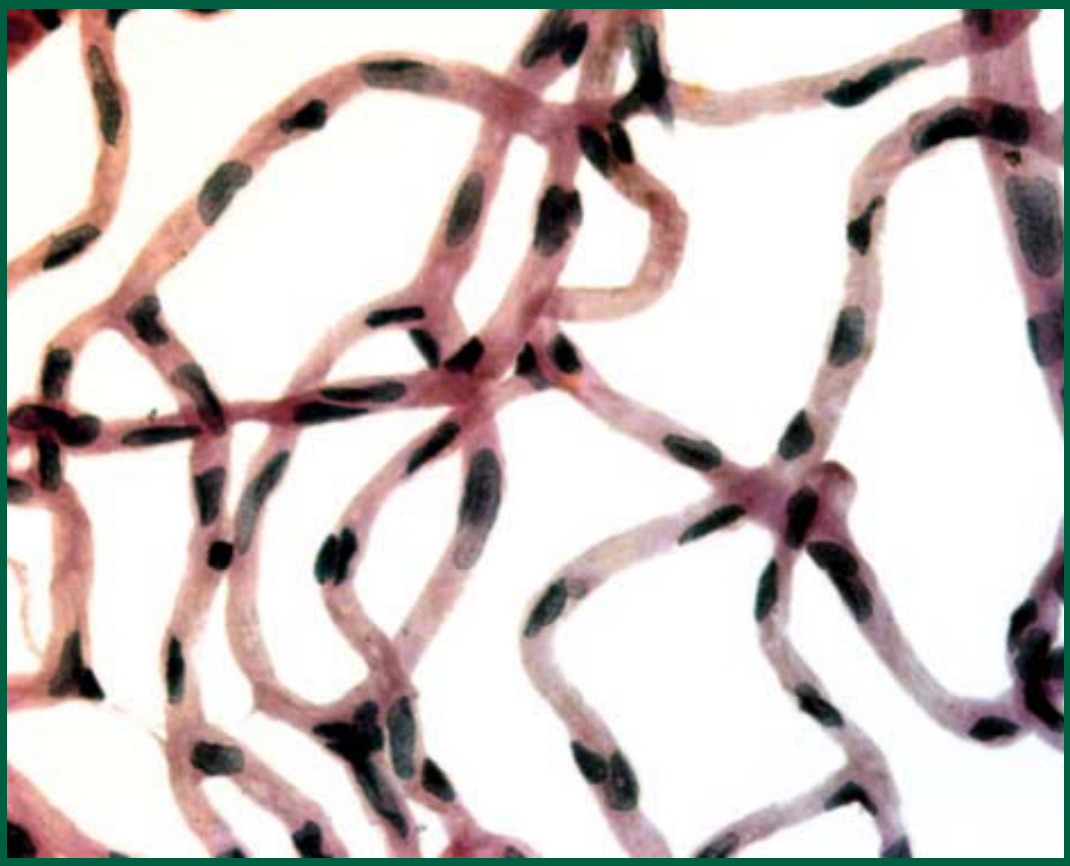

Healthy-looking blood vessels from the eyes of diabetic rats treated with benfotiamine, a B-vitamin related molecule. The therapeutic potential of this molecule represents one promising research advance toward the prevention of vascular complications of diabetes–including diabetic eye disease. Photo: Dr. Xuliang Du and Dr. Michael Brownlee, Diabetes Research Center, Albert Einstein College of Medicine, Bronx, NY. Reprinted with permission from Hammes HP *et al, Nat Med* 9: 294-9, 2003. © 2003 Nature Publishing Group (http://www.nature.com).

Diabetes, Endocrinology and Metabolic Diseases

NIDDK support of basic and clinical research in the area of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, they affect many millions of Americans and profoundly decrease their quality-of-life. Many of these diseases are complex–an interplay between genetic and environmental factors contributes to disease development.

Diabetes is a debilitating disease that affects an estimated 18.2 million people in the U.S.–over 6 percent of the total population–and is the sixth leading cause of death. The number of people with diabetes continues to rise–only a year ago, estimates of the number of persons with diabetes stood at 17 million. Diabetes lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two-to-four-fold, and is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness. In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2002–including costs of medical care, disability, and premature death–was $132 billion. Effective therapy can prevent or delay these complications, but one third of Americans with diabetes are undiagnosed. This has spurred the Department of Health and Human Services to launch the Secretary's "Diabetes Detection Initiative: Finding the Undiagnosed." The goal for this community-based effort is to help identify the several million Americans with undiagnosed diabetes, as well as those at high risk for the disease, and to refer them for follow-up testing as appropriate.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone which is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body completely loses its ability to produce insulin; and type 2 diabetes, in which less insulin than needed is produced, and the body becomes resistant to its signals.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes. It most often occurs in children, but may appear at any age. Type 1 diabetes is an autoimmune disease, in which the immune system mistakenly attacks and destroys the beta cells of the pancreas. These beta cells, which are found within tiny cell clusters called islets, are the body's sole producers of insulin. If left untreated, type 1 diabetes results in death from starvation despite high levels of glucose in the bloodstream. Thus, patients require lifelong insulin administration–in the form of multiple daily injections or *via* an insulin pump–in order to regulate their blood glucose levels. Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for patients to control blood glucose levels as well as they would if they had functional beta cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working on new beta cell replacement therapies meant to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for up to 95 percent of diabetes cases in the U.S. Type 2 diabetes is associated with several factors, including older age and a family history of diabetes. It is also strongly associated with obesity: more than 80 percent of people with type 2 diabetes are overweight or obese. Type 2 diabetes occurs more frequently among minority groups, including African Americans, Hispanic Americans, Native Americans, and Native Hawaiians. In patients with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. Gradually, the pancreatic beta cells secrete less and less insulin, and the timing of insulin secretion becomes abnormal. To control glucose levels, treatment approaches include diet, exercise, and medications; some patients also need to take insulin. There are also millions of individuals who have a condition called "pre-diabetes," in which blood sugar levels are higher than normal, but not as high as in diabetes. This population is at high risk of developing diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial has shown that patients with pre-diabetes can dramatically reduce their risk of developing full-blown diabetes with improvements in lifestyle or with drug treatment.

Type 2 diabetes was previously called "adult-onset" diabetes because it was predominantly diagnosed in older individuals. However, due to an increase in overweight in children, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. This is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early disease onset are at greater risk with respect to complications. Second, maternal diabetes during pregnancy–either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy–confers an increased risk of diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, health care providers may find it increasingly difficult to strictly control a patient's blood sugar and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to drastically worsen the enormous health burden that diabetes already places on the U.S.

The NIDDK is vigorously pursuing research to understand the mechanisms that lead to the development of diabetes and its complications, as well as ways to prevent, treat, and cure the disease. This research is being propelled by emerging technological advances that enable scientists to gather a large amount of data in a short period of time. The impact of new technology is underscored by the recent use of high-throughput DNA sequencing to complete the Human Genome Project. Other novel experimental approaches–such as tools to assess changes in gene and protein expression in organs and tissues affected by diabetes and use of molecular libraries of thousands of compounds to identify potential therapeutic agents–are powerful tools to study disease rapidly. This will speed progress toward understanding, and ultimately curing, diabetes and many other metabolic and endocrine diseases within the NIDDK mission.

ADVANCES IN PREVENTING VASCULAR COMPLICATIONS OF DIABETES

Organs and tissues throughout the body are fed and cleansed by the blood *via* a complex network of capillaries, small blood vessels, and major veins and arteries. Compared with the rest of the population, patients with type 1 or type 2 diabetes have an increased risk for developing injury to these small and large blood vessels. This vascular damage can lead to serious health complications. Injury to the small blood vessels, or microvasculature, can cause blindness, kidney failure, and nerve damage, while injury to the large blood vessels, or macrovasculature, can lead to cardiovascular disease and stroke. Heart disease is the leading cause of death in persons with diabetes. Studies have shown that sustained high blood glucose (sugar) levels, or hyperglycemia, are a major factor in the development of many of

these complications. Researchers are building upon both fundamental investigations of how glucose damages blood vessels, and clinical investigations of its effects on health, to devise strategies to prevent or intervene in diabetes-induced vascular damage.

Reduction in Atherosclerosis from Intensive Blood Glucose Control: In one recent advance, investigators from the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated an important link between blood glucose levels and macrovascular injury. The EDIC is a follow-up study to the landmark Diabetes Control and Complications Trial (DCCT), a large-scale multi-center clinical trial that demonstrated that tight control of blood glucose levels through intensive therapy can reduce the risk of developing small blood vessel complications causing kidney, eye and nerve damage in type 1 diabetes patients. The EDIC study continues to demonstrate enduring benefits of intensive therapy in these patients nearly a decade after the trial ended–most recently, its impact on the blood vessels that supply the heart and brain. (Please see the "Story of Discovery," "Preventing or Delaying Complications Of Diabetes: 20 Years of Study by the DCCT/EDIC Research Group.") While the DCCT proved that glucose control could prevent or delay small vessel damage, controversy remained about the effect of high glucose on the large vessels damaged in cardiovascular disease. Now, results from EDIC have shown that, in contrast to patients on standard therapy, patients who received intensive therapy in the DCCT developed less thickening of the wall of the carotid artery–the artery on which the brain depends for blood flow. Thickening of this artery is an important measurement of atherosclerosis. Reduced calcification, another marker of vascular damage, was also seen in the coronary arteries of the intensively treated group. These significant results demonstrate the importance of strict blood glucose control in preventing damage to large blood vessels, as well as small vessels.

Medicating the Microvasculature: Researchers are also gaining ground in pioneering potential treatments to combat vascular damage. In a recent study, scientists tested the ability of a vitamin-B related molecule, called "benfotiamine," to stop the adverse effects of high blood sugar levels on microvascular complications. Exploiting accrued knowledge about the biochemical pathways that are important in the development of glucose-induced vascular complications, the group hypothesized that benfotiamine could simultaneously block several of these pathways. They found that this was in fact the case, through experiments in both a cell culture model system and in retinas taken from diabetic rats. But was there an impact of this treatment on the development of disease? When the researchers directly tested the effect of benfotiamine in diabetic rats, they found that treated rats did not develop diabetic eye damage. In contrast, untreated rats developed the disease. These promising results in an animal model of diabetes provide an important first step in determining its therapeutic usefulness of benfotiamine for humans. If the results can be replicated in humans, this research could lead to a potential therapeutic agent that may enable diabetes patients to prevent development of diabetic eye disease and possibly other vascular complications.

The NIDDK is supporting numerous basic and clinical investigations like these to address the causes of, prevention of, and interventions for diabetes-associated vascular complications. The Institute is also currently collaborating with the National Heart, Lung, and Blood Institute to support the clinical study, Action to Control Cardiovascular Risk in Diabetes (ACCORD). The goal of ACCORD is to test the best approaches to lowering the risk of heart disease and stroke in adults with type 2 diabetes. ACCORD will compare the effect on cardiovascular outcomes of intensive or standard* blood sugar control, in combination with either aggressive control of blood pressure or blood fats. Moreover, to foster promising research on diabetes complications

* The current "standard" is based upon the more intensive recommendations from the DCCT and a clinical trial of blood sugar control in type 2 diabetes, the UKPDS.

more effectively, the NIDDK recently established a Working Group for Diabetes Complications (see also the "Kidney, Urologic, and Hematologic Diseases" chapter). The goals for this group are to provide seamless integration of NIDDK activities related to complications, including workshops, initiative planning and oversight of existing projects and trials; to establish liaisons with other Institutes and to develop activities that will increase interest in diabetes complications in other scientific communities; and to lead future strategic planning activities on diabetes complications. Through all of these efforts, the NIDDK seeks to ensure continued progress in research leading toward improved clinical management of diabetes complications.

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CONTINUED INSIGHTS FROM THE DIABETES PREVENTION PROGRAM: SUSTAINED BENEFITS OF METFORMIN

As demonstrated by the EDIC follow-up to the DCCT clinical trial, investment in well-designed, large-scale clinical trials can yield important scientific fruits for many years. Similarly, a wealth of insight into the factors influencing onset of type 2 diabetes is continuing to arise from ancillary and follow-up studies to the Diabetes Prevention Program. The Diabetes Prevention Program (DPP) was a clinical trial that aimed to determine the relative effectiveness of drug or lifestyle modification in delaying or preventing the development of type 2 diabetes in an at-risk population. Over 3,000 people participated in the DPP, 45 percent of whom were from racial and ethnic minorities disproportionately affected by type 2 diabetes, and 68 percent of whom were women. The DPP reported that the incidence of diabetes in individuals with impaired glucose tolerance (or "pre-diabetes") could be reduced by 58 percent with intensive lifestyle modifications, and by 31 percent with metformin, an insulin-sensitizing drug, compared with standard medical advice and placebo.

Following the DPP, researchers examined participants who had received metformin or placebo and had not developed diabetes during the trial to learn more about how the drug worked to prevent diabetes. The goal was to determine whether the drug therapy had masked the development of diabetes, and its benefit would disappear if the medication was withdrawn, or if the effect were more lasting, and would persist after cessation of therapy. Patients were instructed to discontinue their medication–either placebo or metformin–for one to two weeks prior to further evaluation. After this "washout" period, the patients received an oral glucose tolerance test, a test that would reveal whether they had diabetes. Statistical analysis revealed that about one quarter of the 31 percent reduction in diabetes incidence seen with metformin therapy in the DPP was attributable to effects of the drug that do not persist when it is withdrawn. However, even after the washout, the incidence of diabetes was reduced by 25 percent in the metformin group. Thus, this study demonstrated that metformin therapy does provide some benefits that can persist after short term drug withdrawal. These observations are important for determining the role of metformin in the clinical management of pre-diabetes.

Extending the value of this clinical trial, several other components of the NIH and the Centers for Disease Control and Prevention (CDC) have joined the NIDDK in supporting a long-term follow-up study to the DPP, called the DPP Outcomes Study (DPPOS). The goal of the DPPOS is to determine the durability over time of the effect of the original

DPP interventions on onset of type 2 diabetes and their effects on diabetes-associated complications–particularly cardiovascular disease–in members of the large, diverse, and well-characterized cohort of DPP participants. It is hoped that results from the DPPOS will ultimately help improve clinical strategies to prevent the onset and/or progression of type 2 diabetes and diabetes complications in the millions of Americans already at-risk.

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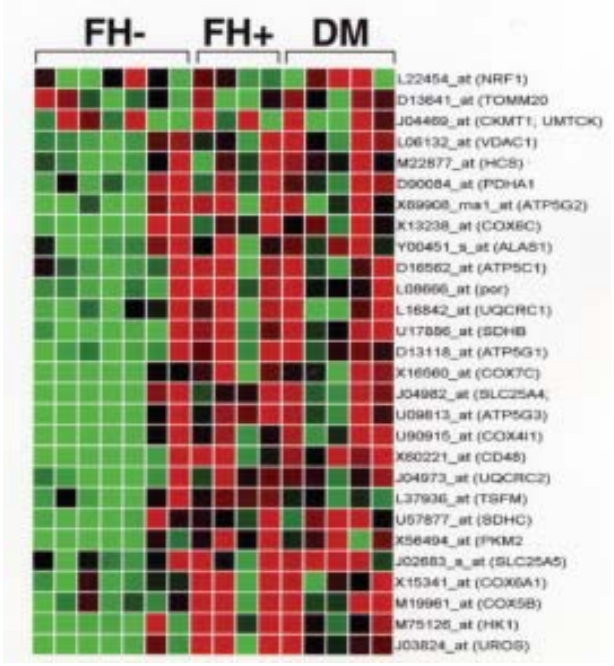
NOVEL USE OF MICROARRAY TECHNOLOGY FOR IDENTIFYING GENES INVOLVED IN TYPE 2 DIABETES

Both genetic and environmental factors contribute to the development of type 2 diabetes. The genetic contribution is likely due to multiple "susceptibility genes," each of which modestly increases risk. Because multiple genes are likely to be involved type 2 diabetes, scientists have used a powerful and efficient research tool, called "gene microarray technology (GMT)," or simply "microarrays," to identify genes that may contribute to disease development. GMT is a method for rapidly analyzing the expression of thousands of genes. It enables researchers to readily compare differences in gene expression in healthy and diseased tissues and cells.

However, although GMT is a powerful survey tool for finding individual genes whose expression changes in human disease, it is difficult to determine which of the modest changes in expression of multiple genes is important. Because there is already high variation in the expression of identical genes from person to person, it is statistically challenging–using the limited number of patient samples usually involved in these studies–to determine which small changes are potentially involved in a disease and which are due to normal population variation (see also the sidebar, "Human Genome Variation and the Genetics of Common Human Disease," in the



Gene microarray technology permits researchers to rapidly compare expression of multiple genes among different individuals. In this diagram, color indicates relative increases (green) or decreases (red) in gene expression. As shown, the expression of many genes involved in cellular energy production (listed at right) is relatively lower in muscle tissue from persons with a family history of diabetes (columns under FH+) or diabetes (DM) as compared to individuals with neither (FH-). Photo: Dr. Mary Elizabeth Patti, Research Division, Joslin Diabetes Center, Boston, MA. Reprinted with permission from Patti ME *et al, Proc Natl Acad Sci USA* 100:8466-71, 2003. © 2003 National Academy of Sciences, U.S.A.

"Cross-Cutting Science" chapter). Thus, researchers are developing novel approaches to capturing and analyzing microarray data that will help them discern when subtle changes are significant. These approaches are being developed by exploiting knowledge of the coordinated regulation of gene expression in discrete biological pathways and by enhancing statistical methods used to analyze the data from microarrays.

Two recent advances employed novel GMT approaches for finding genes that may be important in the development of type 2 diabetes. In one study, researchers investigated the expression of genes in skeletal muscle biopsies from healthy diabetic and non-diabetic individuals, both with and without a family history of diabetes. The expression of many genes was altered modestly in diabetic

patients and in those with a family history of diabetes. Using several special software programs, the researchers were able to uncover significant patterns of change in groups of genes that are related by function. Strikingly, when the scientists studied the resulting genes whose expression was decreased in diabetes, they found that many of them were part of a single pathway. This group of genes plays an integral role in a biological process involving the mitochondria–the power source of cell activity. The expression of this group of genes is regulated by a single master gene, *PGC-1*. Independently, another research team examined differences in skeletal muscle gene expression between diabetic and non-diabetic men using a new analytical strategy for GMT that they designed, called "Gene Set Enrichment Analysis." This team also found that genes regulated by PGC-1 were differentially expressed in the two groups.

These studies represent an ideal melding of basic knowledge of individual genes and gene pathways with high-throughput technologies to answer questions that neither could answer alone. They have not only described a novel approach that other researchers can use to identify additional type 2 diabetes susceptibility genes, but they have also provided insight into the pathogenesis of the disease. Obtaining new knowledge about genes and biological pathways that are important in disease development can be used to understand the underlying defects in diabetes as a basis for determining additional therapeutic targets for prevention or treatment. By demonstrating the importance of PGC-1, which may be a therapeutic target for type 2 diabetes, the researchers have paved the way to the discovery of other potential targets.

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DUAL MECHANISM OF ACTION OF TYPE 2 DIABETES DRUG CANDIDATE

Insulin is critical for the body's use of blood glucose (sugar) as a cellular fuel. Problems in cellular processes involving insulin are apparent in type 2 diabetes patients, who are impaired in their ability both to produce and to respond to insulin. One result is that the liver produces too much glucose, sustained high levels of which lead to development of diabetic complications. Research has shown that an enzyme, called "glucokinase" (GK), is central to regulating glucose metabolism in the pancreas and the liver. Researchers implicated GK in diabetes when they showed that errors in the glucokinase gene were responsible for the development of a certain form of type 2 diabetes, called Maturity Onset of Diabetes in the Young (MODY). In addition, researchers have characterized the importance of GK in diabetes by genetically engineering mice to lack the GK gene in the liver and the pancreatic beta cells. Because of this central role of GK in glucose regulation and diabetes, researchers have considered GK as a possible therapeutic target for type 2 diabetes.

With this knowledge in hand, scientists hypothesized that a drug that would "activate," or increase the enzymatic activity of, normal GK would help to restore normal glucose levels in type 2 diabetes. Toward this goal, they screened 120,000 different drugs and identified a single one that activated GK. The drug dramatically and effectively restored normal glucose levels in diabetic mice. Importantly, the drug achieved this by a dual mechanism: it

stimulated insulin production by pancreatic beta cells and inhibited glucose production by the liver. This is the first identified therapeutic agent to have an effect on both insulin production and insulin action–two processes that are severely impaired in type 2 diabetes.

This study is a key example of how NIH-investment in basic research has directly enabled researchers to identify a therapeutic agent for type 2 diabetes. Only because of basic research on the importance of GK in regulating glucose levels in the pancreas and the liver, and also its role in MODY, could researchers hypothesize that therapeutically targeting this enzyme might be effective in treating diabetes. The novel dual mechanism of action of this drug, which attacks the defects in type 2 diabetes at both the level of the pancreas and the liver, makes this a promising potential treatment approach for type 2 diabetes in humans.

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NEW INSIGHTS INTO ENDOCRINE PANCREAS GENE EXPRESSION

Historically, type 2 diabetes researchers have thought that the defect in the ability of beta cells to produce the proper amount of insulin, and the inability of muscle, fat, and liver to respond to the insulin–known as insulin resistance–are distinct problems. Now, however, there is evidence to suggest that the two defects may be related. A gene, called *Foxo1*, may be an important link.

Using genetically engineered mice, investigators showed that they can prevent diabetes in a mouse model of type 2 diabetes by reducing expression of the *Foxo1* gene product. Investigating how this might occur, they showed through several experiments that *Foxo1* was important in shutting off in beta cells the *Pdx1* gene–a gene that has been found to play an important role in promoting pancreatic cell development. The researchers also have evidence that *Foxo1* activity is regulated by insulin. Based upon these results and other research studies, they have proposed a scientific model in which, in the presence of functional *Foxo1*, there is no expression of the *Pdx1* gene and beta cells do not develop or proliferate; conversely, when insulin is present, insulin stops the *Foxo1* from working, and *Pdx1* is expressed–permitting development and/or proliferation of beta cells. Thus, if cells, including beta cells, become insulin resistant, then insulin can no longer inhibit *Foxo1* activity and enable beta cell development or proliferation. If this model is correct, *Foxo1* may link insulin action and beta cell development, making it a promising therapeutic target for promoting beta cell growth.

Understanding the underlying mechanisms of beta cell development is central to developing therapies for both type 1 and type 2 diabetes. For example, a major barrier to islet transplantation is a shortage of viable islets. If scientists uncover the mechanisms to turn progenitor cells into islet cells, then more cells for transplantation research can be made in the laboratory to help overcome the current shortage. This process will be enhanced by the PancChip 4.0, a microarray cDNA chip specific to the pancreas, which has been developed by researchers of the NIDDK-supported Endocrine Pancreas Consortium. This important research tool is widely accessible to diabetes researchers and will facilitate the identification of additional important genes in pancreatic cell development. Many of these genes may be promising therapeutic targets, just as *Foxo1* is a promising target for promoting beta cell growth. Greater knowledge of genes involved in endocrine pancreas development, coupled with improved tools to study them, will help researchers put together missing pieces of the puzzle of pancreatic cell growth and development.

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MODULATING AUTOIMMUNITY–IMPLICATIONS FOR TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease in which the patient's own immune system mistakenly attacks and destroys the beta cells of the pancreatic islets, the sole producers of insulin. To prevent autoimmune destruction of body cells, it is very important that the immune system distinguishes between "self," or one's own cells, and "non-self," or foreign matter. The body has a way to ensure this recognition happens, which involves destroying any immune cells that will react with "self" cells. A recent study showed that a protein, called AIRE, plays a role in this process. Researchers genetically engineered mice to lack AIRE, and found that those mice developed autoimmune disease. Furthermore, they found that AIRE turned on genes that had a role in the process of destroying immune cells that will react with "self" cells. Researchers can use these results as a basis to elucidate the processes that are important in development of human autoimmune diseases–including type 1 diabetes.

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REMOVING BARRIERS TO ISLET AND ORGAN TRANSPLANTATION

For patients with type 1 diabetes, replacing the destroyed beta cells through transplantation of fresh, undamaged islets that can restore normal insulin production offers the hope of a real cure. However, there are still significant barriers in pursuing this research avenue that could limit its widespread use in clinical application: (1) inadequate supplies of islets, and (2) limitations of current methods to prevent transplant rejection and recurrent autoimmunity. Barriers in the area of transplant rejection are present not only with islet transplantation, but also with organ transplantation in general. Transplant recipients are put on a strict regimen of immunosuppressive drugs–drugs that stop the immune system from working to its full potential–in order to prevent them from rejecting the transplant. However, these drugs can have severe side effects, and can lead to an increase in morbidity and mortality. Therefore, researchers are actively pursuing novel transplantation technologies and improved immunosuppressive therapeutic strategies both to increase organ acceptance and to decrease the adverse side effects of drug treatment.

Encapsulation–A Biological Cloak of Invisibility: Researchers investigating ways to prevent islet transplant rejection are making strides in their work with a technique known as "encapsulation." Encapsulation is used to coat cells with a material that makes them resistant to attack by the body's immune system, thereby obviating the need for immunosuppressive drugs. Encapsulation is challenging because the cell coating must permit exchange of signals, such as glucose and insulin, but block access of the immune system to the transplanted cells. Scientists have tried for years to improve the composition of the coating to achieve these goals. Recently, scientists used a modified encapsulation method to coat immature pig islets. They then transplanted the islets into diabetic mice to determine whether they would mature, grow and start to produce insulin. The encapsulated pig islets were not destroyed by the mouse's immune

system, for up to 20 weeks after transplantation (when the experiment was ended). The islets were able to function properly and produce insulin.

Modeling Mice into Men: New insights are emerging from the observation that, although methods to prevent transplant rejection may work very well in rodent models, the same methods do not work well in non-human primates or in humans. Researchers have found that the ability of the immune system to accept or reject a transplanted organ depended on immune cells that developed because of prior exposure to viruses. They tested mice that had either been virus-free or infected with viruses before transplantation. The mice treated with viruses better mimic a human, because humans have been exposed to many viruses and bacteria during their lifetimes. Both sets of mice were then given immunosuppressive drugs. The mice infected with the viruses were more likely to reject their transplants. The researchers identified the cells in the immune system that were causing this transplant rejection in the virally-infected mice, and they used a drug, called DSG, to stop the immune cells from working. Treatment with DSG increased transplant acceptance.

New Strategies for Immunosuppression: While new approaches to transplantation are going forward, improvements are also being sought for handling immune system rejection of islets and organs. Researchers recently tested a new immunosuppressive regimen in patients receiving kidney, liver, pancreas, or intestinal transplants. They were able to increase the interval between doses of immunosuppressive drugs given to the patients after transplantation (for example, from daily to once a week). This advance, in combination with pre-treating the patients with immunosuppressive drugs before their transplant surgery, has decreased organ rejection and improved the quality-of-life of the patients. Importantly, these results were not dependent on the type of organ transplanted, which suggests that these new approaches can yield wide-reaching benefits for organ transplantation recipients.

Collectively, these studies have demonstrated that novel strategies can improve transplant acceptance over current protocols. In one study, the new methods were tested on human transplant recipients, so the success can be directly translated into improved treatment strategies for patients. The other studies in animal models show much promise, and will have to be extended to non-human primates and humans. These new methods have the potential to increase organ acceptance and decrease the severe side effects of immunosuppressive therapy in order to improve quality-of-life.

The NIDDK will continue to foster progress in this area through its support of the Immune Tolerance Network (ITN), an international consortium led by the National Institute of Allergy and Infectious Diseases (NIAID) that is dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and also to research to prevent rejection of transplanted kidneys and pancreatic islets. The NIDDK has also recently launched a new initiative through which it intends to stimulate research focusing specifically on the biology of human beta cells and human pancreatic islets. These large-scale initiatives complement ongoing efforts by individual basic and clinical research scientists committed to improving health outcomes for people with diseases, including type 1 diabetes, that may be cured through the gift of an organ and/or tissue transplant.

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CLINICAL EFFORTS TO FIGHT DIABETES IN YOUTH

The onset of diabetes in youth–whether type 1 or type 2 diabetes–has long-term consequences for the health and development of the child. The NIDDK is supporting new and continuing clinical initiatives to reduce the burden of diabetes on youth in the U.S. To combat the alarming rise in diagnosis of type 2 diabetes in children and adolescents, the NIDDK plans new trials to identify the best interventions available treat and to prevent type 2 diabetes in youth. A multi-center trial, TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth), will compare three approaches to therapy of type 2 diabetes, and STOPP-T2D (Studies to Treat or Prevent Pediatric Type 2 Diabetes) is conducting pilot studies for a school-based trial directed at preventing the risk factors for type 2 diabetes in middle school children. The NIDDK is also collaborating with the National Institute of Child Health and Human Development (NICHD) to stimulate research on the precursors of the "metabolic syndrome" in children and adolescents. Greater knowledge of this clustering of metabolic disorders, which in adults predicts the development of type 2 diabetes and/or coronary heart disease, may lead to new therapies to prevent its development in youth, or to mitigate its consequences later in life.

The NIDDK will also continue vigorous support of research on type 1 diabetes. Support will continue for TrialNet–a nationwide network of clinical trial centers that supports the development and implementation of clinical trials of agents to prevent or slow the progression of type 1 diabetes. Another study, The Environmental Determinants of Diabetes in the Young (TEDDY), will analyze the infectious agents, dietary factors, and other environmental conditions that might trigger type 1 diabetes in genetically susceptible individuals. A major new clinical trials network will expand support for clinical trials on islet transplantation in type 1 diabetes patients. With the continued Congressional support for research on type 1 diabetes through the Special Statutory Funding Program for Type 1 Diabetes Research, the NIDDK is spearheading a series of initiatives to understand, treat, prevent and cure type 1 diabetes, together with other NIH Institutes and other agencies within the Department of Health and Human Services. More information on efforts made possible through this program is available on the worldwideweb at http://www.niddk.nih.gov/fund/diabetesspecialfunds/.

USING SMALL MOLECULES TO CORRECT CYSTIC FIBROSIS

Cystic fibrosis (CF) is a disease caused by mutations in the gene encoding the CFTR protein. The most common mutation, called ΔF508 (delta F508), causes cells to produce a misfolded protein that is unable to move to its proper location at the cell membrane, or function properly as a chloride ion channel. These abnormalities cause patients to have impaired lung function, caused by thick mucous secretions and bacterial infection, as well as digestive problems.

While the CFTR protein is expressed in high levels in the kidney, mutations in CFTR have little or no effect on kidney function. To help understand this paradox, researchers studied mouse kidney cells expressing the mutant CFTR grown under a special condition. This condition, called "hyperosmotic stress," mimics the environment for cells in the fluid filtering parts of the kidney. This hyperosmotic stress had the effect of correcting the mutant CFTR protein folding defect. They further showed that a small molecule, GSNO, which is a substrate for an abundant enzyme in the kidney, also promoted mutant CFTR protein maturation and function. These results may explain why CF patients do not have impaired kidney function, and demonstrate the feasibility of using a small molecule approach to promote proper folding and cellular trafficking of mutant CFTR protein as a therapeutic treatment. Another research group also used a small molecule

approach, and screened 100,000 small molecules. They identified six classes of molecules that were able to restore the ion channel function to ΔF508, using a cell culture model system. Both of these studies successfully used small molecules to correct defects in the ΔF508 mutant protein in cell culture, which suggests that small molecule intervention may be a useful approach for treating CF.

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BONE HEALTH AND OSTEOPOROSIS

Although seemingly static, bone is constantly being broken down and reformed in a process called "remodeling." A person's skeleton is completely remodeled every 10 years. The protein-mineral complex of bone is created by one set of cells called osteoblasts, and broken down by another set of cells called osteoclasts. Many factors influence the synthesis and demolition of bone by these cells, including nutrition, hormones, the immune system, medications, and exercise. Building and maintaining good bone health are important for proper development of body architecture and strength in youth, and for preventing potentially debilitating bone fractures in older age. The NIDDK supports basic and clinical research on the hormonal regulation of bone and mineral metabolism in health and disease, and the exploitation of this knowledge to develop approaches to maintaining bone mass and preventing bone loss.

Novel Assay for Measuring Protein Involved in Phosphate-Wasting Disorders: Phosphate is a compound obtained from food that is necessary for maintaining bone health. When the body cannot properly use the phosphate, phosphate-wasting disease can develop, such as autosomal dominant hypophosphatemic rickets (ADHR), X-linked hypophosphatemia, and oncogenic (cancer-related) osteomalacia. Patients who suffer from these three diseases have similar clinical symptoms, such as defective bone growth. Research has shown that ADHR is caused by errors in a protein called fibroblast growth factor 23 (FGF-23). The role of FGF-23 in regulating phosphate levels in healthy people is currently unknown. In addition, since X-linked hypophosphatemia and oncogenic osteomalacia are clinically similar to ADHR, it is possible that FGF-23 also plays a role in those diseases. However, a current limitation in understanding the function of FGF-23 is that there is no easy way to measure a person's FGF-23 protein levels precisely.

Researchers recently developed a novel assay, or test, in order to measure the levels of FGF-23 in the blood. They used this assay to measure FGF-23 levels in healthy people, and also in patients with X-linked hypophosphatemia and oncogenic osteomalacia. They found that most patients with either X-linked hypophosphatemia or oncogenic osteomalacia have much higher levels of FGF-23 in their blood than people without bone disease, suggesting that FGF-23 plays a role in regulation of phosphate levels in healthy people. Interestingly, after surgery to remove tumors causing oncogenic osteomalacia, the FGF-23 levels return to normal.

This new assay may be a very useful tool to diagnose patients with phosphate-wasting disorders. For example, patients with oncogenic osteomalacia often have tumors that are very small and difficult to locate. This assay could be used to measure FGF-23 levels in blood sampled at different locations in the body in order to help find the tumors. The assay could also be used to monitor the health of these patients after

tumor removal–if the FGF-23 levels start to increase, then the tumor may have returned. In addition to these promising clinical applications, researchers can now use the assay to study FGF-23 in the laboratory to understand more fully the underlying mechanisms by which the protein normally regulates phosphate levels.

Hormone Treatment for Osteoporosis: Osteoporosis is a disease characterized by low bone mass and bone deterioration. According to the National Osteoporosis Foundation, 10 million people in the U.S. have osteoporosis and an additional 34 million people have low bone mass, which increases their risk for developing the disease. Although the disease strikes both men and women, approximately 80 percent of patients with osteoporosis are women. Osteoporosis occurs when new bone is not formed as quickly as old bone is broken down. NIDDK-supported researchers previously identified parathyroid hormone (PTH) as a key hormone responsible for regulating the osteoblast cells involved in bone formation. PTH both stimulates new bone formation and promotes bone breakdown; careful studies demonstrated that with intermittent administration, the net effect is an increase in bone formation. Because of this beneficial effect, PTH was recently approved as an effective treatment for osteoporosis. Another hormone, PTH-related protein (PTHrP), is similar in many respects to PTH, but has not been tested for its ability to treat osteoporosis.

Researchers recently conducted a 3-month clinical trial of 16 post-menopausal women with osteoporosis to determine if PTHrP treatment had any effect on bone formation. All of the women were on menopausal hormone replacement therapy (MHT) and given vitamin D and calcium supplements during the study. A subset of the women was treated with PTHrP while others were given placebo. The researchers found that the women treated with PTHrP had a 4.7 percent increase in their spine bone mineral density (BMD), a measurement of bone mass. The women treated with the placebo had only a 1.4 percent increase in BMD. This study showed that, over a short period of time, PTHrP could significantly increase bone formation in post-menopausal women who have osteoporosis. Because this was a short-term study with few patients, these results must be confirmed in a clinical study with more patients over a longer time frame to determine if PTHrP can produce beneficial effects long-term. Further studies may compare PTHrP and PTH to define their relative risks and benefits, and establish whether PTHrP represents an alternative bone forming agent that could be used to to stimulate new bone formation in patients with osteoporosis.

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SUSTAINED BENEFITS OF INSULIN-SENSITIZING DRUG THERAPY IN HIV-POSITIVE INDIVIDUALS WITH METABOLIC COMPLICATIONS AND FAT REDISTRIBUTION

Before the advent of highly active anti-retroviral therapy (HAART), individuals with Acquired Immunodeficiency Syndrome caused by the human immunodeficiency virus (HIV-AIDS) often developed a wasting syndrome characterized by catastrophic weight loss. The widespread adoption of HAART has markedly improved survival in HIV-infected individuals and the incidence of AIDS wasting syndrome has declined dramatically. Unfortunately, in many cases, HAART is associated with a different set of metabolic complications that can also be life-threatening, including elevated

blood lipid (fat) and cholesterol levels, insulin resistance, and abnormal distribution of body fat (lipodystrophy). These metabolic abnormalities are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. Researchers have previously found that short-term (three month) treatment with metformin (a drug approved to improve glucose metabolism and insulin sensitivity in patients with diabetes) decreases insulin resistance and improves several cardiovascular risk factors in HIV-positive patients with fat redistribution. However, the risks and benefits of prolonged metformin therapy for these patients have been largely unknown.

The metabolic and cardiovascular benefits of continued metformin therapy for HIV-infected patients with lipodystrophy have now been examined in a follow-on study to the earlier clinical trial. Researchers found additional benefits of metformin in participants in the original three-month trial treated with metformin for an additional six months. Significant reductions were found in levels of tissue plasminogen activator (tPA) antigen levels in the blood–a marker for cardiovascular disease risk–as well as in waist circumference and body mass index, and insulin levels. Although metformin moderately improves lipid levels in type 2 diabetes, lipids were not affected by continued metformin therapy in patients with the metabolic complications of HIV.

Future studies will help to determine if higher doses of metformin are more effective, as well as to assess whether metformin therapy reduces the likelihood of the development of full-blown cardiovascular disease or type 2 diabetes in HIV-positive patients with metabolic complications and fat redistribution.

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STORY OF DISCOVERY

Preventing or Delaying Complications of Diabetes: 20 Years of Study by the DCCT/EDIC Research Group

In type 1 diabetes, the patient's own immune system mistakenly attacks and destroys the beta cells of the pancreatic islets, the sole producers of insulin. Without insulin, the tissues of the body cannot absorb or use glucose (sugar), the major cellular fuel. Type 1 diabetes patients require insulin administration for survival. Insulin, however, is a treatment for the disease and not a cure. Diabetes slowly damages major organs in the body, such as the eyes, kidneys, and cardiovascular system. Thus, it is imperative to better understand and intervene in the development of diabetes complications to improve longevity and quality-of-life of type 1 diabetes patients.

Impressive research progress toward combating diabetes complications was achieved through a large clinical trial which the NIDDK launched in 1983. The Diabetes Control and Complications Trial (DCCT) was a multi-center clinical trial of over 1,400 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of disease. Patients on intensive treatment kept their blood glucose levels and hemoglobin A1c (HbA1c) levels (which reflect average blood glucose levels over a 2- to 3-month period) as close to normal as safely possible with frequent monitoring of blood glucose, and at least three insulin injections a day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections a day, with once-a-day urine or blood glucose testing. The result was a large difference in the mean HbA1c levels in the two groups and a striking difference in their development of microvascular complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease, by 35 to 76 percent compared with conventional treatment. This dramatic, positive result has had a profound impact on clinical practice for the management of type 1 diabetes: it led to the development of clinical guidelines by the American Diabetes Association and other groups; it spurred the creation of the National Diabetes Education Program to disseminate the findings to the public; and it stimulated multifaceted research efforts to develop tools and therapies that enable patients to achieve tight control of blood glucose levels.

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

Now, 10 years after the end of the DCCT, further seminal insights are emerging regarding long-term benefits of intensive blood glucose control. In May 2002, EDIC investigators reported that the 6.5 year

period of intensive treatment during the DCCT continued to reduce the risk of eye disease as long as 7 years after the study ended. Building on this exciting finding, a study in October 2003 showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group eight years after the end of the DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the patients after completion of the DCCT. Analysis shows these long lasting differences in development of complications can be explained by the difference in control of glucose levels between the two treatment groups during the DCCT.

While DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye and nerve problems, controversy remained about the effect of glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlated with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven. In June 2003, the DCCT/EDIC research group showed that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared to the patients in the former conventional therapy group. This was demonstrated using both ultrasound to measure thickening of the wall of the carotid artery and also electron beam computed tomography (EBCT) to measure coronary calcification. Twenty years after the beginning of the DCCT, there is now evidence that intensive glucose control prevents damage to large blood vessels. This is a significant finding because CVD causes death in two-thirds of patients with diabetes.

These findings of the DCCT/EDIC research team raise interesting questions about the "metabolic memory" that enables the beneficial effect of intensified blood glucose control to persist long after the period of intensive therapy has ended. The biologic basis of metabolic memory–how a difference in glucose control for a finite period can have striking effects long after the conclusion of the study–has been explored in a symposium that marked the 20th anniversary of the initiation of the DCCT. Held at the NIH in April 2003, the symposium, "Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back," included an overview of the DCCT/EDIC trials, as well as presentations from leading investigators studying diabetic complications. These investigators are vigorously pursuing possible explanations for the enduring effects of intensive therapy that outlast the period of improved glucose control. One possibility is suggested by the demonstration of longstanding tissue changes associated with high blood sugar, particularly the attachment of end products of sugar metabolism to collagen, a component of the matrix that surrounds most cells. Continued efforts by scientists will unravel the underlying molecular mechanisms by which elevated glucose levels damage small and large blood vessels, and the tissues and organs that are affected. The symposium underscored that, even though the results of the DCCT/EDIC studies show that intensive therapy is beneficial for long-term prevention of complications, a severe limitation to the practice of intensive therapy is the potential for acute episodes of hypoglycemia, or low blood sugar. Thus, it is imperative that researchers seek new methods to improve blood glucose monitoring and insulin delivery, or develop new beta cell replacement therapy to cure type 1 diabetes.

STORY OF DISCOVERY

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

PATIENT PROFILE

Dan Lamb

For Dan Lamb and Many Others, Participating in the DCCT/EDIC Has Been a Life-Altering Experience

"For those of us with diabetes, it was amazing to see the results of 20 years of research," Dan Lamb recalls. Dan and several other participants in the Diabetes Complications and Control Trial, mostly from Iowa and neighboring states, had gotten together in the summer of 2003 for a 20-year reunion. Many had not seen each other in years. One fellow participant came up to Dan the night of the reunion dinner and introduced himself. "I had been this guy's camp counselor many years ago," says Dan, "and when I found out then that he had diabetes, I strongly advised him to get involved with the study. His coming up to me all these years later to tell me the important role the study played in his life, and how appreciative he was that I had pointed him in that direction was extremely heart-felt. It made me feel as if I had made a real difference in someone's life."

Dan Lamb

The Diabetes Control and Complications Trial (DCCT), conducted from 1983 to 1993, included 1,441 volunteers with type 1 diabetes and was conducted in 29 medical centers in the United States and Canada. The goal of the trial was to determine whether or not tight control of blood sugar levels could prevent or delay microvascular complications of the disease. As a result of the DCCT, researchers determined that intensive control of blood sugar dramatically reduces the incidence of eye, nerve, and kidney disease in people with type 1 diabetes. (Please see the accompanying "Story of Discovery," "Preventing or Delaying Complications of Diabetes–20 Years of Study by the DCCT/EDIC Research Group.") Referring to those who had attended the summer reunion, Dan says that most had good stories to tell. "Even those who had a rougher time with their diabetes had good things to say about their experience in the study," he adds.

Today, nearly everyone who participated in the DCCT is now part of an NIDDK-sponsored follow-up study called the Epidemiology of Diabetes Interventions and Complications (EDIC). The EDIC study has followed several diabetes-related health outcomes in DCCT participants since the end of the trial. It is reaffirming the importance of beginning, as early as possible, intensive treatment to control blood sugar.

PATIENT PROFILE

Taking Part in the DCCT

Dan Lamb has been an athlete all his life. As a youngster, he played soccer and football, and also swam. Today, as a 34-year-old, Dan still plays soccer on an adult league and likes to go skiing with his family. With athletics seemingly in his blood, he wasn't about to let being diagnosed with type 1 diabetes at age 10 stop him from playing sports. Much to the chagrin of his mother and his physician, shortly after his diagnosis, Dan signed up for peewee football. Although regular exercise is now considered important for all people with diabetes, "Back then, physical activity wasn't recommended for people with [type 1] diabetes," says Dan.

At the same time that Dan was determined to play sports despite his type 1 diabetes, Dan's mother was just as determined to take care of her son's new-found health care needs. Wanting to be as informed as possible about diabetes, she got involved with the American Diabetes Association. Five years later, after coming upon an NIDDK announcement of a clinical trial that was recruiting volunteers, Dan's mother enrolled him in the DCCT at age 15.

Results of the Diabetes Control and Complications Trial (DCCT) demonstrate that, by strictly monitoring and controlling their blood sugar, people with type 1 diabetes can significantly reduce their risks of developing eye, kidney, and nerve complications.

The DCCT trial was testing the hypothesis that, in persons with type 1 diabetes, more intensive control of blood sugar would significantly prevent or delay the onset or progression of eye, nerve, and kidney disease that are common complications of the disease. The DCCT trial participants were randomly assigned to one of two treatment groups. Dan was randomized into the "intensive" therapy group, which controlled blood sugar levels using a variety of treatment approaches, including different insulin preparations, "jet injectors," and glucose memory meters. As part of the study protocol, and in an effort to simulate the activity of a normal pancreas, Dan's insulin shots went from one or two a day to four shots a day. "I took insulin with my meals and before bed, and recorded my blood sugar results daily," says Dan. For the 10-year duration of the study, Dan was seen once a month at the DCCT clinic to which he was assigned in Iowa, where, he says jokingly, he was "poked and prodded" and given instructions on how to aggressively control his glucose levels. In contrast to this intensive therapy, DCCT participants in the parallel "control" group followed what was then a conventional monitoring and treatment regimen. To determine how well the DCCT participants controlled their blood glucose levels throughout the trial, DCCT clinicians regularly administered a blood test called the HbA1c test. This test measures blood levels of a molecule called HbA1c. HbA1c measurements reflect average blood glucose levels for a 2-to-3 month period, and are given as percent values. The goal for DCCT participants in the intensive

Loren Kirkpatrick
(Intensive treatment group)
"I saw a patient recruitment announcement for the DCCT in the newspaper. I'd never participated in anything like this before. I greatly appreciated the DCCT's approach to teaching us volunteers as much as possible about how to manage our diabetes."

Becky Murphy
(Intensive treatment group)
"After participating in the DCCT for nine years and the ongoing EDIC follow-up study for 11, I feel that I'm being studied by the best medical teams there are…I also feel that these studies will help many, many other people who currently have diabetes, as well as those yet to be diagnosed with the disease."

treatment group was to achieve and maintain an HbA1c measurement as close to 6.0 percent as possible, which would indicate sustained blood glucose levels within a normal, healthy range. At the end of the DCCT, there was a dramatic difference in the HbA1c values between the two treatment groups: participants in the intensive treatment group had an average HbA1c of 7.2 percent, while participants in the conventional treatment group had an average HbA1c value of 9.0 percent. Most importantly, the lower HbA1c values correlated directly with reduced risk for microvascular complications. As soon as the trial ended, those in the control group were instructed in intensive therapy, and both groups were strongly encouraged to use the intensive therapy for life. Since then, glucose control has drawn closer and been similar between the two groups, with better control in the former conventional treatment group, and looser control in the former intensive treatment group.

Dan's experience has been even better than the average for the intensive treatment group, and he has maintained excellent HbA1c values since the end of the trial: Dan started the DCCT in February 1984 with an HbA1c measurement of 10.4 percent. Over the last 10 years, Dan's HbA1c has averaged 6.9 percent. Currently it is 6.5 percent. "As a result of the DCCT, I lowered my numbers relatively quickly and have been able to maintain that level over a long period of time," Dan says. "Had I not been part of the DCCT, I probably would not have paid attention to my diabetes as closely as I have, nor possess the same understanding of the disease and its complications that I have now. The study has been a huge part of my life, and has contributed greatly to my success as a person with diabetes." As a result of the DCCT and a separate study of persons with type 2 diabetes, it is now recommended that all persons with diabetes try to maintain HbA1c values as close to normal as safely possible, at 7.0 percent or less.

Findings of the DCCT Study

The DCCT found that lowering average blood glucose levels for several years **reduces the risk** of:

- *Eye disease by 76 percent*
- *Kidney disease by 50 percent*
- *Nerve disease by 60 percent*

The EDIC

Dan says that the EDIC follow-up study is quite different from the DCCT, but just as valuable. "Instead of once a month, I come in once a year. The physicians review what I've been doing and where I'm at. They [measure my HbA1c values], take a look at my eyes, kidneys and neurological functions and see if I'm staying within a good range of glucose levels," he says. According to Dan, who, as a result of both the DCCT and EDIC, has been followed through his high school, college, marriage, and now his fatherhood years, he still wants that information. "I never

Photo: Melikian Studio

Ruth Thomasian
(Intensive treatment group)
"Before entering the DCCT, I had difficulty managing my diabetes. I'd practically given up being able to deal with erratic blood sugars. The DCCT experimental protocol provided me the ability to take charge of my health and control my blood sugars. I'm thrilled to participate in the EDIC follow-up study to learn more about the benefits of taking charge of my diabetes."

Ralph Dinneen
(Intensive treatment group)
"The DCCT has helped me to reduce the health complications of diabetes, which has improved my life. I could not have asked for a better opportunity than to have participated in the DCCT and now the EDIC."

miss my annual appointment, and I plan on staying with the EDIC for as long as it continues." Currently, Dan's father, mother and brother are also taking part in an ancillary study to the EDIC follow-up in order to help researchers gain a clearer understanding of the genetic aspects of diabetes.

After living with type 1 diabetes for nearly 25 years, Dan has had no complications as a result of his disease. But he also realizes his good fortune. "I'm lucky that my sugar levels stay very much on an even keel," he says. "I have relatives, including an aunt, who did everything according to the book, but had difficulty maintaining good control."

The Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study is revealing the durability of the benefits of stricter blood sugar control and the importance of beginning intensive treatment to control blood sugar as early as possible. So far, the continuing benefits of DCCT intensive therapy observed in EDIC participants include:

- *Reduction in progression of diabetic eye disease by 66 to 77 percent*
- *Reduction in the risk for development of or progression to diabetic kidney disease by 84 percent*
- *Reduced progression of diabetes-related atherosclerosis*

Benefits in Balance

Strict control of glucose levels comes with its own risks, including dangerously low blood sugar, or hypoglycemic episodes, which in severe cases can result in life-threatening comas. In fact, in the DCCT, the intensive treatment group had three times the rate of episodes of serious low blood sugar reactions compared to the control group. Thus, balance is key: While it is recommended to keep blood sugar as close to normal as safely possible to prevent long-term complications, physicians and patients need to be aware of the risks of hypoglycemia that accompany intensive glucose management, especially for those who may be at increased risk of problems due to hypoglycemia. Some individuals–young children, individuals with severe heart disease, or those with hypoglycemia unawareness–may be at increased risk of problems due to hypoglycemia, and thus, for them, it may not be appropriate to manage glucose as intensively. Even though Dan periodically has hypoglycemic episodes, he says that he's always been able to recognize them coming on early and treats them with glucose tablets, or sometimes with orange juice or a sugar-based soda. As far as Dan is concerned, the benefits that come from maintaining tight control over blood sugar far outweigh the potential risks of hypoglycemia. "There's just no substitute for a healthy heart, eyes that are able to focus and work correctly, and kidneys that function well," says

Steve Cook
(Conventional treatment group)
"There were times it seemed like an inconvenience to be part of the DCCT study, but in retrospect the inconvenience was minor in comparison to what I learned about my health and the impact that lifestyle has on diabetes. I'm convinced I'm still not totally aware of all the benefits I received by taking part in both the DCCT and EDIC."

Coretha Rozendaal
(Intensive treatment group)
"I didn't know it before entering the DCCT, but I had something called 'dawn syndrome,' a condition in which my blood sugars would automatically rise, starting at 3 in the morning. The insulin pump offered to me in the trial corrected the condition. The pump certainly has made my life a lot easier, and both the DCCT and EDIC have helped me learn about diabetes, its complications, and what could happen if I don't take care of myself."

Dan. “I know people who have lost their eyesight or have had pancreas transplants because of their diabetes. Living with diabetes is tough, and sometimes people are unable or unwilling to control their blood sugars.”

The message Dan would like to convey to others with diabetes is: “Make sure you’re educated about the disease; follow your doctor’s advice; and take good care of yourself.” As an adult athlete, Dan continues to stay in shape and eat right. “My kids and my wife mean the world to me,” says Dan. “I can’t imagine losing my eyesight and not seeing them grow up, and that’s a distinct possibility for people with diabetes.” He advises everyone he knows with diabetes to “exercise, watch your diet and maintain your blood sugar levels so that you can experience those important moments of your life.” And for Dan, that includes attending his DCCT group’s 40 year reunion–20 years from now.

If doctors and patients adopt stricter standards regarding the monitoring and control of blood sugar, it is likely that we can prevent or delay the development of long-term complications in the estimated 18.2 million Americans with diabetes, both type 1 and type 2, and minimize the risk of hypoglycemia.

Jake Pokita
(Conventional treatment group)
“Because of the study, I’m more in tune with my body. I can tell when my blood sugar is low and when it is high. I have access to the best doctors and latest technologies and treatments. It’s really made a difference.”

Diabetes Education at NIDDK: The National Diabetes Education Program

Although making new discoveries about diseases and how to prevent them is a critically important aspect of the NIH mission, the process of discovery cannot benefit Americans if research findings are not put into practice to improve health. Thus, disseminating new knowledge through education programs directed at healthcare providers and the public is also an important part of the NIH mission. The National Diabetes Education Program (NDEP) is a health information and education service that was launched in 1997 to improve diabetes management and thus reduce the morbidity and mortality from diabetes and its complications. The NDEP is sponsored by the NIDDK and by the Division of Diabetes Translation of the Centers for Disease Control and Prevention (CDC). The program's goals and objectives support major federal government public health initiatives, such as "Steps to a Healthier U.S." and the President's "Healthier U.S." programs.

On November 13, 2003, Health and Human Services Secretary Tommy G. Thompson announced that the number of Americans with diabetes had reached an all-time high. It is estimated that 18.2 million Americans have diabetes and that 90 to 95 percent of these individuals have type 2 diabetes. Of the 18.2 million persons with diabetes, approximately 5.2 million have undiagnosed or unrecognized diabetes.

In response to the startling 2003 numbers, Secretary Thompson announced a new community-based program, "The Diabetes Detection Initiative: Finding the Undiagnosed (DDI)". With the support of the NDEP, the DDI will utilize health education/communication and community health interventions to increase the number of at-risk individuals that undergo risk assessment and, if appropriate, receive blood testing to determine if they have diabetes and need the necessary follow-up. Appropriate information about risk reduction will also be given to individuals who are identified with pre-diabetes or considered to be high-risk. The DDI is supported by several federal agencies, including the CDC and the NIH.

The new DDI program is built on previous clinical studies and ongoing NDEP initiatives. Scientific and clinical studies have demonstrated that if diabetes is well managed, the potentially devastating complications of this disease can be prevented or delayed. However, diabetes must first be diagnosed to be effectively treated and managed. Thus, it is critically important to identify the millions of people with unrecognized diabetes early in the course of the disease, so that they can benefit from earlier interventions to reduce both the microvascular and macrovascular diseases that can occur from diabetes. This early identification has the potential to reduce morbidity and mortality, improve quality of life, and lower the financial costs to individuals and society that result from diabetes complications.

A national diabetes prevention campaign, launched on November 20, 2002, by Secretary Thompson, is being coordinated by the NDEP. The program, entitled "Small Steps, Big Rewards," represents the first major NDEP effort to translate the Diabetes Prevention Program (DPP) results on a national level. The DPP found that modest weight loss and regular physical activity, such as brisk walking for 30 minutes a day five times per week, could cut the risk of developing type 2 diabetes by more than half in people at high-risk for diabetes. These lifestyle changes worked for people of every ethnic or racial group who participated in the study, and they were especially successful for people over age 65. The program emphasizes the practical application of the DPP findings and includes lifestyle-change tools for those at risk, patient education materials for healthcare providers,

web-based resources for both healthcare providers and consumers, and TV, radio and print public service announcements. The NDEP will be tapping its partners at local, state and national levels for help in disseminating the new program's message, and will also recruit businesses and consumer-based programs as partners in this effort.

While working to increase awareness about diabetes and effective means for prevention, the NDEP continues to promote a core campaign, "Be Smart About Your Heart: Control the ABCs of Diabetes." This campaign is designed to make people with diabetes aware of their high risk for heart disease and stroke–the leading causes of death in these patients–and the steps they can take to dramatically lower that risk. The campaign emphasizes that good diabetes management is more than lowering blood glucose (best measured by the HbA1c test). Control of blood pressure and cholesterol is crucial to help prevent heart disease and stroke in people with diabetes.

Because diabetes disproportionately affects minority groups and older adults, the NDEP has developed tailored campaigns for these special population groups. Educational materials, public service announcements (PSAs), and other products have been developed for African Americans, American Indians and Alaskan Natives, Hispanic/Latinos, Asian Americans and Pacific Islanders and senior citizens. NDEP partner organizations representing these audiences help develop and deliver these health messages.

Working with its many partners and community contacts, the NDEP hopes to close the gap between what is known about the best diabetes treatments and what is actually practiced at doctors' offices and health clinics throughout the U.S. A new online comprehensive resource, *www.betterdiabetescare.nih.gov*, is designed to help health care providers, educators, policy makers and purchasers make changes in systems of care. The website provides tools and materials to help improve patient outcomes. Another online resource, *www.diabetesatwork.org*, helps businesses and managed care companies to assess the impact of diabetes in the workplace. It also provides easy-to-understand information for employers to help their employees manage their diabetes and take steps toward reducing the risk for diabetes-related complications. Ultimately, the NDEP aims to help reduce the illness and deaths associated with diabetes and its complications.

PATIENT PROFILE

Krystle Kelly

Living with Type 2 Diabetes as a Teen

Going through adolescence is tough enough. Being a 19-year-old girl with type 2 diabetes makes the going that much tougher. Just ask Krystle Kelly. Diagnosed with the disease at age 13, Krystle's high school classmates tease her about what she eats and are aghast when she has to prick her finger to check her blood-sugar, or glucose, levels. As for those fast-food franchises where teens like to hang out, these establishments present a real risk for someone with Krystle's disease. In addition, her diabetes increases her appetite, which makes it doubly difficult for her to control her weight. "The kids in school call me the peanut butter girl because I eat a lot of peanut butter, and go 'ooh, that's sick' when they see me eat cottage cheese for lunch or prick my finger to check my blood. I try to tell them what diabetes is," says Krystle, "but they don't understand."

At age 19, it may be of little consolation to Krystle, but the fact is she's not alone in her adolescent fight against type 2 diabetes. Once a disease diagnosed in adults, type 2 diabetes is rising dramatically among children, especially minority adolescents, including African Americans, Hispanic Americans, and Native Americans. Currently, there are no national population-based data. However, studies conducted in several cities across the United States indicate that the percentage of children with newly diagnosed diabetes who are classified as having type 2 diabetes has risen from less than five percent before 1994 to 30-50 percent in subsequent years.

Krystle Kelly

Why this dramatic surge?

Type 2 diabetes in children, as in adults, is closely linked to a sedentary lifestyle, a family history of the disease, and obesity–and the prevalence of obesity in adolescents has nearly tripled in the past 20 years. According to recent estimates, 15.3 percent of children six to 11 years old, and 15.5 percent of adolescents 12 to 19 years old were overweight in 2000 in the United States.

Overweight children are at increased risk of developing type 2 diabetes during childhood and later in life. Genetic susceptibility, as well as lack of physical activity and unhealthy eating patterns, all play important roles in determining a child's weight. They also contribute to a child's risk for type 2 diabetes and other complications of being overweight.

Living with Type 2 Diabetes as a Teenager

Krystle was never obese as a child, but she was overweight by 10 or 15 pounds–enough to be considered a risk factor for diabetes. She also had another risk factor that could not be ignored; her father has type 2 diabetes. He was diagnosed in his early 30s. So at around age 13, when Krystle began feeling tired and lethargic, never wanting to do anything, her family had her tested for the disease. Her first blood test turned out negative. However, the second time she was tested, the test proved positive for type 2 diabetes. "I was upset and angry when I found out I had diabetes," says Krystle. As a result of her father's having the disease, she knew what it was like to live with type 2 diabetes "and I just didn't want to go through that." Despite her anger and disappointment, Krystle has made a noble effort to control her weight and blood-sugar levels through exercise, diet and medications in order to stay healthy. But it has not been easy.

"Having this disease is extra hard when you're a teenager," says Krystle's mom, Sharan Kelly. "It's more difficult for kids like Krystle to be accepted by their peers," she says. "The dietary choices teens are constantly confronted with are certainly not good choices for teens with type 2 diabetes, and the fact that kids with diabetes want to avoid being embarrassed by their classmates whenever they need to prick their fingers means they're not taking as good care of themselves as they should." It also has a lot to do with the day and age we live in, adds Mrs. Kelly. "I must confess that when you're a family with two working parents, some nights it's hard to put a balanced meal on the table."

Being the parent of a teen with type 2 diabetes also presents a constant concern. "I'm always worried about the potential long-range complications of this disease as Krystle gets older," says Mrs. Kelly. "I feel like I'm always hounding her, but that's because I understand the complications better than she does." And Mrs. Kelly has every reason to be concerned. Complications of diabetes can result in heart disease, stroke, high blood pressure, blindness, kidney disease, nervous system disease, amputations, and dental disease, as well as other health difficulties. To date, there is no cure for diabetes.

Because there is no known cure for type 2 diabetes, researchers agree that the best one can do is to bring his or her blood-sugar levels into a healthier target range through diet, weight loss, physical activity, stress reduction, and diabetes medication. Therapies that reduce blood pressure and cholesterol are also critical for decreasing the risk of developing complications.

Treating the Disease

So far, Krystle manifests no complications as a result of her diabetes. One factor may be that she tries to exercise at least three or four times a week. "I'm a member of the YMCA, I walk, and ride my bike or roller blade as often as I can," says Krystle. Exercise has been shown to improve insulin sensitivity in people with type 2 diabetes.

If exercise is a good thing for Krystle, the worst thing about having diabetes for her is "the eating part." Her favorite foods are bread, pasta and desserts. At 5-feet 4-inches tall and 146 pounds, Krystle is 10 to 15 pounds overweight, and has remained in that range for several years. Although she stays in fairly good control of her diet, "We're

constantly counting carbohydrates," says Mrs. Kelly. "Some days she eats the wrong foods and her blood sugar rises. Other days she'll eat the right foods, but too much of it." Portion control is a problem for most people with diabetes. The disease increases appetite, which makes the person feel hungry. This can often lead to bad eating habits.

Fortunately, the advent of new medications and technologies is helping people with type 2 diabetes control their blood-sugar levels. Up until recently, for example, Krystle took two types of insulin: one a quick acting insulin before meals or for corrections in between meals to help bring down her sugar levels; the other, a longer-acting insulin to help regulate her blood glucose levels throughout the day and night. She also continues to take metformin, an oral diabetes medication, at breakfast and dinner. Today, almost one-third of the people with type 2 diabetes take some form of insulin to effectively control their sugar levels.

However, many people with type 2 diabetes, including Krystle, who require insulin are now opting to use an insulin pump. "Krystle just loves the pump," says Mrs. Kelly. "It's freed her from all the paraphernalia needed for insulin injections, as well as given her a lot more independence because she's no longer held to the rigid schedule of these injections. It's made a world of difference."

The NIH is funding clinical trials to prevent and treat type 2 diabetes in children. The trials will focus on developing cost-effective interventions to prevent diabetes that can be widely applied in schools and communities across the country, and on determining how best to use diabetes medications to treat children with type 2 diabetes.

Despite these pharmaceutical and technological advances, much more still needs to be done. The NIH is funding clinical trials to prevent and treat type 2 diabetes in children. These studies will try to develop ways to stem the rising tide of type 2 diabetes in children and to treat the disease safely and effectively in those who do develop it. The prevention trials will focus on developing cost-effective interventions that can be widely applied in schools and communities across the country.

"For children like Krystle, who already have type 2 diabetes, it's critical to give the safest, most effective therapy as early as possible," says the NIH study chair Francine Kaufman, MD. "Yet we can't assume that the therapies used in adults have the same safety and efficacy profiles for children," adds Dr. Kaufman, who also is past-president of the American Diabetes Association and director of the Comprehensive Diabetes Center at the Childrens' Hospital of Los Angeles.

The overriding concern is that the longer a person has diabetes–meaning, the earlier the onset–the greater the chances of developing the disabling, life-threatening complications that go along with diabetes. "We are seeing young people in their late teens who are already developing the complications of type 2 diabetes," says Dr. Kaufman. As far as 19-year-old Krystle is concerned, "I just hope they find a way to get rid of this disease."