited block of HLA genes (DRB1, DQA1, and DQB1) will improve the genetic prediction of type 1 diabetes.
- Seven new HLA gene variants (alleles) have been discovered in the study and named; another has been submitted for naming; and several additional new DQB1 alleles have been detected.
- Discovery that a TGF-beta-1 gene variant predisposes type 1 diabetes patients to nephropathy.
- The GoKinD clinical data have provided new information on the potential use of a protein called Cystatin C as an indicator of renal disease.



Type 1 diabetes is associated with serious medical complications. These complications can negatively affect the body in a variety of ways and include: (A) blindness; (B) kidney disease; (C) stroke; (D) heart disease; (E) atherosclerosis (clogged arteries); and (F) nerve damage leading to foot ulcers and amputation. The Epidemiology of Diabetes Interventions and Complications (EDIC), Genetics of Kidneys in Diabetes (GoKinD), and Family Investigation of Nephropathy and Diabetes (FIND) studies are examining the genes that predispose patients to, or protect them from, developing certain complications. *(Illustration credit: F. Netter, MD, C. Machado, MD, and ICON Learning Systems. Netter medical illustration adapted with permission of Elsevier. All rights reserved.)*

Anticipated Outcomes

The diagnosis of type 1 diabetes does not automatically predestine a patient to all of the complications associated with the disease. Although the patient may be genetically susceptible to developing the disease itself, he or she may have a genetic composition that possibly confers protection from some disease complications, while increasing the risk of others. With more complete knowledge of the genetic factors that contribute to different complications, the patient's doctor may be able to intervene early to prevent or delay specific complications. For example, a patient genetically predisposed to diabetic nephropathy could employ clinical strategies such as carefully controlling blood pressure and taking ACE-inhibitors or angiotensin receptor blockers, which lower protein in the urine and are thought to directly prevent injury to the kidney's blood vessels. The synergy of the genetics research in EDIC, FIND, GoKinD, and the Type 1 Diabetes Genetics Consortium (T1DGC) (see Goal I) has promoted significant progress in the effort to identify and predict the natural history of type 1 diabetes and its complications in patients.

In addition to the gene discovery and genetic associations with diabetes complications under way with EDIC, FIND, and GoKinD, each of these consortia also serve as a resource for future efforts: tissue, genetic samples, data, and analytic methods from each Consortium are stored in a repository or database. The large and diverse sample and data collections—with families, cases, and controls—will become a widely-used resource for genetic study of susceptibility to diabetic complications. The availability of immortalized cell lines for each participant provides a renewable source of DNA, allowing future investigators to explore novel hypotheses or analytical approaches (such as whole genome association tests) that may be limited by current technology.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of these three consortia with respect to their components focused on genetics of complications at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- Human genetic studies are extremely challenging because of the difficulty in recruiting a patient with diabetes who has developed complications, as well as two or more family members with type 1 diabetes. These studies would be considered virtually impossible with a standard NIH single-investigator (R01) grant mechanism.
- These consortia provide extraordinarily valuable collections with strengths in sample size and in heterogeneity. Despite achievement of lower than target recruitment numbers, there is a rich collection of material, including that from one of the largest collections of sibling-paired subjects for genetic analysis of diabetic kidney disease.
- Enrollment is often an issue in these kinds of studies, and it is not uncommon for genetics studies to have difficulty meeting recruitment goals. The panel noted that the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations and Institutional Review Board (IRB) requirements may have contributed to slower than projected enrollment.
- The search for genes involved in renal complications is especially promising because of the epidemiology findings: approximately 30 percent of diabetes patients develop nephropathy within 15 years, while patients who have not developed nephropathy in 15 years rarely do so later, suggesting a genetic difference.

Actions Taken in Response to Expert Panel Recommendations

The following actions were taken 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, the consortia supported by the *Special Funding Program* that study the genetics of diabetes complications (EDIC, FIND, and GoKinD) participated in a coordination meeting with the T1DGC. 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 can be accessed at: www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf

Recommendation: Create a Single, Coherent, Accessible Database Combining the Studies

- The NIDDK Database Repository has created a single website (www.niddkrepository.org/niddk/jsp/public/kidney.jsp) that summarizes the major characteristics of each of the four genetics studies. It also provides links to relevant study websites and publications, and a table comparing the data collected in the four studies. When data from high-density genotyping of samples in the collection become available, those data will be reposited in a single database at the NIDDK Database Repository.

Recommendation: Share Lessons Learned About Methods for Effectively Addressing Recruiting Limitations

- A manuscript is in preparation by GoKinD recruiters that presents GoKinD recruitment data and explores the issues that result in barriers to recruitment.

Recommendation: Despite Achievement of Lower Than Target Recruitment Numbers, There is a Rich Collection of Material, Including That from One of the Largest Collections of Sibling-Paired Subjects for Genetic Analysis of Diabetic Kidney Disease

- The FIND family study exceeded recruitment goals, collecting genetic information from 2,367 individuals, who form over 2,000 pairs of siblings from 896 families.

Recommendation: Use Guidelines Developed by the T1DGC as a Model for Standardizing Release of Materials

- All four consortia have agreed to release samples and data by mid-2007 for completed collections.

Ongoing Evaluation

To ensure continued and ongoing evaluation of the study design and the progress of FIND and EDIC, the NIH has established External Advisory Committees (EAC). Each EAC is composed of investigators with scientific expertise relevant to research conducted by the Consortium, but who are not members of the Consortium. Please see a full description of "Ongoing Evaluation" of EDIC in the previous section.

The FIND EAC meets semi-annually to review the progress of the study. The advisors comment specifically on activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, and central laboratories and reading centers), review data to ensure its quality, advise on procedures for analysis, and review proposed significant modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

The GoKinD Executive Committee oversees the day-to-day operation of the study and consists of representatives from academia, government, and voluntary organizations. An external Steering Committee (SC) consisting of scientific and lay reviewers meets once a year to review the study and make recommendations.

Coordination with Other Research Efforts

The consortia studying the genetics of complications coordinate their efforts with each other and 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 Studies of Genetics in Type 1 Diabetes:

- EDIC, FIND, and GoKinD participated in a coordination meeting with the T1DGC (see "Actions Taken in Response to Expert Panel Recommendations" for a description of coordination efforts).
- Key personnel from the FIND study serve in official advisory capacities for GoKinD.

Developing Interoperable Databases for Data Sharing:

- A series of ongoing database coordination meetings between FIND, EDIC, and GoKinD are seeking to standardize vocabularies allowing investigators to search data across databases.
- The NIDDK is coordinating an integrated database of the parameters in the genetic studies of kidney disease in diabetes, which will include EDIC, GoKinD, and FIND.

Designing and Creating Animal Models of Disease for Basic Research from Genetics Data:

- The Animal Models of Diabetic Complications Consortium (AMDCC) semi-annual meeting on March 22-24, 2005, included presentations by FIND, GoKinD, and EDIC to initiate collaborations such that data originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will in turn validate the findings of the genetics consortia.

EDIC Administrative History	
Date Initiative Started	1994
Date *Special Program* Funding Started	1998
Participating Components	NIDDK
EDIC is a long-term follow-up study to the Diabetes Control and Complications Trial (DCCT) of 1,441 patients with type 1 diabetes conducted between 1983 and 1993.	
FIND Administrative History	
Date Initiative Started	1999
Date *Special Program* Funding Started	2001
Participating Components	NIDDK, NEI, NCMHD
Website	http://genepi.cwru.edu/FIND
Ten percent of the subjects in the FIND family study have type 1 diabetes. Funds from the *Special Funding Program* have permitted expansion of FIND to support ancillary studies searching for genetic determinants of diabetic retinopathy.	
GoKinD Administrative History	
Date Initiative Started	1998
Date *Special Program* Funding Started	1998
Recruitment Ended	2004
Participating Components	CDC, JDRF
Website	www.gokind.org
Saved blood plasma, blood serum, and urine samples are being stored at the CDC repository for use by any investigators in the diabetes research community based on a competitive review process.	

Diabetic Retinopathy Clinical Research Network (DRCR.net)

The DRCR.net is a collaborative, nationwide network of eye doctors and investigators conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy, diabetic macular edema, and associated conditions). The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives while incorporating standardization of multiple study procedures, utilization of novel technology, extensive integration of information technology, and the ability to leverage its resources to bring promising new therapies to evaluation that might otherwise not exist. Principal emphasis is placed on clinical trials, but epidemiology, outcomes, and other research approaches may be supported as well. Diabetic retinopathies are complications associated with both type 1 and type 2 diabetes; DRCR.net, which is funded in part by the *Special Funding Program*, enrolls both type 1 and type 2 diabetes patients. In soliciting site participants, involvement of community-based, as well as academic-oriented partners, has been encouraged.

Highlights of Progress

The progress that DRCR.net has made as of March 1, 2006, includes:

- Establishment of nationwide network including 165 clinical sites spanning 43 states. Community-based clinical sites comprise 61 percent of the network; most major research institution-based programs are also involved.
- An electronic visual acuity test has been distributed to all sites. This FDA-approved test is faster to administer than the standard version, and results are easily incorporated into a database.
- Completed study measuring variability in retinal thickening throughout the day in patients with diabetic macular edema.
- Completed enrollment of trial to evaluate different laser photocoagulation methods for diabetic macular edema.
- Completed enrollment and follow-up (through time of primary outcome) of trial to evaluate peribulbar steroid injection alone and in combination with laser photocoagulation for diabetic macular edema.
- Collaboration with industry on innovative protocol to create a drug that would not otherwise be commercially pursued (preservative-free intraocular steroid); recruitment in this Phase III study is near completion.
- Collaborating with industry on the development of a protocol to evaluate the injection of an anti-VEGF drug for diabetic macular edema.
- Five additional trials for diabetic retinopathy that are either in progress or will be initiated shortly.

A researcher examines a retina with diabetic eye disease. *(Photo credit: National Eye Institute, National Institutes of Health.)*

Anticipated Outcomes

Diabetes (type 1 and type 2) is the leading cause of new blindness in people 20-74 years old.[1] Laser photocoagulation is an effective technique that uses the heat of a laser beam to seal abnormal leaky blood vessels in the retina. While laser photocoagulation can prevent blindness, the technique itself can lead to impaired vision. Therefore, improved technologies are being developed and tested by DRCR.net. One of the most important DRCR.net priorities for the future is to have a portfolio of ongoing clinical trials that not only encompasses a broad diversity of promising new therapeutic approaches, but also addresses the full spectrum of patients with diabetic eye disease. The Network is actively pursuing identification and design of important clinical trials that complement each other in terms of patient eligibility and therapeutic approach. This approach prevents competition between studies for similar patients and expands the opportunities for patients to participate in these investigations. The goal of the Network is to eventually have any patient with diabetes potentially eligible for a DRCR.net study. As a large-scale multicenter network, DRCR.net has been successful at leveraging its resources to work with industry in developing therapies that might not have been otherwise pursued. Appreciation of the Network's benefits has prompted numerous inquires from commercial entities regarding evaluation of new therapies by DRCR.net. These opportunities are being carefully considered to assure that any such study would assess a need judged timely and critical by DRCR.net and would maintain rigorous scientific and ethical guidelines.

DRCR.net contributes to the training and knowledge of the ophthalmologic community with regard to rigorous clinical trials. This is one of the reasons for including a large number of community-based sites, offering them an opportunity to participate and become experienced in these efforts. Such expansion of quality clinical centers helps not only the Network, but patients throughout the country and the overall education of the ophthalmologic community.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of DRCR.net at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- DRCR.net successfully met its goals in getting both private- and academic-based retinal practices involved in clinical trials to study epidemiology, therapies, and outcomes of diabetic retinopathy.
- DRCR.net is a very worthwhile infrastructure, and it is awaiting the emergence of additional innovative therapies to test.
- The panel was concerned that the Data and Safety Monitoring Committee performs both safety monitoring and protocol review (See "Ongoing Evaluation" section below). However, the panel also recognized that the Steering Committee (SC) provides oversight of protocol conduct.

- The network incorporated technological innovations such as an electronic visual acuity test to normalize measurements across centers and electronic Clinical Report Forms.
- DRCR.net could serve as a model for conducting clinical trials for other complications (i.e., kidney, nerve).

Actions Taken in Response to Expert Panel Recommendations

The expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 did not make any recommendations specific to DRCR.net. However, the panel discussed the dichotomy of consequences from the growth of new blood vessels (angiogenesis). Whereas angiogenesis in the eye leads to development of retinopathy, diabetes complications in other tissues are caused by a loss of blood vessels. Therapies to inhibit angiogenesis in the eye may actually provide a remedy for the development of retinopathy. In 2005, a research solicitation supported by the *Special Funding Program* on angiogenesis in type 1 diabetes (see Appendix 1) generated projects to complement the ongoing DRCR.net efforts in angiogenesis.

Ongoing Evaluation

The DRCR.net Data and Safety Monitoring Committee (DSMC) has a dual role of external monitoring of network protocols and of advising the NEI on the merits of the protocols proposed by the Network as well as the Network's progress. The Committee meets in person at least twice a year and convenes by conference call as needed several times a year. The Network provides monthly data reports for the DSMC to review.

Within DRCR.net, there is an Executive Committee that is involved in policy decisions, as well as SCs that are involved in providing oversight for the development and conduct of each protocol. Each meets via conference call on a monthly basis with face-to-face meetings scheduled as necessary. The NEI has representation on these SCs.

In addition, a Protocol Concept Review Committee reviews ideas for protocols and advises the Executive Committee on whether an idea should be accepted for protocol development. If an idea is accepted, a Protocol Development Committee is created that is responsible for developing the protocol and has representatives from various aspects of DRCR.net. If the protocol involves a large randomized trial, it is presented to an External Protocol Review Committee whose members are assigned by the NEI to be advisory to the Institute regarding the protocol.

Additional committees created by the Executive Committee include a Data Collection Committee whose members advise the Network regarding development of efficient data collection procedures, and a Quality Assurance Committee whose members review detailed information prepared by the Coordinating Center regarding quality of enrollment, follow-up, adherence to protocol, timeliness of response to data queries, and other issues judged critical to maintaining excellent quality of Network clinical center activities. Summary reports are provided twice a year to the sites to strive for continued improvement in quality.

Representation on all of these committees by different clinical center investigators helps to ensure broad representation of investigators on most aspects of Network activities.

Coordination with Other Research Efforts

The Network also provides funding for small projects judged critical to the development or implementation of its trials. For example, a bioactivity study on bevacizumab was developed to provide necessary data to the FDA regarding shelf life of the compounded drug.

DRCR.net Administrative History

Date Initiative Started	2002
Date *Special Program* Funding Started	2002
Participating Sites (Offices)	Over 150
Participating Physicians	Over 450
Participating Components	NEI, JDRF
Website	www.drcr.net

DRCR.net consists of three cooperative agreements; participation is open to all qualified investigators/clinicians whose sites have the requisite equipment to conduct a study protocol.

Animal Models of Diabetic Complications Consortium (AMDCC)

The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. Most groups in the Consortium generate mouse models of diabetic complications; however, one site has developed larger animal models by selectively breeding pigs and screening for observable characteristics (phenotypes) of diabetes. In addition to creating animal models, the goals of the AMDCC include defining standards to validate each diabetic complication for its similarity to the human disease, testing the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, and facilitating the sharing of animals, reagents, and expertise between members of the consortium and the greater scientific community via its bioinformatics and data coordinating center.

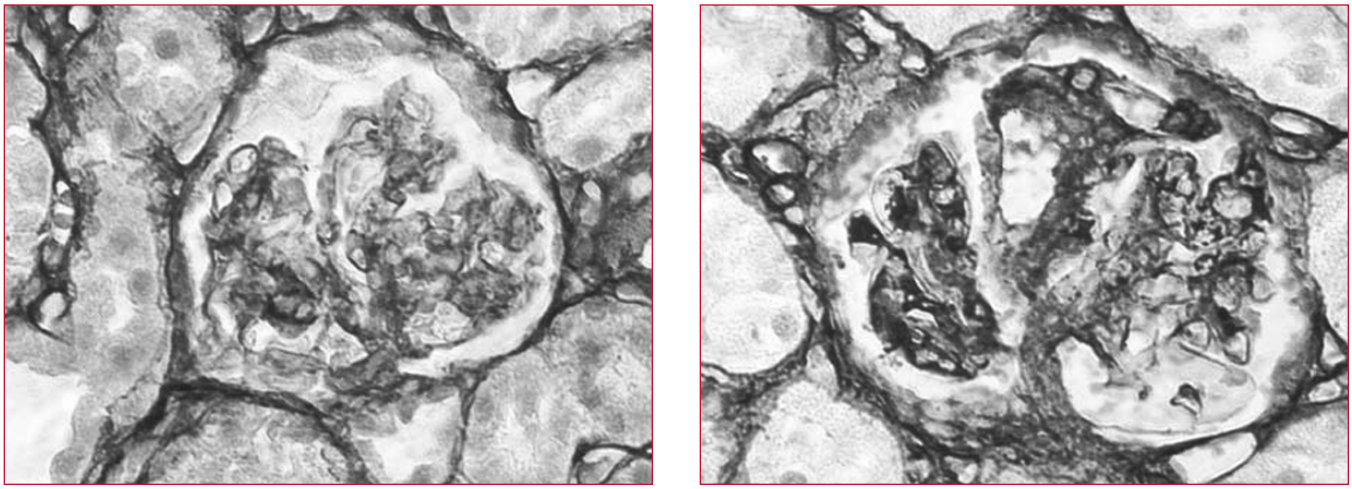
Highlights of Progress

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

- Generated over 60 new mouse models for diabetic complications, including a number of promising models for type 1 diabetic complications of the heart, kidney, and nervous system.
- Generated a new insulin resistant pig model that exhibits hyperglycemia, vascular atherosclerosis, and retinopathy that closely mimics human disease.
- Defined validation criteria for diabetic nephropathy, cardiomyopathy, and micro- and macrovascular disease.
- Developed standardized assays for phenotyping diabetic complications to ensure that data can be easily compared between members of the Consortium and the outside community.
- Built a bioinformatics website featuring a comprehensive laboratory notebook that provides an interoperable phenotype database with statistical and graphical modules. The AMDCC website currently receives about 1,500 hits per month from outside investigators.
- Assembled necessary infrastructure to facilitate sharing of information across the many scientific disciplines involved in complications research and to ensure that animal models developed for one diabetic complication are screened for all relevant complications.

Anticipated Outcomes

Animal models are an important scientific resource because they enable researchers to investigate underlying disease processes that cannot be studied in humans. For example, the demonstration of the key role of immune cells in the destruction of beta cells in type 1 diabetes would not have been possible without animal models. These models also permit assessment of novel therapeutic interventions before they are tested in people. The creation of the non-obese diabetic (NOD) mouse provided investigators with a critical tool for pre-clinical testing of new drugs for type 1 diabetes. Just like people with type 1 diabetes, the NOD mouse has genetic susceptibility due to molecules regulating the immune response; the disease is influenced by environmental encounters; the animal produces autoantibodies against beta cell proteins; and the white blood cells infiltrate the pancreatic islets. In the animal model, beta cell destruction can be attenuated through application of agents capable of influencing the immune response.



Studies from the Animal Models of Diabetic Complications Consortium (AMDCC) have shown that diabetic kidney disease is accelerated in mice that lack a protein, called peroxisome proliferator-activated receptor-alpha (PPAR-alpha). To investigate the role of PPAR-alpha in diabetic kidney disease, researchers studied genetically engineered mice that lacked the PPAR-alpha gene. These images show kidney cortical glomeruli stained for type IV collagen, a marker of diabetic kidney disease, in mice that have the PPAR-alpha gene (left panel) or lack it (right panel). The data suggest that kidney damage is accelerated in the mice without the PPAR-alpha gene. AMDCC researchers have also recently demonstrated that activation of PPAR-alpha by the drug fenofibrate improves diabetes and its kidney complications in a mouse model of type 2 diabetes. *(Images courtesy of Dr. Matthew Breyer. Copyright © 2006 American Diabetes Association. Adapted from* Diabetes*, Vol. 55, 2006; 885-893. Reprinted with permission from The American Diabetes Association.)*

Following this successful approach, the AMDCC is designed to create better animal models of diabetes complications. Because the Consortium has invested in infrastructure to share its resources with the larger scientific community, the impact of its efforts on drug discovery is enormous. For example, a 2006 initiative supported by the *Special Funding Program* is screening compounds already approved by the FDA in cell-based assays for hyperglycemia (please see Appendix 1); compounds identified as potentially useful by a high-throughput screen can then be more intensively investigated in various animal models of diabetes complications to choose the most promising candidates for clinical trials. Animal models also provide an opportunity to identify surrogate markers for diabetic complications. Diagnosing intermediate stages of disease progression is a major challenge inhibiting clinical translation because disease progression is long-term and, at this point, the major focus of the FDA is on endpoints (e.g., death, cardiac events, and stroke). With over 60 new animal models and 50 peer-reviewed scientific publications, the AMDCC has played a critical role in propelling research progress by developing, validating, and distributing animal models with greater fidelity to human type 1 diabetes and its complications.

External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Advisory Committee (EAC) focused on the AMDCC, leading scientific and lay experts were asked to evaluate the progress of the AMDCC 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 AMDCC's major strengths include the validation criteria and standards that were developed by the very strong phenotyping cores and data coordinating center.
- The AMDCC fosters research progress by bringing together leaders in the animal model and diabetic complications fields.

- Strong infrastructure is supported by a functional website for accessing validation criteria and technical methodologies.
- Although the focus has largely been on mouse models, a promising new large animal model has also been developed.
- A major resource provided by the AMDCC has been the "standardization" of measurements/endpoints in various diabetic complications.

Actions Taken in Response to Expert Panel Recommendations

The AMDCC 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: Sustain and Expand the Phenotyping Cores of the AMDCC

- The AMDCC will partner with the NIDDK-supported Mouse Metabolic Phenotyping Centers (MMPCs) to ensure standardized phenotyping across all diabetic complications.

Recommendation: Find Correlations Among Mouse Models Across the Spectrum of Different Complications

- The AMDCC will share a Coordinating and Bioinformatics Unit with the MMPC to ensure that all phenotyping data generated by both consortia are housed together and easily compared across the spectrum of diabetes and its complications.

Recommendation: Create an Outreach Effort To Provide Animal Models or Breeding Pairs to the Research Community

- A Mouse Generation and Husbandry Core will be added to the AMDCC in 2006 to ensure that animal models and breeding pairs are directly available to the research community.

Recommendation: Emphasize Novel Technologies for Phenotyping for Intermediate Stage Diagnoses

- NIDDK recently published a Program Announcement entitled, "Development of Disease Biomarkers" that includes specific language encouraging studies of "diabetes and its complications." Additionally, a new initiative supported by the *Special Funds* calls for innovative research proposals to find and validate biomarkers for diabetic complications.

Recommendation: Include an Immunologist in Oversight of Complications Models

- Immunology expertise will be added to the AMDCC EAC in 2006.

Ongoing Evaluation

The AMDCC is jointly managed by the NIDDK and NHLBI. Program Officers from both Institutes meet every 6 weeks to discuss recent progress and future directions. NIH representatives and AMDCC investigators participate in monthly conference calls; conference calls organized by the nephropathy, cardiovascular, and uropathy subcommittees also occur periodically.

To ensure continued and ongoing evaluation of the study design and the progress of the AMDCC, the NIH has established an EAC. The EAC is comprised of approximately a dozen outside experts who meet with the AMDCC investigators and representatives from the NIH and JDRF for 2 days, every 6 months. The meeting includes an open session where the investigators present their work and a closed session where Program Officers and the EAC evaluate progress and discuss future directions. Following this meeting, the EAC prepares a

written report of its deliberations. This report addresses general progress and productivity within the Consortium, as well as specific strengths and weaknesses of individual projects. The report typically contains a series of critiques prepared by EAC members to which the investigators must provide written responses.

AMDCC investigators must also prepare an Annual Progress Report for submission to the EAC. This document provides a written summary of yearly progress, an appraisal of the interactions between the ongoing projects at each site, and a description of the existing and planned collaborations with other members of the AMDCC.

Coordination with Other Research Efforts

The AMDCC coordinates its efforts with 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.

Synergism with Genetics Consortia:

- One promising example of such coordination occurred at the AMDCC semi-annual meeting in March 2005. This meeting included presentations by members of the three existing diabetes genetics consortia (FIND, GoKinD, and EDIC). The collaborations established during this meeting ensure that the genes implicated by these large genetics studies will direct the creation of new animal models by the AMDCC. In turn, the ability of the AMDCC to confirm the role of these genes in animal models of disease will validate the findings of the genetics consortia.
- Further coordination is evident in the formation of a new partnership between the AMDCC and the NIDDK-supported MMPCs. The mission of the MMPCs is to conduct detailed metabolic phenotyping of genetically-altered mice. Thus, it is a logical extension of both consortia to have all mice generated by the AMDCC shipped to MMPC facilities. This close partnership will not only allow a number of organizational efficiencies, but more importantly, will make certain that all animals generated by the AMDCC are fully phenotyped across each relevant metabolic and diabetic complication.

AMDCC Administrative History

Date Initiative Started	2001
Date *Special Program* Funding Started	2001
Participating Components	NIDDK, NHLBI, JDRF
Website	www.amdcc.org

The AMDCC consists of eight model generation/validation sites, three phenotyping cores, and a bioinformatics/data coordinating center. Most sites are supported by cooperative agreements with the NIH.

EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

In addition to the research consortia previously described, the **Special Funding Program** *supported investigator-initiated research projects addressing particular challenges and opportunities identified by the NIH with the aid of scientific experts at workshops and advisory meetings. Often these recommendations were disseminated to the research community in a Request for Applications (RFA) or Request for Proposals (RFP). (For a list of initiatives supported by the* **Special Funding Program***, please see Appendix 1.) The NIDDK conducted a Grantee Survey (see Appendix 5) to evaluate the impact of the* **Special Funding Program** *on investigators with research project grants principally supported by the* **Special Funds***. The survey was used as a tool to assess the research accomplishments (e.g., publications, resulting patents, impact on patients' health), research collaborations, and impact that the* **Special Program** *had on careers of investigators supported by it. Data from this survey are found in the "Assessment" chapter.*

Impact of *Special Funding Program* on Extramural Grantees

Principal investigators who received grants related to preventing or reversing the complications of type 1 diabetes responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- "I studied diabetic neuropathy over 25 years using electrophysiological techniques. With this grant, preceded by others, I adopted a morphological approach to attempt to quantify the improvement in diabetic neuropathy after pancreas transplantation that I observed clinically. This new approach using confocal microscopy and immunostaining techniques to study sensory nerves procured by skin biopsy started an international trend to use these methods for diagnosis of several neuropathies. My successful attempt to extend this approach to nerves in internal organs, especially the gastrointestinal tract, has kept me in the field of diabetes research."
- "This grant was my first R01 and allowed me to justify dedicated research time and laboratory space. Without doubt, it was a factor in early promotion to Associate Professor (after 4 years on faculty) and tenure. Importantly, work funded by the grant was the basis for the development of research collaborations between the Diabetes/Endocrine and Cardiovascular Divisions and helped jumpstart an entire ultrasound microvascular research core. The work on this grant formed the basis for training multiple fellows, and several young investigator awards at national meetings."
- "This grant was critical for my career, as I am now considered a leading expert in diabetic neuropathy. As a result, diabetes is now the primary focus of my research laboratory, which currently consists of about 30 individuals. I am also now the director of [a clinical diabetes Center of Excellence], overseeing several clinical trials on treatment options for diabetic complications, and have won career achievement awards for my work. Therefore, the success of this NIH grant led to career advancement in both research and the clinic. Diabetic complications will continue to be the main thrust of my work until the end of my career."
- "It was my first clinical grant after many years of bench research, and it made me eager to continue to maintain a clinical arm to my efforts. I thus applied for another clinical grant from the JDRF, which was funded."

- "We have started a small company based upon some of the original findings made through this grant."
- "Since the initial R21 award, I have transitioned my entire research program, not without substantial pain, into the area of diabetic neuropathy. I believe our ability to use proteomics and generate novel conditional transgenic mouse models to investigate the contribution of specific genes toward Schwann cell dysfunction in diabetic neuropathy offers novel approaches that have been lacking in the field. Thus, the momentum provided by the initial award has been substantial and aided my securing additional support from the ADA and the NIH."

Improving Lives of People with Type 1 Diabetes

Diabetes slowly damages major organs in the body, such as the eyes, kidneys, and heart. Impressive research progress toward combating diabetes complications was achieved through a large clinical trial launched by the NIDDK. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial in over 1,400 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of complications affecting the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). Patients on intensive treatment kept their blood glucose levels and hemoglobin A1c (HbA1c) levels (which reflect average blood glucose levels over a 2- to 3-month period) as close to normal as safely possible with frequent monitoring of blood glucose, and at least three insulin injections a day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections a day, with once-a-day urine or blood glucose testing. The result was a large difference in the mean HbA1c levels in the two groups and a striking difference in their development of microvascular complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease, by 35 to 76 percent compared with conventional treatment. This dramatic, positive result has had a profound impact on clinical practice for the management of type 1 diabetes: it led to the development of clinical guidelines by the ADA and other groups; it spurred the creation of the National Diabetes Education Program to disseminate the findings to the public (www.ndep.nih.gov); and it stimulated multifaceted research efforts to develop tools and therapies that aid patients in achieving close control of blood glucose levels.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all patients were encouraged to use intensive treatment. Nearly all patients who participated in the DCCT volunteered for the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to determine the long-term outcome of reducing exposure of the body's tissues and organs to high blood glucose levels.

Over 10 years after the end of the DCCT, further seminal insights continue to emerge regarding long-term benefits of intensive blood glucose control. In May 2002, EDIC investigators reported that the 6.5-year period of intensive treatment during the DCCT continued to reduce the risk of eye disease as long as 7 years after the study ended. Building on this exciting finding, a study in October 2003 showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group 8 years after the end of the DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the patients after completion of the DCCT. Analysis showed these long lasting differences in development of complications could be explained by the difference in control of glucose levels between the two treatment groups during the DCCT.

While the DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye, and nerve problems, controversy remained about the effect of glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlate with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven. Through support in part by the *Special Statutory Funding Program for Type 1 Diabetes Research*, scientists were able to address this critically important topic. In June 2003, the DCCT/EDIC research group showed that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared to the patients in the former conventional therapy group. This effect was demonstrated using both ultrasound to measure thickening of the wall of the carotid

artery and also electron beam computed tomography to measure coronary calcification.

In December 2005, the DCCT/EDIC research group reported that, during an average follow-up time of 17 years, the patients who had been intensively treated during the trial had fewer than half the number of CVD events—heart attacks, strokes, or death due to cardiovascular disease—than those in the conventionally-treated group. These results showed for the first time that intensive control of blood glucose levels has long-term beneficial effects on CVD risk in type 1 diabetes patients. These findings are particularly significant because people with type 2 diabetes are 2-4 times more likely to die from CVD than individuals without diabetes,[2] and patients with type 1 diabetes face a 10-fold increased risk of CVD death.[3,4]

The findings of the DCCT/EDIC research team raise interesting questions about the "metabolic memory" that enables the beneficial effect of intensified blood glucose control to persist long after the period of intensive therapy has ended. Researchers are vigorously pursuing possible explanations for the enduring effects of intensive therapy that persist well beyond the period of improved glucose control. Continued efforts by scientists are also beginning to unravel the underlying molecular mechanisms by which elevated glucose levels damage small and large blood vessels and the tissues and organs that are affected.

Even though the results of the DCCT/EDIC studies show that intensive therapy is beneficial for long-term prevention of complications, a severe limitation to the practice of intensive therapy is the potential for acute episodes of hypoglycemia, or low blood sugar. Thus, researchers supported by the *Special Funding Program* are seeking new methods to improve blood glucose monitoring and insulin delivery and to develop new beta cell replacement therapy to cure type 1 diabetes. Researchers supported by the *Special Funding Program* have already been successful in developing continuous glucose monitoring technology that has been recently approved by the FDA. This technology represents an important current opportunity to help patients implement the recommendations from the DCCT/EDIC that will enable them to achieve significant risk reduction for diabetic complications, while also reducing their risk for episodes of low blood glucose.

The DCCT and EDIC studies have directly and positively affected the manner in which patients and physicians manage diabetes. They have provided conclusive evidence that patients should begin intensive therapy as early as safely possible. By maintaining intensive therapy, patients have significantly reduced development of complications, which directly translates into an improved quality of life. The *Special Funding Program* will continue to support studies to investigate mechanisms by which glucose exerts its devastating effects in the development of complications, with a goal of discovering therapeutic targets to treat or prevent complications.

The DCCT and EDIC studies also demonstrate how the long-term investment in research continues to have a profound impact on the health of patients. Over 20 years after the beginning of the DCCT, researchers are just now demonstrating significant findings that continue to improve the care of type 1 diabetes patients and have implications for type 2 diabetes patients as well. Because the cohort of DCCT patients was too young for examination of cardiovascular complications when the study began, the long-term follow-up was necessary to assess the effect of intensive glucose control on this most life-threatening diabetic complication. Likewise, it is anticipated that the long-term research efforts that have been recently launched with support of the *Special Funding Program* will also result in dramatic and positive benefits for type 1 diabetes patients in the future.

Angiogenesis is a process in which new blood vessels grow from existing ones. This process is critically important to the development and growth of a healthy embryo. It is also important in some cases in a healthy adult. For example, angiogenesis is triggered at the site of a wound to help speed the repair process. However, aberrant angiogenesis can contribute to disease states, and over 70 diseases have been identified in the last two decades which depend on angiogenesis.[5] These diseases include cancer, heart disease, many eye disorders, psoriasis, rheumatoid arthritis, and some diabetic complications. Historically, angiogenesis is most commonly studied in relation to its role in cancer. Cancer research has resulted in significant new insights regarding the underlying molecular mechanisms that control angiogenic processes. Research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research* is building upon and applying this knowledge to study angiogenesis as it relates to diabetes complications, with the ultimate goal of identifying new prevention and treatment strategies.

Angiogenesis and Cancer: From Hypothesis to Therapeutic Agent

In 1971, Dr. Judah Folkman proposed a novel view of the importance of blood vessels in the cancer field when he suggested that tumor growth is dependent on angiogenesis. Subsequent research has confirmed this hypothesis, and scientists have demonstrated that primary tumor growth, as well as the spread of cancer to other parts of the body (metastasis), is dependent on new blood vessel formation. Without new blood vessels, the tumors lack the blood, oxygen, and other nutrients needed for growth.

Dr. Folkman further postulated that inhibiting angiogenesis was a reasonable approach for cancer therapy. He reasoned that if a therapeutic intervention could stop tumors from promoting angiogenesis, then it would in essence "starve" the tumor and inhibit its growth. Since Dr. Folkman's initial observations and hypotheses, researchers have vigorously studied angiogenesis as it relates to cancer. In February 2004, the FDA approved the first cancer drug that works by inhibiting angiogenesis. The drug was approved for treating colorectal cancer. The approval of this therapeutic agent demonstrates how basic research to understand angiogenesis ultimately led to a therapy to treat some cancer patients.

Applying Angiogenesis Research To Reduce the Burden of Diabetic Complications

Although research on angiogenesis has primarily focused on cancer, it is crucial to apply the lessons learned, as well as to expand upon this knowledge base, to benefit research on other diseases which depend on angiogenesis. Research has shown that angiogenesis plays a key role in the development of diabetic complications. Both type 1 and type 2 diabetes share the same disease complications, which include blindness, kidney failure, lower limb amputations, heart disease, and stroke. Even with recent advances in treatment, type 1 diabetes is estimated to lower average life expectancy by 15 years due to the development of these life-threatening and serious complications.[6] Because type 1 diabetes patients develop the disease so early in life, the complications can also develop earlier, be more serious and costly, and dramatically reduce patients' quality-of-life.

The role of angiogenesis varies in different diabetic complications. For example, in diabetic eye disease (retinopathy), blood vessel growth in the eye directly leads to blindness because the new blood vessels are leaky and prone to bleeding. Likewise, research has suggested a role for excessive angiogenesis in the early phase of diabetic kidney disease (nephropathy). Therefore, a therapeutic agent to inhibit angiogenesis could potentially be used to treat these complications. However, in a diabetic wound, the blood vessels at the wound edge are abnormal, and studies in animal models have shown reduced angiogenesis in healing of skin wounds. Thus, an agent to promote angiogenesis selectively may be therapeutically useful to treat this complication. Because there is not a "one size fits all" strategy for treating diabetic complications, additional

research is needed to further elucidate the pathways that lead to abnormal angiogenesis in the different complications of diabetes.

Angiogenesis Research Supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*

To take advantage of the strong angiogenesis research base that has been realized by studying cancer, the *Special Funding Program* has propelled studies on angiogenesis related to diabetic complications, as described below.

Collaborative Studies on Angiogenesis and Diabetic Complications

The *Special Funding Program* has supported an initiative to stimulate research on the abnormal angiogenesis observed in type 1 diabetes and the mechanisms that lead to these abnormalities. The research supported under the initiative could ultimately lead to the development of therapies, biomarkers, and imaging tools to improve the diagnosis and treatment of diabetic complications. Ongoing studies include those to: elucidate the molecular pathways regulating angiogenesis in diabetic kidney disease; develop strategies to restore normal angiogenesis in type 1 diabetes patients to prevent the poor outcome of cardiovascular events (e.g., heart attack, stroke); understand the mechanisms that underlie the impaired function of endothelial precursor cells (cells that have been found to be involved in angiogenesis) in animal models of type 1 diabetes; and study the progression of diabetic retinopathy. Although these studies are still in their infancy, they have potential to provide insights regarding the aberrant angiogenesis observed in the development and progression of diabetic complications. This knowledge could be used to develop novel prevention and treatment strategies which could, in turn, improve morbidity and mortality associated with type 1 diabetes.

Diabetic Retinopathy Clinical Research Network

The NEI-led Diabetic Retinopathy Clinical Research Network (DRCR.net) facilitates the conduct of multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. The Network provides the infrastructure to permit the conduct of multiple concurrent and consecutive studies while retaining the ability to rapidly develop and initiate new protocols.

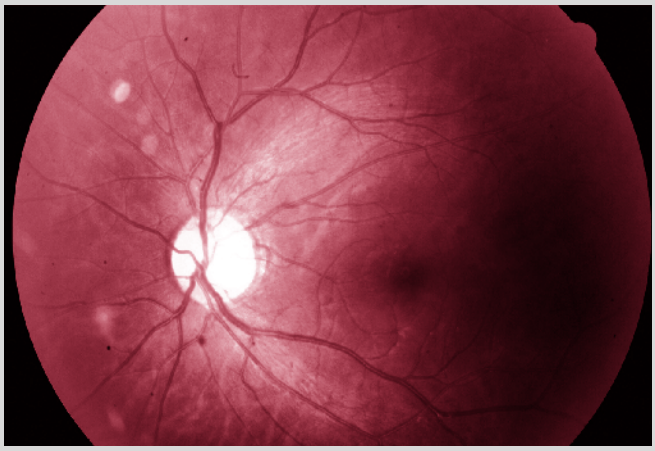


Image of human retina. Excessive angiogenesis (new blood vessel growth) in diabetic eye disease can lead to blindness; therapies to inhibit angiogenesis could possibly be used to prevent or treat this complication. *(Image courtesy of Dr. Ray Gariano.)*

Because excessive angiogenesis in the eye leads to blindness, identifying a therapeutic agent that inhibits angiogenesis can tremendously benefit type 1 diabetes patients. Investigators in DRCR.net are currently collaborating with industry on the development of a protocol to evaluate an injected anti-VEGF drug as a therapy for diabetic macular edema. VEGF, or vascular endothelial growth factor, is associated with promoting angiogenesis in the eye; agents that block its action, such as anti-VEGF drugs, could possibly be used to inhibit angiogenesis. For example, a drug that can bind VEGF has already been approved by the FDA for treating age-related macular degeneration. Further clinical research studies are needed to determine if anti-VEGF drugs are effective on other eye diseases, including diabetic eye disease.

NIH Trans-Institute Angiogenesis Research Program

The potential for angiogenesis research to improve so many lives prompted the formation of the NIH Trans-Institute

Angiogenesis Research Program (TARP) in early 2004. The overall goal of this program is to apply a multidisciplinary approach to research in order to accelerate the discovery of new interventions for a variety of diseases and conditions. Importantly, advances in one disease area may fuel advances in others. The NIH TARP will ensure that discoveries in one disease area are rapidly applied to other disease areas so as to maximize the NIH's investment in angiogenesis research.

Angiogenesis Research in the Future

The angiogenesis research supported by the *Special Funding Program* has the potential to not only benefit type 1 diabetes patients, but also type 2 diabetes patients, who share similar disease complications. Scientific knowledge gained from this research can also help patients suffering from other diseases in which angiogenesis plays a role. Just as angiogenesis research has benefited some cancer patients, it is hoped that similar benefits for type 1 diabetes patients could be realized and that research will uncover novel ways to prevent or treat the devastating and life-threatening disease complications. It is only through continued research that this goal can be realized.

At Age 18, a World-Class Ambassador for Diabetes Awareness

Eighteen-year-old college freshman Dana Lewis of Huntsville, Alabama, always considered herself a good talker. She's put that skill to very good use by helping to raise diabetes awareness not only throughout the U.S., but also throughout the world.

Dana was diagnosed with type 1 diabetes at age 14, and shortly thereafter began speaking at American Diabetes Association (ADA) events on behalf of people with the disease. At age 16, she was ADA's Alabama State Ambassador. A year later, Dana was crisscrossing the U.S. as ADA's National Youth Advocate, regularly meeting with policy makers to increase awareness about type 1 diabetes, and reaching out to her peers, as well as to adults, encouraging them to become involved in the fight against diabetes.

Today, Dana is reaching beyond America's borders, helping to make the entire world more aware of diabetes and its impact on people and society.

International Diabetes Foundation Youth Ambassador

In 2006, the International Diabetes Foundation (IDF) selected 25 youth ambassadors from around the globe, "and I was chosen as one of them," Dana says proudly. Last December, she and her fellow youth ambassadors were invited to participate in the World Diabetes Congress held in South Africa, where they helped pass a United Nations Resolution that proclaims every November 14th, starting in 2007, as World Diabetes Day.

"This U.N. Resolution is one of the biggest and most important things that's happening to make the world more aware of diabetes and its consequences," says Dana. She is proud to be a part of this global effort

Dana Lewis

that is encouraging nations from around the world to develop national policies for the prevention, treatment, and care of diabetes. But when she was first diagnosed with type 1 diabetes 4 years ago, her initial reaction was quite different.

Taking Good Care of Herself—and Others

Except for telling a few very close friends, Dana kept the fact that she had type 1 diabetes a secret from others for 4 or 5 months after her diagnosis. "I was scared of diabetes because my grandmother had been diagnosed with the type 2 form of the disease when I was 9 or 10 years old. Diabetes was a curse word to me," she says. "It took me a while to get used to being 'different,' and I didn't want to tell anyone that I had it."

Then one day, sitting in an advanced geometry class in high school, Dana suddenly made a complete turnaround. "I just all of a sudden said to myself that I want to get an insulin pump; I want to find a cure for this disease; I want to do whatever I can."

And given all of her diabetes-related activities, she's made good on that promise to herself.

Not only does Dana talk the talk; she walks the walk. She is acutely aware that tight regulation of blood sugar levels helps to prevent or delay the development of life-threatening complications related to diabetes, which include eye, kidney, nerve, and heart disease. Therefore, exercise, eating the right foods, and frequently testing her blood sugar levels are part of her daily routine.

"I take good care of myself," says Dana, "and I don't have any complications from my diabetes." Dana has two older brothers, but she is the only one in her family who has type 1 diabetes. "My mom keeps a close watch on my brothers for any symptoms, but so far they are both diabetes-free," she says.

Diabetes also has put Dana very much in touch with her body and herself. "I find that when I get stressed, my blood sugar goes up." To help prevent this problem, she spends part of every day by herself, just relaxing, perhaps reading or writing, which are two of her favorite things. To control her blood sugar levels, Dana also uses an insulin pump and is meticulous about checking her blood sugar levels at least 12 times a day.

In addition to taking care of herself, Dana is a strong advocate for finding ways to help others with their diabetes. "No matter what you do," she says, "doing something for someone else is better for you than anything. Volunteering is what puts diabetes in perspective for me."

To help teens like herself, Dana, when she was still in high school, created a support group, called "Teen Team," which served as a venue for members to share their experiences. "Support groups provide an opportunity to meet other teens who have diabetes and to learn how they are managing and juggling the disease with everything else that's going on in their busy lives," she says. She encourages young people to contact a local diabetes education center or doctor's office to help get a support group up and running in their school or community.

"I feel strongly that young people with diabetes not only need to take good care of themselves, but they also need to advocate for research that will one day cure us of this disease," says Dana. She believes that her double major in public relations and political science at the University of Alabama will help her in her advocacy work on behalf of people with diabetes. She continues to speak at ADA events and encourages people to participate in America's Walk for Diabetes and the Tour de Cure to help find a cure for the disease.

Thankfully, Dana is healthy and active right now. "I live my life the way I do in spite of having diabetes, not because of it! I plan to make a difference in the fight against diabetes, and I'm working very hard to encourage as many young people as I can to get involved and to advocate for more research."

With all the improvements in research and technology, Dana has high hopes that a cure for diabetes will be found in her lifetime. In the meantime, she will do whatever she can to manage her disease, as well as advocate on behalf of others with diabetes.

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

The 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).*

Molecular Mechanisms of Common Pathways in Diabetic Complications

Identify Molecular Pathways of Hyperglycemia Damage:

- Discover the factors controlling hyperglycemia-induced reactive oxygen species (ROS) formation and adaptive and maladaptive cellular responses to increased ROS.
- Identify the molecular events controlling receptor for advanced glycation endproducts (RAGE) expression and endogenous soluble RAGE production.
- Discover the mechanisms by which hyperglycemia impairs bone marrow progenitor cell function, especially vascular cell progenitors needed to repair wounds and revascularize ischemic heart muscle, peripheral nerves, and lower limbs.
- Identify the mechanisms of vascular proliferation in diabetic retinopathy.
- Discover the mechanisms leading to diabetic neuropathy that can occur through impaired blood vessel function and other causes, such as advanced glycation endproducts (AGE) formation and alterations in nerve growth factor signaling.

Clarify Mechanisms Linking Fuel Utilization and Heart Disease:

- Characterize the factors controlling increased fatty acid accumulation and mitochondrial oxidation in the development of diabetic cardiomyopathy and accelerated atherosclerosis, as well as the mechanisms by which this cellular lipotoxicity induces cell damage.

Understand the Systems Biology of Diabetic Complications:

- Apply a systems biology approach to research on diabetic complications.

Metabolic Memory

Discover the Molecular Mechanisms of Metabolic Memory:

- Study epigenetic factors involved in metabolic memory.
- Investigate the role of mitochondria in metabolic memory.
- Understand the regulation of the antioxidant response element.

Genetic Factors

Identify Genes Conferring Susceptibility and Resistance to Diabetic Complications:

- Determine the genes that increase susceptibility to diabetic complications.
- Discover genetic modifiers for diabetic complications.

Animal Models

Develop More Human-like Animal Models of Diabetic Complications:

- Develop human-like mouse models for diabetic complications.
- Utilize large animal models of diabetic complications.

Biomarkers and Surrogate Endpoints to Facilitate Clinical Trials

Identify Biomarkers or a Combination of Biomarkers for Earlier Detection of Cell and Tissue Damage:

- Validate newly developed biomarkers.
- Discover specific molecular targets and innovative technologies for early biomarker development.

Validate Surrogate Endpoints for Assessing the Progression of Complications in Clinical Trials:

- Develop surrogate endpoints for clinical trials in diabetic complications.

Therapies To Improve Patient Health

Identify Therapeutics That Prevent or Reverse the Development and Progression of Diabetic Complications:

- Use high-throughput screening of molecular libraries to find new therapeutics for diabetic complications.
- Improve the high-throughput assays for diabetic complications.
- Apply the latest advances in drug development technology to diabetic complications.
- Encourage the translation to human application of promising new therapies.

Mitigate Psychosocial Complications and Comorbidities of Diabetes To Improve Quality of Life:

- Clarify the bidirectional influences of depression as a complication and potentially modifiable risk factor for type 1 diabetes complications.

Combine New Technology for Diabetes Management with Behavioral and Translational Research:

- Design family-based interventions to improve patient management of diabetes.
- Identify strategies to improve adherence to therapy in adolescents and young adults with type 1 diabetes.

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