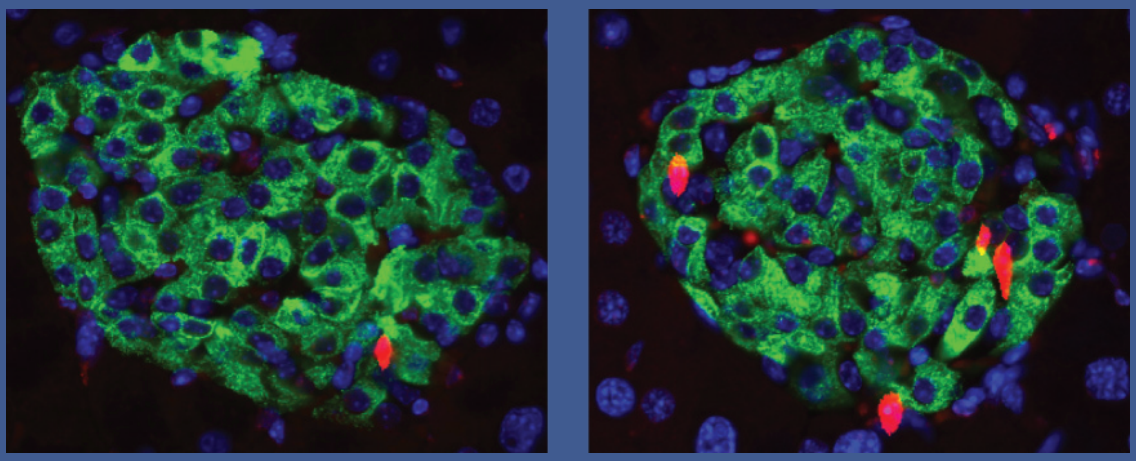

In research described in this chapter, scientists discovered telomere shortening can play a role in metabolic diseases like cardiovascular disease and type 2 diabetes. Telomeres are specialized regions that "cap" the ends of chromosomes to protect critical DNA sequences from being lost each time a cell replicates its DNA and divides. As cells age, telomeres erode, leading to damaging consequences. The effect of telomere shortening is particularly apparent in a mouse model of diabetes. With unaltered telomeres (left), there were relatively few dying cells (red) among the insulin-producing beta cells (green). However, when cells in this mouse model are genetically modified to have short telomeres, scientists observed an increase in cell death (right), as well as loss of beta cell function, and glucose intolerance similar to human diabetes. Short telomeres may increase diabetes risk and serve as a biomarker that can help explore new treatments or prevention strategies.

Images provided by Dr. Mary Armanios, and from Guo N, Parry EM, Li L-S, Kembou F, Lauder N, Hussain MA, Berggren P-O, and Armanios M: Short telomeres compromise β-cell signaling and survival. PLoS One 6: e17858, 2011.

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, these diseases and conditions affect many millions of Americans and can profoundly decrease 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 25.8 million people in the United States—or 8.3 percent of the total population—and is the seventh leading cause of death.[1] Diabetes lowers average life expectancy by up to 15 years,[2] increases risk of death from cardiovascular disease 2- to 4-fold, and is the leading cause of kidney failure, lower limb amputations, and, in working-age adults, blindness.[1] In addition to these human costs, the estimated total financial cost for diabetes in the United States in 2007—including costs of medical care, disability, and premature death—was $174 billion.[1] Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.[1]

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that 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. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that is similar to type 2 diabetes but unique to pregnancy. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery.

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of adults and the majority of children and youth with diagnosed diabetes.[1] It most often develops during childhood, but may appear at any age. Type 1 diabetes is an autoimmune disease, in which the immune system launches a misguided attack and destroys the insulin-producing beta cells of the pancreas. If left untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. 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 to near the normal levels achieved by functional beta cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working to develop beta cell replacement therapies to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.[1] Type 2 diabetes is associated with several factors,

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[1] 2011 National Diabetes Fact Sheet. Centers for Disease Control and Prevention. Atlanta, GA.

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

including older age and a family history of the disease. It is also strongly associated with obesity; more than 80 percent of adults with diabetes are overweight or obese.[3] Type 2 diabetes occurs at elevated rates among minority groups, including African Americans, Hispanic and Latino Americans, American Indians, and Native Hawaiians.[1] Gestational diabetes is also a risk factor: women who have had gestational diabetes have a 35 to 60 percent chance of developing diabetes—mostly type 2 diabetes—in the next 10 to 20 years.[1]

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic beta cells lose their ability to secrete enough insulin to restore balance, and the timing of insulin secretion becomes abnormal causing blood glucose levels to rise. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 79 million adults in the United States who have a condition called "prediabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes.[1] This population is at high risk of developing diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a 7 percent reduction in body weight. Moreover, follow-up research has shown that this benefit of reduced diabetes risk can persist for at least 10 years.

Type 2 diabetes was previously called "adult-onset" diabetes because it is 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 than those who develop the disease later in life. 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 type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes 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, patients may find it increasingly difficult to strictly control their blood glucose levels and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

The NIDDK is supporting research to better understand metabolism and 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. Exploring interrelationships between some of these diseases is an important and informative facet of this work—for example, diabetes is becoming an increasing problem for people with cystic fibrosis, as life expectancy for these individuals has improved due to advances in cystic fibrosis treatment. In parallel, based on knowledge from past scientific research investments, the Institute is vigorously pursuing studies of prevention and treatment approaches for these diseases.

MOLECULAR MECHANISMS OF REGULATING THE BODY'S BLOOD GLUCOSE LEVELS

FGF19 Lends Insulin a Hand: A new discovery is reshaping our understanding of the way the body's hormones control blood glucose. While the hormones insulin and glucagon have long been known to respond to the influx of glucose with a meal or to fasting between meals, scientists recently found that another hormone, FGF19, adds a new dimension to this regulation as food makes its way through the digestive tract. During periods of fasting, the pancreas secretes glucagon, which signals the liver to liberate glucose stored there in the compound glycogen, and release it into the bloodstream. When we eat, glucose and other nutrients are transported from the digestive system into

[3] *Eberhardt MS, et al. MMWR 53: 1066-1068, 2004.*

the blood, and the pancreas begins to release insulin. Insulin is a signal to our cells to take up glucose, and in the liver it also suppresses glucose release, induces restoration of the glycogen supply, promotes protein synthesis, and inhibits the action of glucagon. This two hormone picture became a bit richer with the discovery more than a decade ago that GLP-1, a hormone produced by cells of the upper small intestine when food begins to pass through the stomach, serves to signal to the pancreas that a bolus of nutrients is on the way, boosting the insulin response. That discovery led to development and approval of several important new medications for type 2 diabetes.

The new discovery concerns FGF19, a hormone produced by cells in the final portion of the small intestine (the ileum). FGF19 is secreted in response to bile acids—a group of compounds released from the gall bladder to aid in the digestion of fats. The bile acids accompany digesting food through the intestines, so their presence in the ileum indicates that the digestive process is nearing completion. FGF19 induces the gall bladder to rebuild its supply of bile acids, and this was thought to be the hormone's major purpose. Now researchers have shown that, like insulin, FGF19 signals the liver to synthesize glycogen and protein and reduce glucose production and release. Experiments using the human FGF19 hormone in mice show it helps keep blood glucose levels down, restores the liver glycogen supply in mice that have uncontrolled diabetes, and helps moderate blood glucose and insulin levels in mice fed a diet that tends to promote diabetes. In contrast, mice lacking the mouse equivalent of FGF19 have elevated blood glucose and abnormally low liver glycogen supplies. In healthy humans, insulin levels typically reach their highest point within an hour after eating, whereas the signal to produce FGF19 comes relatively late in the digestive process. Therefore, its levels and impact peak about 3 hours after a meal, shortly before liver glycogen supplies typically reach their zenith. Thus, insulin quickly and potently causes glucose uptake and storage at the initiation of a meal, whereas FGF19 provides a later signal to sustain the insulin-initiated response, continuing production of glycogen and protein and repression of liver glucose synthesis until absorption of a meal is complete. The researchers found that FGF19 stimulates glycogen synthesis in a manner that is completely independent of insulin, and that messages from the two hormones are carried into liver cells by distinct sets of "signal transduction" molecules. These findings suggest it may be possible to help people with diabetes control their blood glucose by developing new medications that act through the same mechanism as FGF19.

Kir S, Beddow SA, Samuel VT, et al. FGF19 as a postprandial, insulin-independent activator of hepatic protein and glycogen synthesis. Science 331: 1621-1624, 2011.

Potthoff MJ, Boney-Montoya J, Choi M, et al. FGF15/19 regulates hepatic glucose metabolism by inhibiting the CREB-PGC-1α pathway. Cell Metab 13: 729-738, 2011.

New Insight into Liver Glucose Production:

Researchers have uncovered a cellular pathway in mice and fruit flies that may represent a novel target for treating high blood glucose levels. One function of the liver in humans and many animals is to stabilize the body's glucose levels between meals, when glucose isn't being supplied by food, by producing its own glucose and releasing it into the bloodstream. In type 2 diabetes, this function goes awry, contributing to chronically elevated blood glucose. Normally, liver cells detect when glucose levels are falling via glucagon, a pancreatic hormone that counterbalances insulin and signals fasting, and respond by "turning on" genes involved in glucose production. Many of these genes are under the control of gene regulatory factors collectively called FOXO. In a recent study in mice and in isolated cells (from mice and humans), researchers found that three intracellular proteins, called class IIa histone deacetylases (HDACs), regulate activation of FOXO—and thereby help "turn on" glucose production genes—in a glucagon-dependent fashion. This newly identified mechanism significantly expands what is known about glucose production by liver cells. Intriguingly, a second, overlapping research team studying a simpler organism, the fruit fly, uncovered a similar role for class IIa HDAC activation of FOXO and FOXO-controlled metabolic genes in the insect equivalent of fat and liver. Because this molecular mechanism for increasing energy production under fasting conditions appears to be highly conserved from insects to mammals, scientists think it is likely to exist in humans as well. To determine whether the class IIa HDACs play a role in regulating blood glucose, the first research team

studied their activity in diabetic mice. They found that when they experimentally reduced the amounts of these HDACs in the livers of different mouse models of type 2 diabetes—both genetic and diet-induced—the mice showed significant improvements in both blood glucose levels and glucose tolerance tests. The results of these studies thus not only reveal a new and possibly highly conserved molecular pathway regulating glucose production by the liver, but also suggest that, if this pathway exists and functions similarly in humans, targeting the activity of class IIa HDACs could turn out to be a new therapeutic approach for type 2 diabetes.

Mihaylova MM, Vasquez DS, Ravnskjaer K, et al. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. Cell 145: 607-621, 2011.

Wang B, Moya N, Niessen S, et al. A hormone-dependent module regulating energy balance. Cell 145: 596-606, 2011.

New Hypothesis To Explain Type 2 Diabetes—It Might Begin with the Beta Cell: Recent research links diet and obesity to direct effects on insulin production in the pancreas, suggesting a new hypothesis that may help explain how type 2 diabetes develops. The predominant scientific view today is that, in susceptible people, obesity triggers a chronic, low level inflammatory process that induces insulin resistance. Insulin resistance increases the demand on the insulin-producing beta cells of the pancreas. When the beta cells are unable to make sufficient insulin to restore balance, blood glucose levels rise. Thus, the insulin resistance comes first, and its consequences eventually impinge on the beta cell. The new findings turn that view around, by demonstrating how a high-fat diet can inhibit proper beta cell function in both mice and humans, and trigger symptoms associated with type 2 diabetes.

Beta cells secrete insulin in response to glucose molecules passing through glucose transporter proteins located in the cells' outer membranes. These transporter proteins are therefore critical to beta cell function. To remain stably embedded in the membrane and perform their vital task, glucose transporters must be modified by an enzyme called GnT-4a. Previous work determined that mice lacking the *GnT-4a* gene develop diabetes, and also that a high-fat diet reduces GnT-4a levels in the cell. The new research shows that, compared to healthy beta cells, beta cells from mice with diabetes induced by a high-fat diet did not produce enough GnT-4a to keep an adequate supply of glucose transporters in the beta cell membrane. Moreover, GnT-4a and glucose transporter levels were also abnormally low in beta cells obtained from deceased human donors with type 2 diabetes. As expected, these GnT-4a-deficient beta cells from mice and humans did not respond with robust insulin secretion in the presence of elevated glucose. This phenomenon could also be induced in healthy human beta cells by exposing them to a specific form of fat molecule that mimics the effects of a high-fat diet. To further understand the potential impact of reduced GnT-4a in the diabetes disease process, the researchers generated mice with a genetic change that keeps levels of GnT-4a constant in beta cells, even when the mice eat a high-fat diet. Such a diet did cause mice with constant GnT-4a to become obese, but they did not develop diabetes. Although the animals' blood glucose levels rose higher, when fed high-fat food, than those fed a more healthful diet, their glucose levels did not rise as dramatically as those of normal littermates eating high fat. The mice that always produce GnT-4a in their beta cells also did not develop other common features of diabetes. In particular, they did not develop fatty livers or severe insulin resistance. Thus, continued pancreatic production of GnT-4a not only rescued the ability of the mouse pancreas to respond to glucose despite a high-fat diet, but also it improved the response to insulin in the animals' other organs and tissues. While the mechanisms for that effect remain unclear, it suggests that abnormal beta cell function may play an important role earlier in the development of type 2 diabetes than had previously been appreciated. It also highlights the importance of GnT-4a for maintaining healthy blood glucose levels, and suggests the enzyme may potentially be a useful target for pharmaceutical approaches to treating type 2 diabetes.

Ohtsubo K, Chen MZ, Olefsky JM, and Marth JD. Pathway to diabetes through attenuation of pancreatic beta cell glycosylation and glucose transport. Nat Med 17: 1067-1075, 2011.

INSIGHTS INTO THE LINK BETWEEN AGING AND METABOLISM

Molecular Link Between Energy Intake and Lifespan/Aging: Researchers have discovered a molecular connection between energy intake, lifespan, and the aging process. Previous research in animal

models, such as in the roundworm *Caenorhabditis elegans* (*C. elegans*), has shown that reducing calories extends lifespan. Two nutrient- or energy-sensing proteins found inside cells, called AMPK and calcineurin, regulate lifespan in the worm, but it was unknown how they exert their effects.

Using a *C. elegans* model system, researchers identified a critical protein target of AMPK and calcineurin, called CRTC-1. When the scientists depleted CRTC-1 using genetic techniques, the worms lived longer, suggesting that the protein is also a regulator of lifespan. CRTC-1 is a type of protein that controls whether genes are turned on or off. Further experiments demonstrated that AMPK and calcineurin had opposing effects in regulating the extent to which CRTC-1 was chemically modified (phosphorylated), which in turn controlled whether CRTC-1 could turn on its target genes. Additionally, a protein that interacts with CRTC-1, called CREB, was found to be an important component in this lifespan-regulating pathway because depleting the worm's CREB protein also prolonged its life. Because AMPK, CRTC, and CREB are known to play a role in metabolism in mammals, the scientists hypothesized that these proteins were regulating metabolism-related genes to control the worm's lifespan. Surprisingly, this was not the case. Rather, the worm genes regulated by AMPK/CRTC-1/CREB were involved in a type of stress in a cellular component called the endoplasmic reticulum (ER). Research has suggested that aging-related changes to the ER stress response contribute to diseases such as type 2 diabetes, cancer, and neurodegenerative diseases. This observation provides a possible molecular explanation for how nutrient levels could affect the aging process and longevity. Importantly, the pathway involving CRTC-1/CREB is evolutionarily conserved from worms to mammals, suggesting that these findings may be relevant to people. This research provides new insights into the molecular pathways that link energy intake to aging and lifespan, and illuminates new targets for potential intervention against age-related conditions such as type 2 diabetes.

Mair W, Morantte I, Rodrigues APC, et al. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. Nature 470: 404-408, 2011.

The Long and the Short of It—How Aging Impairs Metabolism: Two recent studies provide insight into how aging leads to decreased organ function and increased risk for certain metabolic diseases, like cardiovascular disease and type 2 diabetes. From decades of research, two theories emerged to explain how aging is linked to metabolic disease and organ failure. In one theory of aging, organs with cells that divide at a high rate are unable to repopulate dead cells, leading to organ failure. A separate theory of aging emerged from studies of mitochondria—the "powerhouses" of the cell that generate most of a cell's energy through metabolic pathways. Mitochondria also have their own DNA, which is different from the rest of a cell's DNA and contains genes needed for mitochondrial function. Aging, it is thought, results from an accumulation of mutations or alterations of the mitochondrial DNA over time, which leads to decreased energy production and damage to the cell. Therefore, in tissues that do not regularly repopulate their cells, such as the heart, liver, and brain, this loss of energy leads to aging.

In a recent study, scientists demonstrated that these two theories about aging-related disease are linked in that they are two facets of the single process of aging. The link comes from telomeres, specialized structures at the ends of DNA. Within a cell, DNA is packed into chromosomes. To ensure that critical DNA sequences near the ends of chromosomes are not lost each time a cell replicates its DNA and divides, telomeres "cap" the ends of chromosomes. Over time, however, these regions are eroded, prompting the cell to stop replicating and even to initiate a death process. To investigate effects of telomere shortening on cell function and aging, scientists studied mice that were genetically engineered to have short telomeres and found that shortened telomeres were associated with a decrease in mitochondrial mass and impaired mitochondrial function. The mice also showed evidence of heart disease and liver dysfunction, characteristics of aging. These important results link the effects of aging on the cell's DNA through telomere dysfunction with decreased function of the mitochondria.

In another study, a different group of researchers looked specifically at the effects of shortened telomeres on β (beta) cells in the pancreas. β cells produce the hormone insulin which helps the body use glucose for energy. Loss of β cell function is a hallmark of diabetes. The scientists found that mice genetically engineered to have short telomeres had impaired secretion of insulin and resulting high levels of glucose in the blood. Importantly, the β cell mass was not decreased in these mice; rather, the short telomeres led to changes in gene expression (whether genes are "on" or "off") that affected multiple cellular processes involved in insulin secretion. This provides critical information about why β cell function declines with age in many people.

Together, these studies identify a role for telomere shortening and resulting mitochondrial dysfunction in age-related metabolic diseases like type 2 diabetes. While these results need to be confirmed in humans, this knowledge could lead to new treatments or prevention strategies for such diseases.

Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 470: 359-365, 2011.

Guo N, Parry EM, Li L-S, et al. Short telomeres compromise β-cell signaling and survival. PLoS One 6: e17858, 2011.

Turning Back Time on Beta Cell Age: Scientists discovered a mechanism for the decline in β (beta) cell proliferation as mice and humans age and identified a potential new strategy to induce β cell regeneration. β cells, which produce the vital hormone insulin, are destroyed by the immune system in people with type 1 diabetes and may not function normally in people with type 2 diabetes. Identifying ways to replace the lost β cells to restore the body's insulin-producing capacity would benefit people with type 1 and type 2 diabetes, and is a major goal of research. As mice and humans age, the ability of their β cells to divide and make new β cells (or "proliferate") diminishes. Therefore, understanding how the β cells lose this ability could lead to strategies to prevent this loss or even to reverse the process and promote expansion of β cells.

A protein called platelet-derived growth factor receptor-α (Pdgfr-α) is found on the surface of cells and is known to regulate cell division and survival; however, its role in β cells has been unknown. In this study, scientists discovered that levels of Pdgfr-α decreased as mouse β cells aged. To further investigate Pdgfr-α's role, the researchers genetically altered the mice, to ask what happened to β cells if Pdgfr-α levels were reduced prematurely. They found that not only did β cell proliferation diminish in these mice, but that they also had decreased β cell mass and impaired glucose control. Because Pdgfr-α was critical to β cell development in young mice, the scientists speculated that the protein might also control β cell regeneration in adult mice. When mice are given a specific chemical, a significant number of their cells are destroyed, but the remaining β cells proliferate and restore the mass, allowing scientists to study β cell regeneration. Using this tool, the researchers observed high levels of Pdgfr-α in the remaining adult β cells, coincident with an increase in proliferation. However, in the mice genetically altered to have reduced Pdgfr-α levels, the remaining adult β cells failed to regenerate, leading the mice to develop severe diabetes. Now knowing that Pdgfr-α is necessary for β cell regeneration, the scientists investigated whether increasing Pdgfr-α activity could reverse the age-dependent β cell loss. Genetically modifying adult mice to have continual Pdgfr-α activity delayed β cell loss, and instead promoted growth of new β cells and increased β cell mass.

Importantly, the scientists demonstrated that Pdgfr-α and other proteins required for its activity are present in human β cells and undergo a similar age-dependent decline in levels. Stimulating human juvenile cultured β cells with a protein that turns on Pdgfr-α activity led to increased β cell proliferation, indicating that Pdgfr-α may regulate new β cell growth in aging β cells in humans as well as mice. The exciting discovery of mechanisms that regulate age-dependent loss of β cells could provide scientists with new avenues for modulating growth of human β cells to promote their regeneration and replace those lost in diabetes.

Chen H, Gu X, Liu Y, et al. PDGF signalling controls age-dependent proliferation in pancreatic β-cells. Nature 478: 349-355, 2011.

IMPROVING DIABETES SCREENING

New Blood Test May Improve Assessment of Type 2 Diabetes Risk: Research in the emerging field of metabolomics has revealed a new approach

for determining who is at greatest risk for developing type 2 diabetes. Several factors are known to increase a person's type 2 diabetes risk. These include overweight or obesity, age, and a family history of the disease. In addition, blood tests can identify people whose blood glucose is intermediate between normal and diabetic levels—people with glucose levels in this range are said to have prediabetes, because they are at significantly higher risk of type 2 diabetes than peers with lower blood glucose. More than a third of Americans—roughly 79 million people—are considered to have prediabetes by this definition, according to 2011 estimates. These intermediate levels of blood glucose, however, are not a perfect predictor of disease risk; indeed, many people with prediabetes will not go on to develop diabetes in their lifetimes. So a better test for diabetes risk would be invaluable for helping direct scarce preventive health care resources to those who need them most.

To address that need, researchers have turned to the new field of metabolomics, the study of the many chemical compounds our bodies produce in the course of daily life. Looking for a chemical signature of diabetes risk, the researchers compared the blood from a group of 189 people who developed type 2 diabetes over the course of an earlier, 12-year study, to blood from 189 people in the same study who did not develop the disease, but who were otherwise similar in terms of age, blood glucose levels, and degree of overweight. The researchers discovered that blood levels of five different amino acids were higher in people who went on to develop diabetes years later, and confirmed the result in a second set of people. (Amino acids are the building blocks of protein molecules.) By combining tests for three of the five amino acids, they were able to identify a subgroup of people whose risk of diabetes is about six times greater than that of people with otherwise similar risk factors, but lower amino acid levels. The scientists then confirmed the relationship of the amino acid levels to diabetes risk by performing the test in two more sets of people. This re-test not only confirmed the relationship of the amino acids to diabetes risk, it showed that it holds true even in people with comparatively low blood glucose, who are therefore considered to be at relatively low risk of diabetes based on blood glucose alone. This research raises intriguing questions as to the molecular mechanism that ties these amino acids to development of diabetes. If an affordable clinical version of the test is developed, it may one day greatly improve the ability of health care providers to identify people most likely to benefit from diabetes prevention therapy.

Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 17: 448-453, 2011.

Health and Cost Benefits of Genetic Testing for Neonatal Diabetes Mellitus: Research suggests that genetic testing for neonatal diabetes mellitus would not only improve patients' quality of life, but also result in cost savings. Neonatal diabetes mellitus (NDM) is a rare form of diabetes that occurs in the first 6 months of life. It is called "monogenic" diabetes because it is caused by defects in a single gene (as compared to type 1 and type 2 diabetes, in which risk is related to multiple genes). In about one-half of babies with NDM, the condition is transient and disappears during infancy but can reappear later in life; in the other half, the condition is lifelong and is called permanent neonatal diabetes mellitus (PNDM). Research on the genetics of PNDM has shown that over 40 percent of the cases result from defects in one of two different genes (*KCNJ11* or *ABCC8*). Knowledge about how those genes function in the body led to the discovery that people with defects in one of those genes could be treated with oral sulfonylurea therapy rather than injections of insulin—a less burdensome treatment approach that results in better glucose control. However, PNDM can be misdiagnosed as the more common type 1 diabetes, so some patients who could be taking sulfonylureas are instead put on insulin therapy. Thus, scientists are considering whether routine genetic testing—particularly for children under 6 months of age who have been diagnosed with diabetes—should be done to identify individuals who carry one of the PNDM-causing genes so that they are correctly diagnosed with this form of the disease.

In new research, scientists used a conceptual model comparing a policy of routine genetic testing with no testing, to develop estimates of total medical costs and health outcomes over 30 years resulting from correctly diagnosing children with PNDM or misdiagnosing them with type 1 diabetes. The analysis showed that routine genetic testing could result in quality of life benefits that increase over time, and also save approximately $12,500 over 10 years, and $30,400 over 30 years. Improved quality of life is due to factors such as using a less

burdensome therapy and having a reduced lifetime risk for complications. Reduced costs stem from factors such as lower health care costs for treating complications. This research suggests that genetic testing in neonatal diabetes is a medical advance that would improve patients' quality of life and save money. It also highlights the potential economic benefits of implementing personalized genetic medicine approaches.

Greeley SAW, John PM, Winn AN, et al. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. Diabetes Care 34: 622-627, 2011.

New Insights on When To Screen Children for Type 1 Diabetes Risk Factors: Researchers have defined a time period during which to screen children for risk of developing type 1 diabetes. In the disease, a misguided attack of the immune system—known generally as "autoimmunity"—leads to destruction of the insulin-producing β (beta) cells of the pancreas. A feature of the onset of autoimmunity is the body's development of antibodies to β cell proteins. These antibodies are called "autoantibodies" because they recognize proteins within the body, rather than invading pathogens. Importantly, they typically appear before overt symptoms of type 1 diabetes and thus serve as useful clinical predictors of the disease. Blood tests for the presence of autoantibodies can accurately identify relatives of people with type 1 diabetes who are at high or moderate risk of developing the disease within 5 years. At-risk people identified by screening may be eligible for trials to test promising prevention strategies.

Although it is known that diabetes autoantibodies frequently develop in childhood, less is known about the relationship between age and onset of autoimmunity. To gain insights into this relationship, scientists studied children 3 to 18 years of age who participated in the NIDDK's Diabetes Prevention Trial-Type 1 (DPT-1). All of the children were relatives of people with type 1 diabetes. In the trial, the children were initially screened for the presence of autoantibodies. Of the 42,447 children screened, 3,235 had autoantibodies. Those who did not have autoantibodies were invited to return for re-screens. Of the 11,813 children who returned, 469 (4 percent) had autoantibodies. Further analysis showed that risk for developing autoimmunity was highest in early childhood, with risk decreasing by 5 percent each year. If children tested positive for autoantibodies, most of them (75 percent) did so by age 13. These findings suggest that, in relatives of people with type 1 diabetes, annual screenings should begin in early childhood and continue through early adolescence to identify the majority of children who are at increased risk for developing the disease and who may be eligible for prevention trials.

Vehik K, Haller MJ, Beam CA, et al. Islet autoantibody seroconversion in the DPT-1 study: justification for repeat screening throughout childhood. Diabetes Care 34: 358-362, 2011.

TYPING DIABETES IN YOUTH

New Approach to Characterization of Pediatric Diabetes Type: Scientists developed a marker-based approach to classifying diabetes type in youth. Current classification of diabetes type predominantly falls into one of two categories: type 1 or type 2 diabetes. Although both of these are metabolic disorders, they have different causes and different options for treatment. In type 1 diabetes, a misguided autoimmune attack specifically targets the insulin-producing beta cells of the pancreas and destroys them. People with type 1 diabetes, therefore, do not produce insulin and require insulin injections. In type 2 diabetes, the body becomes less sensitive to the action of insulin and may eventually stop producing insulin. Therefore, approaches to treating people with type 2 diabetes who continue to produce some insulin of their own include improving their response to insulin, increasing its production by the pancreas, reducing release of glucose by the liver, and other approaches. Previously, diagnosis of diabetes type was generally driven by the age of onset, since onset of type 1 diabetes most often occurs in children and adolescents, among whom type 2 diabetes was once unknown. However, type 2 diabetes is now increasingly being diagnosed in children and adolescents. In addition, the obesity epidemic has clouded classification, as the presence of obesity no longer automatically indicates type 2 diabetes, since youth with type 1 diabetes are increasingly obese. Finally, cases of "hybrid" diabetes—with aspects of both type 1 and type 2—have been reported. Diabetes classification is therefore particularly challenging in young people. Moreover, an increasing number of treatment options are available, particularly for people with type 2 diabetes, and some

people with type 2 diabetes require insulin treatment. An accurate understanding of the underlying disease characteristics is needed to ensure that people receive the proper treatment.

To improve diabetes classification and better understand these disorders, scientists in the SEARCH for Diabetes in Youth Study measured markers of autoimmunity and insulin sensitivity in over 2,000 individuals under 20 years of age with recently diagnosed diabetes. The presence or absence of the markers led to the recognition of four groups of youth with diabetes, and allowed the researchers to explore how other factors varied across these groups. As expected, young people whose diabetes was identified as autoimmune and insulin-sensitive had been considered to have type 1 diabetes by their physicians and had traditional characteristics of type 1 diabetes: an average age of onset at 9.3 years; relatively low prevalence of obesity; treatment with insulin; and mostly of non-Hispanic white origin. Those whose diabetes was identified as nonautoimmune and non-insulin sensitive had been diagnosed with type 2 diabetes by their physicians and had traditional characteristics of type 2 diabetes: a higher probability of belonging to a racial/ethnic minority; a typically later age of onset (after onset of puberty); and a high prevalence of obesity.

Youth in the autoimmune and non-insulin sensitive group mostly had been diagnosed by their own doctors as having type 1 diabetes, although they had an older average onset age (12.9 years), a smaller proportion of non-Hispanic white ethnicity, and a higher prevalence of obesity. As this group did not differ significantly in other measures from youth with autoimmunity who are insulin-sensitive, the scientists hypothesize that this group represents individuals with type 1 diabetes who are obese, which is accompanied by abnormal metabolic function causing insulin resistance. It would be valuable to study further this group to determine whether their clinical course is different from insulin-sensitive youth with type 1 diabetes, including the development of diabetes-related complications. Most of the participants in the final group, nonautoimmune and insulin-sensitive, had originally been diagnosed with type 1 diabetes. These youth had many characteristics consistent with this diagnosis: early age of onset (9.4 years); mostly non-Hispanic white origin; and a low prevalence of obesity. The scientists hypothesize that this group could represent people with type 1 diabetes who lacked the traditional markers of autoimmunity at the time of testing.

The results of this study offer researchers and clinicians a marker-based method for diabetes classification and provide definitions of diabetes type using this approach. In this study, most pediatric diabetes fell into groups that align with traditional descriptions of type 1 and 2 diabetes, and provider classification agreed well with this approach. In addition to providing information to improve diabetes type diagnosis, this approach will allow scientists to better understand the course of diabetes in youth.

Dabelea D, Pihoker C, Talton JW, et al. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 34: 1628-1633, 2011.

GENETICS OF TYPE 2 DIABETES INFORMS PREVENTION STRATEGY

Gene Variants Influence the Effectiveness of a Diabetes Prevention Approach: Geneticists have recently shown that variants of a gene called *SLC47A1* can have a significant impact on the ability of the medication metformin to prevent diabetes. Metformin is a well-tolerated, generic medicine that has for decades been the first-line treatment for most people with type 2 diabetes. The NIDDK's landmark Diabetes Prevention Program (DPP) clinical trial tested two approaches to preventing type 2 diabetes in a multi-ethnic group of people at high risk for the disease: metformin, and a lifestyle modification approach designed to achieve 7 percent weight loss through diet and exercise. The DPP found that both interventions were effective at delaying or preventing the development of diabetes. The lifestyle intervention was particularly so, reducing the rate of diabetes by 58 percent compared to a control group that received standard counseling and a placebo. Metformin reduced risk of diabetes by 31 percent relative to the same control group. Recent advances in understanding the genetics of type 2 diabetes now provide the opportunity to assess the interaction between risk genes and the DPP interventions, which may one day enable personalized care to optimize prevention of the disease in those at risk.

The new study investigated genetic variations in (or near) any of 40 genes that had been previously identified as affecting risk for diabetes, as well as genes in which mutations cause rare forms of diabetes and genes involved in drug metabolism. Specifically, the researchers determined whether any of the genes had a significant impact on which DPP participants developed diabetes, and whether any influenced the effectiveness of metformin or the lifestyle intervention. Although they found that several of these gene variants seemed to be increased in the patients that went on to develop diabetes, none achieved clear statistical significance. Although this finding may seem to be at odds with previous research, there are several reasons why this was not unexpected. Because the cohort of the DPP was known to be at particularly high risk of diabetes, for example, as a group they were expected to be enriched in high-risk variants of many of the genes. And importantly, most of the participants in the DPP received interventions that helped prevent diabetes, effectively blunting the impact of genes which ordinarily contribute only modestly to the risk of diabetes.

The researchers also found that the lifestyle intervention was effective regardless of genetic risk factors. Thus, even people with a high genetic risk of type 2 diabetes can reduce their likelihood of developing the disease by maintaining a healthful lifestyle. But intriguingly, the researchers found that while metformin was quite effective for preventing diabetes in the majority of the DPP participants, about a third of the group, those with a distinct version of *SLC47A1*, appeared to receive no diabetes protection at all from the medication. *SLC47A1* encodes a protein known to be involved in clearing metformin from the body, and, in a prior study, the gene had been found to influence the ability of metformin to control diabetes in people who already have the disease. The new research supports and extends that result, showing the gene also can affect diabetes prevention. Taken together with the earlier study, this research suggests that while metformin is highly effective for lowering blood glucose and/or preventing diabetes in the majority of people to whom it is prescribed, almost a third of patients may have a response to metformin that is less robust. A genetic test may one day be available to help tailor diabetes prevention or therapeutic approaches to specific people, and the characterization of genes associated with diabetes may lead to new therapeutic strategies. Importantly, no genetic or demographic characteristic has yet been found to render the DPP lifestyle intervention ineffective: research continues to show that it is a powerful approach for preventing type 2 diabetes in people at high risk for the disease.

Jablonski KA, McAteer JB, de Bakker PIW, et al. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the Diabetes Prevention Program. Diabetes 59: 2672-2681, 2010.

RESEARCH ON NEW THERAPIES FOR TYPE 2 DIABETES

Designing New and Improved Type 2 Diabetes Drugs: Researchers have identified experimental drugs that are as effective in mice as current medications for type 2 diabetes, but cause fewer side effects. A hallmark of type 2 diabetes is that cells become resistant, or less sensitive, to the action of insulin. Some current type 2 diabetes drugs target a protein called PPARγ, which is known to regulate insulin sensitivity. The drugs make the body more sensitive to insulin but come with unwanted side effects, such as fluid retention, weight gain, bone loss, and an increased risk of heart failure. In previous research, scientists discovered that a specific chemical modification (phosphorylation) to PPARγ leads to the abnormal regulation of a number of genes related to obesity and insulin sensitivity in mice. They also found that the current diabetes drugs block this modification in people with type 2 diabetes, thus countering insulin resistance. However, the drugs also broadly stimulate PPARγ, which the scientists thought was responsible for the negative side effects.

In new research, the scientists built on this finding to search for drugs that block phosphorylation of PPARγ without broadly stimulating it, with the hope that the drugs would improve insulin sensitivity without causing the unwanted side effects. Toward that goal, the scientists selected a compound that binds strongly to PPARγ, but does not broadly stimulate it. Next, they generated a series of similar compounds and searched for ones that blocked phosphorylation of PPARγ. They focused on one promising compound that, when tested in diabetic mice, improved insulin sensitivity without

causing fluid retention or weight gain. The compound also had no detrimental effect on bone formation in cultured laboratory cells, whereas current drugs do interfere with bone formation in the cells. Although additional research is needed before potential new drugs could be tested in people, this exciting finding suggests that it may be possible to develop a new class of type 2 diabetes drugs that improve insulin sensitivity but that have fewer negative side effects.

Choi JH, Banks AS, Kamenecka TM, et al. Antidiabetic actions of a non-agonist PPARγ ligand blocking Cdk5-mediated phosphorylation. Nature 477: 477-481, 2011.

Natural Product Has Potential To Combat Type 2 Diabetes: Scientists have identified a natural product that improves metabolic abnormalities associated with type 2 diabetes in mice, and are now testing the product in people. Fatty liver is strongly associated with insulin resistance and type 2 diabetes. One possible approach to reduce fatty liver is through promoting bile acid synthesis. Bile acids are made in the liver and have a role in processing dietary fats; high levels of bile acids reduce fatty liver. A protein called LRH-1 is known to regulate bile acid synthesis; it is one of a group of proteins called nuclear receptors, which regulate diverse aspects of metabolism. Researchers looked for compounds that could activate LRH-1 and potentially promote bile acid synthesis and reduce fatty liver. Through screening, they identified compounds called phosphatidylcholines (PCs) that activated LRH-1. PCs are a type of lipid (fat) and a major component of cellular membranes; they are found in many foods such as eggs and soy. Although not all PCs activated bile acid synthesis, one particular PC, called DLPC, did, and the scientists also further studied it because it is a natural product. In two mouse models of insulin resistance, DLPC treatment increased bile acid levels, decreased fatty liver, and increased insulin sensitivity. In contrast, DLPC treatment had no effect on mice that were genetically engineered to lack LRH-1 in their livers, suggesting that DLPC was exerting its beneficial effects through LRH-1 either directly or indirectly. While the precise mechanism underlying DLPC's effects remains to be determined, the research suggests that DLPC is a promising compound for the prevention or treatment of metabolic disorders, such as type 2 diabetes. Based on the findings, the researchers have begun a human clinical trial to explore the potential benefits of DLPC treatment in people with prediabetes.

Lee JM, Lee YK, Mamrosh JL, et al. A nuclear-receptor-dependent phosphatidylcholine pathway with antidiabetic effects. Nature 474: 506-510, 2011.

Vitamin D May Help More Than Just Bones—It May Also Help Prevent Diabetes: Results from a clinical trial suggest that vitamin D supplementation could aid efforts to delay development of type 2 diabetes in people at high risk. In addition to known risk factors such as family history, older age, and obesity, nutrient status may contribute to the development of type 2 diabetes. For example, several studies had previously suggested that lower vitamin D status or lower calcium intake may be associated with greater risk for diabetes. However, whether improving levels of these nutrients could have any effect on risk reduction had not been rigorously tested. In a recent clinical trial, researchers investigated whether, in adults at high risk for type 2 diabetes, short-term vitamin D and/or calcium supplementation could improve three indicators of diabetes risk: an assessment of pancreatic beta cell function; insulin sensitivity; and blood glucose measures such as HbA1c, a test that indicates average blood glucose levels over the previous 2 to 3 months.

Ninety-two women and men were randomly assigned to one of four daily supplement groups. People in these groups received either (1) placebo, (2) vitamin D supplements only, (3) calcium supplements only, or (4) both vitamin D and calcium supplements for 16 weeks. During that time, participants were asked to maintain their normal diets, but to avoid taking vitamin D, calcium, or other supplements of their own, beyond what was provided for the study. When the researchers compared measurements taken at the start of the trial period to those at the end, they found that the "disposition index"—a calculation that is used to assess how well the insulin-producing beta cells compensate for altered insulin sensitivity—not only improved significantly in participants who received vitamin D supplements, but it also worsened in those who did not. Changes in insulin sensitivity and in HbA1c did not differ significantly between the groups during the course of the trial, although researchers observed a slight trend toward improved HbA1c in people who received vitamin D. The use or lack of calcium supplements

did not appear to affect any of the risk indicators. Because declining beta cell function is an early step in progression to type 2 diabetes, therapies that improve or preserve function could help stave off disease.

While longer-term, larger studies will be necessary to further assess the effects of vitamin D and to determine levels of supplementation that are potentially both safe and effective, the results of this study suggest that addition of vitamin D supplements might turn out to be a simple intervention that can help prevent or delay progression to type 2 diabetes in people at high risk.

Mitri J, Dawson-Hughes B, Hu FB, and Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. Am J Clin Nutr 94: 486-494, 2011.

DELAYING PROGRESSION OF TYPE 1 DIABETES

Results from Clinical Trials Testing Strategies To Halt Type 1 Diabetes: Researchers in the NIDDK's Type 1 Diabetes TrialNet reported results from two clinical trials aimed at slowing progression of type 1 diabetes. Both trials tested agents that could potentially intervene in the immune attack that destroys insulin-producing β (beta) cells. The goal of the trials was to stop the immune system from destroying remaining β cells—and thus preserve insulin production—in people with newly diagnosed type 1 diabetes. This goal is important because preservation of insulin production is associated with reduced risk for diabetes complications.

The first trial tested a drug called abatacept, which affects immune system cells (T cells) that are known to be involved in type 1 diabetes. Scientists tested whether administering infusions of the drug over a 2-year period could slow progression of the disease in people with new-onset type 1 diabetes. The results showed that abatacept slowed disease progression for 6 to 9 months compared to placebo. After that time, the effect of the drug diminished, and rate of loss of insulin production was similar in the abatacept and placebo groups. However, because of the initial beneficial effects of the drug, after 2 years, people in the abatacept group produced 59 percent more C-peptide, a marker of insulin production, compared to people in the placebo group. These results suggest that abatacept slowed disease progression and preserved patients' β cell function. A second trial focused on a protein called GAD, which is a known target in the immune system attack on β cells in type 1 diabetes. Researchers tested a vaccine against GAD to see if it could dampen the immune response and slow disease progression in newly diagnosed patients. The results showed no difference in C-peptide production after 1 year in people who received the vaccine compared to people who received placebo, demonstrating that the GAD vaccine did not slow type 1 diabetes disease progression.

These results show that, in people with new-onset type 1 diabetes, abatacept slowed disease progression and preserved patients' insulin production, while a GAD vaccine had no effect. Because additional research is needed to understand better the importance of the benefits compared to the risks of treatment, abatacept is not recommended for treating type 1 diabetes in clinical practice at this time. However, the abatacept trial shed light on the biology of type 1 diabetes which could lead to more effective and safer future therapies. For example, the observation that abatacept was effective in the first 6 to 9 months after disease diagnosis suggests that it may be valuable to explore therapies affecting T cells early in the course of disease. It also suggests that combination therapy, which may involve the use of different agents at different stages of disease progression, may be beneficial. Thus, in addition to identifying a possible new therapy for type 1 diabetes, the results may also help to inform the design of future clinical trials to combat the disease.

Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 378: 319-327, 2011.

Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 378: 412-419, 2011.

UNDERSTANDING BARRIERS TO TYPE 1 DIABETES CARE

Finding Ways To Combat Self-imposed Insulin Restriction in Women with Type 1 Diabetes:

Researchers have identified factors linked with some women's decisions to take insufficient insulin to properly manage their type 1 diabetes (insulin restriction). Some women with type 1 diabetes intentionally take less insulin than prescribed by their doctors—usually because of the fear of gaining weight and problems with diabetes self-care—and thus do not achieve optimal blood glucose control. Insulin restriction is a serious health issue because good blood glucose control reduces the risk of long-term diabetes complications. Indeed, researchers conducted an 11-year follow-up study of women with type 1 diabetes, 30 percent of whom reported restricting insulin at baseline. In this previous research, they discovered that insulin restriction was associated not only with increased rates of diabetes complications, but also with increased risk of premature death. These findings underscore the need to find ways to prevent or help women stop insulin restriction to improve their health.

In new research, the same group of scientists examined the same population of women, but looked at factors associated with decisions to start or stop insulin restriction over the 11-year follow-up period. The results showed that women who stopped restriction reported improved diabetes self-care, fewer problems with diabetes self-management, and less fear that taking insulin would cause weight gain. In contrast, women who started insulin restriction were fearful of weight gain. Overall, fear of weight gain and problems with diabetes self-care were core issues associated with women's decisions to start or stop insulin restriction. The researchers also looked at actual weight gain and found that the result was the exact opposite of the fears: women who stopped restricting did not gain weight, while the insulin restrictors gained weight. This observation could potentially be used by doctors as a tool to help women with type 1 diabetes manage concerns about weight gain, and thus help avoid insulin restriction. Overall, this study sheds light on core issues surrounding women's decisions to restrict insulin and highlights the importance of health care providers' assessing and addressing insulin management as well as any weight concerns or symptoms of eating disorders when treating women with type 1 diabetes. These insights could also inform future research to develop and test new intervention strategies that could more effectively prevent insulin restriction and help those who use this practice to return to healthier insulin administration and to address related weight and other concerns, so that they could enjoy better health.

Goebel-Fabbri AE, Anderson BJ, Fikkan J, Franko DL, Pearson K, and Weinger K. Improvement and emergence of insulin restriction in women with type 1 diabetes. Diabetes Care 34: 545-550, 2011.

DIABETES COMPLICATIONS

Predicting and Slowing Development of Cardiovascular Disease in Type 1 Diabetes:

Researchers have made advances in identifying biological predictors and a strategy to slow progression of cardiovascular disease in people with type 1 diabetes. Type 1 diabetes, like type 2 diabetes, is associated with an array of serious, long-term complications, such as cardiovascular disease. In people with and without diabetes, plaque—made of fat, cholesterol, calcium, and other molecules found in blood—can build up in a person's arteries, leading to a condition called atherosclerosis. As the plaque collects and hardens, it can narrow the arteries, reduce the flow of oxygen-rich blood to parts of the body, and potentially lead to heart attack or stroke. People with diabetes have a greatly increased risk for cardiovascular disease.

In a recent study, researchers investigated the long-term effects of intensive blood glucose control on the progression of atherosclerosis in participants of the NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up study, called the Epidemiology of Diabetes Interventions and Complications (EDIC). The DCCT showed that intensive control of blood glucose levels reduced the risk of complications of the kidneys, eyes, and nerves in people with type 1 diabetes. Previous results from EDIC demonstrated that people who had been intensively treated during the DCCT had fewer than half the number of cardiovascular disease events than those who received treatment that was conventional at the time. In the recent study, the researchers found

that people in the intensive glucose control group had slowed atherosclerosis progression 6 years after the end of DCCT compared to the conventional group, but that this slowing did not continue in years 6-12. Since development of atherosclerosis in the intensive group progressed more slowly in years 1-6 following the end of the DCCT, this group still demonstrated an overall beneficial effect of the prior intensive treatment 13 years after the DCCT. These results support the recommendation that people with type 1 diabetes implement early and continued intensive blood glucose control to slow atherosclerosis.

In other recent studies, researchers examined whether the presence of a marker called "oxidized low-density lipoprotein," or oxLDL, could predict risk for cardiovascular events. LDL, sometimes called "bad" cholesterol, carries fats in the blood to parts of the body. Modified forms of LDL are recognized by immune system proteins which bind them; these complexes are known as "oxLDL-IC." In both studies, the researchers measured oxLDL-IC levels in samples collected from a subset of participants in the DCCT when they first joined the trial. Then, they examined whether there was a correlation between oxLDL-IC levels and signs of atherosclerosis that were measured in the same people after 8 to 20 years as part of EDIC. Both studies found that increased levels of oxLDL-IC were predictive of later atherosclerosis in people with type 1 diabetes. In one of the studies, the researchers found that another immune complex with a differently modified LDL was also associated with signs of later atherosclerosis. Not only do these studies suggest a pathogenic role for modified LDL immune complexes, but they also indicate that measures of these factors may help to identify people at high risk for cardiovascular disease.

After the DCCT ended, more than 95 percent of the participants enrolled in the EDIC follow-up study. As reported in these three advances, because of the long-term commitment of these participants, researchers are adding new knowledge to the understanding of cardiovascular disease and demonstrating the importance of intensive blood glucose control in people with type 1 diabetes.

Lopes-Virella MF, Baker NL, Hunt KJ, et al. Oxidized LDL immune complexes and coronary artery calcification in type 1 diabetes. Atherosclerosis 214: 462-467, 2011.

Lopes-Virella MF, Hunt KJ, Baker NL, et al. Levels of oxidized LDL and advanced glycation end products-modified LDL in circulating immune complexes are strongly associated with increased levels of carotid intima-media thickness and its progression in type 1 diabetes. Diabetes 60: 582-589, 2011.

Polak JF, Backlund J-YC, Cleary PA, et al. Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes 60: 607-613, 2011.

Study Links Prediabetes with Periodontal Disease: Dentists have long known that their patients with diabetes (both type 1 and type 2 diabetes) have an elevated risk of periodontitis, defined as chronic inflammation of the soft tissue around the teeth and deterioration of the network of the fibers that connect teeth to the surrounding bone. In addition to the swollen, tender gums that bleed easily and are the first manifestations of periodontitis, the progressive diminishment of the attaching fibers can lead to tooth loss. It is not yet known why diabetes and periodontitis are frequently associated with one another. One possible explanation is that elevated glucose levels in oral tissues might create an environment conducive to promoting gum disease. Alternatively, the inflammation that is characteristic of periodontitis might promote insulin resistance. Indeed, both of these hypotheses could be correct, with the two diseases reinforcing one another. Interestingly, new research shows that periodontitis is also associated with increased levels of glucose below the threshold for diabetes. To better understand the relationship between oral health and elevated blood glucose, researchers assessed the periodontal health and fasting plasma glucose levels of more than 12,000 participants in the National Health and Nutrition Examination Survey III. The examiners used two different measures of oral health that are commonly used to diagnose periodontitis—"clinical attachment loss" and "pocket depth"—and stratified the participants into equally sized groups ranging from very healthy to serious periodontitis for each measure. Then they looked for the presence of type 2 diabetes and prediabetes (which refers to blood glucose levels that are elevated, but not as high as in diabetes, a condition associated with increased risk

of later developing type 2 diabetes) in each group. As expected, diabetes was most prevalent in the group with the most serious periodontitis (by either measure). Interestingly, there was also a strong correlation between prediabetes and periodontitis. Although it is tempting to conclude from this that periodontitis often precedes and may therefore promote diabetes, it is important to note that this study did not follow the participants over time, so the researchers could not determine whether fasting glucose levels rose from prediabetic to diabetic levels more quickly in people with periodontitis than in those without it. In any case, the results underline the importance of determining the biological link between these chronic inflammatory diseases through further research. The findings are also of clinical importance, because they suggest that screening for periodontal disease, along with a concerted effort to improve and maintain oral health, may be particularly important not only for people with diabetes, but also for those with prediabetes. Further, because periodontitis is now clearly known to be a risk factor for elevated blood glucose levels, it may be advisable for people with the disease to consider testing for undiagnosed diabetes or prediabetes.

Choi Y-H, McKeown RE, Mayer-Davis EJ, et al. Association between periodontitis and impaired fasting glucose and diabetes. Diabetes Care 34: 381-386, 2011.

NEW INSIGHTS ON RARE METABOLIC DISEASE

Potential New Treatment for Niemann-Pick Type C: Scientists have identified a class of drugs that corrects a defect in cells from people with a rare genetic disease called Neimann-Pick type C (NPC). NPC is a disease in which the body cannot properly break down lipids, which include cholesterol and other fats. This leads to too much cholesterol in the liver and spleen, and excessive amounts of other fats in the brain; NPC is thus referred to as a lipid storage disease. NPC may be diagnosed at any age, but is most often diagnosed in middle to late childhood. NPC is a fatal disease, with children often living only until their teenage or early adult years. Previous research identified two genes—*NPC1* and *NPC2*—that are linked to NPC; defects in the *NPC1* gene account for about 90 percent of NPC cases. In new research, scientists focused on a class of drugs called histone deacetylase (HDAC) inhibitors to examine if they could prevent or reduce the excess fat accumulation in NPC cells. Many HDAC inhibitors have been tested in people with a variety of diseases and have been found to be safe; two HDAC inhibitors have been approved by the U.S. Food and Drug Administration for treating certain forms of cancer. In the study, researchers used cultured human cells that had a mutation in the *NPC1* gene. Before treatment with HDAC inhibitors, cholesterol was trapped within the cells. Dramatically, after treatment, cholesterol was no longer trapped, and the cells appeared to function like normal, unaffected cells. In contrast, HDAC inhibitors were ineffective in treating human cells carrying a defect in the *NPC2* gene, suggesting that the beneficial effect may be specific to cells with an *NPC1* gene defect. HDAC inhibitor therapy will have to be tested in clinical trials of NPC patients, but this exciting research has opened up a new avenue for possibly treating some people with this rare, devastating disease.

Pipalia NH, Cosner CC, Huang A, et al. Histone deacetylase inhibitor treatment dramatically reduces cholesterol accumulation in Niemann-Pick type C1 mutant human fibroblasts. Proc Natl Acad Sci USA 108: 5620-5625, 2011.

Diabetes Research Strategic Plan: Building on Advances, Seizing Opportunities

In late February 2011, the NIDDK announced the publication of a new blueprint for diabetes research supported by the NIH and other federal agencies. Entitled *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee*, this multi-faceted strategic plan identifies compelling opportunities for research over the next decade on diabetes and its complications. Spanning basic, clinical, behavioral, and translational research, the report features advances, key questions, and future directions in 10 major diabetes research areas. It also addresses the need for technological and human resources to accelerate discovery. Developed with input from researchers, patient advocates, and the public, the report is a guide for research efforts that can benefit the tens of millions of Americans who are living with, or at risk for, diabetes and its complications.

Organization and Purpose

The *Strategic Plan* is framed around major scientific areas representing important opportunities in research on all forms of diabetes. These 10 areas are overlapping but complementary in scope:

- Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications
- Type 1 Diabetes and Autoimmunity
- The Beta Cell
- Type 2 Diabetes As a Multi-Dimensional Disease
- Obesity
- Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia
- Clinical Research and Clinical Trials
- Special Needs for Special Populations
- Diabetes Complications
- Clinical Research to Practice: Translational Research

Each of the 10 chapters in the *Strategic Plan* addressing these areas of scientific opportunity includes an introduction, summaries of recent research advances, key questions and future directions (goals) for research, and a closing section describing how the research directions outlined in the chapter may transform the health of people with or at risk of diabetes. The *Strategic Plan* also includes a chapter that outlines resource and infrastructure development needs to support the implementation of the future directions for diabetes research.

Tackling diabetes from multiple angles, the goal of the *Strategic Plan* is to accelerate discovery on several fronts, including the relationship between obesity and type 2 diabetes, and how both conditions are affected by genetics and environment; the autoimmune mechanisms at work in type 1 diabetes, and the emerging role of the immune system in type 2 diabetes; the biology of beta cells, which release insulin in the pancreas and represent potential for therapy or a cure; the development of artificial pancreas technologies that could help to alleviate the burden of therapy on people with type 1 diabetes while preserving their health; prevention

of diabetes health complications that affect the heart, eyes, kidneys, nervous system, and other organs; and reduction of the impact of type 2 diabetes on groups disproportionately affected by the disease, including the elderly and racial and ethnic minorities in the United States. Through seizing upon opportunities outlined in the *Strategic Plan*, the hope is to more quickly erase the scourge of diabetes and improve the health of patients, their families, and the Nation.

Origin of the *Diabetes Research Strategic Plan*

In 1999, the congressionally established Diabetes Research Working Group issued a comprehensive plan for diabetes research, entitled *Conquering Diabetes: A Strategic Plan for the 21st Century*. This report was the culmination of the vigorous efforts of the Working Group, a committee of leading extramural diabetes experts. In the years since that plan was released, there have been major advances in the understanding of diabetes, new tools and technologies have been developed, and strategies for diabetes prevention and treatment have been expanded. Many of these scientific successes are directly linked to ideas and goals set forth in the 1999 plan, which has served to guide the NIH's planning activities for fostering discovery in diabetes. In 2002, the NIDDK published *A Scientific Progress Report on the Diabetes Research Working Group's Strategic Plan*, which highlighted program efforts, research advances, and scientific opportunities.

In 2006, the NIH published *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*, a report that described opportunities that would inform research on many areas of commonality between type 1 and type 2 diabetes, but with a primary focus on type 1 diabetes research. This report was developed under the auspices of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), a statutory committee established in 1974. Chaired by the NIDDK, the DMICC facilitates cooperation, communication, and collaboration on diabetes efforts across the federal government.

In late 2008, the DMICC determined that the time was right to embark on an update of both previous diabetes research plans by identifying the most promising, up-to-date, high-priority opportunities for diabetes research that could build on recent advances and be accomplished over the next 5 to 10 years. The ensuing effort resulted in the new *Diabetes Research Strategic Plan*.

A Collaborative Planning Process

The *Strategic Plan* was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing diabetes research. These volunteers were assembled into working groups to address each of 10 scientific areas of important opportunity related to diabetes. An additional working group composed of representatives from each of the other 10 groups addressed overarching needs for scientific expertise, tools, technologies, and shared research resources. Each working group was chaired by a scientist external to the NIH and was composed of additional external scientific experts, as well as representatives of DMICC member organizations and diabetes voluntary organizations. Working groups met through conference calls and electronic exchanges to assess the state of the science and identify advances and emerging opportunities in their scientific areas.

An overarching *Diabetes Research Strategic Plan* Leadership Group was formed of the chairs of the 11 working groups and representatives from the federal government and diabetes voluntary organizations. This overarching working group met in person on July 7, 2009, to review progress of the scientific working groups and ensure that the *Strategic Plan* was comprehensive and addressed the most compelling opportunities for prevention, therapy, and cure of diabetes and its complications. In 2010, a draft of the *Strategic Plan* was posted on the NIDDK web-site to provide an opportunity for broad public input prior to completion and publication of the final plan.

Implementation of the *Diabetes Research Strategic Plan*

The *Diabetes Research Strategic Plan* is part of a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities for diabetes research are identified. The DMICC will continue to play a key role by assessing progress toward the research goals described

in the *Strategic Plan*. The NIH will also continue to solicit broad external input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH, other DMICC member organizations, and the scientific community will use the research questions and future directions described in the *Strategic Plan* as a scientific guidepost to enhance fundamental understanding of diabetes, improve current treatment strategies, and identify ways to prevent or cure diabetes and its complications.

Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee is available electronically on the NIDDK web-site at *http://diabetesplan.niddk.nih.gov*

Hard copies of this *Strategic Plan* may also be ordered from the National Diabetes Information Clearinghouse at *http://catalog.niddk.nih.gov*

The Special Statutory Funding Program for Type 1 Diabetes Research

The *Special Statutory Funding Program for Type 1 Diabetes Research (Program)* is a special appropriation dedicated to supporting research on the prevention and cure of type 1 diabetes. On behalf of the Secretary of the U.S. Department of Health and Human Services (HHS), the NIDDK administers the *Program* in collaboration with multiple NIH Institutes and Centers and the Centers for Disease Control and Prevention (CDC). This funding program augments regularly appropriated funds that the NIH receives for diabetes research.

NIDDK Director Dr. Griffin Rodgers received the 2011 JDRF Children's Congress Hero Award—the JDRF's top honor—for his steadfast commitment to research on type 1 diabetes. Pictured with Dr. Rodgers (center) are JDRF Chairman, Board of Directors Mr. Frank Ingrassia (left) and JDRF President and CEO Mr. Jeffrey Brewer (right).
Photo credit: Juvenile Diabetes Research Foundation International

Renewal of the *Program*—
New Research Opportunities

Special funding for type 1 diabetes research was initially provided in fiscal year (FY) 1998 for $30 million a year, and has since been renewed and augmented. In December 2010, the *Program* was renewed for $150 million each year for FY 2012 and 2013. Since 1998, the *Program* has provided $1.89 billion for research on type 1 diabetes.

To receive input on emerging research opportunities that could be pursued with the recent *Program* reauthorization and funding renewal, the NIDDK convened a panel of scientists from across the country and others with expertise in type 1 diabetes in May 2011. The panel was asked to provide input on draft concepts, put forth by the NIH and CDC, for initiatives that could be supported with the funds. Based on input from the panel, and with consideration of research opportunities outlined in the recent *Diabetes Research Strategic Plan* (see this chapter), the NIH plans to pursue several new initiative concepts in FY 2012-2013.

Evaluating the *Program*—
Research Advances and Innovation

The law that previously renewed the *Program* also mandated that an evaluation of the *Program* be submitted to the Congress by January 1, 2011. To meet this requirement, the NIDDK submitted the evaluation report to the Congress in December 2010. This report describes the unique, innovative, and collaborative research consortia and clinical trials networks enabled by the *Program*, as well as the scientific accomplishments that have emerged.

As described in the evaluation report, assessment of the *Program* indicated that it has produced significant scientific advances; yielded robust scientific output; led to issuance of new patents; promoted development of resources for use by the broad scientific community; fostered clinical research; and attracted new scientists to the study of type 1 diabetes. In addition, the evaluation report contains profiles of people participating in clinical research supported by the *Program* and profiles of scientists whose studies have been supported by the special funds, including the late Dr. Mark Pescovitz. This report can be found at *www.t1diabetes.nih.gov/evaluation2010*

NIDDK Director Dr. Griffin Rodgers Testifies to Congress on Type 1 Diabetes Research

On June 22, 2011, NIDDK Director Dr. Griffin P. Rodgers was invited to testify about progress in type 1 diabetes research before the Senate Committee on Homeland Security and Governmental Affairs. The hearing, entitled "Transforming Lives Through Diabetes Research," was chaired by Senators Joseph Lieberman and Susan Collins. Dr. Rodgers spoke of research made possible by the *Program*, including progress from studies to identify the environmental factors that cause type 1 diabetes, and advances in developing and testing artificial pancreas systems. A hearing on type 1 diabetes research is held every 2 years in conjunction with the Juvenile Diabetes Research Foundation International (JDRF) Children's Congress. The previous day, Dr. Rodgers received the 2011 JDRF Children's Congress Hero Award for his work in advancing type 1 diabetes research and improving the lives of people affected by the disease.

At a June 2011 congressional hearing on type 1 diabetes, JDRF Children's Congress delegates (foreground) listened to testimony from (at table, left to right) JDRF Celebrity Advocate Co-chair, and actor, Mr. Kevin Kline; NIDDK Director Dr. Griffin Rodgers; and Chair of the FDA Artificial Pancreas Critical Path Initiative, Dr. Charles Zimliki. Several of the children also spoke at the hearing, describing their experiences with this disease and the importance of research (see Patient Profile in this chapter).
Photo credit: Juvenile Diabetes Research Foundation International

Coordinating the Coordinators: NIDDK Brings Together Type 1 Diabetes Study Coordinators To Exchange Ideas and Best Practices

People who have or are at risk for type 1 diabetes have made enormous contributions to research on this disease by participating in clinical studies. Their efforts clearly demonstrate a commitment to finding a way to prevent or cure the disease and to helping others who are or may be diagnosed. Alongside these passionate participants work another group of people dedicated to this cause—the type 1 diabetes clinical study coordinators. The NIDDK broke new ground in September 2011 with its first joint study coordinator meeting for several type 1 diabetes clinical research studies supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*. Coordinators from The Environmental Determinants of Diabetes in the Young (TEDDY); the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC); Type 1 Diabetes TrialNet; Search for Diabetes in Youth (SEARCH); and Trial to Reduce IDDM in the Genetically at Risk (TRIGR) met to exchange ideas and best practices, share challenges, and discuss professional development.

Although each of these studies aims to change the course of type 1 diabetes in the United States and around the world, they have different goals. For example:

- SEARCH is providing nationwide data on the percent or proportion of children with diabetes (prevalence), the rates of development of childhood diabetes (incidence), and whether these rates and the clinical course of diabetes in children and youth are changing over time.
- The TEDDY and TRIGR studies aim to identify the environmental triggers of type 1 diabetes, to inform the development of prevention approaches. These two studies have enrolled newborns who are at high genetic risk for the disease, and will evaluate potential triggers such as viruses and hygiene (TEDDY) and a protein in cow's milk (TRIGR).
- TrialNet is testing strategies to prevent or delay progression of type 1 diabetes in people at high risk for or newly diagnosed with type 1 diabetes.
- DCCT/EDIC continues to examine the benefit of intensive blood glucose control on the development of complications in people who have had type 1 diabetes for more than 30 years.

Though these studies include people at different stages of disease progression and of varying ages, they are all long-term studies that are dependent on participants to achieve their goals.

The study coordinator is an integral component of any type 1 diabetes clinical study. These studies require dedicated staff to find, recruit, screen, and enroll individuals. For example, studies related to type 1 diabetes prevention require screening tens or hundreds of thousands of people to identify those eligible for enrollment. Once participants are enrolled, it is critical that they remain active in the study and carry out the protocol as planned. Coordinators wear any number of different hats, working tirelessly to recruit and retain study volunteers, collecting key samples and data from participant visits, maintaining excellent data quality, providing critical input to protocol development, and even designing ancillary studies.

For DCCT/EDIC coordinators specifically, this effort has been nearly 3 decades of dedication—a key reason why about 95 percent of the original participants of the DCCT are involved in its EDIC follow-up study. The landmark DCCT/EDIC demonstrated that intensive control of blood glucose levels can have long-lasting effects toward reducing the onset and progression of diabetes complications involving the kidney, eyes, nerves, and heart. These findings revolutionized clinical management of type 1 diabetes and translated into dramatic health benefits for all people with type 1 diabetes. At the conclusion of DCCT, participants were recruited to EDIC. EDIC study coordinators have faced significant challenges in conducting this long-term investigation. For example, participants move geographically and "burn out" with the demands of participating in a study, and EDIC staff

changes over time. However, EDIC study coordinators have found ways to meet these challenges, such as by developing flexible scheduling, maintaining strong participant-staff bonds, and always leaving the door open so that participants who need to take a break from the study can return at any time. The role of the EDIC study coordinator has evolved as well; study coordinators have a dynamic role and are voting members of the study group, chair study committees, and serve as co-investigators on several ancillary studies. This increased autonomy, accountability, and responsibility have contributed to high job satisfaction, high-quality data collection, and exemplary patient retention, making EDIC an excellent model for other clinical studies in type 1 diabetes.

The other studies represented at the September 2011 meeting also face significant challenges. Study protocols can be demanding, requiring study coordinators to encourage volunteers to remain engaged. For example, participation in TEDDY requires families to dedicate a significant investment of time and effort, which can become overwhelming. Parents need to stay motivated in collecting their child's stool samples and taking their child for blood draws on a regular basis, which are key components of the study. Indeed, hundreds of thousands of samples have already been collected for analysis or storage for future analysis of possible triggers of type 1 diabetes. Some TrialNet protocols require participants to receive multiple infusions of a drug over 2 years; others involve daily infusions for 14 consecutive days and still others call for overnight stays in the clinic. Additionally, these studies are long term, requiring participants to stay involved with the study for years, even decades. For example, SEARCH asks children to return for follow-up clinical visits 1, 2, and 5 years after the initial visit. TRIGR is following children until age 10 with annual clinical visits after 2 years, whereas TEDDY is following children until age 15 with continued sample collection and clinical visits. The study coordinators also have an important role in easing anxiety experienced by study participants and their families. For instance, in TrialNet, volunteers are asked to participate in repeat screenings and to return year after year even if they currently have no signs of the disease, in order to identify individuals at risk for developing type 1 diabetes, and to offer them an opportunity to participate in prevention trials. This annual screening can be anxiety provoking, with the possibility of finding out that the individual or their child has signs of type 1 diabetes. However, the study coordinators are there to help families cope with anxiety. The challenges of keeping participants motivated in demanding protocols, retaining volunteers for decades of follow up, and providing support through stressful procedures are important considerations for the study coordinators.

The meeting provided an opportunity for coordinators to share their studies' resources and creative solutions to problems and develop ways to improve efficiency, cooperation, and, ultimately, study success. In breakout sessions, they brainstormed new recruitment and retention tools like social media, the role study coordinators can play in study design, and professional development strategies. Group discussions highlighted several opportunities for enrichment and coordination, including the formation of a network of type 1 diabetes study coordinators to increase communication and collaboration among the studies. The study coordinators also suggested future meeting topics, reflecting the synergy generated by meeting face-to-face. By convening the meeting to create opportunities to improve the recruitment and retention of participants and to invigorate the study coordinators, the NIDDK recognizes the value and commitment of each and every participant and study coordinator, and remains dedicated to the goals of preventing and curing type 1 diabetes.

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HEALTHY Schools, Healthier Students

Thirty years ago, type 2 diabetes, which often develops in people with overweight or obesity, was referred to as "adult onset" diabetes because it most often develops in people who are middle-aged or elderly. In fact, at the time, type 2 diabetes was unknown in children; when diabetes struck in childhood, it was type 1 diabetes, often referred to as "juvenile" diabetes. Unfortunately, the trend in this country toward larger waistlines is not restricted to adults. National data indicate that about 17 percent of children between 6 and 19 years of age are obese, and another 15 percent are overweight. Rates of obesity are even higher in those who are economically disadvantaged and in ethnic minority groups. Type 2 diabetes now represents 33 percent of newly diagnosed diabetes cases in 10 to 19 year olds, and accounts for the majority of new cases of diabetes among adolescents in certain racial/ethnic groups. With the hope that extensive changes throughout schools and related communications efforts could help improve adolescents' food choices and physical activity levels—and thus reduce risk factors for type 2 diabetes, including obesity—the NIDDK spearheaded a large study with thousands of participating students. The results of this study, called HEALTHY, showed that the school-based intervention had the most benefits for those students who had been the most at risk.

Childhood Obesity: A Worrisome Development

As part of the extensive planning and development of the HEALTHY study, researchers considered the many serious health issues associated with type 2 diabetes and obesity. The development of type 2 diabetes among young people has significant personal and public health consequences, as these youth are likely to develop the eye, kidney, nerve, and cardiovascular complications of diabetes during what should be the most productive period of their lives. An additional concern for young women with the disease is that diabetes during pregnancy significantly increases the risk of complications for both mothers and their babies; and children born to women with either type 2 diabetes or gestational diabetes are themselves at significantly elevated risk for developing type 2 diabetes, an effect which may potentially reinforce the increasing rate of type 2 diabetes among youth. Further, the recent NIH-supported Hypoglycemia and Adverse Pregnancy Outcomes Study showed that risk for many of the adverse pregnancy outcomes associated with gestational diabetes is increased even below the threshold blood glucose level considered to define diabetes. Rather, those risks are lowest at the lowest blood glucose levels, and rise continuously with increasing blood glucose levels. These findings suggest that it will benefit the health of future mothers (and their children) to reach their child-bearing years with weight, glucose levels, and other diabetes risk factors as close as possible to normal. And ominously, a growing body of research evidence is showing that being obese during childhood increases the risk for serious health problems throughout a person's life. For example, obese young people who do not develop type 2 diabetes as children remain at substantially elevated risk of developing the disease as adults. Also, as they enter middle age they are more likely than their lower body mass index (BMI) peers to develop conditions such as high blood pressure and other aspects of the metabolic syndrome, and atherosclerosis (thickening of arterial walls, sometimes called "hardening of the arteries"), a hallmark of heart disease that can presage heart attacks and strokes.

Going to School To Promote Health

Researchers and public health professionals who are focused on the childhood obesity problem are seeking practical approaches to help as many children as possible avoid obesity and the many serious problems that can stem from it. From this perspective, schools

have great potential to play a role in reducing pediatric diabetes risk, because no other institution has as much contact time with youth. Schools can add class curricula aimed at enhancing knowledge about science and health, and they can implement environmental changes that target modifiable risk factors for obesity and type 2 diabetes, such as diet and physical activity. Several studies in recent years have sought to measure the effects of school-implemented changes to diet, activity, and the curriculum.

Working with teachers and administrators in schools with students of several age groups, researchers have examined efforts that restricted availability of sugared beverages, lowered fat content in school lunches, changed physical education curricula, and introduced science and nutrition education materials. Several studies have tested interventions with multiple components, from the lunch room, to the classroom, to the gymnasium. Although some shorter studies (*i.e.*, interventions lasting for a few months) seemed to at least temporarily improve one or more measures of pediatric health, longer studies have generally demonstrated only modest effects.

Yet, if a practical and effective program to improve student health can be developed, middle schools may be a key place to implement it. Children in the sixth through the eighth grades are generally 11 to 14 years old and in early adolescence. This is, of course, a period of physical maturation and metabolic change as well as emotional and mental growth and development. Research has shown that as youth of this age group progress through puberty, hormonal changes not only alter their body composition, but also tend to lower their insulin sensitivity, suggesting this may be a key period along a potential pathway to type 2 diabetes. Students at this age are developmentally capable of beginning to assume personal responsibility for behavior and choices, and indeed diet and physical activity behaviors are often in flux during adolescence. Thus, middle school may afford a key opportunity to encourage healthful behaviors.

Making HEALTHY Changes at Schools

The NIDDK, with supplementary support from the American Diabetes Association, worked to develop and test a comprehensive but practical approach schools could take to try to improve the health of their students. The result was HEALTHY, a study which evaluated a 3-year, multi-component, school-based program to decrease risk factors for type 2 diabetes. Because children from lower income households or who are from racial/ethnic minorities are at substantially elevated risk for both obesity and type 2 diabetes compared to higher income and/or white peers, schools selected for HEALTHY either had to have at least 50 percent of their students eligible for federally subsidized, free or reduced-price meals, or be made up of at least 50 percent minority students. In fact, the averages for participating schools were much higher: over 70 percent of the students who were in the HEALTHY cohort were eligible for free or reduced-price meals, and over 70 percent were minorities.

During the fall semester of 2006, the researchers recorded the initial height and weight of more than 6,000 sixth graders from the participating schools who wished to participate and whose parents consented, and also measured the students' fasting insulin and blood glucose levels. The results of those tests were sobering, and highlight health disparities in risk factors for pediatric type 2 diabetes. Sixteen percent of the students had relatively high levels of blood glucose while fasting (prediabetes), and almost 7 percent had elevated fasting insulin levels. The highest percentage of prediabetes and elevated fasting insulin levels was observed in Hispanic American students. Overall, nearly half of the sixth-grade students in schools participating in the HEALTHY study were considered overweight or obese according to their BMI. This is higher than the national average of U.S. children, but similar to rates observed in other predominantly minority populations. Among the students in the

study, the Hispanic American children had the greatest percentage of overweight/obese individuals, followed by African American children.

The HEALTHY intervention consisted of four integrated components—nutrition, physical activity, behavioral knowledge and skills, and communications and social marketing—each of which was carefully pilot-tested before the formal study began. The nutrition component targeted the quantity and nutritional quality of foods and beverages that were served throughout the school environment (cafeteria, vending machines, à la carte options, snack bars, school stores, fundraisers, and classroom celebrations). The physical education component was designed to increase the amount of time students spent in moderate-to-vigorous physical activity, defined as activity sufficient to raise the heart rate to 130 beats or more per minute. Behavioral knowledge and skills were promoted with the use of a classroom-based program, FLASH (Fun Learning Activities for Student Health), which targeted self awareness, knowledge, behavioral skills, and peer involvement to promote behavior change. The various components of the intervention were integrated by having a theme each semester that targeted specific behaviors (*e.g.*, drink more water and fewer sweetened beverages; engage in more physical activity and less sedentary activity) that could be addressed across all intervention components. The study worked with marketing and creative design experts to develop a brand, logo, activities, and materials that effectively linked these behavior messages. In the latter half of the study, students worked with study staff to produce photographs, artwork, audio messages, and video clips that reinforced the intervention in a way that reflected student perspectives and local sensibilities. Rounding out the communications approach, HEALTHY researchers worked to engage the entire school staff in promoting healthy behaviors.

Of the 42 qualifying schools that participated, 21 were randomly assigned to receive the intervention, while the remaining 21 served as comparison ("control") schools. HEALTHY targeted sixth graders, who received the intervention through the end of the eighth grade. All students in the sixth grade in the intervention schools were exposed to the intervention. However, the study only collected data from students who provided their assent, as well as the written consent of a parent. The intervention began in the spring of 2006, and proceeded through the end of eighth grade, in 2009, when outcome data were again collected in all schools. Except for data collection, the study sponsored no activities in the comparison schools. Over 6,000 students—59 percent of the student body—agreed to participate in the sixth grade and most (over 4,600 students) were re-assessed at the end of the study in eighth grade. (The great majority of those who were measured only in sixth grade had moved to other schools before the end of the study.)

A Trove of Intriguing and Encouraging Findings

The results of HEALTHY were reported in the *New England Journal of Medicine*. The Physician Section of the American School Health Association and the American Academy of Pediatrics Council on School Health later declared the paper to be among the 13 most important school health papers published in 2010. Study investigators reported the surprising finding that the intervention and comparison schools both saw a reduction of about 4 percent in the overall proportion of students who were either overweight or obese. The HEALTHY program also resulted in statistically significant reductions in other risk factors for type 2 diabetes in the intervention schools, including elevated levels of insulin in the blood, and a waist circumference above the 90th percentile. Despite the difference in insulin levels, the study did not find a difference in average blood glucose levels between the two groups of schools.

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Perhaps the most exciting outcome of the study, however, was that the intervention significantly lowered the obesity rate in the children at highest risk for type 2 diabetes—those who were already overweight or obese in the sixth grade: these students had a 21 percent lower risk for being obese at the end of the eighth grade if they were in the intervention schools than if they were in the comparison schools. In the HEALTHY study, the children who were obese at the outset were the most likely to have also begun with elevated levels of both glucose and insulin. Encouragingly, this group of children seems to have particularly benefited from the HEALTHY program: fasting insulin and waist size fell to a significantly greater degree in intervention schools compared to control schools among students who began the study overweight or obese.

The HEALTHY results are particularly notable given the mixed results seen with other school-based interventions. Indeed, the reduction in obesity achieved by the schools using the HEALTHY program in the children who were most at-risk stands in sharp contrast to the modest obesity effects generally observed in intensive, clinic-based, behavioral-treatment programs. Importantly, the HEALTHY program achieved these successes in a cohort consisting largely of children whose race, ethnicity, and socioeconomic status are risk factors for obesity and diabetes. That success may be related to the comprehensive approach HEALTHY took to target both diet and physical activity, strategically incorporating multiple environmental and behavioral strategies.

There may be other reasons, too, that the intervention worked well for those students who were overweight or obese at the beginning of the study. Before HEALTHY began, study investigators expected that this group would be the hardest to reach. However, it is possible that the intervention resulted in greater improvements in diet and activity in these high-risk children, since they may well have had higher food consumption and lower levels of physical activity before enrollment than did the children who were not overweight. Also, HEALTHY provided the intervention to the entire school, perhaps preventing some of the stigmatization that would have occurred if the intervention had been targeted selectively to the most overweight and obese children. In addition, HEALTHY's schoolwide changes may have made it easier for these children to make healthful choices than interventions that have been less comprehensive about addressing environmental factors that promote obesity. Although parents were not the target of the HEALTHY intervention, newsletters and other messaging were sent home to families. Perhaps parents of overweight and obese children may have been more responsive to intervention messages. Whatever the reason for the enhanced effect in this subgroup, wide-scale implementation of the approach could have significant benefits for children at highest risk for type 2 diabetes.

Understanding Results Observed at Comparison Schools

Certainly among the most intriguing HEALTHY study observations was the finding of an overall decrease in the number of overweight and obese children in both the control and intervention schools, when considering all of the children, including those who were normal weight at the outset of the trial. This was surprising, because in previous studies, rates of overweight and obesity generally continued to rise in control/comparison groups. Moreover, national statistics at the time that HEALTHY was being planned suggested that obesity rates were rising among youth. More recent data, however, indicate that childhood obesity rates may have leveled off in the United States. Also, although HEALTHY implemented no school-based activities at the control schools, all students who participated in data collection in sixth grade received a health "report card," with advice about seeking medical follow-up if there were abnormalities in weight, blood pressure and glucose,

insulin or lipid values. It is possible that parents in comparison schools acted on these results.

This potential explanation is bolstered by a report from Arkansas that suggested a leveling off of obesity rates among children after implementing BMI screening in the schools by school nurses, and notifying parents of the results. A recent report from California, however, did not show any change in BMI or obesity with BMI reporting, so its impact and influence in the HEALTHY study remain unclear. Numerous local, state, and federal mandates addressing childhood obesity during the HEALTHY study period may also have influenced the results in both control and intervention schools. Enhanced public concern about obesity among children may well have resulted in significant programming changes in the comparison schools. Indeed, physical education class time did increase in the HEALTHY control schools during the course of the study, and an equal number of intervention and comparison schools eliminated vending machines by the end of the study. Further research is needed to better understand factors currently affecting, and potentially stabilizing, rates of overweight and obesity among youth.

Offering HEALTHY Changes to More Schools

The HEALTHY program can potentially be implemented in other middle schools. Importantly, the physical education and FLASH components of the intervention were taught by the regular teachers, although the research team provided training. Cafeteria staff members also received training and were encouraged to promote messaging about nutritional quality. All HEALTHY materials for each of the five intervention semesters, including the physical education curriculum, FLASH student and teacher workbooks, nutrition messaging, and all posters and other social marketing materials are available at no cost at *www.healthystudy.org* These materials may provide helpful resources to staff at other schools seeking to implement environmental changes or school programs that promote messaging and behaviors that support healthy lifestyles among youth.

Genomic Variation and the Inherited Basis of Type 2 Diabetes

Dr. David Altshuler

Dr. David Altshuler is a world leader in the study of human genetic variation, using tools and information from the Human Genome Project to discover the underlying causes of type 2 diabetes and other common diseases. Dr. Altshuler earned his Ph.D. in 1993 from Harvard University and his M.D. in 1994 from Harvard Medical School. He completed his internship, residency, and clinical fellowship in Endocrinology at the Massachusetts General Hospital. A founding member of the Broad Institute of Harvard and MIT, he serves as a Director of the Broad Program in Medical and Population Genetics, as well as the Broad Institute's first Deputy Director and Chief Academic Officer. He is also a Professor of Genetics and Medicine at Harvard Medical School in the Department of Molecular Biology at the Center for Human Genetics Research, as well as the Diabetes Unit at the Massachusetts General Hospital.

Dr. Altshuler has been a lead investigator in multiple public-private partnerships that have established a foundation for disease genetic research: the Single Nucleotide Polymorphism (SNP) Consortium, the International HapMap Project, and the 1000 Genomes Project. His work has contributed to the discovery of over 100 gene variants that are associated with the risk of type 2 diabetes, cholesterol levels, heart attack, prostate cancer, systemic lupus erythematosus, and rheumatoid arthritis. In 2011, Dr. Altshuler received the prestigious Stern Award from the American Society for Human Genetics, which is given in recognition of major scientific achievement in human genetics that has occurred in the last 10 years. At the September 2011 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Altshuler described the research his team is pursuing, in collaboration with researchers around the world, to identify the causes of type 2 diabetes, its fundamental biology, and ultimately to develop more effective approaches to prevention and therapy. While most NIDDK-supported research has been and continues to be "hypothesis-driven" research, Dr. Altshuler described how new, transformative technologies can be used for discovery research to uncover new and unexpected disease pathways.

Rationale for a Human Genetic Approach: From the Patient to Biology and Medicine

Why use a human genetic approach to understand and ultimately guide treatment of disease? Dr. Altshuler focused on human genetics as a method for discovery—uncovering new causes of disease not previously discovered by other approaches.

Dr. Altshuler started by noting the vast majority of research is (appropriately) hypothesis-driven, building on previous observations. In today's world, these observations most often derive not from patients, but from experiments in cells and animal models. Moreover, drug development focuses to a large extent on these well-characterized hypotheses. And yet, experience has shown that the vast majority of candidate therapies that enter human clinical trials fail due to lack of efficacy, toxicity in humans, or other challenges. Dr. Altshuler argued that hypothesis-driven research is inherently hypothesis-limited research—and, to the extent that many important biological processes and disease mechanisms in humans remain to be identified, our ability to understand and treat disease will similarly be limited.

He posited that a new approach is needed to improve our knowledge of disease mechanisms in humans, and that this will ultimately boost the success rate for candidate therapeutics. Dr. Altshuler explained

that human genetic sequence data, technologies, and methods have recently become sufficiently advanced to identify robust genetic risk factors for common diseases. Starting with the human patient, scientists cast a wide and unbiased net across the genome, searching for whatever genes contribute to disease risk. These genetic risk factors point to new components of pathophysiology, and Dr. Altshuler argued that, however new and unexpected they may be, their relevance to humans argues for their being understood and pursued. The major challenge going forward is to invent methods to harness the resulting discoveries to develop diagnostic tools and therapeutic targets.

Dr. Altshuler next described his and colleagues' work to apply these approaches to type 2 diabetes.

Mapping of Genes and Variants Associated with Type 2 Diabetes—Background and Update

Within a population, about half of an individual's risk for type 2 diabetes is thought to be due to genetic factors inherited from his or her parents. So, how do researchers discover the specific genes and gene variants responsible for this inherited risk? Dr. Altshuler explained that, for many years, it was assumed that the genetic mutations that underlie inherited disease were rare and had very large effects. This was based on experience with single gene disorders such as cystic fibrosis and muscular dystrophy. In such cases, researchers developed a highly successful approach called family-based linkage studies to discover gene variants that tracked with disease. That approach had been successful in understanding the genes underlying literally thousands of rare single gene disorders. But, type 2 diabetes is not a single disease. Rather, it is a constellation of disease syndromes, or forms, some very rare, all leading to a final common diagnostic marker—hyperglycemia, or high levels of glucose in the blood. Only in rare families is diabetes caused by a single gene mutation. These include perhaps 10 genes contributing to rare families with early onset and/or severe forms of type 2 diabetes. Mutations in these genes explained only a percentage or two of the cases of type 2 diabetes seen in the clinic.

Based on the analogy to these rare single gene disorders, in the 1990s investigators applied family based linkage studies to the common forms of type 2 diabetes. Unfortunately, these studies failed to identify robust and reproducible discoveries of specific genes that contribute to the common forms of type 2 diabetes.

Around the year 2000, data from the NIH-led Human Genome Project (HGP) and the technologies developed to bring it to fruition helped launch a new approach to discovering genetic contributors to type 2 diabetes and other complex diseases. Rather than drilling down in multiple stages to find single genes, researchers sought to look out across the entire genome and ask: are there genetic variations that are more (or less) common in people with the disease as compared to people without the disease? These studies are called Genome Wide Association (GWA) studies.

Such studies required researchers to compare variation in the genetic blueprint among thousands of people. Each copy of the human genome is made up of three billion chemical units—the nucleotides adenine, thymine, cytosine, and guanine, represented by the letters A, T, C, and G. Researchers have known for decades that 99.9 percent of these nucleotides are the same when any two people are compared—that is, about one in every one thousand letters in one person's genome will differ from that of another person. Dr. Altshuler explained that the vast majority of the genetic variation in each individual human genome is common, not rare. That is, there are specific sites, spread across the human genome, that differ at a high frequency between human beings. This limited number of common variant sites could be catalogued and then tested for association with disease. In such studies, a skew in the frequency of

a particular common variant (*e.g.*, a higher frequency of "G" vs "A" at a particular site in the genome) could serve as a clue that a specific gene(s) in that region is somehow contributing to the disease.

In efforts facilitated by the HGP and new technologies, Dr. Altshuler has been a leader of NIH-supported projects such as the International HapMap Project and the 1000 Genomes Project. These projects were established to comprehensively catalogue common genetic variations between human beings. A database of human DNA variations, called dbSNP, is maintained by NCBI of the National Library of Medicine at NIH. Dr. Altshuler explained that 10 years ago, when the database was first created, it contained less than 1 percent of the DNA variations present in any individual. Today, over 98 percent of the DNA variations present in an individual are in this catalog.

Over the last 5 years, Dr. Altshuler and other investigators have used this information to search for genes contributing to risk of type 2 diabetes. As recently as 2005, there were only a couple of genetic variants known to contribute to the common forms of type 2 diabetes. Since then, over 40 new genetic variants have been discovered and shown to be reproducibly associated with disease risk.[1] In aggregate, these common variants account for about 10 percent of inherited risk of type 2 diabetes—far from complete, but a major increase as compared to the 1 percent or so of inherited risk that was explained 10 years ago.

Dr. Altshuler described an intriguing outcome of the GWA studies of diabetes-associated variants: before embarking on these studies, in 2006 he and his collaborators attempted to compile a list of all known candidate genes that had been hypothesized (through any of a variety of methods) as possibly relevant to type 2 diabetes. Over 600 such genes were identified based on reading papers and examining the results of other types of research.

Later, GWA studies identified a number of gene variants associated with blood glucose and insulin levels in healthy people without diabetes.[2] As expected, the vast majority of the genetic risk factors were in or near genes that were already on candidate gene list. In other words, the previous methods had done a good job of identifying genes that contribute to the inherited variation in blood glucose and insulin in individuals without diabetes.

In contrast, when Dr. Altshuler and colleagues examined the results of the GWA study approach for type 2 diabetes, they found little overlap with the list of 600 candidate genes. These results suggest that the genes underpinning normal glucose metabolism are not necessarily the same genes that contribute to the abnormalities that ultimately lead to type 2 diabetes. Dr. Altshuler proposed that the approaches that generated the pre-2006 list of candidate genes for type 2 diabetes—mostly studies in cells and animal models of glucose metabolism—were very successful at illuminating genes involved in human glucose metabolism in people without diabetes. But, it is possible that these approaches did not fully recapitulate the biological processes that go awry in human type 2 diabetes. Thus, focusing only on genes involved in normal glucose metabolism could limit investigators' ability to discover the genes and processes that contribute to this disease in people.

Can knowledge of genetic variants be employed clinically to help predict disease in individuals? Interesting results have emerged from leveraging clinical trial data. A key advance in diabetes from the last decade was the finding that type 2 diabetes can be prevented or delayed in people with prediabetes through medication or intensive lifestyle change (a program of diet and moderate exercise to induce 5 to 7 percent weight loss). This finding emerged from the Diabetes Prevention Program (DPP), a clinical trial spearheaded by the NIDDK. Now that gene variants affecting diabetes and other related traits have been identified, Dr. Altshuler and colleagues, led by Dr. Jose Florez of

Harvard Medical School and the Massachusetts General Hospital, have been analyzing data from the DPP to ask a key question: are people who have these genetic variants more likely to develop diabetes, or more or less likely to benefit from the DPP interventions?

Beginning with a study of variants in the *TCF7L2* gene[3] and followed by additional investigations of other high-risk variants, it turns out that the intensive lifestyle intervention was, on average, equally effective in DPP participants regardless of whether or not they had a high-risk variant—meaning that a high-risk genotype indicated by these variants can be overcome. Dr. Altshuler observed, however, that there does appear to be a genetic interaction between genotype and interventions that creates a continuum of risk. That is, if a gene variant increases diabetes risk and an intervention lowers it, an individual's risk ends up being intermediate. This continuum of risk versus an absolute "yes/no" risk may turn out to be typical for genetics of complex traits, such that genetics will end up being similar to familiar predictors of the sort that have existed in medicine for a long time—*e.g.*, cholesterol and blood pressure levels as measures of risk for heart disease.

While conducting human genetic studies offers the exciting prospect of new discoveries highly germane to human disease, Dr. Altshuler highlighted three major challenges to characterizing the genetic variant contributions to type 2 diabetes. First, the vast majority of the genes implicated by GWA studies are novel and thus previously unstudied. Second, the body tissue or tissues in which each gene might act are not yet clear —thus, researchers do not know what tissue to start with to get at how the gene functions, and how variants contribute to disease. Third, most of the genetic variants found through GWA studies are "non-coding," that is, the genome sequence variant does not appear to be within the part of the gene that codes for a protein product. Thus, it is difficult to pinpoint what is the actual causal gene—*i.e.*, the gene affected by the variant (either a nearby gene, or a gene that is otherwise affected by the variant). Researchers will need to overcome these challenges as they work to connect novel genetic variants to the biology of type 2 diabetes.

Dr. Altshuler reported that even as the results of the GWA studies he described are being interpreted, a second technological revolution is under way that makes it possible to use sequencing to find not only common variants within a population, but also less common and so-called "private" variants that are specific to an individual or family. Two NIDDK-supported, international diabetes projects are leading the way in the application of these new "next generation" sequencing technologies to try to further illuminate this disease. One, "GoT2D," is a research consortium established to develop and evaluate a variety of next generation sequencing approaches and methods for gene discovery in type 2 diabetes. The study, co-funded by the Wellcome Trust, the NIDDK, and the NIH's National Human Genome Research Institute (NHGRI), with additional support from the American Recovery and Reinvestment Act, is now examining genetic data from 2,800 people of European ancestry chosen from the extremes of diabetes risk. The other project is "Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multiEthnic Samples," or T2D-GENES, a research consortium supported by the NIDDK and the NHGRI. Because the vast majority of genetic variant studies have been performed in populations of European ancestry, T2D-GENES is probing both the genetic differences that exist in different racial and ethnic groups and the role of different environments, different behaviors, *etc.*, in interacting with genetic risk for diabetes, by conducting DNA sequencing and other studies across a variety of samples from people of different ancestries and current geographic locations.

Dr. Altshuler noted that the pace of discovery in this field has been remarkable. Only 4 years ago, there had been few discoveries in type 2 diabetes, while now, with next generation sequencing, the

number is poised to expand rapidly beyond the over 40 candidates found in just the last few years. Researchers studying other diseases have made similar rapid increases in gene discovery within this short time period. With such a steep increase in information and new clues to disease, it will likely be 5 or 10 years until researchers have sorted through the enormous amounts of data to get a clearer picture of how genetic variants affect disease and the insights they can provide.

From Genes and Genetic Variants to Biology and Medicine

For diabetes and other diseases, what should researchers do with the genetic variants and associated genes that have already emerged from the exploratory approach of modern human genetic studies, and those that appear to be forthcoming? Dr. Altshuler emphasized that researchers need to turn their focus to understanding the biological functions of these genes and how they influence disease. Dr. Altshuler described three ways the research community can follow up on the wealth of data that has come from GWA and other sequencing studies:

- Generate biological hypotheses from the genetic findings to discover connections between genes and diseases, and pursue them.
- View sequence variations as "nature's randomized trial" for disease biomarkers that are potentially being targeted for therapeutics. That is, researchers could investigate whether or not genetically driven perturbation of a biologic factor affects disease outcome, thereby informing the likelihood that a drug developed to do the same thing might work.
- Investigate where and how prediction based on DNA information can improve or augment what researchers and clinicians can do today with other measures.

In terms of discovering connections between genes and pathophysiology, leveraging research findings from different lines of inquiry will help to make these connections more rapidly. For example, if a human genetic variant of interest for type 2 diabetes discovered by GWA studies or next generation sequencing is associated with a gene already being studied mechanistically in animal models, research teams can collaborate to see if the mouse model shows similar diabetes-related traits that will make it worth investigating as a model system for processes important in human diabetes.[4] Dr. Altshuler described one such project already under way that is showing promise for understanding the role of a gene, called *IMP2*, in type 2 diabetes. Variants in other genes that interact with *IMP2* have also been associated with type 2 diabetes in GWA studies and show interesting effects on glucose metabolism in non-diabetic humans,[1] strengthening the case for fleshing out the biology of these genes and the mechanism(s) by which they are contributing to diabetes risk.

Looking to the Future

Dr. Altshuler concluded by reasserting that human genetics offers an approach to develop new hypotheses about human biology not only in the context of rare syndromes linked to one or a few genes, but also for common diseases in which the genetic contributions are myriad and complex. While for decades the absolutely rate-limiting step has been the inability to go from a disease to a gene, recent advances in knowledge and technologies have helped scientists make very substantial progress in that regard for complex diseases—and, with the new sequencing technologies, it appears the field is poised for even more rapid growth. The challenge of the next 10 years for human genetic studies for type 2 diabetes and other common, complex diseases will be how to choose which follow-up experiments to do, which genes to study, and what approaches to take—a process that will take the effort and collaboration of many researchers.

[1] *Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 42: 579-589, 2010.*

[2] *Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 42: 105-116, 2010.*

[3] *Florez JC, Jablonski KA, Bayley N, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 355: 241-250, 2006.*

[4] *Zhu H, Shyh-Chang N, Segrè AV, et al. The Lin28/let-7 axis regulates glucose metabolism. Cell 147: 81-94, 2011.*

PATIENT PROFILE

Jack Schmittlein

Living with Type 1 Diabetes–A Disease That "Never Takes a Vacation"

Jack Schmittlein

On October 4, 2004, Jack Schmittlein's life changed forever. It was on that day that Jack, at age 6, was diagnosed with type 1 diabetes.

"Instead of being a carefree kindergartner, I was faced with pricking my fingers 8 to 10 times a day, counting carbs [carbohydrates], and taking insulin shots," says Jack, now an articulate 13 year old. So articulate, in fact, that he was invited by Congress to testify at a hearing entitled "Transforming Lives Through Diabetes Research" in June 2011. The hearing was held in conjunction with the Juvenile Diabetes Research Foundation International's (JDRF) Children's Congress.

What was it like to testify before members of the U.S. Congress? "Awesome!" says Jack. "It was a once-in-a-lifetime experience, and I felt honored to be speaking for all the other kids who have type 1 diabetes." Jack gave eloquent testimony about what it is like living with type 1 diabetes and the importance of pursuing research toward a cure for the disease.

"Instead of being a carefree kindergartner, I was faced with pricking my fingers 8 to 10 times a day, counting carbs [carbohydrates], and taking insulin shots," says Jack.

About Type 1 Diabetes

Type 1 diabetes is an autoimmune disease in which the immune system destroys cells in the pancreas that make insulin, a hormone required by the body to use sugar from food as a cellular fuel. People with type 1 diabetes must carefully monitor blood sugar levels, which Jack does by pricking his finger to get a small drop of blood to be tested. They must also administer insulin, either through injections or an insulin pump.

A constant challenge faced by people with the disease is matching food intake (which is why Jack counts carbs), physical activity, and insulin doses in order to maintain healthy blood sugar levels. Dramatic rises and drops in blood sugar can have immediate and life-threatening consequences, as Jack and his family are well aware. At the same time, NIDDK-supported research has shown that carefully controlling blood sugar levels over the long term is crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, nerve, and heart disease. Therefore, managing diabetes is a difficult and delicate balancing act of trying to control blood sugar levels, particularly in terms of avoiding dangerous bouts of very high or low blood sugar.

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A Disease That "Never Takes a Vacation"
The constant burden of managing type 1 diabetes means that the disease permeates every facet of a family's life.

"Every night my dad takes the late shift to check my blood sugar level after I've gone to sleep," says Jack. "And every morning my mom is there to wake me up and make me check my sugar level as the first thing I do each and every morning." In other words, "Managing diabetes is hard work that lasts 24 hours a day, every day," explains Jack.

"There are days when we're just not in charge of this disease," says Jack's mom, Denise. "Despite how controlled we try to keep it, diabetes wins a lot of the time."

A couple of years ago, the Schmittleins went on a vacation that included an excursion trip to swim with stingrays. Jack was excited. When they arrived by boat at the designated spot, "I jumped into the water," he says. He suddenly felt his blood sugar go extremely low. He immediately became dizzy and couldn't swim. Fortunately, his mom, Denise, was able to get him safely back into the boat while dad, Marc, stayed with Jack's younger brother, Cole. "My sister, Alexis, got left in the deep water with a bunch of stingrays coming at her. She still hasn't forgiven me," Jack says with a brotherly chuckle.

But the day only got worse. The Schmittleins discovered that Jack's insulin pump had broken, so the entire family needed to return to shore. They spent the next 2 days scrambling to get a replacement pump while Jack instead had to take insulin shots every time he ate. "Diabetes never takes a vacation!" says Jack.

"There are days when we're just not in charge of this disease," says Jack's mom, Denise. "Despite how controlled we try to keep it, diabetes wins a lot of the time."

Raising Awareness About Type 1 Diabetes
Jack has been actively involved in raising awareness about type 1 diabetes, and his outreach efforts have been remarkable. In addition to testifying before Congress, he was selected by the JDRF to be its 2010 Youth Ambassador for Connecticut and Western Massachusetts. He has spoken at JDRF diabetes fundraising events, including the Promise Ball, where he was the keynote speaker to an audience of more than 750 people, and Walk for a Cure, where he has spoken twice and been a team captain four times. He's also helped to organize a fundraising walk at school for 600 of his fellow students.

Why does Jack work so hard at raising awareness about type 1 diabetes and advocating for a cure? "I can only imagine what it would be like to not have to check my sugar as much, not have to measure everything I eat, and not have to tell my insulin pump how much insulin I need," he says. It would also mean that Jack, who loves sports, wouldn't have to come out in the middle of his basketball or football games to test his blood sugar. In other words, he is waiting for the day when he can take a permanent vacation from having type 1 diabetes.

Another motivation for Jack has been his best friend since second grade, who would keep him company on walks to the school nurse's office every day for blood sugar checks. "On the way, we'd try to guess what my sugar numbers would be," recalls Jack. When they were in fourth grade, Jack's best friend was also diagnosed with type 1 diabetes. Jack says that his friend's diagnosis is "just one more reason why I work to raise awareness about type 1 diabetes."

Hope Through Research
Right now, Jack is putting a lot of hope in what is called an artificial pancreas, or a "closed-looped system," still under development, in which a computer would

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calculate insulin dose based on blood sugar levels and deliver insulin automatically through an insulin pump, mimicking the function of a real pancreas. This type of system could reduce or eliminate much of the everyday burden of managing type 1 diabetes. The NIDDK is vigorously supporting research toward the development of an artificial pancreas that could help Jack and other people with type 1 diabetes.

"I'm really looking forward to the day when I can say, 'I used to have diabetes.'"

"An artificial pancreas would help prevent my blood sugar from dropping and give me insulin if my blood sugar gets too high," says Jack. "It's going to be the next best thing to a cure. It will give me my life back so I can just feel like a kid, instead of a kid with diabetes," he adds hopefully.

In the meantime, Jack and his family will need to be vigilant and continue to cope with type 1 diabetes each and every day. "This disease is all consuming," says Denise. But, she notes that many things have helped her family cope with the disease, including getting support from other families living with type 1 diabetes, having a good relationship with Jack's doctor, and remaining optimistic that Jack can function with this disease and live a full and long life. Her advice to other parents is: "Don't let this disease define your child. Let them be a kid!"

As for Jack, his advice to his peers is: "If you're a kid and get diagnosed with type 1 diabetes, don't overreact…just be responsible for yourself and you'll be fine."

But he quickly adds, "I'm really looking forward to the day when I can say, 'I used to have diabetes.'"