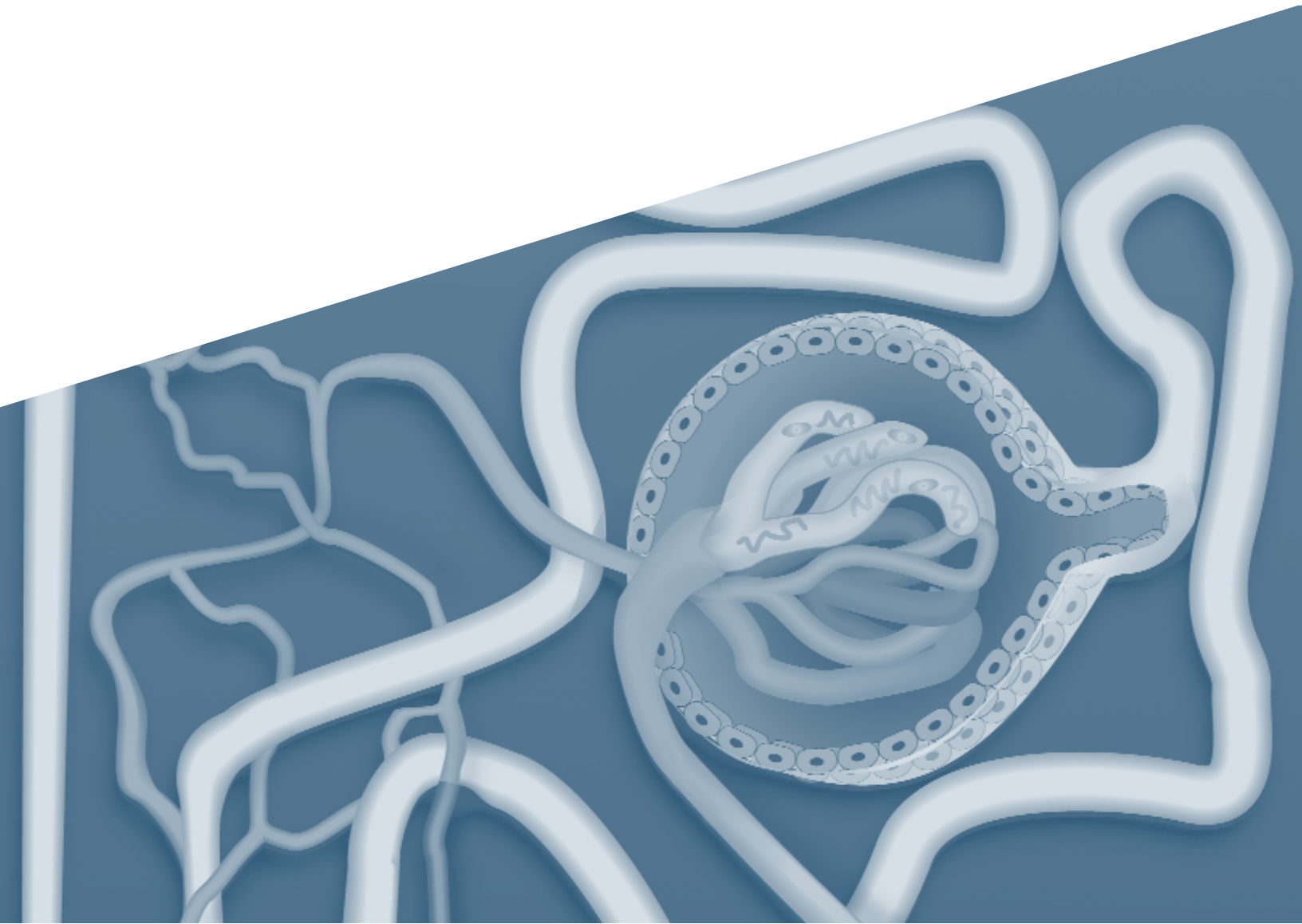
GOAL V

PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES



Persistent elevation of blood glucose—hyperglycemia—in type 1 diabetes leads to devastating health complications affecting nearly every organ system in the body. Diabetes damages the microvasculature, networks of small blood vessels embedded in tissues, leading to: diabetic retinopathy—eye disease—the leading cause of new blindness in the U.S.; nephropathy—kidney disease—which can lead to irreversible kidney failure, known as end-stage renal disease; and neuropathy—nerve disease—an often painful condition contributing to foot ulcers which can lead to limb amputation in extreme cases. Macrovascular complications involving larger blood vessels give rise to cardiovascular disease and increase the risk of heart attack and stroke. In addition, diabetic individuals are at increased risk of gum disease and other oral complications, pregnancy-related complications, and impaired gastrointestinal, bladder, and sexual function.

The Diabetes Control and Complications Trial (DCCT), which ended in 1993, demonstrated that intensive glucose control can reduce the long-term risk for microvascular and neurologic complications of type 1 diabetes. Nonetheless, even with optimal diabetes care, such complications constitute a significant health burden for diabetic patients and compromise the quality-of-life in this population. Therefore, uncovering the molecular mechanisms by which high glucose causes vascular damage and designing novel therapies to reverse this damage remain high research priorities.

The Special Statutory Funding Program for Type 1 Diabetes Research has created exciting new opportunities for the research community to advance the study of many diabetic complications. Long-term clinical studies on the biology and treatment of diabetic eye, kidney, nerve, and cardiovascular disease are now under way. The development of new research tools—including improved animal models, state-of-the-art imaging techniques, and optimized surrogate marker assays—will greatly enhance future research progress. Importantly, the scientific and clinical accomplishments that emerge from the complications research supported by the special funds will benefit individuals afflicted with any form of diabetes, including both type 1 and type 2 diabetes.

Graphic
Kidney nephron diagram.

(Credit: Maryetta Lancaster, for NIH Medical Arts and Photography Branch)

MAJOR RESEARCH CONSORTIA AND RESOURCES

With the marked increase in special statutory funds that became available in FY 2001, major research consortia, trial networks, resources, and research solicitations were launched in FY 2001 and FY 2002. Brief descriptions of the research efforts and expected outcomes of initiatives supported in whole or in part by the special funds are presented below. More detailed scientific plans are available in Appendix 3.

Genetics of Kidneys in Diabetes (GoKinD) Study

Kidney disease associated with type 1 diabetes is thought to have a significant genetic component. Identification of the genetic basis of diabetic kidney disease will reveal new targets for therapy to prevent this devastating complication. However, the large sample sets needed to study the genetics of kidney disease in type 1 diabetes are not currently available. The GoKinD Study, led by the CDC in collaboration with the JDRF, will develop a set of 4,300 DNA samples from patients with type 1 diabetes, with and without kidney disease, and their family members. Planning for this long-term study began in FY 1998, and patient recruitment and sample analysis were launched in FY 2001.

Epidemiology of Diabetes Interventions and Complications (EDIC) Study

Two thirds of people with diabetes die of cardiovascular disease. Although intensive glucose control has been proven to reduce the risk of eye, nerve, and kidney disease in type 1 diabetes, its value in preventing heart disease and stroke has not been established. This initiative will support studies, using surrogate markers, to assess the effects of intensive therapy on cardiovascular disease risk in the 1,400 patients at 27 centers who participated in the landmark Diabetes Control and Complications Trial. This small group of extremely well-characterized, long-term research volunteers is now enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The effect of type 1 diabetes and its therapy on urologic health will also be addressed in EDIC. The new cardiovascular and urologic components of EDIC began in FY 2002 using the special statutory funds, and will continue for 3 years, with the potential for subsequent extension beyond this period to assess actual cardiovascular events in addition to markers of risk. The EDIC complications study is sponsored by the NIDDK.

Studies To Identify Genetic Associations in Patients with Microvascular Complications

Both diabetic eye and kidney disease may have genetic components, although it is not known whether the underlying genetic roots are the same for the two conditions. The special statutory funds allowed the addition of a retinopathy component to the ongoing Family Investigation of Nephropathy and Diabetes (FIND) Study that is searching for genes involved in diabetic kidney disease. Six study centers will recruit over 3,300 patients, including more than 1,300 for the retinopathy study, over 3.5 years. In contrast to the GoKinD and EDIC studies, which exclusively recruit type 1 diabetic patients, FIND is searching for the genetic associations of complications in individuals with either type 1 or type 2 diabetes. This research effort is supported by the NIDDK, NEI, and NCMHD.

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

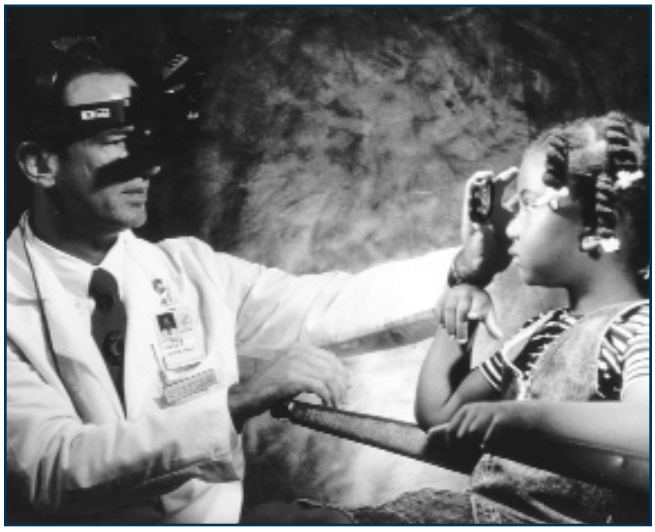
Macular edema secondary to diabetic retinopathy—eye disease—is a major cause of visual loss in patients with diabetes. The Diabetes Macular Edema Clinical Trials Network will plan, implement, and conduct multi-center clinical research and clinical trials of new, potential treatments for diabetic macular edema. NEI, the primary sponsor, established this network in FY 2002 and will support it for a period of 7 years.

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

A lack of good animal models has been an impediment to research on the long-term micro- and macrovascular complications of diabetes. Animal models can be used to conduct preliminary tests of new therapies and studies at the molecular, cellular, and tissue level that are not feasible in humans. Thus, an urgent research priority is to derive, characterize, and validate animal models that mimic human disease and that can be used to test therapeutic, prevention, early detection, or diagnostic imaging strategies for diabetic complications. The Animal Models of Diabetic Complications Consortium (AMDCC), which was established by the NIDDK and NHLBI in FY 2001 for a period of 5 years, will expedite the development of both mouse and large animal models. Six of the nine principal investigators of the AMDCC are supported by the special funding program.

Improving the Clinical Measurement of Hemoglobin A1C

Measurement of hemoglobin A1C (HbA1C) reflects the long-term control of blood glucose levels. Persistent, suboptimal HbA1C results, which indicate poor glucose control, correlate with the development of long-term diabetic complications. A lack of comparability of HbA1C test results among methods and laboratories is a major obstacle to the effective implementation of a national strategy to reduce the complications associated with diabetes through proper glycemic control. The CDC provides continuous technical support and assistance to the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry (IFCC) programs to improve and standardize HbA1C laboratory measurements over time. This CDC-led effort, which began in FY 1998, is an important research resource that continues to advance the standardization of HbA1C measurement.



After the eyes are dilated, an indirect ophthalmoscope provides the eye care professional with a wider view of the retina. Regular eye exams are an important part of diabetes clinical care. The Diabetic Macular Edema Clinical Trials Network is investigating potential new treatments for diabetic eye disease–a major cause of vision loss in the U.S.

(Photo Credit: National Eye Institute)

HIGHLIGHTS OF SCIENTIFIC DISCOVERIES

Many significant scientific advances have emerged from investigator-initiated research that began in the early years of the special statutory funding program. Highlights of these discoveries are provided here. More extensive discussion of initiatives and their research progress can be found in Appendix 3. Some grants or programs supported by the early initiatives are still in progress and the full impact of these projects on preventing the complications of type 1 diabetes may not be realized for several years. It is premature to assess accomplishments of the newly formed consortia or investigator-initiated research grants awarded in FY 2001 or FY 2002.

New Paradigms for Understanding the Development of Diabetic Complications

- Diabetic patients are at increased risk of macrovascular complications, including the formation of lesions that can block blood vessels. Maintaining healthy blood vessels involves a continual balance between proliferation and programmed cell death of vascular smooth muscle cells (VSMC). High glucose was shown to reduce the level of VSMC programmed cell death in a diabetic rat model. This finding provides new insight into the mechanism of diabetic cardiovascular disease, in which high glucose may tip the balance toward proliferation and accumulation of VSMC in vascular lesions.

- Complement is an immune defense system comprised of approximately 30 proteins circulating in the blood. A link between complement activation and diabetic vascular complications had been previously postulated, but the mechanism of this link was not known. Researchers have now defined the molecular pathway by which high glucose levels cause complement activation. Interestingly, the complement protein targeted and modified by high glucose in humans is slightly different in other species. Identifying this subtle, but crucial, variation may help to explain why no animal model of diabetes exhibits the full range and extent of complications observed in humans. This knowledge may aid scientists in the development of new animal models that more closely mimic the development of human diabetic complications.

- Pericytes—a cellular component of small blood vessels—are thought to be damaged early in the progression of diabetic eye disease. Researchers found that diabetic patients produce autoantibodies that attack pericytes. This finding demonstrates a role for the immune system in diabetic eye complications. Moreover, immune system involvement may explain why some patients develop retinopathy despite good blood glucose control.

Novel Therapeutic Targets or Strategies for Preventing or Reversing Diabetic Complications

- Adult bone-marrow derived stem cells are capable of differentiating into blood vessel-forming cells. Researchers showed that, when such stem cells are injected into the fluid inside the eye, these cells extensively and stably incorporate into the network of vessels in the retina. These findings create an exciting new paradigm for treatment of diabetic eye disease. Genetically modifying the stem cells before injection into an eye would permit these cells to deliver therapeutic molecules at the exact site of disease over a prolonged period of time.

- Researchers have investigated the role of adult stem cells in maintenance and repair of heart and blood vessel disease and have shown that treatment with stem cells can improve blood vessel repair in animal models. Additionally, these studies have demonstrated that adult stem cell function is impaired in diabetes,

suggesting that stem cell dysfunction may contribute to diabetic cardiovascular complications. This research has important implications for therapy of a variety of diabetic complications and suggests that adult stem cells may prove useful for treating heart attack and stroke in both diabetic and non-diabetic patients.

- Diabetes causes serious oral complications, including impaired wound healing in the mouth and increased periodontal disease. Saliva from diabetic individuals was shown to have significantly reduced levels of a protein—epidermal growth factor (EGF)—that is important in maintenance of oral health. Moreover, in the NOD mouse model of type 1 diabetes, researchers demonstrated that diabetic animals had a reduced rate of tongue wound healing, which could be accelerated by addition of EGF to the drinking water. Thus, topical application of EGF could potentially be developed as an effective therapy for oral complications of diabetes.

- Diabetes results in extensive vascular damage that can lead to a variety of organ complications. Activation of an enzyme found in the cell nucleus–poly (ADP-ribose) polymerase (PARP)—has been implicated in the pathogenesis of stroke, heart attack, inflammation, and other conditions. Researchers discovered that PARP activation in blood vessels increases when the pancreatic islets are destroyed in either chemically-induced or genetic models of type 1 diabetes in rats and mice. However, treatment of these animals with a novel inhibitor of PARP—called "PJ34"—restored normal vascular function, even in the presence of severely high glucose levels. Thus, PJ34 is an exciting candidate for therapy of diabetic vascular complications in humans.

- Two nerve growth factors, prosaposin and prosaptides, are being studied as possible treatments for diabetic neuropathy. Preclinical studies showed that these molecules can prevent or attenuate electrophysiological, biochemical, and structural disorders in peripheral nerves in a diabetic rat model. These results have been extended to establish the prosaptide "TX14(A)" as a promising therapeutic candidate that could both rapidly alleviate pain and prevent chronic progression of diabetic nerve disorders. Importantly, TX14(A) affects pain perception only in diabetic, but not control, animals, which suggests that diabetic pain may be induced through a novel molecular pathway rather than through existing pain processing mechanisms. This finding has significant implications for the treatment of diabetic pain. As a result of this basic research supported by the special funding program, clinical trials of the use of TX14(A) against neuropathic pain in diabetic individuals are being pursued through other sources.

- Vascular dysfunction was studied in blood vessels that supply the sciatic nerve in diabetic rats. Researchers demonstrated that problems in this vascular bed occur early in the course of diabetes, and they began to uncover the molecular defects at work in this complication. Significantly, treating diabetic rats with several types of antioxidants was shown to prevent vascular and neural dysfunction due to diabetes, which suggests that the early stage of diabetic neuropathy is primarily a vascular disease associated with increased oxidative stress. These findings imply that antioxidants, such as alpha-linoleic acid, may hold promise for the clinical treatment of diabetic neuropathy.

- Currently, no methods exist to directly treat diabetic neuropathy, a progressive loss of nerve function that can result in pain, numbness, digestive problems, and other serious complications. Investigators found that nerves of diabetic rats have reduced levels of a protein known as "desert hedgehog"–a member of the "hedgehog" family of proteins that are critical to the development of the nervous system. Treating these animals with another member of the family, "sonic hedgehog," restored many parameters of nerve

function, although this therapy did not improve the diabetic condition itself. These findings suggest that hedgehog proteins are viable targets, and potential therapies, for specifically treating the nervous system complications of diabetes.

New Animal Models for Research on Diabetic Complications

- Heart muscle cells in diabetic individuals have an impaired ability to metabolize glucose. Researchers characterized the role that decreased glucose transport plays in causing cardiac complications in diabetes. A new mouse model was created, in which GLUT4—the major cardiac glucose transport protein—was genetically deleted. Loss of GLUT4 resulted in cardiac hypertrophy—an enlarged heart—and a reduced ability to respond to ischemic injury. Thus, two major characteristics of impaired glucose uptake in the diabetic heart could be accounted for by decreased glucose transport. Therapeutic strategies that increase glucose uptake into the heart are likely to reduce certain cardiac complications of diabetes.

Clinical Research on Diabetic Complications

- Results from the 1998-2000 EDIC cardiovascular study demonstrate that atherosclerosis develops more slowly with age in type 1 diabetic individuals whose blood sugar has been kept near normal by intensive treatment of their diabetes. Moreover, the risk of atherosclerosis in type 1 diabetes was shown to be increased by higher blood pressure and cholesterol and by smoking, just as it is in non-diabetic individuals. Thus, complications resulting from premature atherosclerosis, such as heart attacks and strokes, may be prevented by intensive treatment to keep blood sugar, blood pressure, and cholesterol levels as low as is safely possible.

- Although diabetic neuropathy appears to have many underlying causes, ultimately, ischemia—an obstruction in the blood flow—is a final, common pathology. Researchers observed a substantial reduction in the expression of thrombomodulin—an anti-clotting factor on the surface of blood vessel cells—in nerve microvasculature of diabetic patients with neuropathy relative to non-diabetic individuals. Down-regulation of thrombomodulin in diabetic neuropathy may contribute to microvascular ischemia that damages nerves.

Diabetes is the leading cause of lower limb amputations. Nerve and vascular damage can result in loss of feeling, poor circulation, and impaired healing of wounds or infections on the feet. For this reason, regular foot exams to identify problems early and reduce the risk of amputation are an important part of diabetes care. The Special Statutory Funding Program for Type 1 Diabetes Research supports investigator-initiated research on the neurological complications of diabetes.

(Photo Credit: National Diabetes Education Program)

EXTERNAL EVALUATION

This section provides commentary from leading scientific experts within the diabetes research community who assessed the accomplishments of the special statutory funding program and from researchers who participated in the use of the special funds. A complete description of the evaluation process and the use of evaluative data regarding the special funding program is available in the Assessment chapter and Appendix 2.

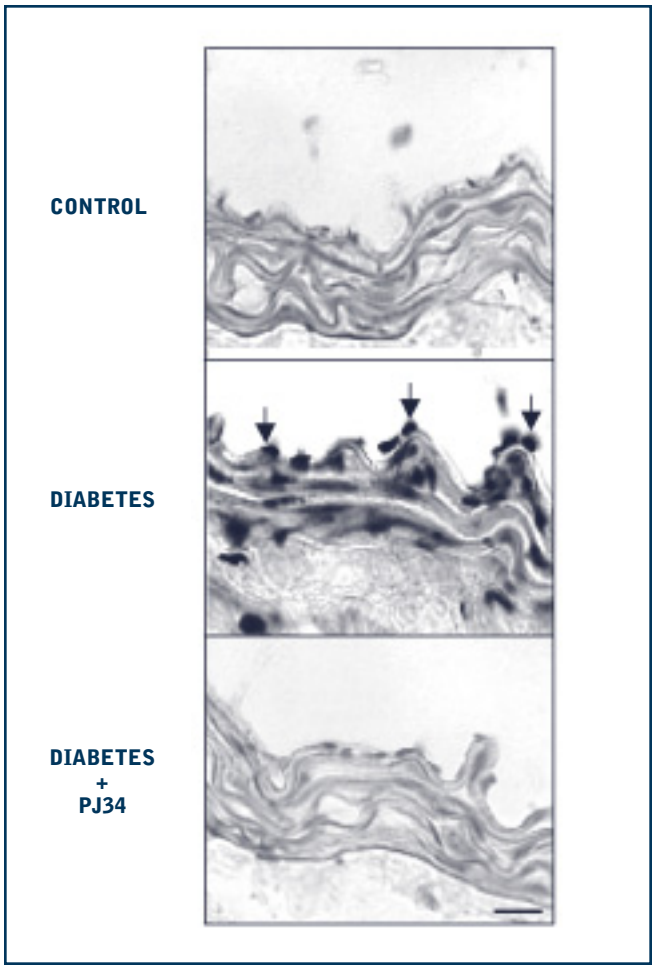
Advisory Panel

A panel of scientific and lay experts on type 1 diabetes research convened at the NIH in May 2002 to review the use of the special statutory funds. Comments from the advisory panel regarding research on diabetic complications include:

- The advisory panel identified the Diabetes Control and Complications Trial (DCCT), which showed that close glycemic control can ameliorate microvascular and neurologic complications in type 1 diabetes, as a tremendous advance in the clinical management of this disease. Nonetheless, the panel also recognized that complications account for the vast majority of diabetes-associated medical costs and that much more research on prevention and treatment of diabetic complications will be necessary to make a positive impact on the quality-of-life of diabetic individuals.

- Research on diabetic complications spans a complex and diverse array of investigations. The panel members proposed many ways to focus the field on common goals and to maximize the research resources available to the community.

- The panel was very enthusiastic about the availability and sharing of animal models that will be a key feature of the Animal Models of Diabetic Complications Consortium. The group identified several opportunities for leveraging the infrastructure created by the consortium and for optimizing the use of animal models in the study of complications affecting multiple organs.



These images of blood vessel walls show the difference in activation of the poly (ADP-ribose) polymerase (PARP) enzyme activity in tissue from non-diabetic, control mice (*top panel*), diabetic animals (*middle panel*), and PJ34-treated diabetic animals (*bottom panel*). PARP activation has been linked to several diabetic complications, including stroke, heart attack, and inflammation. Blood vessels from diabetic mice show evidence of PARP activation in the cell nuclei (*see arrows indicating stained nuclei in middle panel*). However, treatment with a novel PARP inhibitor, "PJ34," blocks PARP activation in diabetic mice (*note loss of nuclear staining in bottom panel*). Although more research is necessary to translate these findings to human diabetes, PARP may represent a new target for the treatment of diabetic microvascular complications. This work was supported in part by the Special Statutory Funding Program for Type 1 Diabetes Research.

(Photo Credit: Reproduced from Nature Medicine, 2001, 7(1): 108-113, by copyright permission of the Nature Publishing Group.)

- The field of diabetic complications research is very diverse, yet has many potential commonalities. The panel was concerned with the lack of cohesion among investigators in the field and, thus, encouraged the further development of mechanisms to facilitate productive interactions. The advisors suggested that this subject would benefit significantly from the establishment of a research consortium similar to the Beta Cell Biology Consortium (*see Goal III*) for basic studies related to cell replacement therapies.

Extramural Grantees

Principal investigators who received grants or grant supplements related to diabetic complications responded to a survey asking, in part, about the value of this grant or funding source. Representative remarks include:

- "Research is a costly and time consuming endeavor. However, every little thing that we learn helps us gain a better understanding of the mechanisms involved in the development of diabetes. Without this funding, my laboratory would never have been able to pursue this cause."

- "This supplement allowed an existing study to ask several very important scientific questions related to diabetic complications that were not part of the initial study. This is an extremely productive use of funds because it leverages the investment in the core study to allow important questions to be addressed using technology that was not available at the time the initial study was planned."

- "The timing of this financial stimulus could hardly have been better. It provided an additional creative momentum at a time when the diabetes basic and clinical science research communities were poised to take advantage of recent spectacular advances in molecular and genetic understanding of diseases. This added support puts prevention and cure of type 1 and type 2 diabetes—both are needed—within our grasp."

- "This grant allowed my laboratory to pursue and be productive in diabetes research. Although components of the work...were areas in which my lab had a proven track record, we had no published experience in applying our expertise to the field of diabetic neuropathic or autonomic complications. The funding of this RFA was a very significant opportunity for the lab to 'grow' into this new field. We plan to continue this line of work."

- "[This was] an excellent mechanism to merge NIH and private foundation support for clinically critical areas of research. [It was a] particularly valuable approach with the limited funding provided by the NIH for patient oriented research. This grant has been a catalyst for the testing of hypotheses that have been generated in experimental animal studies in humans. Furthermore, we believe it has provided sufficient preliminary data to develop a large scale clinical research program focusing on the genetics of cardiovascular complications of diabetes."

- "This grant allowed me to pursue and develop the most promising therapeutic agent for treating diabetic neuropathy that I have encountered in 17 years of research into diabetic neuropathy."

- "This was a terrific opportunity and has—I believe—jump-started a new research field. The outcome of this research has the potential of achieving a paradigm-shift in our understanding of diabetes complications."

- "I have previously been funded on numerous NIH grants, but this specific project allowed me to adapt procedures and skills developed in other fields...to the field of diabetes. Further, this project allowed me to link my studies in experimental animal models...with my participation in human multi-center clinical trials of diabetic neuropathy."

- "This funding opportunity has led me to focus attention on the disease and pathogenic mechanisms in the disease that I would not otherwise have explored....These kinds of programs can be very valuable for bringing important health related topics to the attention of basic scientists."

- "This grant mechanism has been extremely important as I make the transition to diabetes research. My prior expertise in physiology, neuroscience, and neuroendocrinology gave me the tools to ask the questions that are the focus of my research; however, I was not aware of the many problems and complications associated with the effect of type 1 and type 2 diabetes on the nervous system. It is crucial to continue development of our basic science knowledge by studying these interface areas between disciplines as was so carefully done in this initiative on diabetes and the brain."

- "The majority of NIH funding requires a very specific mechanistic (usually molecular) hypothesis as the basis of a proposal that can preclude studies of agents that have therapeutic potential but for which the mechanisms of action are unclear. This can delay assessment of the therapeutic potential of such agents and prevent their development for clinical use. This type of RFA was an ideal venue for examining the potential of [these agents] and the support has been rewarded by the ongoing development of these agents for clinical approval and use, even though we are still not clear of their precise molecular mechanisms of action."

Diabetes is the leading cause of end-stage kidney disease in the U.S. This patient is receiving dialysis to remove wastes from her blood, a function that her kidneys can no longer perform. The Genetics of Kidneys in Diabetes (GoKinD) and Family Investigation of Nephropathy and Diabetes (FIND) studies are searching for genes that contribute to diabetic kidney disease. In addition, the Special Statutory Funding Program for Type 1 Diabetes Research is supporting pilot trials of novel therapeutic agents for the study of diabetic nephropathy.

(Photo Credit: Richard Nowitz for NIDDK)

PREVENTING OR DELAYING THE COMPLICATIONS OF DIABETES: THE EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC) STUDY

People with diabetes who intensively manage their blood sugar levels were shown to reduce dramatically their risk of eye, kidney and nerve damage in the major NIH-funded Diabetes Control and Complications Trial (DCCT). Now a DCCT follow-up observational study, called the Epidemiology of Diabetes Interventions and Complications (EDIC), has confirmed the long-term benefits of intensive blood sugar control. Major reductions in diabetic complications were found to continue 7 years after the DCCT ended.

The DCCT was a multicenter clinical trial of over 1,400 people with type 1 diabetes. Completed in 1993, the trial compared intensive versus conventional treatment of blood glucose levels. The DCCT proved conclusively that intensive therapy significantly reduced the risk of microvascular complications, including retinopathy, nephropathy, and neuropathy compared with conventional treatment. 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 self-monitoring of blood glucose, and at least three insulin injections a day or an insulin pump. Conventional treatment consisted of one or two insulin injections a day, with once-a-day urine or blood glucose testing. After spending an average of 6.5 years in the DCCT, patients' HbA1C levels averaged 7.2 percent in the intensive treatment group, and 9.1 percent in the conventional treatment group; the normal range is 4 to 6.1 percent.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all participants were encouraged to use intensive treatment. The EDIC study was established to follow the DCCT participants to determine the long-term outcome of reducing exposure of the body's tissues and organs to high blood

Complications of Diabetes[1]

- **Blindness:** Diabetic eye disease (retinopathy) is the leading cause of new blindness in U.S. adults, resulting in 12,000 to 24,000 new cases of blindness each year.
- **Irreversible Kidney Failure:** Diabetic kidney disease (nephropathy) is the most common cause of end-stage kidney failure, accounting for 43 percent of new cases, and this proportion is projected to grow. In 1999, over 38,000 people with diabetes began treatment for end-stage renal disease and over 114,000 underwent dialysis or kidney transplantation.
- **Amputations:** About 60 to 70 percent of people with diabetes have damage to the nervous system (neuropathy). Severe forms of diabetic nerve disease—coupled with circulatory failure in the foot and leg—lead to foot ulcers and about 82,000 amputations annually in the U.S. More than 60 percent of non-traumatic lower leg amputations in the U.S. occur in people with diabetes.
- **Heart Attacks and Strokes:** Premature cardiovascular disease is the cause of death in two thirds of patients with diabetes. Heart disease (atherosclerosis) is accelerated in individuals with diabetes, who have a two- to four-fold increased risk for developing macrovascular disease and suffer a two-fold excess in morbidity and mortality following a heart attack compared to individuals without diabetes.

1 *National Diabetes Statistics.* Available at: www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#13.

glucose levels. In this ongoing study, patients receive care from their own physicians, while researchers continue to track them annually, monitoring changes in their eyes, kidneys, nerves, heart and blood vessels.

The exciting new finding reported in May 2002 was that the period of intensive treatment during the DCCT continued to positively influence the health of participants in that treatment group for as long as 7 years after the study ended. The continued significant reduction in complications in the former intensive treatment group, compared with the former conventional treatment group, occurred despite nearly identical blood glucose control in the two groups after completion of the DCCT. During the EDIC study, when intensive therapy was encouraged for all participants, researchers found that the average HbA1C level in the former DCCT intensive treatment group *increased* from 7.2 to 8.1 percent, while that of the former conventional treatment group *fell* from 9.1 to 8.3 percent. The difference in average HbA1C levels of the two populations became statistically non-significant by 5 years into the EDIC study. The investigators will continue following the research patients for at least another 4 years.

"We knew from the DCCT that intensive management—with the aim of keeping blood glucose levels as close to normal as possible—is extremely effective at reducing the complications of diabetes," says Dr. David Nathan, who co-chair's the DCCT/EDIC research group. "From EDIC, we now know that the benefits of intensive control continue for years. The take-home message is that the earlier intensive therapy begins and the longer it can be maintained, the better the chances of reducing the debilitating complications of diabetes." Dr. Nathan is Director of the Diabetes Center at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School.

"The benefits of intensive treatment add up like interest on an investment," said Dr. Saul Genuth, the other co-chair of the DCCT/EDIC research group. "The longer that diabetic patients can keep practicing intensive treatment and keep their glucose levels down, the longer the benefits will accumulate." Dr. Genuth is Professor of Medicine at Case Western Reserve University's School of Medicine and University Hospitals of Cleveland. Indeed, this finding raises interesting questions about the "metabolic memory" that enables the beneficial effect to persist long after the period of intensified blood glucose control has ended. The biologic basis of this metabolic memory—how a difference in glucose control for a finite period can have striking effects long after the study (and the difference in glucose control between the two groups) ended—will be explored in a symposium to mark the 20th anniversary of the initiation of the DCCT.

Despite the success of the DCCT and EDIC studies, major challenges remain. As seen in EDIC, with the tools currently available outside the supervision of a clinical trial, even the most highly motivated and trained patients often cannot achieve the levels of glucose control that are proven to reduce the risk of complications. Thus, researchers are vigorously exploring other ways, such as cell-based therapy, to restore blood glucose levels to patients with diabetes and thus prevent or delay complications. Recent exciting success with one such approach, islet transplantation, underscores the critical importance of research to expand availability of insulin-producing pancreatic islets for transplantation and to develop improved methods of immune suppression or tolerance to prevent the body's immune system from rejecting such transplants. Researchers are also seeking new methods for assessing and monitoring glucose control, new forms of insulin and methods for its delivery, and new classes of medicines for treating high blood glucose levels.

DCCT Conventional Therapy Methods

- Clinical goals: No symptoms of hyperglycemia or hypoglycemia
- One or two insulin injections per day
- Daily self monitoring of blood glucose
- Quarterly HbA1C
- Pregnant women treated intensively
- Diet and exercise education
- Quarterly clinic visits

Concomitantly, scientists are unraveling the molecular mechanisms by which elevated glucose levels damage blood vessels and the tissues and organs that are affected by diabetes. Already, classes of medications that alter production or action of a key signaling molecule involved in regulation of blood pressure have been shown to block progression of the kidney disease of diabetes. A novel pharmacologic agent under development for diabetic eye and nerve disease targets a signaling molecule that may play an important role in mediating glucose toxicity. This promising medication has slowed development of eye and nerve disease in animal models of diabetes and is now moving into clinical trials *(see Goal VI sidebar on Bench-to-Bedside Research).* Further delineation of the cell signals involved in glucose toxicity is a key step toward defining additional molecular targets for drug development, which can lead to new medicines to block diabetes complications.

In addition to generating knowledge that may lead to prevention of microvascular complications in people with type 1 diabetes, one of the major goals of the EDIC study is to learn more about the factors that cause macrovascular disease so that it, too, might be prevented. People with diabetes are at especially high risk for developing cardiovascular complications, including heart disease, stroke, atherosclerosis, cardiomyopathy, congestive heart failure, and poor circulation in the legs. Cardiovascular complications are now the leading causes of illness and death among the nation's diabetic population.

By examining the effect of glycemic control on cardiovascular disease, the EDIC study will help reveal whether intensive blood glucose control can contribute to preventing cardiovascular complications caused by type 1 diabetes. The Special Statutory Funding Program for Type 1 Diabetes Research will be used to apply state-of-the-art techniques to measure cardiovascular disease, which is an increasing concern as the EDIC cohort ages. A newly-developed, non-invasive procedure called "coronary calcium scanning" will be used to directly assess atherosclerosis in the coronary arteries of people in the EDIC cohort. Calcium is deposited in places where atherosclerosis exists, so the higher the "calcium score"

measured in this test, the more atherosclerosis is present in the coronary arteries. This study will determine whether coronary calcium score was affected by intensive therapy in the same way as the microvascular complications. The score will be interpreted in the context of other risk factors that might be present, such as gender and age, blood pressure, cholesterol levels, C-reactive protein, smoking history, exercise level, body weight, family history of coronary heart disease, status of kidney function, and electrocardiogram results. Thus, coronary calcium score may be a surrogate marker that can provide important information about the development of macrovascular disease in people with type 1 diabetes, before onset of clinical events such as heart attack and stroke.

Communicating the message of EDIC's findings to physicians and patients is critical. "This study is good news for people with diabetes. EDIC adds to the growing body of scientific evidence that people who aggressively control their diabetes can make a huge difference in their health," says Dr. Rodney Lorenz, Chairman of the Department of Pediatrics at the University of Illinois School of Medicine. Dr. Lorenz is Vice Chair of the Diabetes in Children and Adolescents work group, and Chair of the Evaluation work group, for the National Diabetes Education Program, which is co-sponsored by the NIDDK and the CDC, along with over 200 non-federal partnership organizations.

Writing Team for the DCCT/EDIC Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 2002; 287: 2563-2569.

DCCT Intensive Therapy Methods

- Three or more daily injections or insulin pump
- Four or more blood glucose tests daily
- Frequent dietary instruction to help achieve goals
- Monthly clinic visits
- Integrated team care

IMPROVED SURVIVAL IN TYPE 1 DIABETES

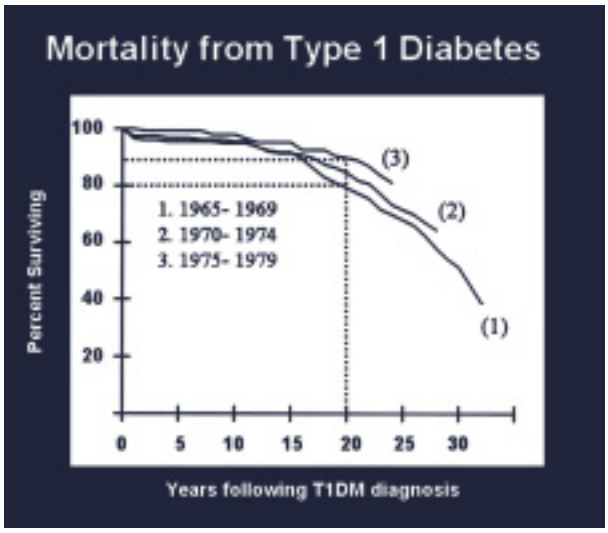
Five to 10 percent of the 11.1 million Americans with diagnosed diabetes have type 1 diabetes. Prior to the introduction of insulin in the 1920s, death shortly after diagnosis was inevitable. Since then, death rates in Americans with type 1 diabetes have improved steadily, but remain markedly increased above those of the general population.

Within a Pittsburgh-based cohort of 1,075 patients with type 1 diabetes diagnosed between 1965 and 1979, a sharp drop in mortality over time was found by comparing subgroups diagnosed between 1965-69, 1970-74, and 1975-79. Between 10 and 20 years duration of diabetes, 8.4 percent of subjects died in the 1965-69 cohort, compared to only 3.5 percent in the 1975-79 cohort (p=0.03). These data show the long-term survival of children with type 1 diabetes has improved, most likely representing better glycemic and blood pressure control since the early 1980s.

NIH-supported research led to the development of a key blood test (hemoglobin A1C) for monitoring glycemic control, improved methods of insulin delivery, and other therapies that improved blood glucose control. NIH-supported research also led to improved therapies for hypertension, which have been key to improved survival of those with type 1 diabetes.

Further reductions in mortality can be expected as the findings of subsequent clinical trials are incorporated into practice. For example, the results of the Diabetes Control and Complications Trial (DCCT), completed in 1993, showed that further improvement in glycemic control (over what was standard care at the initiation of the trial in the mid-1980s) significantly reduced eye, nerve and kidney complications.

The most recent data from the long-term follow-up of DCCT study participants suggest that surrogate measures of cardiovascular disease may be improved in those in the intensive treatment arm of the trial. Since premature cardiovascular disease is the major cause of death in diabetes, this preliminary finding suggests that the prognosis will continue to improve for those more recently diagnosed with type 1 diabetes.



Life-table analyses by temporal trend of individuals with type 1 diabetes diagnosed in Allegheny County, PA, between 1965 and 1979. Participants in the study were separated into three groups based on the date of their diagnosis. The graph shows the survival curves of each group. Analyses of the data at 20 years post-diagnosis show a significant improvement in mortality in the 1975-1979 group (line 3) when compared to the 1965-1969 group (line 1). Improved diagnosis and treatment are considered to be major factors contributing to the decline in mortality rates.