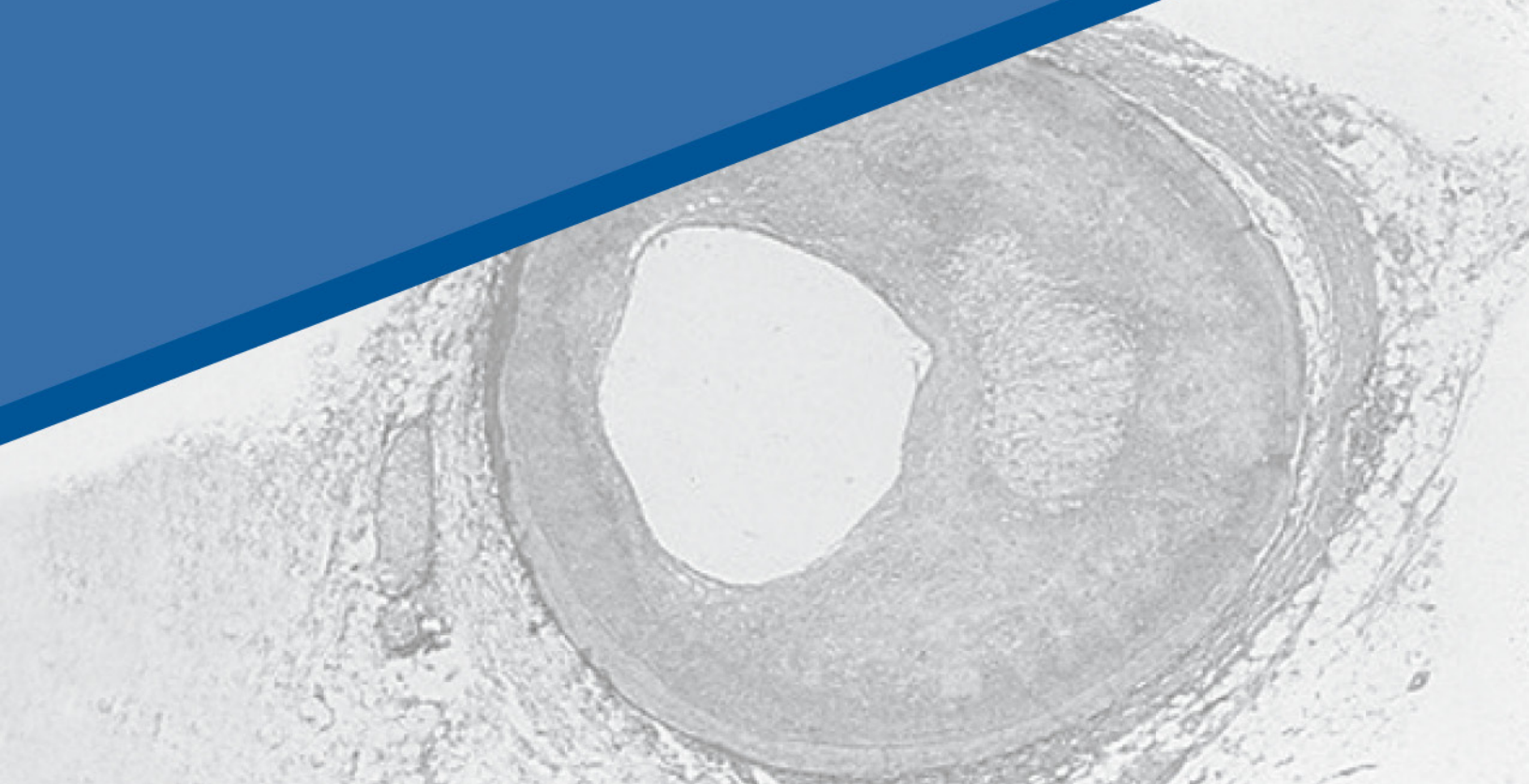
GOAL V

PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES



Persistent elevation of blood glucose (sugar) levels, despite insulin therapy, slowly damages the body's organs and can lead to life-threatening diabetes complications. Until the prevention or cure of type 1 diabetes is possible, the *Special Statutory Funding Program for Type 1 Diabetes Research* is vigorously supporting research toward preventing and treating the complications of the disease. In addition to the significant research progress described in this chapter, information on the program evaluation related to Goal V can be found in Appendix A (Allocation of Funds), Appendix B (Assessment), and Appendix C (Evaluation of Major Research Consortia, Networks, and Resources).

Insulin therapy enables survival for people with type 1 diabetes, by signaling their cells to take up needed glucose from the blood. One might expect this circumvention of the need for pancreatic insulin to allow people with the disease to live as long as people who do not have diabetes. Unfortunately, type 1 diabetes, like type 2 diabetes, is associated with an array of common complications that can be costly, debilitating, and deadly, and can shorten life. Diabetes ravages nearly every part of the body, including the heart, eyes, kidneys, nerves, lower limbs, mouth, and digestive and urologic systems. In the United States, diabetes is the leading cause of vision loss in working age adults, nontraumatic lower limb amputations, and kidney failure.[24] Heart disease risk is increased up to 10-fold in people with type 1 diabetes compared to the general age-matched population.[25] Type 1 diabetes is estimated to shorten the average life span by 15 years.[26] Until the prevention or cure of type 1 diabetes is possible, therefore, intensified research toward preventing and treating the complications of the disease is critically important. The *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program* or *Program*) has enabled significant progress toward combating diabetes complications.

[24] Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

[25] Krolewski AS, Kosinski EJ, Warram JH, et al: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 59: 750-755, 1987; Dorman JS, Laporte RE, Kuller LH, et al: The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality results. Diabetes 33: 271-276, 1984.

[26] Portuese E and Orchard T: Mortality in Insulin-Dependent Diabetes. In *Diabetes in America* (pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH, 1995.

Graphic: Image of artery occluded by lipid buildup which contributes to cardiovascular disease—a devastating complication of type 1 diabetes. Image credit: National Heart, Lung, and Blood Institute, NIH.

HIGHLIGHTS OF RECENT RESEARCH ADVANCES RELATED TO GOAL V

Continued Benefits of Improved Blood Glucose Control: The Diabetes Control and Complications Trial (DCCT) showed that intensive control of blood glucose levels reduced the risk of damage to small blood vessels and nerves in people with type 1 diabetes. The follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continues to demonstrate the long-term benefits of intensive therapy. Patients who had been intensively treated during the trial had fewer than half the number of cardiovascular disease 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 cardiovascular disease risk in people with type 1 diabetes. These findings have revolutionized the management of type 1 diabetes and the fruits of this research are resulting in improved health outcomes for people with type 1 diabetes: DCCT/EDIC researchers recently demonstrated that intensive control of glucose beginning as soon as possible after diagnosis can greatly improve the long-term prognosis of type 1 diabetes.

Long-term Clinical Trials Revealed the Phenomenon of "Metabolic Memory" in People with Diabetes: The DCCT/EDIC studies have shown that participants who intensively managed their blood glucose during the trial have maintained a lower risk of complications for more than 15 years, even though after the trial ended their glucose control gradually became indistinguishable from that of the participants who had received standard glycemic control measures. This apparent long-term benefit of a relatively short period of intensive glucose control has been termed metabolic memory. These results underscore the importance of intensive glucose management from the earliest stages of diabetes and point to the need for research in epigenetics and other potential mechanisms contributing to metabolic memory.

The Repair and Regeneration Process Is Impaired in Diabetes: Many of the serious complications associated with diabetes—including chronic, non-healing foot ulcers and poor recovery from impaired blood supply to the heart, brain, and/or limbs—stem from inadequate growth of new blood vessels where and when they are needed. A critical component of normal vessel growth is a population of cells called circulating endothelial progenitor cells (EPCs). Several recent studies report that diabetes is associated with impairments in EPC number and function, as well as problems in other stem cell populations involved in wound healing. Trials are under way to test injection of a person's own EPCs to promote blood vessel growth in sites where it is needed. Recent studies on wound healing in response to restricted blood supply show that a protein called hypoxia-inducible factor (HIF)-1alpha is a critical regulator of new blood vessel formation. HIF-1alpha, and other molecules involved in the repair process, might serve as targets for therapeutic intervention to promote wound healing in people with diabetes.

Value of Ranibizumab in Treating Diabetic Macular Edema: Diabetes has multiple effects on the vasculature. A paucity of small blood vessels prevents wound healing leading to amputation, but in the eye, diabetes leads to excessive new blood vessel formation. A recent Diabetic Retinopathy Clinical Research Network (DRCR.net)

comparative effectiveness research study found that a drug that blocks vascular endothelial growth factor (VEGF), ranibizumab (Lucentis®), in combination with laser therapy, was substantially better than laser therapy alone or laser therapy with a different drug, at treating diabetic macular edema, a swelling in the eye that often accompanies and aggravates diabetic retinopathy. Nearly half of the patients receiving ranibizumab showed a substantial improvement in vision, compared to 28 percent receiving only laser treatments. This class of drugs could become the new standard of care for diabetic macular edema.

Development of a Mouse Model of Diabetic Nephropathy: Recent studies have implicated dysfunctional endothelial nitric-oxide synthase (eNOS) as a common pathogenic pathway in diabetic vascular complications. Researchers in the Animal Models of Diabetic Complications Consortium (AMDCC) have shown that eNOS deficiency in a widely used mouse model of type 2 diabetes causes profound glomerular changes with increased proteinuria, marked thickening of the glomerular basement membrane, mesangial expansion, prominent nodular sclerosis and an impressive reduction in glomerular filtration rate—all critical features of human diabetic nephropathy that had been missing from previous mouse models. Similar phenotypic changes were observed in a mouse model of type 1 diabetes. This is the first mouse model to exhibit all of the classic pathologic lesions of diabetic nephropathy observed in humans. The finding that endothelial eNOS loss produces a phenotype similar to diabetic nephropathy suggests that therapies targeted toward preservation of endothelial function may be useful in preventing or attenuating this complication in humans.

Importance of Intensive Blood Glucose Control in Preventing Complications

The NIDDK's landmark DCCT provided dramatic evidence that type 1 diabetes-related "microvascular" complications of the kidneys, eyes, and nerves can be prevented or greatly delayed through intensive control of blood glucose levels. The DCCT results also served to establish that these complications arise from the long-term effects of chronically elevated blood glucose rather than, for example, from the absence of some putative protective compound made by pancreatic beta cells. The initial DCCT results, published in 1993, therefore laid the groundwork for subsequent efforts to prevent or reduce the complications of type 1 diabetes.

Continuing To Learn from DCCT Participants: The scientific benefits of the DCCT continue today through a follow-on effort with DCCT participants called the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which is led by NIDDK and supported in part by the *Special Diabetes Program*, and which continues to yield important, life-saving data. EDIC, and some of its numerous major findings to date, are described in greater detail below and in the Story of Discovery later in this chapter. In subsequent studies, EDIC found that intensive blood glucose control could also prevent the "macrovascular" (heart-related) complications that are the most common cause of death among people with diabetes. These findings

have revolutionized management of type 1 diabetes and translated into dramatic health benefits. DCCT/EDIC scientists and other researchers recently reported that intensive control of blood glucose levels as soon as possible after diagnosis can greatly improve the long-term outcomes for people with type 1 diabetes, and result in reduced rates of complications. Thus, the fruits of type 1 diabetes research are paying off with respect to critical improvements in care.

Improving Care through Standardized Hemoglobin Assays

The DCCT also established and validated hemoglobin A1c (HbA1c) as a key marker of blood glucose control. Because HbA1c is an excellent indicator of how well a person's blood glucose has been controlled over the course of recent weeks and months, it has become enormously important as a tool for assessing the efficacy of new interventions, as well as for helping doctors and patients adjust their therapeutic regimen to obtain the best possible results. The utility of the test is dependent upon accuracy and reliability in measures of HbA1c. Another initiative supported in part by the *Special Diabetes Program*, the National Glycohemoglobin Standardization Program (NGSP), works to ensure that commercial HbA1c tests are accurate, free from artifactual errors due to naturally occurring variations in hemoglobin structure, and standardized to the methods used in the DCCT. This effort, which is supported by CDC and NIDDK, is critical to people with all forms of diabetes treated in the United States, and means that an HbA1c test result from one lab can meaningfully be compared to one from another.

Standardization of HbA1c test results has facilitated the implementation of vital public health campaigns such as the National Diabetes Education Program's "Know Your Number" and "Control Your Diabetes. For Life." campaigns, co-led by NIDDK and CDC, which emphasize the importance of HbA1c control to extend life and reduce complications. Standardized laboratory HbA1c tests have now also been proposed as an alternative to fasting blood glucose tests for the diagnosis of type 2 diabetes, to help identify some of the many undiagnosed people with diabetes and pre-diabetes who would benefit from life-saving treatments. This is only practical because of the improvements in HbA1c testing that have been brought about through the NGSP.

Preventing or Delaying Diabetic Vision Loss

Blindness is a debilitating complication of diabetes. Laser photocoagulation is an effective therapy to prevent progression of diabetic retinopathy to blindness, but the technique itself can lead to impaired vision. Thus, new therapeutic options are needed and are being tested in the DRCR.net. Led by NEI and supported in part by the *Special Diabetes Program*, DRCR.net is facilitating multicenter clinical research on diabetic retinopathy, diabetic macular edema, and other associated conditions, and has launched 15 studies. A recent DRCR.net comparative effectiveness research study found that a therapeutic called ranibizumab, in combination with laser therapy, was substantially better than laser therapy alone or laser therapy with a different drug, at treating diabetic macular edema, a swelling in the eye that often accompanies and aggravates diabetic retinopathy. Ranibizumab with laser therapy often resulted in substantial improvements in vision among patients, and could become the new standard of care for diabetic macular edema. Ranibizumab works by inhibiting VEGF, a protein which contributed to diabetic macular edema by promoting blood vessel growth in the eye. The *Special*

Diabetes Program has also supported key basic research on VEGF and other factors affecting blood vessel growth.

Understanding the Risk Factors for Diabetic Complications

While the DCCT established that chronic hyperglycemia is a major risk factor for kidney disease and other complications of type 1 diabetes, some people with relatively well controlled blood glucose still develop certain complications, and some with more poorly controlled blood glucose do not. Therefore, it is believed that other factors may influence the risk of developing complications.

Epidemiologic Studies Provide Insight: SEARCH for Diabetes in Youth (SEARCH) is a multicenter, epidemiologic study led by CDC and supported by NIDDK and the *Special Diabetes Program* (see Goal I). Data collected by SEARCH is enabling studies to delineate the risk factors for diabetes complications in a racially and ethnically diverse population of youth with diabetes. For example, SEARCH has demonstrated that youth with type 1 diabetes and suboptimal control of their blood glucose levels had abnormal lipid (fat) profiles—indicators of heart disease risk—even after a short duration of disease. High prevalence of cardiovascular disease risk factors, including obesity, dyslipidemia, and hypertension, has been documented in youth with type 1 diabetes, as well as youth with type 2 or hybrid diabetes. These studies point to the complexity of the metabolic factors involved in diabetes and the need for careful monitoring of glucose, lipid, and blood pressure levels for people of all ages with type 1 diabetes. For more information on the use of SEARCH data to inform understanding of heart-related complications of diabetes, see the Investigator Profile of Dr. Dana Dabelea later in this chapter.

Large-scale Studies on the Genetics of Diabetes Complications: Predispositions to specific complications within families suggest that some of the additional risk may come from genetics, but at the outset of the *Special Diabetes Program* in 1998, little was known definitively about the genetics of diabetes complications. To investigate the genetic underpinnings of diabetes complications, NIDDK's Family Investigation of Nephropathy and Diabetes (FIND) Consortium, and the JDRF's Genetics of Kidneys in Diabetes Study (GoKinD), also supported in part by the *Special Diabetes Program*, have taken different, complementary approaches to identifying genetic factors that predispose people with diabetes to—or protect them from—developing diabetic nephropathy (kidney disease). Based on the evidence that diabetic kidney disease results from chronically elevated blood glucose levels in both of the major forms of diabetes, the FIND study collected genetic material from participants with either type 1 or type 2 diabetes. This approach may make it easier to detect factors that influence genetic susceptibility in minority patients. Using genome-wide scans of these samples, FIND researchers identified four regions where subtle variations correlated with an increased risk of diabetic kidney disease. These findings confirmed earlier studies and identified a new region of interest. In addition, support from the *Special Diabetes Program* is enabling efforts to look for genes affecting the likelihood of diabetic eye disease using FIND genetic samples, thereby increasing the value obtained from these samples. FIND represents

the first large-scale study of the genetic determinants of retinopathy.

GoKinD, in contrast, is a collection of samples from people who have both type 1 diabetes and kidney disease, as well as control samples from people with type 1 diabetes and other similar characteristics, but without kidney disease. The resulting data from GoKinD and DCCT/EDIC have been used by numerous investigators in various analyses to identify genetic regions associated with a disease, or to replicate promising findings from other studies, or to refine analytic methods. For example, genome-wide association data from the GoKinD collection has led to the identification of genes/genetic regions association with diabetic nephropathy, including *FRMD3*, *CARS*, and *ELMO1*. In another example, the DCCT/EDIC research group confirmed and helped define versions of the angiotensin converting enzyme gene that affect the likelihood of developing diabetic nephropathy.

Maximizing the Value of Collected Data and Samples: In addition to the genes and genetic associations with diabetes complications that have been discovered and are still emerging from DCCT/EDIC, FIND, and GoKinD, each of these consortia also serves as a resource for future efforts: tissue, genetic samples, data, and analytic methods from each study are stored in a repository or database. The large and diverse sample and data collections—with families, cases, and controls—are widely-used resources 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. Identification of genes associated with diabetes complications may not only greatly improve understanding of the disease process, but also provide important new targets for therapy.

Advancing the Study of Diabetic Complications through Animal Models

Animal models of human disease often provide vital clues into the molecular pathways of disease and represent a critical tool for helping translate basic discoveries about disease pathobiology into candidate therapeutics for testing in clinical trials. While there were several notable animal models of type 1 diabetes when the *Special Diabetes Program* began, there were no animal models that faithfully recapitulated the pathology of human diabetic complications. The AMDCC was therefore established to develop and characterize such models. The AMDCC, which is supported by NIDDK, NHLBI, and the *Special Diabetes Program*, has made important strides in producing animal models that mimic human diabetic nephropathy, cardiovascular disease, and neuropathy. These models are advancing understanding of why complications occur, and how they can better be treated and prevented. For example, mouse models created through the AMDCC much more closely match the clinical pathology of human diabetic kidney disease than previous models had, and are helping tease out the key molecular players that lead to kidney damage in diabetes. Other work has helped further understanding of the molecular events that increase risk of cardiovascular disease in people with diabetes. Additionally, AMDCC researchers found that the therapeutic rosiglitazone helped prevent nerve damage in a mouse model of diabetic neuropathy.

Summary

People with diabetes are leading longer, healthier lives with a reduced likelihood and severity of complications due to strides in medical treatment that derive from research advances such as the findings of DCCT/EDIC, which were made possible in part through support from the *Special Diabetes Program*. To realize further progress, the *Program* also supports research on the underlying causes of diabetic complications, including research on the genetic factors that may predispose or protect patients from developing certain complications. Numerous genes have now been identified, which is opening up avenues for new prevention and treatment approaches. This knowledge can pave the way toward personalized therapies based on patients' genetic profiles. The *Special Diabetes Program* also supported research that identified an improved treatment approach for treating diabetic eye disease. By supporting a broad research portfolio on the complications of diabetes, the *Special Diabetes Program* has already enabled significant progress, with additional insights expected in the future as research builds on the progress made to date.

RESEARCH CONSORTIA AND NETWORKS RELATED TO PREVENTING OR REDUCING THE COMPLICATIONS OF TYPE 1 DIABETES

Evaluation of research consortia and networks supported by the *Special Diabetes Program* and related to Goal V is found in Appendix C. Highlights of these are summarized below.

Epidemiology of Diabetes Interventions and Complications (EDIC): EDIC is a prospective study of the clinical course and risk factors associated with the long-term complications of type 1 diabetes, in 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. EDIC follows both the "conventional" and "intensive" treatment groups from DCCT, although all participants are now recommended to follow the intensive therapy guidelines.

Genetics of Diabetic Complications: Genetics of Kidneys in Diabetes Study (GoKinD) has facilitated investigator-driven research into the genetic basis of diabetic nephropathy by creating a resource of genetic samples from people who have both type 1 diabetes and renal disease and "control" patients who have type 1 diabetes but no renal disease. The Family Investigation of Nephropathy and Diabetes (FIND) Consortium carries 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 people with diabetes. Five to ten percent of the people in FIND have type 1 diabetes. A genetics component of the EDIC 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.

Diabetic Retinopathy Clinical Research Network (DRCR.net): The DRCR.net is a collaborative, nationwide network of eye doctors and investigators conducting clinical research on 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, including standardization of multiple study procedures, utilization of novel technology, extensive integration of information technology, and the ability to leverage resources to evaluate promising new therapies that might otherwise not be tested. The Network has spearheaded 15 protocols. Because diabetic retinopathies are associated with both type 1 and type 2 diabetes, DRCR.net enrolls both type 1 and type 2 diabetes patients.

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. In addition to creating animal models, the AMDCC sets standards to validate each experimental animal model of diabetic complications for its similarity to the human disease; tests the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications; and facilitates the sharing of animals, reagents, and expertise between members of the Consortium and the greater scientific community via its bioinformatics and data coordinating center. The AMDCC has developed about 40 animal models of type 1 diabetes that closely mimic various aspects of the human complications of diabetes.

Story of Discovery:
The DCCT/EDIC Research Group: Improving the 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 NIDDK in 1983. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial in 1,441 people with type 1 diabetes. Completed in 1993, the trial compared the effects of intensive versus conventional treatment of blood glucose levels on the development of microvascular complications (those affecting the small blood vessels in the eyes, kidneys, and nerves). Participants in the intensive treatment group 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 through a regimen that included frequent monitoring of blood glucose and at least three insulin injections per day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections per day, with once-a-day urine or blood glucose testing. The two treatment groups achieved markedly different average HbA1c levels over the course of the trial, and strikingly different rates 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 what was then 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 American Diabetes Association 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.

Long-term Benefits of Intensive Blood Glucose Control

Upon completion of the DCCT, participants who had received conventional treatment were taught the intensive treatment methods, and all were encouraged to use intensive treatment, although the intervention itself stopped. Nearly all who participated in the DCCT volunteered for the follow-on 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.

In 2002 and 2003, EDIC investigators reported that the period of intensive glucose control during the DCCT continued to reduce risk for microvascular complications 7 to 8 years after the end of DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the two treatment groups after completion of the DCCT. The phenomenon of long-lasting effects of a period of intensive or non-intensive glucose control has been termed "metabolic memory," and it suggests that implementing intensive glucose control as early in the course of type 1 diabetes as possible could help people avoid life-threatening complications. More recent results showing that new cases of retinopathy among participants who received the intensive treatment are beginning to approach the number of new cases in the control group, however, suggest that metabolic memory may wane over time.

While the DCCT proved that blood glucose control could prevent small vessel damage, the effect of glucose control on cardiovascular disease (CVD) was unknown. Through support in part by the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program* or *Program*), scientists were able to address this critically important topic. In December 2005, the DCCT/EDIC research group reported that, during an average period of 17 years since their enrollment in the DCCT, people 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 showed for the first time that intensive control of blood glucose levels has long-term beneficial effects on CVD risk in people with type 1 diabetes. These findings are particularly significant because people with the disease face a 10-fold increased risk of CVD death compared to the general age-matched population.[27]

More than 17 years after the end of the DCCT, insights continue to emerge regarding the long-term benefits of intensive blood glucose control. In 2009, DCCT/EDIC researchers found that, after 30 years of diabetes, DCCT participants randomly assigned to intensive glucose control had about half the rate of eye damage compared to those assigned to conventional glucose control (21 percent versus 50 percent). They also had lower rates of kidney damage (9 percent versus 25 percent) and cardiovascular events (9 percent versus 14 percent) compared to those receiving conventional glucose control. These findings suggest that, with early intensive therapy to control blood glucose levels, the outlook for people with type 1 diabetes is better than ever.

Research To Understand and Combat Hypoglycemia

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. The immediate effects of hypoglycemia can be severe, including changes in cardiovascular and central nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and death. Thus, researchers supported by the *Special Diabetes Program* are seeking new methods to keep blood glucose low, but not dangerously low, through improved blood glucose monitoring and insulin delivery, and through beta cell replacement therapy to potentially cure type 1 diabetes. Researchers supported by the *Program* have already been successful in contributing to the development of continuous glucose monitoring technology that has been approved by the U.S. Food and Drug Administration (FDA) (see Goal IV). Other research is ongoing to develop artificial pancreas technology, which represents an important current opportunity to help people with diabetes implement intensive blood glucose control.

Encouraging news about the long-term effects of hypoglycemia emerged from evaluation of EDIC participants 12 years after the conclusion of the DCCT. The study revealed no link between multiple severe hypoglycemic reactions and impaired cognitive function. This result means that people with type 1 diabetes do not have to worry that acute episodes of hypoglycemia will damage their mental abilities and impair their long-term abilities to perceive, reason, and remember.

[27] Krolewski AS, Kosinski EJ, Warram JH, et al: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 59: 750-755, 1987; Dorman JS, Laporte RE, Kuller LH, et al: The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality results. Diabetes 33: 271-276, 1984.

New Insights into the Genetics of Diabetes Complications

The DCCT and EDIC studies have also provided an enormous wealth of information on the genetics of diabetes complications and related questions. Genetic samples taken during the DCCT, for example, helped researchers to identify a region of the genome near the *SORCS1* gene that is associated with HbA1c levels. Other genetic regions were also found to be associated with HbA1c levels, and some of the regions were also associated with low blood glucose levels. These results could be used to identify people at risk for poor blood glucose control and aid in developing their personalized treatment plans. Genetic data from DCCT/EDIC have also proved useful in other ways, by providing control data for use in other studies, and therefore represent a significant scientific contribution that goes beyond the study of diabetes and its complications.

A Long-term Investment in Research Improves the Lives of People with Type 1 Diabetes

The DCCT and EDIC studies demonstrate how the long-term investment in research continues to have a profound impact on the health of patients. Almost 30 years after the beginning of the DCCT, researchers are still demonstrating significant findings that continue to improve the care of people with type 1 diabetes and also have implications for people with type 2 diabetes. 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 launched with support of the *Special Diabetes Program* will also result in dramatic and positive benefits for people with or at-risk for type 1 diabetes in the future.

Investigator Profile

Dana M. Dabelea, M.D., Ph.D.

SEARCH-ing for Diabetes in Youth and Studying the Natural History of Heart Disease

Dana M. Dabelea, M.D., Ph.D.

Dana M. Dabelea, M.D., Ph.D., is an Associate Professor in the Department of Epidemiology, School of Public Health, at the University of Colorado Denver. She is one of six principal investigators and serves as national vice-chair person for the SEARCH for Diabetes in Youth (SEARCH) study, which is led by CDC with support from NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research. *SEARCH is identifying cases of diabetes in youth less than 20 years of age in six geographically dispersed populations in the United States, including Colorado. This profile describes some of SEARCH's remarkable progress and how Dr. Dabelea is capitalizing on the SEARCH infrastructure to study the natural history of heart disease in youth with type 1 diabetes.*

"I have been doing diabetes research for nearly 20 years and was first attracted to diabetes research because of my clinical training as a diabetologist," says Dr. Dabelea. In particular, she is interested in pediatric diabetes. "I believe that diabetes research—and especially pediatric diabetes research—is very important because kids have a higher lifetime burden of diabetes than adults. By studying younger people with diabetes, we increase our chances of finding risk factors for the disease and for disease progression before it's too late and before chronic complications develop," she adds. This interest led her to participate in the SEARCH for Diabetes in Youth (SEARCH) study. She moved from Romania to Colorado specifically to work on SEARCH, demonstrating her personal commitment to participating in this important research study.

New Insights into Childhood Diabetes

While substantial increases in the incidence (number of new cases) of type 1 diabetes have been reported in Europe, reliable data on whether the rates of childhood diabetes in the United States are changing over time, or even how many children in the United States have diabetes, were lacking. To address this gap in knowledge, the SEARCH study was launched in 2000.

"SEARCH is unique," says Dr. Dabelea. "It is the only comprehensive population-based study of childhood diabetes by type in a population with a diverse racial background in the U.S. and, I dare to say, in the world. Some of the other registry studies in Europe are based on youth with type 1 diabetes of Caucasian origin. SEARCH is unique in that it includes various racial and ethnic backgrounds and both types of diabetes."

Dr. Dabelea notes that many new insights are emerging from SEARCH. For example, for the first time, SEARCH

defined the prevalence (total number of cases) of childhood diabetes in the United States: 1 of every 523 youth had physician-diagnosed diabetes in 2001. SEARCH also determined the incidence of diabetes in American youth: annually, about 15,000 youth are diagnosed with type 1 diabetes and about 3,700 youth are diagnosed with type 2 diabetes. Thus, SEARCH is providing new insights not only on type 1 diabetes, but also on type 2 diabetes, which is an emerging health problem in youth driven by increasing rates of obesity. In fact, Dr. Dabelea explains that "With the epidemic of obesity and the younger age of onset in both type 1 and type 2 diabetes, the lines between the two major forms of diabetes are becoming blurred." In other words, although most children are accurately diagnosed with type 1 or type 2 diabetes, a subset of children may have clinical characteristics that overlap between the two major forms of diabetes, making it difficult for physicians to easily determine diabetes type. To address this issue, SEARCH is leading an effort to classify diabetes type in youth by developing clinical definitions and epidemiologic definitions of diabetes type, which is important not only for SEARCH research, but also for clinical purposes to ensure that all children are accurately diagnosed and given the proper treatment.

SEARCH is also shedding light on the complications of diabetes in youth, and, "The findings are not necessarily painting an optimistic story," says Dr. Dabelea. For example, SEARCH found that youth with diabetes have a high prevalence of risk factors for kidney disease and heart disease. Although these findings are troubling, Dr. Dabelea notes that they are important because they tell us that "Even at a young age, in a population with short duration of disease, we are seeing risk factors for chronic complications that will develop later. We must start programs that address this increased risk and try to prevent the development of chronic complications." Dr. Dabelea is building on the observations from SEARCH to further study heart disease in type 1 diabetes.

Studying the Natural History of Heart Disease in Youth with Type 1 Diabetes

Heart disease risk is increased by up to 10-fold in people with type 1 diabetes compared to the general age-matched population—a statistic that underscores the importance of identifying and implementing strategies to prevent this life-threatening complication. Research from the NIDDK's landmark Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study showed that early and intensive blood glucose control prevented or delayed future heart-related complications of type 1 diabetes. However, achieving good glucose control is difficult for many patients. "SEARCH has found that a high percentage of youth with diabetes, especially those of minority racial/ethnic backgrounds, have poor glycemic control," says Dr. Dabelea.

Furthermore, little is known about when the course of heart disease actually begins in people with type 1 diabetes. This knowledge is important to inform decisions about when additional therapy to prevent heart disease—such as treatment with statin medications that lower LDL (bad) cholesterol—should be started. For example, does the development of heart disease begin in childhood or adulthood? If it begins in childhood, should statin therapy be introduced at a young age? SEARCH data show that physicians rarely prescribe statin medications to their young patients with type 1 diabetes.

"Prevalence of statin use is very, very low in the SEARCH population," notes Dr. Dabelea. "It is possible that we may need to intervene earlier in life than in adulthood and at lower lipid and blood pressure levels to prevent chronic complications from developing." However, more research is needed to inform those types of recommendations.

Dr. Dabelea is capitalizing on the SEARCH infrastructure to conduct an ancillary study that can begin to address these important questions. "The study is enrolling a subset of SEARCH children, adolescents, and young adults with type 1 diabetes and non-diabetic controls from Colorado and Ohio and is comparing the prevalence of sub-clinical cardiovascular abnormalities in these two groups," explains Dr. Dabelea. "We are looking at carotid intimal-medial thickness (carotid IMT), which is a marker of atherosclerosis, and at arterial stiffness, which is a stiffening of both the large and small vessels that occurs early in the progression of heart disease. Such abnormalities can be detected early in life in teenagers and young adults before heart events even occur. That is why we are interested in studying this population that doesn't have heart disease, but who may have early signs of pre-clinical heart disease."

The first part of the study will examine whether there are any differences in carotid IMT and arterial stiffness between youth with type 1 diabetes and non-diabetic youth. "We suspect that we will find differences," Dr. Dabelea predicts, "and if there are differences, we will explore whether they could be explained by glycemic control, obesity, a family history of heart disease, or other factors." This study also has a longitudinal component, which will examine whether there is progression in arterial stiffness in youth with type 1 diabetes over time. This research can contribute much needed knowledge about the natural history of heart disease in youth, which could inform recommendations about when preventive strategies, such as introducing statin therapy, should begin.

Capitalizing on the SEARCH Infrastructure

To conduct the ancillary study, Dr. Dabelea is collaborating with SEARCH colleagues in Ohio and also taking advantage of the existing SEARCH infrastructure. She cites numerous advantages to conducting her research as an ancillary study to SEARCH, rather than starting a new study. "The children and youth participating in a study like SEARCH are already attending baseline and follow-up visits and are committed to participating in the study," Dr. Dabelea explains. "When you tell them about the possibility of participating in an ancillary study, you have a very receptive population."

Another benefit is that Dr. Dabelea can utilize the existing SEARCH network system for the ancillary study. "The network system includes providers throughout the state of Colorado and at each of the other SEARCH sites, so when we want to start an ancillary study, it is easy to talk to providers and participants—you don't have to start that network from scratch," she says. Furthermore, Dr. Dabelea already has a wealth of SEARCH data that can be incorporated into the ancillary study. "We don't have to spend time and resources collecting those data *de novo*," she notes. Thus, Dr. Dabelea is able to build on the investment that has been made in SEARCH, with support from the *Special Diabetes Program*, to maximize research progress and address key questions related to the management of type 1 diabetes.

Looking to the Future

Dr. Dabelea believes that it is important to continue collecting data through SEARCH, to paint a better and broader picture of childhood diabetes in the United States. "SEARCH is unique," she explains, "and diabetes in youth is an important problem with many public health implications." Dr. Dabelea also has a vision for using SEARCH data to benefit children with diabetes. "SEARCH has increased our understanding of childhood diabetes and its complications. We hope that in the next several years, the knowledge provided by SEARCH will translate into better quality of care and better quality of life for children with type 1 diabetes, and maybe someday to successful prevention of the disease."

Patient Profiles

Robert Watts and Sallie Cartwright

Participating in a Landmark Clinical Trial that Improved Vision

Blindness is a debilitating complication of diabetes that has a profound impact on people's quality of life. To combat this complication, the *Special Statutory Funding Program for Type 1 Diabetes Research* supports clinical research to accelerate the development of new therapies and treatments for diabetic eye disease (retinopathy). One major research effort is the Diabetic Retinopathy Clinical Research Network (DRCR.net), which is led by NEI and supported in part by the *Special Diabetes Program*. The DRCR.net is a nationwide collaboration of eye doctors and scientists conducting research on diabetes-induced retinal disorders. Because diabetic retinopathy is a complication associated with both type 1 and type 2 diabetes, DRCR.net enrolls people with both forms of diabetes into its studies. In April 2010, the DRCR.net announced the results from its landmark comparative effectiveness clinical trial showing that a new therapy combining eye injections of the drug ranibizumab with laser treatment to the eye was more effective than the standard practice of laser treatment alone. This profile includes the personal stories of two people—one with type 1 diabetes and the other with type 2 diabetes—who achieved significant vision improvement in this clinical trial.

About the Trial

The goal of the DRCR.net trial was to translate recent discoveries about a molecule that affects blood vessel growth and permeability into potential new treatment approaches for diabetic retinopathy. Diabetic retinopathy is caused by changes in blood vessels in the retina, the part of the eye that detects light and produces signals that enable the brain to "see" images—thus functioning much like the sensor in a digital camera, or like camera film. One condition that can affect people with diabetic retinopathy is called diabetic macular edema. In this condition, blood vessels in the eye leak fluid in an area of the retina responsible for sharp central vision, causing swelling and blurring sight. Regular eye exams are important to help detect this and other diabetic eye problems early and protect vision. Diabetic retinopathy can be treated with laser surgery to the eye, significantly reducing the development of severe vision loss. However, laser treatment itself can lead to some diminution of vision. New approaches are thus highly desirable. A normal body protein called vascular endothelial growth factor, or VEGF, has emerged as a prime suspect in some of the blood vessel problems seen in diabetic retinopathy, including blood vessel "leakiness." Researchers decided to test whether administration of a drug (ranibizumab) that inhibits VEGF activity, in combination with laser treatment, could benefit people with diabetic retinopathy.

The DRCR.net trial included a total of 854 eyes of 691 participants. The reason that there are more eyes than people is because some people had only one eye treated, while others had both eyes treated. Each eye was randomly assigned to one of four treatment groups: sham injections (containing no medicine) plus prompt laser treatment; ranibizumab injections plus prompt laser treatment; ranibizumab plus deferred (for a short time) laser treatment; or injections of corticosteroid medication known as triamcinolone, plus prompt laser treatment. However, if a person was receiving treatment in both

eyes, then one eye was treated with laser and sham injections and the other eye was treated with laser and a medicine (ranibizumab or triamcinolone).

For the first 12 weeks of the study, the participants received treatment based on their assigned group. After that time and for the remainder of the study, retreatment followed a detailed algorithm. In general, treatment was continued until a participant's vision or retinal thickness returned to normal, or until additional treatment did not improve vision or retinal swelling. Once retreatment was withheld, it typically was resumed if retinal thickness worsened at a subsequent visit.

The exciting results demonstrated that nearly 50 percent of eyes treated with ranibizumab and either prompt or deferred laser treatment showed a substantial visual improvement after 1 year, compared to 28 percent of eyes that received the standard laser treatment plus sham injections. In some instances, the combination treatment reversed a person's vision impairment, an advance that has greatly improved quality of life for those individuals. Many in the field refer to this finding as the most significant treatment advance in diabetic retinopathy in 25 years.

Robert Watts

Robert Watts was diagnosed with type 1 diabetes at the age of 24, and he has been injecting himself with insulin for the past 46 years. Robert admits that he works hard at taking care of himself and monitoring his blood sugar levels. He tests his blood sugar levels seven or eight times each day, and he believes that it is because of this constant monitoring that he has not yet experienced many of the common complications from diabetes.

However, 10 years ago, Robert began to notice that his vision was declining. "The street signs became difficult to read when I was driving at night, and it became challenging to read the numbers at the bottom of my television screen during a sporting event," he recalls. "When I went to my eye doctor a little over 3 years ago, he told me that my vision was going to continue to deteriorate. He told me about a clinical trial that was testing a new course of therapy for people with my condition, and I wanted to learn more." Robert was fortunate that his doctor was participating in DRCR.net, and he was able to receive information about the trial quickly.

"It was an easy decision to enter the trial," says Robert. "I have four grandchildren, ages 14, 13, 9 and 6. I want to see them grow up. I love them more than anything, and that is why I try to take good care of myself." Robert also recognized the opportunity he had been given to help others with diabetes. "I knew that by participating in this trial, I would be helping the researchers gather more

information about diabetic retinopathy that would help them develop new treatments for others," he says.

"My vision has improved big time," Robert says proudly.

Robert enrolled in the trial 3 years ago and, since the start of the trial, he has visited his doctor every month for an exam that lasts approximately 2 hours. Robert was one of the trial participants who received treatment in one eye only. He received ranibizumab injections in combination with laser treatment. During the time that Robert was receiving the treatment, he remembers that the procedure was not pleasant. "After my monthly exam, if the research team determined that I needed to receive the treatment, it would involve a needle in my eye," Robert notes. "It was not a procedure that I looked forward to. But there was a team of people in the doctor's office who took great care of me. That made it a lot easier." Robert attributes his positive experience in the trial to his doctor and his team. "I have lots of tests done at each visit," he says. "The team is very professional and works together. They are outstanding." Even his wife, a retired nurse, has commented on the care Robert has received. "My wife took me to each appointment and was always by my side. She is a retired nurse and has been so impressed with the quality of care I have been receiving as a participant in the trial."

"After about a year of receiving the treatment, my vision improved greatly," Robert remembers. "I keep going back to the doctor monthly for my exams, but I haven't had to have a treatment in about a year and a half. My vision has improved big time," Robert says proudly.

Sallie Cartwright

Shortly after Sallie Cartwright and her husband moved to Maryland 4 years ago, she noticed a problem with her vision. "I realized when I was driving that I couldn't see the road signs and my first thought was that I needed driving glasses," remembers Sallie. "Reading became increasingly difficult. I had trouble reading the phone book and my prescription bottles. But the hardest thing for me," she recalls, "was not being able to read music properly. I am a retired professional musician and sharing my musical skills still brings joy to me."

When Sallie went to the eye doctor, she received an unexpected diagnosis. After a thorough examination, the ophthalmologist told her that her right eye was worthless and her left eye was legally blind. He said that glasses would not help her and that she needed to go to a retina specialist as soon as possible. The vision problems she was experiencing were a complication of her type 2 diabetes.

Shortly after that visit, Sallie went to a retina specialist recommended by her ophthalmologist. During her first

visit, she learned about a DRCR.net clinical trial that was testing a new therapy to treat diabetic retinopathy. She was told that she was eligible to participate in the trial and what would be involved if she chose to participate. Sallie remembers that the decision to enter the trial was not an easy one to make. "I have had severe allergies to food and medicines since I was a child, so the decision to participate was a difficult one," she recalls. "I had no idea how I was going to react to the medication I would be given. Over the years I had been rushed to the emergency room for adverse reactions to drugs and nearly lost my life several times." Sallie has been married to a research scientist for 45 years, so her knowledge of the importance of clinical research played a big role in her decision to participate. She says, "With the professionalism, caring, kindness, commitment and dedication to healing and research of the retina specialist to whom I was referred, I felt that it was my obligation to participate and possibly help others. I was willing to take a personal risk for the opportunity to help so many."

Sallie had both eyes treated as part of the trial. One eye was treated with ranibizumab injections plus laser, while the other eye was treated with sham injections plus laser. Happily for Sallie, her vision dramatically improved in both eyes since she enrolled in the trial—she now sees "20/20" and is back to reading music and playing the piano. She says, "Everyone is so excited when I have my vision tested and I am reading 20/20. The research team and support staff are like a big cheering squad for me. Throughout the trial, they have always been professional, caring, and incredibly dedicated. The quality of care I have received has been exceptional."

"For my eyes to go from worthless and legally blind to being able to see at 20/20 without glasses is incredible," says Sallie.

When asked about her experience in the trial, Sallie pauses and searches for the right words. Expressively she says, "My experience during this trial is hard to describe. For my eyes to go from worthless and legally blind to being able to see at 20/20 without glasses is incredible."

For more information on the DRCR.net, please visit: www.drcr.net

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL DIABETES PROGRAM*

The *Special Statutory Funding Program for Type 1 Diabetes Research* has fueled the emergence of a wide range of research opportunities. These opportunities were identified in a strategic planning process as being critically important for overcoming current barriers and achieving progress in diabetes research. Key questions and research opportunities relevant to type 1 diabetes, including those related to preventing and reversing diabetes complications, are outlined in Appendix F.