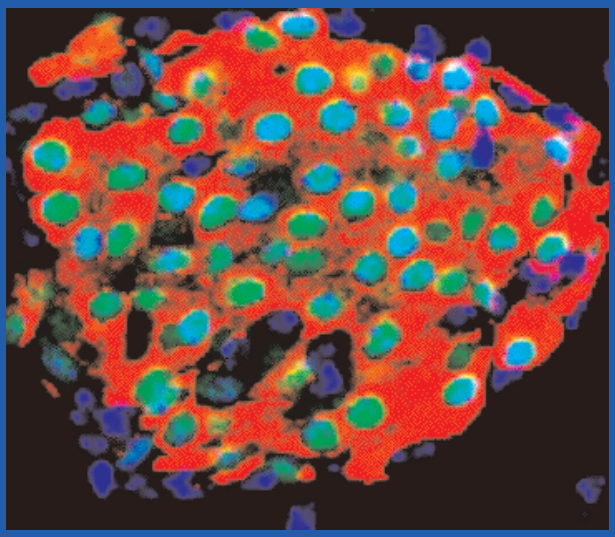

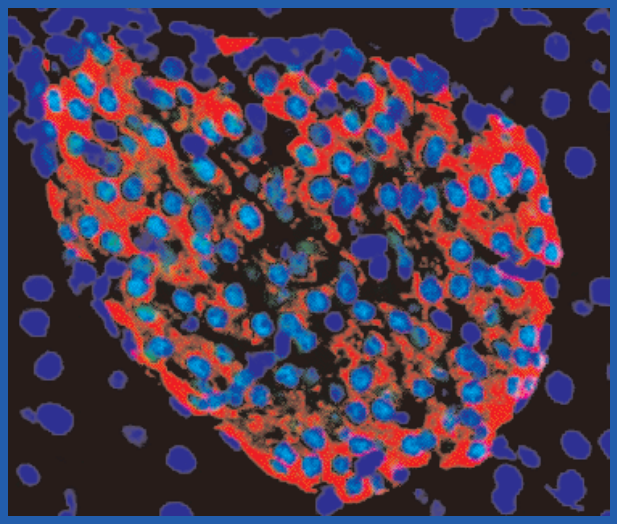

People with type 2 diabetes are less responsive than healthy people are to insulin—the hormone secreted when blood sugar rises. Many people with type 2 diabetes also produce reduced amounts of insulin, compounding the problem of insufficient insulin signaling. Recent research has indicated that an important underlying characteristic of those with the disease is that they have a reduced level of a protein called ARNT in their islets, the structures in the pancreas that produce insulin. These two images show histologic staining of a normal mouse islet (left) and an islet from a mutant mouse that lacks the *ARNT* gene (right). The genetic material (DNA) of the cells in the islets is marked by a blue fluorescent dye. The normal islet shows both the ARNT protein (marked with green fluorescent dye) and adequate production of insulin (marked with red fluorescent dye). In contrast, the mutant mouse islet that lacks the ARNT protein (green staining is absent) produces less insulin (red staining).

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Diabetes, Endocrinology, and Metabolic Diseases

NIDDK support of basic and clinical research in the areas 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 20.8 million people in the U.S.—over 7 percent of the total population—and is the sixth leading cause of death. 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 approximately one third of Americans with diabetes are undiagnosed.

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 loses its ability to produce insulin; and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production.

Type 1 diabetes affects approximately 5 to 10 percent of individuals with diagnosed diabetes. It most often develops during childhood, 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 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 could 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, American Indians, 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, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, 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 supporting research to better understand the mechanisms that lead to the development and progression of diabetes and the many other endocrine and metabolic diseases within the Institute's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

UNDERSTANDING TYPE 1 DIABETES

Insulin as an Autoantigen in Type 1 Diabetes: Recent exciting reports have suggested that the hormone insulin may be the critical initiator of the autoimmune destruction of insulin-producing pancreatic beta cells that leads to type 1 diabetes. Patients with the disease are known to have antibodies directed against insulin, and these antibodies are used to identify individuals at risk for the disease. However, it has been unclear whether insulin itself is the "key" autoantigen that triggers the autoimmune attack. Two new lines of evidence have now emerged—one in a genetically engineered mouse model of diabetes and the other using isolated T cells (a type of cell in the immune system) from pancreatic lymph nodes of people with and without type 1 diabetes. The first study found that diabetes did not develop in a type 1 diabetes mouse model engineered to express an insulin molecule not recognized by the mouse's immune system. The second study found that T cells from the lymph nodes of people with type 1 diabetes had large numbers of cells that recognized insulin, but those from non-diabetic persons did not. This research suggests that the immune systems of patients who are susceptible to developing type 1 diabetes do not respond appropriately to insulin—a hormone essential for life that all humans naturally produce. This derangement in recognizing insulin may provoke the immune system's misguided destruction of the body's own insulin-producing cells.

These studies are not the first to examine a possible role for insulin in the development of type 1 diabetes. The Diabetes Prevention Trial-Type 1 (DPT-1) studied whether injected or oral insulin administration could prevent or delay type 1 diabetes in persons at high- or moderate-risk for the disease. While the DPT-1 did not find an overall protective effect of injected or oral insulin, a subset of trial participants who had higher levels of insulin autoantibodies seemed to benefit from oral insulin treatment, though this result was not definitive. Plans are now underway for a trial to build upon the suggested benefit of oral insulin therapy in people with elevated insulin autoantibodies. This trial will be conducted by the Type 1 Diabetes TrialNet—an international network of investigators, clinical centers, and core support facilities that supports the development and implementation of clinical trials of agents aimed at slowing the progression of type 1 diabetes in new-onset patients and at preventing the disease in at-risk patients.

Kent SC, Chen Y, Bregoli L, Clemmings SM, Kenyon NS, Ricordi C, Hering BJ, and Hafler DA: Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope. Nature 435: 224-228, 2005.

Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, Yu L, Wegmann DR, Hutton JC, Elliott JF, and Eisenbarth GS:

Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. Nature *435: 220-223, 2005.*

The Diabetes Prevention Trial-Type 1 Study Group: Effects of oral insulin in relatives of patients with type 1 diabetes. Diabetes Care *28: 1068-1076, 2005.*

Continued Benefits of Improved Blood Sugar Control: The landmark Diabetes Control and Complications Trial (DCCT) showed that intensive control of blood glucose levels reduced the risk of damage to small blood vessels and nerves in people with type 1 diabetes. The follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continues to demonstrate long-term benefits of intensive therapy in these patients, and over 1,300 volunteers continue to participate. The EDIC study is now examining rates of cardiovascular disease among trial participants. During an average follow-up time of 17 years, the patients who had been intensively treated during the trial had fewer than half the number of cardiovascular disease events—heart attacks, strokes, or death due to cardiovascular disease—than those in the conventionally-treated group. These results show for the first time that intensive control of blood glucose levels has long-term beneficial effects on cardiovascular disease risk in type 1 diabetes patients. These findings are particularly significant because cardiovascular disease is the cause of death in two-thirds of patients with diabetes.

Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, and Zinman B for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med *353: 2643-2653, 2005.*

ADVANCES AND EMERGING OPPORTUNITIES IN TYPE 1 DIABETES RESEARCH: A STRATEGIC PLAN

In January 2005, the NIDDK convened an *ad hoc* planning and evaluation meeting of external scientific and lay experts in type 1 diabetes to perform a mid-course assessment of many currently funded type 1 diabetes research programs, and to identify future research opportunities within this context. One of the recommendations emanating from this meeting was to initiate a much broader review of the entire state-of-the-science with respect to type 1 diabetes, including recent research advances and emerging opportunities. In response to this recommendation, the NIDDK Director announced in March 2005 that the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), chaired by the NIDDK, would spearhead a new type 1 diabetes strategic planning effort. The membership of this Committee includes all NIH components involved in diabetes research, as well as other relevant federal agencies.

The purpose of the Strategic Plan is to serve as a scientific guidepost to the NIH and to the investigative and lay communities by identifying compelling research opportunities that will inform the priority-setting process for the type 1 diabetes research field and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. The Strategic Plan is planned for release in Summer 2006.

INSIGHTS INTO TYPE 2 DIABETES

Gene Expression Changes Associated with Type 2 Diabetes: Although key aspects of the underlying disease process in type 2 diabetes are different from type 1 diabetes, both forms of the disease have in common a dysfunction of the insulin-producing beta cells of the pancreas. In advanced type 2 diabetes, it is not well understood how beta cells lose their ability to secrete insulin in response to high blood sugar (glucose) levels. To study the molecular mechanisms, scientists compared gene expression patterns in pancreatic islets—where beta cells reside—from people with type 2 diabetes and from those with normal blood glucose control. They observed a marked decrease in expression of a gene called *ARNT* (or *HIF1beta*) in patients with type 2 diabetes. *ARNT* encodes a transcription factor, a protein that can regulate the expression of many other genes. In cultured islet cells and a mouse model, diminished expression of *ARNT* or its absence in pancreatic islets resulted in defects in glucose-dependent insulin release and changes in gene expression patterns similar to those seen in patients with type 2 diabetes. *ARNT* controls many genes involved in diabetes, and these observations suggest a key integrating role for *ARNT/HIF1beta* in the

beta cell dysfunction that is associated with human type 2 diabetes.

Gunton JE, Kulkarni RN, Yim S, Okada T, Hawthorne WJ, Tseng YH, Roberson RS, Ricordi C, O'Connell PJ, Gonzalez FJ, and Kahn CR: Loss of ARNT/HIF1beta mediates altered gene expression and pancreatic islet dysfunction in human type 2 diabetes. Cell 122: 337-349, 2005.

THE DIABETES PREVENTION PROGRAM—STILL YIELDING BENEFITS

DPP Continues To Underscore the Benefits of Preventing Type 2 Diabetes: Additional analyses of data from a landmark clinical trial have revealed more detailed information about the impact of the interventions. Researchers are continuing to gain new insights from the Diabetes Prevention Program (DPP) clinical trial, which examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk for this disease. The DPP compared intensive lifestyle modification, treatment with the drug metformin, and standard medical advice. Published in 2002, the DPP results showed that participants who received the lifestyle intervention had a dramatically reduced risk—by 58 percent—of developing type 2 diabetes. Metformin reduced diabetes risk by 31 percent. New data analyses show that hypertension, a classic risk factor for cardiovascular disease, was present in about 30 percent of all participants at the beginning of the study, and increased in the patients who received either placebo or metformin. However, hypertension significantly decreased in the lifestyle intervention group. Levels of recently identified, non-traditional risk factors for cardiovascular disease—such as C-reactive protein and fibrinogen—were lower in the metformin and lifestyle groups, with a larger reduction seen in the lifestyle group. About half of all DPP participants had a condition known as the "metabolic syndrome," which is defined by the presence of several conditions that increase risk for the development of type 2 diabetes and cardiovascular disease. Both lifestyle modification and metformin therapy reduced the development of the metabolic syndrome, with lifestyle modification more effective. Years later, the DPP continues to yield important insights into the prevention of type 2 diabetes in at-risk people.

Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, Marcovina S, Mather K, Orchard T, Ratner R, and Barrett-Connor E: Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. Diabetes 54: 1566-1572, 2005.

Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, and Fowler S: The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 142: 611-619, 2005.

Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, and Temprosa M: Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care 28: 888-894, 2005.

PROTEOMIC AND METABOLOMIC APPROACHES TO THE DIAGNOSIS OF DIABETES

Biomarkers: The NIDDK supports an ongoing initiative to identify new biomarkers related to type 2 diabetes and pre-diabetes. Early diagnosis is crucial for reducing the overall burden of type 2 diabetes in the U.S. Many proteins and metabolites such as peptides, lipids and sugars may be modified in individuals with elevated glucose, a feature of pre-diabetes and diabetes. Disease-related changes in the protein profile of a cell (the proteome) and the metabolite profile (the metabolome) are ideal targets for new diagnostic techniques. Several novel proteomic and metabolomic technologies will be used to analyze plasma samples of pre-diabetic and diabetic patients. A simplified and less burdensome approach to the diagnosis of diabetes and pre-diabetes would facilitate increased recognition and improved care of these conditions.

METABOLIC PATHWAYS PLAY A KEY ROLE IN HEALTH AND DISEASE

Link Found Between a Saturated Fat Diet and Unhealthy Blood Fat: Researchers are uncovering the metabolic pathways that link several health problems. For example, elevated levels of fat and cholesterol in the blood are significant known risk factors for cardiovascular disease (CVD). Similarly, diets high in saturated and *trans* fats are strongly associated with high levels of fats and

LDL cholesterol ("bad" cholesterol) in the blood. In studying these types of associated health problems, scientists recently discovered a link between a diet high in saturated fat, changes in gene expression in the liver, and levels of fat and cholesterol in blood. In mice fed large amounts of saturated fat, they noted increased expression of a set of genes involved in fat synthesis in the liver, including one that augments the expression of many genes involved in fat metabolism, *PGC-1beta*. The protein encoded by this gene works with members of another family of genes (SREBP transcription factors) to help regulate fat synthesis in the liver. The *PGC-1beta* gene also influences the activity of a nuclear hormone receptor in the liver (LXR), which is involved in lipid and cholesterol metabolism in rats. A treatment to boost the *PGC-1beta*- regulated protein in the liver was found to reduce fat levels in liver, but to raise them in the blood, thereby suggesting that the protein activates pathways leading to fat export. The *PGC-1beta* gene therefore seems to lie at the nexus of two important pathways of fat metabolism in the liver: fat synthesis and export. These studies suggest that the *PGC-1beta* gene may be a good target for novel therapies aimed at reducing elevated circulating fat levels that arise from diets high in saturated fats.

Lin J, Yang R, Tarr PT, Wu PH, Handschin C, Li S, Yang W, Pei L, Uldry M, Tontonoz P, Newgard CB, and Spiegelman BM: Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. Cell 120: 261-273, 2005.

Newly-discovered Links Between Inflammation and Mediators of Metabolism: In recent years, researchers have uncovered intriguing links between the molecular mediators of inflammation and a number of human diseases. The enzyme IKK-beta is a central coordinator of inflammatory responses through its activation of the transcription factor NF-kappaB. Researchers studying severe muscle wasting that is often seen in AIDS, diabetes, and end-stage heart and kidney diseases, engineered mice that had a constitutively active form of IKK-beta in their skeletal muscle. These mice developed severe wasting, and inhibition of NF-kappaB activity could partially reverse this condition. Mice with the "always on" form of IKK-beta in their livers developed metabolic patterns similar to type 2 diabetes, with high blood sugar, severe insulin resistance in their livers, and moderate insulin resistance in muscle; drugs that block IKK-beta and NF-kappaB activity were able to ameliorate these conditions. In another study, mice were engineered to lack IKK-beta in either their livers or in myeloid cells, a type of white blood cell. In response to a high fat diet or obesity, mice lacking IKK-beta in their livers retained insulin sensitivity in this organ, but developed insulin resistance in muscle and fat. In contrast, mice lacking IKK-beta in their myeloid cells retained global insulin sensitivity under the same conditions. These observations suggest that IKK-beta acts locally in liver cells but systemically through myeloid cells to influence insulin sensitivity. Taken together, these results identify IKK-beta as a key player in modulating metabolism and insulin sensitivity. These studies also provide evidence that IKK-beta-mediated inflammation links obesity to insulin resistance. Drugs that target the inflammatory signaling pathway may be useful in treating both muscle wasting and insulin resistance.

Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, and Karin M: IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 11: 191-198, 2005.

Cai D, Frantz JD, Tawa NE, Jr., Melendez PA, Oh BC, Lidov HG, Hasselgren PO, Frontera WR, Lee J, Glass DJ, and Shoelson SE: IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell 119: 285-298, 2004.

Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, and Shoelson SE: Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 11: 183-190, 2005.

Umbilical-Cord Blood Cell Transplantation Slows Krabbe Disease Progression: Researchers have tested the use of umbilical-cord blood cell transplantation to treat Krabbe disease. This disease is a rare, inherited degenerative disorder of the central and peripheral nervous systems that is uniformly fatal, with many children dying before the age of two. It results from a deficiency in the enzyme that breaks down the molecule galactocerebroside, which is an important component of nerve tissue, leading to its accumulation and subsequent nerve damage. There is no cure for the disease, but replacing the missing enzyme in the brain has been predicted to be therapeutic.

Researchers have recently used umbilical-cord blood transplantation from closely-matched, but not identical,

donors to combat the disease. The hope was that transplanted cells in the cord blood would migrate to the brain and provide the missing enzyme and thereby halt nerve damage. The researchers treated two groups of newborns; one group was diagnosed with Krabbe disease before or at birth on the basis of family history and was transplanted in the first 6 weeks of life, and the other was diagnosed at the onset of clinical symptoms of the disease after birth and was transplanted in the first 6 months to 1 year of life. After 3 years of follow-up, when most untreated Krabbe patients would have died, survival was 100 percent for the newborns transplanted in the first 6 weeks of life, and 43 percent for infants transplanted after the onset of symptoms. Infants who underwent transplantation before the onset of symptoms did not develop the neurological impairment characteristic of the disease. Those who did not undergo transplantation until after the appearance of symptoms did not show neurological improvement. This research demonstrates the greatest benefit results from early intervention before clinical manifestations of Krabbe disease. Newborn screening should be considered for Krabbe disease to identify infants who would benefit from early transplantation.

Escolar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, Wenger DA, Pietryga D, Wall D, Champagne M, Morse R, Krivit W, and Kurtzberg J: Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 352: 2069-2081, 2005.

NIDDK AIDS RESEARCH

Research supported by the NIDDK has made important contributions to the current understanding of many of the metabolic complications associated with HIV infection and highly active anti-retroviral therapy (HAART). These complications include HIV- and HAART-related lipid dysregulation, insulin resistance, and abnormal body fat distribution. These complications are risk factors for serious diseases, such as diabetes and cardiovascular disease. The NIDDK also supports research to define the causes of liver disease associated with HIV. Areas of interest include the delineation of interactions between HIV and hepatitis B and C viruses, and the development of means to prevent and treat liver disease in HIV-infected persons. In addition, the NIDDK supports studies of the neurological, gastrointestinal, endocrine, renal, liver, and hematologic manifestations and complications of HIV infection. The NIDDK also maintains a highly productive intramural program on structural biology. Scientists seek to determine the structures of biologically significant proteins relative to HIV infection, replication, and integration.

Cardiovascular Disease Risk in HIV-Infected Women: New findings may help researchers overcome the metabolic complications sometimes associated with HIV infection and the highly active antiretroviral therapy used to treat the infection. It is not clear whether these complications arise from HIV infection per se, components of the antiretroviral therapy, or a combination of the two. These metabolic complications include lipid (fat) abnormalities, insulin resistance, and abnormal distribution of body fat. They are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. These metabolic abnormalities have been previously well-studied in HIV-positive men, but relatively little information is available regarding their impact on women. A recent study shed light on cardiovascular risk factors in HIV-infected women relative to HIV-negative women. The infected women had higher levels of C-reactive protein (a marker of inflammation) and triglycerides (circulating fat levels); showed elevated 2-hour oral glucose levels after a glucose tolerance test; and had increased fasting insulin levels. Additionally, HIV-infected women had more abdominal visceral fat and less extremity fat than HIV-negative controls. Thus, the HIV-infected women had significantly increased risk factors for cardiovascular disease and abnormal fat distribution. These findings are expanding the knowledge base on which future studies may be framed for devising HIV treatment regimens that address metabolic complications of HIV infection and/or antiretroviral therapy.

Dolan SE, Hadigan C, Killilea KM, Sullivan MP, Hemphill L, Lees RS, Schoenfeld D, and Grinspoon S: Increased cardiovascular disease risk indices in HIV-infected women. J Acquir Immune Defic Syndr 39: 44-54, 2005.

Collaborative Islet Transplant Registry — Second Annual Report Published

Episodes of dangerously low blood glucose, or hypoglycemia, were greatly reduced in people who received islet transplants for poorly controlled type 1 diabetes, according to an analysis of outcomes in 138 patients who had the procedure at 19 medical centers in the United States and Canada. This is one of the conclusions of the Collaborative Islet Transplant Registry (CITR), which tracks many factors affecting the success of this experimental procedure in people with severe type 1 diabetes. The CITR released its second annual report (*http://www.citregistry.org*) in September 2005.

In the islet transplantation procedure, islets—which are clusters of cells that include the insulin producing beta cells—are extracted from a donor pancreas and infused into the portal vein of the recipient's liver. In a successful transplant, the islets become embedded in the liver and begin producing insulin.

The CITR reported that, one year after their last islet infusion, 58 percent of recipients no longer had to inject insulin. Those who still needed insulin a year after their last infusion had a 69 percent reduction in insulin requirements. One infusion of islets, though not always enough to keep blood glucose in the normal range, generally lowered insulin needs and alleviated episodes of severely low blood glucose in most patients.

Despite the progress seen in islet transplantation in recent years, it is still an experimental procedure currently reserved for adults who are unable to control their diabetes with conventional therapy. Islet recipients must take immunosuppressive drugs to prevent their immune systems from rejecting the transplant. Because of the adverse side effects of these drugs, the patients chosen for the procedure were those who had the greatest need and potential for benefit, such as those with a history of being unaware of hypoglycemia.

The scarcity of islets poses another major obstacle to wider testing of islet transplantation as a treatment for type 1 diabetes. Only about 3,500 pancreata are suitable for transplantation, and many of these organs are used for whole organ transplantation. To improve the potential of cell replacement therapy for diabetes, NIH-funded research is focusing on understanding the insulin-producing beta cell and its regeneration and on efforts to develop alternative sources of beta cells. Researchers are also working on ways to coax the immune system into accepting donor cells or tissues without suppressing the entire immune system.

The CITR's mission is to expedite progress and promote safety in islet transplantation by collecting, analyzing, and communicating data on islet transplantation. Single copies of the CITR report may be ordered free of charge from the registry (*http://www.citregistry.org*) or from NIDDK's National Diabetes Information Clearinghouse by calling 1-800-860-8747, or through the website at *http://catalog.niddk.nih.gov/detail.cfm?ID=824&CH=NDIC*

The National Diabetes Education Program (NDEP)

Through education and awareness campaigns and other health information dissemination efforts, the National Diabetes Education Program (NDEP) aims to improve treatment and outcomes for people with diabetes, to promote early diagnosis, and to help prevent the onset of diabetes. The program develops information and education messages and materials for people with diabetes and their families, health care providers, payers and purchasers of health care, health care system policy makers, and the general public—including people with undiagnosed diabetes and those at risk for the disease. The NDEP is jointly sponsored by the NIDDK and the Division of Diabetes Translation of the Centers for Disease Control and Prevention, both of the U.S. Department of Health and Human Services, and also involves the participation of over 200 public and private partner organizations.

In 2005, the NDEP continued to promote campaigns focusing on diabetes prevention and control. A key target audience for these messages is older adults. The NDEP launched its newly revised campaign for seniors to help them manage their diabetes. One campaign, "The Power to Control Diabetes Is in Your Hands," provides older adults with information on how to control their disease by regular self-monitoring of blood glucose and by following the "ABCs" of diabetes care to prevent or delay its serious complications. The "ABCs" refer to monitoring of hemoglobin A1c levels, blood pressure and cholesterol levels. The campaign also provides older adults with information on the newest Medicare benefits and how these benefits can help them manage their disease to live a long and healthy life. Educational materials include a consumer brochure, available in English and Spanish, and a community action kit, a comprehensive resource designed to assist community organizations in helping their older adult members living with diabetes.

Another NDEP campaign, "Small Steps. Big Rewards. Prevent Type 2 Diabetes," is based on the findings of the NIH-sponsored Diabetes Prevention Program (DPP) clinical trial. This trial demonstrated that the risk of developing type 2 diabetes can be significantly reduced through modest weight loss, of five to seven percent of body weight, along with exercise, such as 30 minutes of moderate physical activity five days per week. These lifestyle changes were most effective in adults over 60 years of age. In 2005, the NDEP reached out to older adults at risk for type 2 diabetes with the campaign, "It's Not Too Late To Prevent Diabetes. Take Your First Step Today," and developed tailored materials for seniors to motivate them to make modest lifestyle changes to prevent the disease.

In 2005, the NDEP added a new target audience to promote diabetes prevention messages—women with a history of gestational diabetes mellitus (GDM) and their children. An expert panel was convened to review the latest science on this topic, and a communication plan has been developed that targets health care providers and women with a history of GDM to educate them about how to lower their risk. The NDEP plans to launch this campaign in the spring of 2006 with educational materials for consumers and health professionals. For children at risk for developing type 2 diabetes, a new tip sheet, "Lower Your Risk for Type 2 Diabetes," was developed to alert at-risk children and adolescents and their families to take action to delay or prevent the onset of type 2 diabetes. To help teens with diabetes learn to cope with the emotional and psychosocial aspects of diabetes, the NDEP children's work group produced a tip sheet, "Dealing with the Ups and Downs of Type 2 Diabetes."

The NDEP has issued a new publication, "New Beginnings: A Guide for Living Well with Diabetes," to help groups facilitate dialogue about diabetes and its complications. This discussion guide, targeting African Americans with diabetes, has been developed to expand on the themes and educational opportunities brought out in "The Debilitator," a docudrama developed by an independent film company. "New Beginnings" was designed to be used by diabetes educators, church groups, clinics, hospitals, families, or anyone interested in talking about diabetes and its impact on African Americans.

In other activities, the NDEP continues to partner with the American Diabetes Association for the health awareness

campaign, "Be Smart About Your Heart: Control the ABCs of Diabetes," in order to promote the link between diabetes and cardiovascular disease. In 2005, tailored materials were developed for American Indians and Alaska Natives, the newest target audience for the campaign. Versions of the campaign are also tailored for Hispanic and Latino Americans and for Asian Americans and Pacific Islanders. In November 2005, the NDEP partnered with the American Podiatric Medical Association on World Diabetes Day to promote messages about people with diabetes taking care of their feet to prevent lower-limb amputations.

The NDEP website addressing systems change to improve diabetes care can be accessed at: *http://www.betterdiabetescare.nih.gov*. The website is completing an update with new resources and tools. The NDEP is collaborating with the Indiana University School of Medicine (IUSM) to provide a continuing education component (CE) to the website through IUSM's reflective learning program. The NDEP website for the workplace continues to include updated information on diabetes management and prevention topics for businesses and has new educational materials available in Spanish. It can be accessed at: *http://www.diabetesatwork.org*.

With the help of its 200 partners, the NDEP continues to reach millions of people with its messages. In 2005, messages about NDEP made more than 177 million media impressions through broadcast and print outlets, and the NDEP website received more than 1.6 million visits. To date, over one million copies of NDEP's educational materials have been distributed through the National Diabetes Information Clearinghouse.

The NDEP evaluation work group continues to collaborate with its partners to collect data and track progress toward the program's goal and objectives. Both process and outcome data measures are being monitored to help with program planning of future activities, campaigns and materials. The NDEP also conducts a semiannual online, web-based partner activity survey that shows how partners are disseminating program messages and resources.

The NDEP also offers other patient education materials, and resources and tools designed for health care professionals. The NDEP has begun an initiative to determine the economic impetus for diabetes prevention and control. Further information on all NDEP campaigns, activities and materials can be found on the NDEP website, accessible at: *http://www.ndep.nih.gov*.

Glucagon-like Peptides Yield New Diabetes Therapies

By deciphering how the body maintains normal blood sugar levels, researchers are finding clues to combat diabetes. In healthy individuals, the beta cells of the pancreas respond to elevated levels of sugar in the blood by releasing insulin, and the insulin, in turn, causes cells to absorb sugar. The pancreas reacts to low levels of blood sugar, on the other hand, by releasing glucagon from its alpha cells, triggering the liver to release part of its store of sugar into the blood and turning off insulin production. These are crucial steps in normal metabolism. In diabetes, this exquisite regulation is disturbed either by loss of cells that produce insulin (type 1 diabetes) or by inadequate amounts of insulin to compensate for diminished responsiveness of cells to the hormone—mostly in muscle and fat (type 2 diabetes).

This fairly simple paradigm is by no means the whole story, however. In the 1960s, researchers showed that sugar triggers more insulin to be released if the sugar is absorbed through the digestive system rather than injected directly into the blood. The underlying reasons were a mystery, but scientists speculated that the presence of sugar or other food in the gut might trigger the release of some hormone that increases the pancreatic insulin response. The putative insulin production-promoting hormone or hormones were called "incretins." A vital clue to the incretin mystery was uncovered in 1982 by Dr. Joel Habener and colleagues when they cloned the gene that encodes the glucagon protein. Inspection of the gene revealed that it also encodes two other proteins similar, but not identical, to glucagon. These were called "glucagon-like peptides," or GLPs. The NIDDK-supported researchers later demonstrated that a truncated form of one of these, GLP-1, was able to act as an incretin: pancreatic beta cells release more insulin in response to sugar in the presence of GLP-1 than in its absence. Thus "Glucagon-Like Peptide 1" actually has effects somewhat opposite to those of glucagon, in that it helps to lower blood sugar. As expected for an incretin, GLP-1 is produced by intestinal cells when stimulated by the presence of food. In addition to its effect on promoting the insulin response, GLP-1 also has the important effect of slowing stomach emptying, essentially helping a person "feel full." More recently, mounting evidence suggests that GLP-1 can stimulate the multiplication of insulin-producing beta cells, while simultaneously protecting them from so-called "programmed cell death."

Properties of GLP-1 suggested that it might be of potential therapeutic benefit for some people with type 2 diabetes. By boosting their natural insulin secretion in response to food, GLP-1 could reduce their need for injected insulin or other therapies. Unfortunately, scientists soon discovered a major potential barrier to this approach: GLP-1 lasts only a very short time in the blood stream before it is digested by an enzyme called dipeptidyl peptidase IV (DPP IV). A solution to this problem was found in the unlikeliest of places: the venom of a lizard native to the Sonora Desert. At about the same time that the glucagon-like peptides were being discovered by NIDDK grantees, NIDDK intramural scientists studying the so-called "Gila monster" discovered that proteins in the lizard's venom stimulate the release of digestive enzymes by cells of the pancreas. Because the reptile typically goes months between meals, these proteins may serve to "jump-start" its digestive system when it feeds. Among the proteins isolated from the venom was one, designated exendin-4, with considerable similarity to GLP-1. Scientists showed

that exendin-4 and GLP-1 are both capable of stimulating gastric secretions in guinea pigs, though exendin-4 is the more potent of the two. Indeed, two labs have independently demonstrated that both proteins work by stimulating the same cellular receptor. Furthermore, exendin-4 is not digested by DPP IV, and therefore can last much longer in the blood than GLP-1.

The discovery and characterization of the GLPs and of exendin-4 are the fruits of basic research, much of which was funded by NIDDK. Based upon this critical foundation, pharmaceutical companies have developed an important new treatment for patients with type 2 diabetes. A synthetic version of exendin-4 (the manufactured form is referred to as "exenatide," but is chemically identical to exendin-4) was recently tested for therapeutic benefit in industry-supported randomized controlled clinical trials. The studies enrolled patients with type 2 diabetes whose blood sugar was inadequately controlled. Patients then received either standard treatment or standard treatment plus a high or low dose of exenatide. At the conclusion of the studies, those patients who had received exenatide were found to have maintained significantly healthier levels of blood sugar, and those receiving the high dose of the new drug had done better than those with the low dose. Another exciting finding was that the patients who had received exenatide lost weight compared to the control group. A possible explanation for the latter finding is the effect that GLP-1/exendin-4/exenatide have on slowing stomach emptying and creating a sense of fullness. This result is particularly important because type 2 diabetes is associated with overweight and obesity. Again, those receiving the higher dose of exenatide achieved the better result, losing more weight. In April 2005, the Food and Drug Administration approved exenatide as a supplementary treatment for type 2 diabetes in patients whose blood sugar is not otherwise well-controlled.

Scientists are eager to explore potential benefits of exenatide in treating or preventing type 1 diabetes. This disease results when a person's immune system attacks and destroys his or her own insulin-producing pancreatic beta cells. The landmark NIDDK-sponsored Diabetes Control and Complications Trial (DCCT) had demonstrated that a significant percentage of people with type 1 diabetes retain the capacity to produce a small amount of their own insulin. This finding suggests that, in some patients at least, the process of autoimmune beta cell destruction may be modestly offset by beta cell regeneration. NIDDK intramural researchers Drs. David Harlan and Kristina Rother are currently testing whether exenatide can help capitalize on the presumed natural regenerative capability in patients who, although they have had type 1 diabetes for several years, still produce some insulin. Study volunteers are receiving exenatide either alone or in combination with an immunosuppressive drug designed to blunt the continuing autoimmune attack on their beta cells. Researchers in the newly formed Clinical Islet Transplantation Consortium plan to test the value of exenatide in enhancing the viability of transplanted islets, and the Type 1 Diabetes TrialNet is developing studies to assess the potential of exenatide to prevent or delay onset of type 1 diabetes in patients with autoimmunity directed at the beta cell, but who have not yet developed symptoms of the disease. These impressive research advances have rapidly taken a newly discovered protein from the laboratory to an approved drug. Further studies unfolding in this field may extend the clinical utility of this new class of therapeutics.

PATIENT PROFILE

Jodie and Dillon Distel

Participating in Clinical Research To Fight against Type 1 Diabetes

Jodie Distel had just given birth to her son, Dillon, at St. Joseph's Hospital in Denver, Colorado, when she was asked if she would like to participate in something called the Diabetes Autoimmunity Study in the Young, or DAISY. The study, she was told, would initially involve a fairly simple test: Blood from her newborn son's umbilical cord would be screened for genes that could indicate whether he was at high risk for developing type 1 diabetes.

"I didn't know very much about the disease," says Jodie, "but I figured that if taking part in the study might benefit someone else's child or my own son, that it was okay with me." She signed up for the study on the spot.

Within a week after Dillon's birth, Jodie was taken totally by surprise to learn that test results indicated that Dillon was at high risk for developing type 1 diabetes. Later, Jodie recalls, study staff alerted her that it was extremely likely that Dillon would have the disease by the time he was eight years of age. In fact, exactly three days after his seventh birthday, Dillon was formally diagnosed as having the disease.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

Jodie and Dillon Distel

About Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that destroys a person's ability to produce insulin, a critical hormone the body needs in order to convert sugar from food into life-sustaining energy. Type 1 diabetes most frequently strikes people in childhood, adolescence, or young adulthood. It is characterized by elevated levels of blood glucose, or sugar, which lead to other serious health complications, including eye, kidney, and nerve disease. Adults with type 1 diabetes are also at much greater risk of death from heart disease than adults without diabetes.

Because there is not yet a cure for the disease, people with type 1 diabetes face a daily struggle to manage their disease and prevent complications over the long-term. They must monitor their blood sugar levels and administer insulin via shots or an insulin "pump" every day to enable muscle, fat, and other tissues to absorb sugar from the blood for conversion to energy, and to try to keep blood sugar levels in a stable, healthy range. To help patients, their families,

and people at risk for the disease, the NIH is supporting research on type 1 diabetes with the aim of disease prevention, improved interventions, and, ultimately, a cure.

What Is DAISY?

DAISY is one in a group of epidemiological studies that researchers are pursuing to better understand the underlying causes of type 1 diabetes. The study is based at the University of Colorado Health Sciences Center in Denver. Marian Rewers, MD, the lead investigator for the study, says: "With DAISY, we have two primary objectives. One is to find out what causes [type 1] diabetes; the other is to find ways to prevent it."

To those ends, DAISY researchers are following two groups of children at risk for type 1 diabetes. One group was identified through screening a general population of newborns—which is how Jodie and Dillon got involved in the study. The other group consists of children who have a parent or sibling with type 1 diabetes.

Children who participate in DAISY are followed until they receive a clinical diagnosis of type 1 diabetes or until age 15, whichever comes first. Follow-up includes interviews with the parents to determine a child's diet and exposure to certain viruses, as well as periodic blood tests for three different antibodies against insulin-producing pancreatic islet cells, starting at nine months of age. Like the initial genetic screening, the antibody tests are used to predict risk of developing type 1 diabetes. The presence of antibodies indicates that the autoimmune process has begun. Dillon's blood tests were negative for antibodies against the insulin-producing islet cells until he reached the age of two, at which time he began showing an elevated level of one antibody. Subsequently, his blood was tested more frequently, every 3 to 6 months. At three-and-a-half years of age, he began showing an elevated level of two antibodies. Other markers for diabetes began to change, as well. Over time, Dillon's levels of a marker called HbA1c began to show an upward trend. Finally, his blood sugar levels became elevated. On December 13, 2004, Dillon was diagnosed with type 1 diabetes. He started on a low dose of insulin, and is currently doing very well; as of January 2006, he has never been hospitalized for diabetes-related conditions. With only about one-quarter of the insulin dose it usually takes at his age, physicians are currently able to keep Dillon's levels of the HbA1c marker at a level consistent with improved long-term health outcomes in persons with type 1 diabetes.

Dillon's case appears to support previous observations that early diagnosis helps, to some degree, to preserve the body's own insulin production. This may be in part due to avoiding a condition called diabetic ketoacidosis (DKA). DKA is a dangerous metabolic condition caused by profound insulin deficiency. Prior to diagnosis, many patients with undetected type 1 diabetes will develop DKA, which, if untreated, places them at risk of diabetic coma and death. However, the severe metabolic disturbance of DKA is not only life-threatening, but also further damages any residual insulin-producing cells. Early detection thus helped Dillon to avert both DKA and DKA's negative impact on his already compromised ability to produce insulin—and, by doing so, likely contributed to his need for less aggressive insulin therapy at diagnosis.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Dillon's mother, Jodie. Now, looking back, she adds that: "participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

The benefits of early detection and preservation of the body's capacity to produce insulin can last many years. In the landmark Diabetes Control and Complications Trial (DCCT), for example, participants who had preserved insulin secretion not only had better blood glucose control and lower insulin requirements, but also had a 50

percent lower risk of eye complications and a 65 percent lower risk of severe hypoglycemia, or low blood sugar (a risk patients face as a result of insulin treatment).

Thus, early detection of type 1 diabetes can provide both immediate and longer term health benefits. "Dillon is in a much better situation than if we had not participated in the study," says Jodie. In addition to testing a child's blood for antibodies and elevated sugar levels, the families of the children who participate in DAISY are educated about what to expect in the way of symptoms, how to do blood sugar tests at home, and more.

By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

As part of the DAISY research efforts, "one of the best things we do is to educate families, from the time their child's screening indicates high risk, straight through to diagnosis, if that should end up being the case," says Michelle Hoffman, RN, the clinical coordinator for DAISY.

Benefits of the DAISY Study

Since December 1993, the DAISY study has screened more than 33,000 newborns in the Denver, Colorado area for genetic markers that would indicate high risk for type 1 diabetes. Of those, the study has followed more than 2,000 children whose genetic screenings indicated that they were at high risk for developing the disease. Of those, 143 children developed islet cell autoimmunity (ICA)—a condition present in the majority of cases of type 1 diabetes, although people with ICA do not always progress to onset of the disease. Of those 143, 48 have developed type 1 diabetes.[1]

"It should be noted," says Dr. Rewers, "that 90 percent of children in the United States diagnosed with type 1 diabetes are hospitalized at the onset of the disease, and nearly one-third of those enter the hospital with diabetic ketoacidosis (DKA)." According to Dr. Rewers, approximately 100 children die each year of DKA. However, of the 48 children in the DAISY study who went on to develop full-blown type 1 diabetes, only one—an 11-month-old infant—needed to be hospitalized at disease onset.

Therein lies one of the benefits for participants in the DAISY study: By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Jodie lived for seven years with the hope that Dillon would never be diagnosed with type 1 diabetes. However, when the diagnosis came, she was knowledgeable. "Because of the DAISY program I think Dillon and I were prepared to handle Dillon's being diagnosed, and I think we had to go through far less than any other child and family who do not have the benefit of learning and recognizing early indications of this life-changing disease," she says. "From day one, I was told what symptoms to look for and I mentally prepared myself for this day and how I would help Dillon from that day."

Because diabetes is an insidious disease, "most families are blindsided; they don't know what to look for to recognize onset of the disease," says Dr. Rewers. "When eventually diagnosed, the overwhelming majority of these children end up in the hospital, and many are fighting for their lives—at great emotional expense to themselves and their families, and financial expense to our society." He adds, however, that until researchers can discover and develop prevention strategies to arrest disease onset, they do not currently recommend extending screening programs outside of the research setting.

Research Findings

In addition to refining ways to recognize a genetic predisposition to diabetes and to pursue effective family follow-up, DAISY also has been responsible for a number of significant findings. "For example," says Dr. Rewers, "by closely following these children, we've been able to rule out quite a few environmental factors once suspected as triggers for the onset of diabetes."

DAISY has also opened up new areas for investigation. Researchers, for example, are currently investigating whether the introduction of baby cereals may have something to do with the onset of inflammation in the pancreas that leads to diabetes. "We've discovered through DAISY that if babies at increased risk of type 1 diabetes first eat cereal regularly in their diets before four months of age, or after six months, their risk of islet autoimmunity is four to five times higher than if they begin eating cereal between four and six months of age," says Dr. Rewers. (The current American Academy of Pediatrics recommendation is to breast-feed babies and begin introducing iron-enriched solid foods, such as cereal, beginning at six months of age, if the child is ready.[2]) For children who have a specific genetic marker that is known to strongly predispose individuals to type 1 diabetes, the risk appears to be even greater. According to Dr. Rewers, "these children have an overall increased risk of islet autoimmunity six times higher if fed cereal before age four months, and twelve times higher if cereal is delayed beyond six months, than if they are started on cereal at age four to six months." Research is ongoing to tease out the answers to this and other challenging issues regarding possible causes of type 1 diabetes and factors contributing to its onset.

TEDDY—A Collaborative Effort

In addition to DAISY, other studies have contributed many important insights to advance research on environmental factors in type 1 diabetes. However, there are limitations to smaller studies, such as the number of patients that can be recruited in a given location.

To overcome these limitations, the NIH spearheaded the launch of a long-term, international, collaborative effort to identify environmental triggers of type 1 diabetes. This effort, begun in 2002, is called "The Environmental Determinants of Diabetes in the Young," or TEDDY. Funded by the Special Statutory Funding Program for Type 1 Diabetes Research (see *http://www.T1Diabetes.nih.gov*), TEDDY consists of six centers in the U.S., Finland, Sweden and Germany. The creation of the TEDDY consortium allows for a coordinated, multidisciplinary approach; collection of data and information in a standardized manner; greater statistical power than can be achieved in smaller studies; and the creation of a central repository that includes data and biological samples for use by the scientific community.

Researchers participating in TEDDY—including the Denver investigators who have conducted DAISY—are recruiting newborns who are genetically predisposed to developing type 1 diabetes. They are screening newborns from the general population, as well as newborns who have parents or siblings with the disease. The children will be followed until they are 15 years old or until they develop islet autoimmunity or type 1 diabetes. This long-term study will amass the largest data set and samples on newborns at risk for type 1 diabetes anywhere in the world.

"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.

TEDDY was established by the NIDDK, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, the Juvenile Diabetes Research Foundation, and the American Diabetes Association.

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"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.

[1]*These numbers are current as of December 2005.*
[2]*http://aappolicy.aappublications.org/cgi/content/full/pediatrics;115/2/496*

TEDDY is currently enrolling patients. TEDDY enrollment sites in the United States are located in Georgia, Florida, Colorado and Washington state. For more information on enrolling in TEDDY, please see:
http://www.niddk.nih.gov/fund/diabetesspecialfunds/t1d_ctcr/study.asp?StudyID=121

PATIENT PROFILE

Todd Hutchinson

Dealing with Type 2 Diabetes

Fourteen-year-old Todd Hutchinson and his mother, Lisa, live in Tahlequah, Oklahoma, capital of the Cherokee Nation. As capital cities go, Tahlequah, a one-hour drive east of Tulsa, is quite small, with a population of about 15,000. American Indians, including Todd, his mother, and other Cherokee descendants, make up a large percentage of the population. Despite Tahlequah's size, "there are many people with diabetes here," says Lisa, whose own family reflects the severity of the problem. Lisa, Todd, Lisa's father, her sister, as well as other extended family members, including Todd's step-grandmother, have been diagnosed with type 2 diabetes.

According to statistics compiled by the NIDDK and other agencies of the Department of Health and Human Services, American Indians and Alaska Natives are more than twice as likely to have diagnosed diabetes as non-Hispanic whites of similar ages.[1] More disturbing is the fact that, until recently, type 2 diabetes was rarely diagnosed in children and adolescents. However, type 2 diabetes is now diagnosed more frequently within these age groups, particularly among American Indians, African Americans, and Hispanic/Latino Americans. Genetic susceptibility, reduced physical activity, and obesity are viewed as major contributors to this alarming trend—and to personal stories. For example, Todd weighed more than 250 pounds and led a relatively sedentary lifestyle prior to being diagnosed with type 2 diabetes in April 2005, at age 13.

Todd Hutchinson, and his mother, Lisa

Type 2 diabetes is being diagnosed more frequently in children and adolescents, particularly among American Indians, African Americans, and Hispanic/Latino Americans.

Todd is an extraordinarily bright, articulate, studious young man, who aspires to become a physician one day. A couple of months after his diagnosis, he was enrolled in the study of "Treatment Options for Type 2 Diabetes in Adolescents and Youth," commonly referred to as the TODAY study. Begun in March 2004, and funded by NIDDK, TODAY is comparing treatments for type 2 diabetes in children and teens in 13 medical centers and their affiliated sites across the United States. The aim of the study is to identify the best therapeutic strategies to combat this disease in young people. According to Todd and his mother, Todd's participation in the TODAY study has greatly benefited both of them.

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About TODAY

Participants in the TODAY study are young people with type 2 diabetes, a disease characterized by the body's resistance to the action of insulin. The trial is testing two drugs that help to fight the disease by increasing the body's sensitivity to the insulin it produces. In addition, the trial is studying intensive lifestyle changes aimed at lowering weight by cutting calories, improving nutrition, and increasing physical activity.

Young people interested in joining the TODAY study first complete a two-part screening process to determine their eligibility, during which they receive a comprehensive program of standard diabetes education that includes important information about nutrition and physical activity. Following the screening process, eligible participants are then enrolled in a treatment group. The TODAY study has three treatment groups. Participants in one group are provided with the drug metformin alone. Metformin is the only oral drug approved by the Food and Drug Administration to treat type 2 diabetes in children. In the second group, participants are provided with metformin in combination with rosiglitazone, another promising oral drug currently approved only for adults. Participants in the third group receive metformin and also participate in a family-based behavioral weight loss program that focuses on cutting calories and increasing physical activity. Notably, TODAY is the first clinical study to look at the health effects of intensive lifestyle change in youth with type 2 diabetes. It is based upon previous studies in adults, which show that relatively modest weight loss and increased physical activity can substantially reduce blood sugar levels.

Because type 2 diabetes was previously very rare in children, there is very little information on how best to treat it. By supporting major research studies that are aimed at developing optimal treatment of type 2 diabetes in children—like the TODAY trial—the NIDDK hopes to ameliorate this disease and its complications in this most vulnerable population.

Todd was randomly assigned to one of the TODAY study's three treatment groups. Researchers are planning to enroll 750 children and teens, ages 10 to 17, who have been diagnosed with type 2 diabetes within the past 2 years. The trial will last approximately 5 years and is expected to answer urgent questions about which therapy is most effective for treating type 2 diabetes in young people.

Why Early Intervention Is Important

The longer a person has diabetes, the greater the chances he or she will sustain serious damage to blood vessels of the eyes, nerves, kidneys, and heart. Todd's grandfather, for example, had his foot amputated and later became legally blind as a result of complications from diabetes. This aspect of diabetes makes the growing burden of type 2 diabetes in children particularly alarming, because children with this diagnosis have a greater statistical chance of developing medical complications during their lifetimes. Therefore, the prevention of type 2 diabetes in youth is a primary public health goal. However, optimizing type 2 diabetes treatment alternatives is equally critical in order to forestall the onset of complications in children who already have the disease.

One Smart Young Man

It doesn't take long to figure out that Todd Hutchinson, now 14, is a smart and highly motivated young man. In addition to being an avid reader, Todd takes part in extracurricular school activities, such as the Esperanto Club, and fiercely competes in the "tournament of champions" academic competitions in the state of Oklahoma. Todd says that he likes to look up things he doesn't know about on the Internet. So, he investigated when he began experiencing excessive thirst, unexplained weight loss, and extreme hunger in the middle of the night, as well as very dry skin, sleepiness, blurred vision and a tingling sensation in his hands. "I went on the Internet and learned that I was manifesting all the classic symptoms of type 2 diabetes," he says in a sophisticated voice that belies his relatively young age. His mother

adds that: "Todd didn't want to accept the fact that he might have type 2 diabetes." The tipping point came when Todd had surgery for an ingrown toenail and it wouldn't heal. "My mom took me to the doctor, and he found that my blood sugar levels were running between 700 and 1,000 [milligrams per deciliter]," says Todd. The normal range for blood sugar levels for people without diabetes is about 10 times lower. Todd remembers that: "The doctor was amazed that nothing bad had happened to me, and told me and my mom that I could have easily gone into a diabetic coma and died, and that I was very lucky not to have had any serious repercussions."

Todd later enrolled in the TODAY study on the recommendation of his physician. "I enjoy being in the study," says Todd. "It's a little bit of work, but it's well worth it."

Taking Part in the TODAY Study

As a study participant, Todd's health records and other personal information were collected. Todd and his mother also went through an intensive education program that included information about diabetes, the impact of lifestyle and diet on the disease, and the steps that study participants and their families can expect to follow over the next two to five years of the study, including the frequency with which Todd's blood sugar levels must be checked. Todd also keeps a daily journal of his food intake, exercise activities, and more. He says that: "One of my responsibilities is to bring my glucose meter with me wherever I go." Todd is aware of the potential consequences of his disease, and says, "I have a group of friends who help me out a lot, and I've told them what to look for if my sugar gets too high or too low."

As part of the study, Todd has a personal activity leader, or PAL, who comes to his home once a week to monitor his progress and to continue educating Todd and his mother about lifestyle and eating habits and how they affect diabetes. Todd, for example, has gone from eating cheeseburgers and pizzas and drinking two-to-three liters of soda a day ("we call it pop, here," says Todd), to consuming more healthful foods, including vegetables. "My diet has changed tremendously," he says. "I like stir fried vegetables, and one of my favorites is broccoli."

Because he wants to adhere to all the expectations of the study, Todd is engaging in more physical activities, as well. "I ride my bike 10 or more miles a week and I often go on family hikes through the woods." Nearly every day he and his mother walk two miles around a local high school track. As a result, in a matter of months, Todd's weight has gone from 250 pounds down to 171 pounds. "My goal is 160 pounds, which would be a good weight for me," he says. His mother, who was diagnosed with type 2 diabetes seven years ago, adds that the exercising she does with Todd and the information she has received about diabetes as a result of the TODAY study have also benefited her health.

Exercise, change of diet, and weight loss are helping Todd keep his glucose levels in a healthy target range. "The TODAY study has really changed Todd's life," says his mother. Todd agrees. "When I was first diagnosed with type 2 diabetes, I was a bit worried, but I told myself 'you've got it and you can't change that, so you had better deal with it.' The TODAY study has helped me do that. I just hope they find a cure for type 2 diabetes so that kids like me can live our lives as normal kids, without fear of going blind or losing a limb." In the meantime, Todd wants to be part of the solution. "I want to become a physician so I can help other people with diabetes. It's a great ambition of mine." And given his determination, it's surely an ambition this engaging young man with deep American Indian roots can realize.

[1] *National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics fact sheet: General information and national estimates on diabetes in the United States, 2003. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2003. Rev. ed., 2005.*