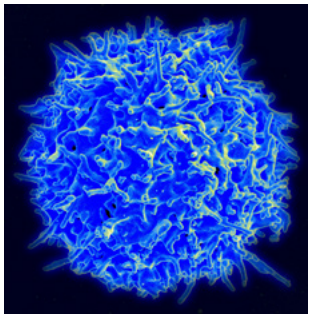

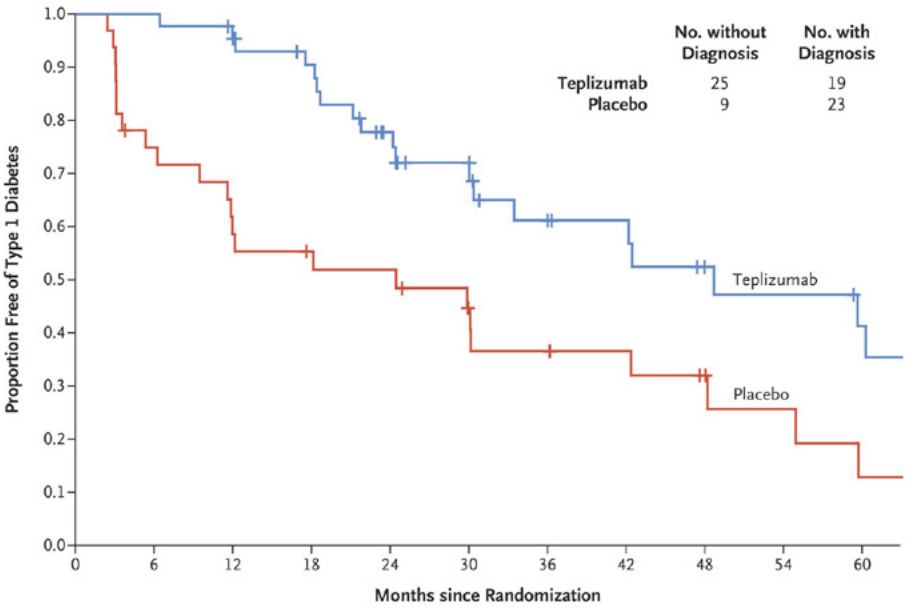

As described in this chapter, a clinical trial conducted by NIDDK's Type 1 Diabetes TrialNet has demonstrated that early preventive treatment with a drug called teplizumab slowed the progression to clinical type 1 diabetes in high-risk individuals without diabetes. Teplizumab targets T cells of the immune system (depicted in left image), which are known to play a role in the type 1 diabetes autoimmune attack. Data from the clinical trial are illustrated in the graph, which shows that over time, more people in the teplizumab treatment group (blue line) were free of type 1 diabetes (*i.e.*, were not diagnosed with the disease) compared to those in the placebo group (red line). This exciting discovery provides the first evidence that clinical type 1 diabetes can be delayed with early preventive treatment.

Graph courtesy of Dr. Kevan Herold, Yale University. From The New England Journal of Medicine, Herold KC, Bundy BN, Long SA,...Greenbaum CJ; Type 1 Diabetes TrialNet Study Group, An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes, 381: 603-613. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. T cell image courtesy of the National Institute of Allergy and Infectious Diseases/National Institutes of Health.

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.

Not only is diabetes chronic and relentless, but its slow accumulation of insults to the body can rob a person of the ability to see, hear, feel, think, and walk. In addition to increasing the risk for complications of vision loss, kidney failure, and amputation, diabetes doubles risk for heart disease, many forms of cancer, some forms of dementia, hearing loss, erectile dysfunction, urinary incontinence, and many other common diseases.[1] NIDDK is vigorously pursuing research to combat diabetes and its associated health consequences.

Diabetes is a debilitating disease that affects an estimated 30.3 million people in the United States—or 9.4 percent of the total population—and is the seventh leading cause of death.[2] Although overall rates of diabetes-related complications have declined substantially in recent years, disease burden remains significant as the number of people with diabetes is still very high.[1] Diabetes can affect many parts of the body and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputation. In addition to these human costs, the estimated total financial cost for diagnosed diabetes in the United States in 2017—including costs of medical care, disability, and premature death—was $327 billion.[3] Effective therapy can prevent or delay diabetic complications, but nearly one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.[2]

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 develops during pregnancy, but in many cases may resolve after pregnancy. However, women who develop gestational diabetes are at greater risk of developing type 2 diabetes later in life. 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 diagnosed diabetes cases in adults, and the majority of diagnosed cases in children and youth.[2] 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 β (beta) cells of the pancreas. If left untreated, type 1 diabetes results in death: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed.

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[1] *Diabetes in America, 3rd ed. Cowie CC, et al., Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2018.*
[2] *Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2017.*
[3] *American Diabetes Association. Diabetes Care 41: 917-928, 2018.*

This disruption of the body's metabolism causes a biochemical chain reaction that can result in a life-threatening condition called diabetic ketoacidosis (DKA). DKA can be deadly if it is not aggressively treated with insulin. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—to regulate their blood glucose levels. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated with type 1 diabetes. However, despite vigilance in disease management and current technologies to test blood glucose levels and administer insulin, it is still not possible for people with type 1 diabetes to manage blood glucose levels as well as functional pancreatic β cells do. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery. In this regard, NIDDK-supported research has contributed to the development or testing of new diabetes management technologies recently approved by the U.S. Food and Drug Administration, including the first commercial "hybrid artificial pancreas" device that automatically links glucose monitoring and insulin delivery, and next-generation continuous glucose monitors, including the first fully implantable device. Researchers are also working to develop β cell replacement therapies, such as islet transplantation, 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.[2] The risk for developing type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.[3] Type 2 diabetes occurs at higher rates among racial and ethnic minority populations in the United States, including African Americans, Hispanic and Latino Americans, American Indians, some Asian Americans, and Native Hawaiians and Pacific Islanders.[2] Gestational diabetes is also a risk factor: about half of women with gestational diabetes will develop type 2 diabetes within 5 to 10 years after giving birth.[4]

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 β 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 managing glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 84 million U.S. adults who have a condition called "prediabetes," in which blood glucose levels are higher than normal but not as high as in diabetes.[2] This population is at elevated risk of developing type 2 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. To a more limited degree, the safe and well-tolerated drug metformin can also help prevent or delay type 2 diabetes. Moreover, follow-up research has shown that the benefits of reduced diabetes risk from weight loss or metformin can persist for at least 15 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 in this population it disproportionately affects youth from racial and ethnic minority populations in the United States. Believed to be related to increasing rates of pediatric obesity, this trend is alarming for many reasons. For example, results from the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial and the Restoring Insulin Secretion (RISE) Pediatric Medication Study showed that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with diabetes duration and management of blood glucose levels, so those with early disease onset are at especially high risk for developing complications. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and 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

[4] *Kim C, et al. Diabetes Care 25: 1862-1868, 2002.*

women could contribute to a cycle of ever-growing rates of diabetes. 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 NIDDK's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

RESEARCH ON TYPE 1 DIABETES

Drug Delays Type 1 Diabetes in People at High Risk:

Results from a recent clinical trial have demonstrated that a treatment targeting the immune system slowed the progression to clinical type 1 diabetes in high-risk individuals. Currently, there is no way to prevent type 1 diabetes, which is caused by an autoimmune attack that destroys the insulin-producing β (beta) cells in the pancreas. Previous research demonstrated that treatment with an anti-CD3 monoclonal antibody (teplizumab) slows β cell loss in people with recent-onset clinical type 1 diabetes; teplizumab targets immune system cells (T cells) that are known to play a role in the autoimmune attack. However, the drug had never been tested in people without clinical disease to see if it could also slow β cell loss earlier in the course of type 1 diabetes and thus prevent clinical disease onset.

To address this gap in knowledge, Type 1 Diabetes TrialNet conducted a trial in which they enrolled 76 mostly White, female and male participants aged 8 to 49 years who were relatives of people with type 1 diabetes; over 70 percent of the participants were 18 years old or younger. The participants did not have clinical type 1 diabetes, but were at high risk for developing it because they had at least two types of diabetes-related autoantibodies (proteins made by the immune system) and abnormal glucose (sugar) tolerance. Participants were randomly assigned to receive either a 14-day course of teplizumab or placebo (no medicine), administered intravenously. The results were striking: during the trial, 72 percent of people in the placebo group developed clinical type 1 diabetes, compared to only 43 percent of the teplizumab group. The median time for people in the placebo group to develop clinical disease was just over 24 months, compared to 48 months in the treatment group. The study is the first to show that clinical type 1 diabetes can be delayed by 2 or more years among people who are at high risk.

The researchers noted that the study had limitations, including the small number of participants, their lack of ethnic diversity, and that all participants were relatives of people with type 1 diabetes, potentially limiting the ability to translate the study to a broader population of people who do not have relatives with the disease but do have other risk factors. Future research could help to address these limitations, as well as shed light on teplizumab's mechanism of action and long-term effects, to build on this exciting finding that clinical type 1 diabetes can be delayed with early preventive treatment.

Herold KC, Bundy BN, Long SA,...Greenbaum CJ; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 381: 603-613, 2019.

Type 1 Diabetes Study Provides New Details on Development of Children's Gut Microbiome:

Researchers investigating possible causes of type 1 diabetes have published new details about how environmental factors such as breastfeeding affect the microbes in the gut (*i.e.*, the gut "microbiome") as children age. The Environmental Determinants of Diabetes in the Young (TEDDY) is an international study investigating what environmental factors might trigger or protect against type 1 diabetes. TEDDY is following almost 6,000 children at high genetic risk of developing type 1 diabetes from their birth through age 15. One factor of interest to TEDDY researchers is the gut microbiome. Previous studies suggested that crosstalk between the immune system and gut microbes in infancy and childhood can be linked to immune-related diseases later in life, such as the autoimmune attack on pancreatic beta cells that occurs during type 1 diabetes. TEDDY scientists are interested in whether or not changes in the gut microbiome affect a child's risk for developing type 1 diabetes. To investigate this, they analyzed donated stool samples from hundreds of girls and boys participating in TEDDY, identifying the bacteria in the children's gut microbiomes and tracking how the types and abundance of these bacteria changed as the children grew. Information on the children's health, diet, geographical location, and other environmental

exposures was then used to explore whether these factors may have affected the gut microbiome and how those effects correlated with the children's type 1 diabetes status.

From this research, one of the largest-ever clinical microbiome studies in infants and children, TEDDY scientists identified three distinct phases of gut microbiome development: a developmental phase (3-14 months of age), a transitional phase (15-30 months of age) where the microbiome diversifies, and a stable phase (31-46 months of age) where the microbiome's composition is largely established. Within these phases, researchers found considerable personal variability between gut microbiomes. Breastfeeding was the most important factor associated with how the gut microbiome developed in the first years of life. For example, the microbiome of infants not receiving breast milk moved more quickly through the developmental phases compared to children receiving any amount of breast milk, even if supplemented with formula or solid foods. Some of the other factors that affected the gut microbiome included probiotic and antibiotic use, geographical location, and having siblings and/or furry pets. Finally, researchers found a possible beneficial effect on risk for type 1 diabetes from bacteria that produce short-chain fatty acid molecules. These molecules are often made during fermentation of indigestible carbohydrates like fiber, and future research will be needed to determine whether these molecules or the bacteria that produce them protect against type 1 diabetes.

The TEDDY cohort is largely White and non-Hispanic, so further work will be needed to determine if these discoveries are applicable to all children. However, these new findings could help inform the development of strategies or therapies to support the development of a healthy gut microbiome in children. They also demonstrate how the ambitious TEDDY study is already expanding our knowledge of child development and the human microbiome, while continuing its search for causative and protective factors for type 1 diabetes.

Stewart CJ, Ajami NJ, O'Brien JL,...Petrosino JF. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 562: 583-588, 2018.

Vatanen T, Franzosa EA, Schwager R,...Xavier RJ. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature 562: 589-594, 2018.

Novel Imaging Technology Sheds Light on How Type 1 Diabetes Progresses: Two studies have used a sophisticated novel imaging technology to visualize the pancreas and gain new insights into how type 1 diabetes progresses—knowledge that could inform strategies to prevent or halt the disease. Type 1 diabetes is an autoimmune disease in which the immune system destroys the insulin-producing β (beta) cells found in clusters called islets in the pancreas. In two recent studies, researchers used a novel technology, called imaging mass cytometry, to analyze pancreases from female and male organ donors with type 1 diabetes of varying disease duration, as well as female and male donors without the disease. The technology allowed the scientists to measure simultaneously over 30 cellular markers and visualize at a single-cell level not only β cells and other pancreatic cell types, but also immune cells involved in the autoimmune attack. This novel technology enabled an unprecedented look not only at the numbers and characteristics of various cell types in the pancreas, but also at how cells interacted with each other, and provides an exciting resource for future studies.

Both studies confirmed that there were significant differences in the number and types of cells found in islets from different individuals. The studies also confirmed that β cell numbers were reduced in pancreases from donors with type 1 diabetes compared to those without disease, although there were differences observed among the donors. For instance, a surprising finding from one of the studies was that two donors with new-onset disease had a similar proportion of β cells in their pancreases as those without disease. This finding suggests that even at type 1 diabetes onset when people are showing clinical symptoms and need to take insulin to lower their blood glucose (sugar) levels, their pancreases may still have high numbers of β cells. Further experiments also suggested that, as type 1 diabetes progresses, the β cells go through an altered state, in which they display fewer characteristic features of β cells, before they are destroyed by the immune system.

The technology also enabled scientists in both studies to begin exploring the immune cell environment that plays a role in type 1 diabetes—looking at many different immune cell types at the same time and cataloging the number and timing of immune cell interactions with pancreatic cells.

For example, one finding was that certain types of immune cells (T cells) were abundant in people with new-onset type 1 diabetes and less abundant in people with long-standing disease, suggesting that the immune system attack is maximal around the time of disease onset and that immune cells leave islets after β cells are destroyed.

By using imaging mass cytometry, these research groups not only painted a new and more vivid picture of type 1 diabetes disease progression, but also demonstrated the promise of this technology to garner new knowledge about the type 1 diabetes disease process. Results from these and future studies could help to inform the development of new therapies to prevent or treat the disease.

Damond N, Engler S, Zanotelli VRT,...Bodenmiller B. A map of human type 1 diabetes progression by imaging mass cytometry. Cell Metab 29: 755-768.e5, 2019.

Wang YJ, Traum D, Schug J,...Kaestner KH. Multiplexed in situ *imaging mass cytometry analysis of the human endocrine pancreas and immune system in type 1 diabetes. Cell Metab 29: 769-783.e4, 2019.*

RESEARCH ON TYPE 2 DIABETES

Study Shows Vitamin D Supplementation Has Little or No Effect on Type 2 Diabetes Prevention: In the largest study to directly examine if daily vitamin D supplementation helps prevent or delay type 2 diabetes in people at high risk for the disease, scientists found no meaningful difference in the rate of type 2 diabetes development between those taking the vitamin D supplement and those taking a placebo pill daily. Previous observational studies reported an association between low levels of vitamin D and increased risk for type 2 diabetes, and smaller studies found that vitamin D could improve the function of beta cells, which produce insulin. To determine whether vitamin D supplementation could prevent type 2 diabetes, the Vitamin D and Type 2 Diabetes (D2d) study enrolled 2,423 adults and was conducted at 22 sites across the United States. All participants had blood glucose (sugar) levels higher than normal but not high enough to be diagnosed with type 2 diabetes, and the group included a range of physical characteristics, including sex, age, and body mass index (a measure of weight relative to height), as well as racial and ethnic diversity, to ensure that the study findings could be widely applicable to people at high risk for developing type 2 diabetes. All study participants had their blood levels of vitamin D measured at the start of the study. At that time, about 80 percent of the participants had vitamin D levels that were considered sufficient at the time.

The study assigned participants randomly to take either 4,000 International Units (IUs) of the D3 (cholecalciferol) form of vitamin D—greater than the average daily recommended intake of 600 to 800 IUs a day, but within limits deemed appropriate for clinical research at the time—or a placebo pill daily. The study screened participants every 3 to 6 months for an average of 2.5 years to determine if they had developed diabetes. At the end of the study, 293 of the 1,211 participants (24.2 percent) in the vitamin D group developed diabetes compared to 323 out of the 1,212 (26.7 percent) in the placebo group. Although a lower proportion of those taking vitamin D developed diabetes, the difference was too small to reach statistical significance. The researchers found no meaningful differences between the two groups regardless of age, sex, race or ethnicity, and they saw no difference in the number and frequency of predicted side effects when they compared the two groups. With the rising numbers of people at high risk for type 2 diabetes, efforts will continue to search for new ways to prevent the disease.

Pittas AG, Dawson-Hughes B, Sheehan P,...Staten M; for the D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. N Engl J Med 381: 520-530, 2019.

Study in African Populations Leads to Identification of Type 2 Diabetes Risk Gene: In a genetic study with participants from sub-Saharan Africa, researchers discovered that variants of a gene not previously known to be associated with type 2 diabetes affect risk for the disease, and also found evidence for how the normal version of the gene may promote metabolic health. To date, genome-wide association studies (GWAS) have identified over 400 genetic regions that may affect risk for type 2 diabetes. However, the majority of GWAS have included at least some people of European descent, and little research has been done focusing exclusively on people of African origin, even though evidence suggests Africans have elevated genetic risk for type 2 diabetes.

In this new study with more than 5,000 female and male participants from Nigeria, Ghana, and Kenya,

variants in or near the gene *ZRANB3* were found to be associated with risk for the disease (as were variants of some genes previously associated with type 2 diabetes through studies in other parts of the world). To determine whether variations in *ZRANB3* itself were responsible for differences in diabetes risk—rather than differences in some other, nearby gene—the scientists sought to learn whether *ZRANB3* may have a role in the body's insulin-producing β (beta) cells. For this analysis, they used—as an experimental model—a strain of zebrafish that produce a fluorescent dye in their β cells so that the cells are comparatively easy to detect and count in the small, partially transparent fish. Targeted elimination of the zebrafish version of *ZRANB3* led to fish developing with about 30 percent fewer β cells, without causing any other obvious effects. Detailed analysis of data from these experiments suggests that initially a normal number of β cells may have been forming, but that some of them died during later development. Another set of experiments showed that the protein encoded by the *ZRANB3* gene—designated ZRANB3—may play an important role in mature β cells, as well: β cells isolated from a mouse pancreas did not secrete as much insulin as they should in response to high glucose (sugar) levels if they lacked the protein. Taken together, these results suggest that the ZRANB3 protein plays key roles in β cell biology and may one day be the target of therapies that help people with diabetes, be they from Africa or elsewhere.

Adeyemo AA, Zaghloul NA, Chen G,...Rotimi CN. ZRANB3 *is an African-specific type 2 diabetes locus associated with beta-cell mass and insulin response.* Nat Commun *10: 3195, 2019.*

Predicting an Individual's Response to a Diabetes Drug: Scientists demonstrated that genetic variation predicts individual responsiveness to the antidiabetic drug rosiglitazone. Rosiglitazone reverses insulin resistance in type 2 diabetes, but its use is limited due to its significant side effects, which can include an increased risk of heart attack and stroke. Additionally, rosiglitazone's beneficial insulin-sensitizing effect is seen in most but not all people, and scientists have been seeking to understand the reasons for these differential responses. With such knowledge, it might one day be possible to develop diagnostic tests to identify who will respond best to the drug and/or have the fewest side effects. In this study, a group of researchers developed a strategy—using stem-cell generated cells to identify human genetic variation—to study the differential response to rosiglitazone and, in doing so, revealed genetic predictors of an adverse response to the drug.

The researchers generated adipocyte (fat) cell lines from tissue samples from five women who had obesity, treated the cell lines with rosiglitazone, and identified genes that were "turned on" in each of the cell lines in response to the treatment. Interestingly, each cell line showed a unique signature of genes that were turned on. For example, 87 genes that were activated in 4 of the lines remained inactive in the fifth; on the other hand, 399 of the genes that were activated by rosiglitazone in 1 of the cell lines remained inactive in the other 4. Because rosiglitazone is known to activate a protein called PPARγ, which binds to DNA to turn genes on, the scientists examined whether genetic differences between the participants affected PPARγ binding in these cell lines. They found specific genetic differences that not only altered PPARγ binding sites, but also accounted for corresponding differences in the responsiveness to rosiglitazone.

One genetic variation was of particular interest to the scientists because it was near a PPARγ-regulated gene whose protein is known to affect cholesterol levels. Treatment with rosiglitazone commonly leads to higher total cholesterol and low-density lipoprotein cholesterol, which may contribute to heart attacks and strokes among people taking the drug, but it is not well understood how rosiglitazone affects cholesterol levels. The scientists found that having a specific genetic variant (designated "C") correlated with PPARγ responsiveness to rosiglitazone in that the nearby cholesterol-affecting gene was turned on, while it was not turned on in individuals with a different variant, "A." The researchers went on to show that these genetic variants also affected cholesterol levels. People with the C variant had higher levels of total and low-density lipoprotein cholesterol in response to rosiglitazone while people who had the A variant near both copies of the cholesterol-affecting gene (cells have two copies of this gene) received the benefits of rosiglitazone treatment (lower blood glucose levels), but much less of the drug's cholesterol-elevating side effect. This result suggests it may one day be possible for clinicians to identify people who may benefit from rosiglitazone without the adverse effects on their cholesterol levels. The study also presents an approach to identify how human genetic variation determines response to a drug and may be an important tool for understanding drug responses in other diseases.

Hu W, Jiang C, Guan D,...Lazar MA. Patient adipose stem cell-derived adipocytes reveal genetic variation that predicts antidiabetic drug response. Cell Stem Cell 24: 299-308.e6, 2019.

RESEARCH ON DIABETES COMPLICATIONS

Long-term Type 1 Diabetes Study Reveals Immune System Links Between Blood Glucose Management and Heart Health: Two recent studies have found new connections between blood glucose (sugar) management and heart health, which may explain the increased risk of cardiovascular diseases (heart disease and stroke) in those with type 1 diabetes. Previous insights about type 1 diabetes and cardiovascular health have come from the landmark Diabetes Control and Complications Trial (DCCT) and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. DCCT/EDIC demonstrated that early and intensive blood glucose control lowered the risk of cardiovascular diseases and cardiovascular-related deaths, though exactly how blood glucose levels affect cardiovascular health was not fully understood.

In new research, scientists further studied the health of DCCT/EDIC participants to examine how blood glucose management influenced these people's risk of cardiovascular disease. In particular, researchers wondered if that risk was mediated through known cardiovascular factors or if there were unknown, diabetes-specific mechanisms at play, as well. The DCCT/EDIC research group investigated this question by analyzing whether or not an increased risk of heart problems could be accounted for by factors such as blood pressure, pulse rate, cholesterol levels, and/or measures of kidney function. Their analyses demonstrated that although having higher blood glucose levels over time was associated with many traditional risk factors for cardiovascular disease, these associations could not completely explain the increased risk seen in some DCCT-EDIC participants. This raised the question of what other factors were mediating the effect of high blood glucose levels on heart health.

Another research group hypothesized that the link between blood glucose levels and the heart is mediated by the immune system. By analyzing biological samples from a subset of DCCT participants, as well as samples from people with type 2 diabetes, scientists found signs of cardiac autoimmunity—*i.e.*, the presence of at least two cardiac autoantibody types—in people who had type 1 diabetes and elevated blood glucose levels (measured as an HbA1c greater than 9 percent). These autoantibodies were not found in people with type 2 diabetes who had similar blood glucose levels. People with type 1 diabetes and cardiac autoimmunity also had a higher risk of both accelerated atherosclerosis and cardiovascular events. Since cardiac autoantibodies developed decades before the cardiovascular complications, such autoantibodies might be useful as early biomarkers of cardiovascular disease risk specifically in people with type 1 diabetes. This study also suggested a new role for autoimmune mechanisms, possibly mediated by inflammation, in the development of cardiovascular complications of type 1 diabetes.

These results break new ground in the study of type 1 diabetes complications, identifying a novel cardiovascular disease pathway specific to type 1 diabetes and further emphasizing the importance of keeping blood glucose levels within a healthy range. More study is needed to clarify how exactly blood glucose levels affect heart health. Such studies could also lead to new insights into cardiovascular disease itself and to methods to detect, prevent, or treat cardiovascular complications in people with type 1 diabetes.

Sousa GR, Pober D, Galderisi A,...Lipes MA. Glycemic control, cardiac autoimmunity, and long-term risk of cardiovascular disease in type 1 diabetes mellitus. Circulation 139: 730-743, 2019.

Bebu I, Braffett BH, Orchard TJ, Lorenzi GM, and Lachin JM; DCCT/EDIC Research Group. Mediation of the effect of glycemia on the risk of CVD outcomes in type 1 diabetes: The DCCT/EDIC study. Diabetes Care 42: 1284-1289, 2019.

GESTATIONAL DIABETES RESEARCH

Folate Supplements May Help Reduce Risk of Gestational Diabetes: New findings from a long-term study in thousands of women suggest that pre-pregnancy dietary supplementation with folate, a B vitamin, can reduce risk of developing gestational diabetes. Gestational diabetes (GDM) is a form of diabetes currently diagnosed during the late second or the third trimester of pregnancy and affects approximately 7 percent of pregnancies in the United States. GDM increases health risks for mothers and their babies both during pregnancy and delivery (*e.g.*, high birth weight babies, delivery complications) and later on in life (*e.g.*, greater risk of type 2 diabetes in

mothers and obesity and/or type 2 diabetes in the child). Research on GDM aims to better understand why and how it occurs and to try to find ways to prevent it. In the present study, researchers examined whether or not risk of developing GDM correlated with the self-reported folate intake—both from food sources and from folate dietary supplements—in over 14,000 women who became pregnant while enrolled in the Nurses' Health Study II over a 10-year period. After controlling for known risk factors for GDM, they found that, when consumed as a dietary supplement, folate was associated with decreased risk of GDM. Moreover, the GDM risk fell as the level of supplementation increased from adequate—*i.e.*, the U.S. recommended daily allowance level—to somewhat higher levels. In contrast, folate from food sources was not found to reduce risk, an observation the researchers attributed to the body being able to use a lower proportion of the folate in food than it can from the synthetic version (folic acid) found in supplements. Therefore, dietary supplementation could represent a simple, cost-effective approach to GDM prevention. Future studies should help to extend these encouraging findings about folate and GDM risk and determine whether there is a safe and effective optimal supplementation dose that has a significant impact on GDM prevention in women.

Li M, Li S, Chavarro JE,…Zhang C. Prepregnancy habitual intakes of total, supplemental, and food folate and risk of gestational diabetes mellitus: A prospective cohort study. Diabetes Care 42: 1034-1041, 2019.

METABOLIC REGULATORS OF HEALTH AND DISEASE

Metabolism, Memory, and the Role of Insulin in the Brain: Gaining new insights into the link between diabetes and higher risk of dementia, scientists discovered, in research in mice, that insulin and the related hormone IGF-1 act in multiple parts of the brain to regulate blood glucose (sugar) levels, memory, and other vital mind and body processes. Insulin and IGF-1 transmit critical biological signals, and prior research showed that impaired insulin and IGF-1 signaling in the brain is associated with diabetes, obesity, and potentially increased risk for Alzheimer's disease and other cognitive problems. But much remains unknown.

To identify areas of the brain important for insulin and IGF-1 control of metabolism and cognitive functions, the researchers generated two groups of mice with reduced signaling by these hormones in specific regions of the brain—the hippocampus and central amygdala, respectively—and examined the effects. They found that, in mice with insulin/IGF-1 signaling deficiencies in either of these brain regions, blood glucose levels rose above normal. Mice with these deficiencies in the central amygdala also could not maintain normal body temperature in a cold environment. From additional experiments, they determined that this effect was likely due to disrupted signaling along nerves that connect the brain to brown fat tissue, which generates heat. Investigating other effects, the researchers found that, compared to normal mice, those with insulin and IGF-1 signaling deficiencies in either of these brain regions did not differentiate between new and familiar objects, and they displayed anxiety-like behaviors. Mice with signaling deficiencies in the hippocampus were also much slower in learning to navigate their way through a maze and had more trouble remembering the route later. In their experiments, the researchers used only male mice to explore the role of insulin/IGF-1 signaling in the hippocampus, and only female mice in studies of the central amygdala. Thus, it is not yet clear whether some of the metabolic and cognitive effects reflect distinct functions of the two brain regions, differences between males and females, or both.

The results from this research in mice illuminate critical roles of the hormones insulin and IGF-1 in multiple areas of the brain and yield new insights into the connections between insulin action, metabolism, learning and memory, and anxiety-like behavior. These findings may lead to new ideas for therapies in humans, not only for diabetes and obesity, but also for Alzheimer's disease and other dementias.

Soto M, Cai W, Konishi M, and Kahn CR. Insulin signaling in the hippocampus and amygdala regulates metabolism and neurobehavior. Proc Natl Acad Sci USA 116: 6379-6384, 2019.

STRIDES IN THE TREATMENT OF CYSTIC FIBROSIS

It has been over 30 years since the discovery of *CFTR*—the gene that is mutated in people with cystic fibrosis (CF)—and 7 years since the U.S. Food and Drug Administration (FDA) approved the first drug capable of rescuing CFTR protein function in people with certain CF-causing mutations. This medication, called ivacaftor, is a "potentiator,"

meaning it enables certain mutant versions of the CFTR protein to fulfill their critical function as a channel that allows chloride ions to travel in and out of various cells, greatly reducing the burden of the disease. Unfortunately, ivacaftor cannot repair damage caused before treatment begins; and, at least by itself, it is only helpful for the 5 percent or so of people with CF that have a version of the protein (resulting from mutations in the gene such as one designated *G551D*) that, although inactive without the drug, is stable and reaches the cell surface where it is supposed to reside. However, research has continued to improve functional rescue of various forms of the CFTR protein and thereby continues to improve the health and quality of life for people with CF. For example, the FDA has recently approved the use of "corrector" drugs that help other mutant forms of the CFTR protein reach the cell surface. These can be combined with ivacaftor to improve CFTR function in people who have CF and have one or two copies of *ΔF508*, the most common disease-causing *CFTR* mutation. The improvements from these treatment regimens are modest, though clinically meaningful, so work has continued to improve upon this therapeutic approach. In the major recent advances described below, researchers examined whether it might be possible to maximize the clinical value of existing therapies like ivacaftor by starting treatment before birth; tested new, triple drug combinations in clinical trials with participants who have the *ΔF508* mutation; and developed new candidate corrector drugs that could potentially raise CFTR channel levels in the majority of people with CF to normal or near-normal levels.

In Utero Treatment May Promote Healthy Development: New research shows that treatment during pregnancy can prevent or reduce developmental complications of CF in an animal model of the disease. While ivacaftor treatment for people with the *CFTR-G551D* mutation greatly improves patient health and quality of life, CFTR activity appears to be important during embryonic development, even before a baby takes his or her first breath—and thus before treatment begins. For example, infants with CF may be born with intestinal blockages so severe that they are life-threatening. Even in cases where this does not happen, defects in the intestines and pancreas can interfere with proper absorption of nutrients, slowing the baby's growth. In addition, men with CF are almost invariably infertile, because the vas deferens and epididymis—ducts that carry sperm from the testes—do not develop properly during gestation. Although ivacaftor is FDA-approved for infants as young as 1 year old who have CF and at least one copy of *G551D*, prevention of these digestive and reproductive consequences of the disease might require treatment to begin earlier—potentially even before birth.

To test this hypothesis, researchers utilized a ferret model of CF, which is much more prone to these developmental issues than are mouse or rat CF models. Ferrets born with *CFTR-G551D* have a very high frequency of serious intestinal blockages; those that survive infancy grow much more slowly than normal due to difficulty absorbing nutrients; and male ferrets with the mutation are sterile. However, the researchers found that if the mothers were treated with ivacaftor during pregnancy, both the digestive system and the male reproductive tract of the offspring developed much more normally. It remains to be determined whether treatment with ivacaftor or other small molecule drugs can safely and effectively promote healthy embryonic and infantile development in people with CF, but these results suggest that such treatments may one day allow much healthier development in children born with the disease and may help advance knowledge about the role of CFTR function during development.

Sun X, Yi Y, Yan Z,...Engelhardt JF. In utero *and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis.* Sci Transl Med *11: pii: eaau7531, 2019.*

Triple Combination Therapies Show Promise for People with the Most Common CF-causing Mutation: Combinations of recently developed small molecule drugs have shown great promise for significantly improving treatment of people who have CF and have one or two copies of the *ΔF508 CFTR* mutation. About 90 percent of people with CF have at least one copy of *ΔF508*, and half have two copies, one from each parent. The effects of the *ΔF508* mutation on CFTR function are profound. Not only does the mutation inactivate the chloride channel, it also has two other serious consequences: it interferes with the protein's biosynthesis, greatly reducing the amount that reaches the cell membrane, where it is needed; and it also renders the protein highly unstable, so that the small amount of CFTR protein that reaches its cellular destination is rapidly degraded. Thus, restoring robust CFTR function in people with *ΔF508* will not only require an improvement in the protein's function, it will also require both an increase in the amount of the mutant protein that cells produce and an improvement in the protein's stability once it reaches the cell surface. To date, no single medication has been identified that is capable of meeting all of these needs.

Previous research had shown that the corrector drugs lumacaftor and tezacaftor are each capable of stabilizing ΔF508-CFTR during biosynthesis so that a significant amount of the protein reaches the cell surface. That alone is not enough to provide clinical benefit, since the protein remains inactive; but when combined with the potentiator ivacaftor, either corrector can provide a modest but measurable improvement in ΔF508-CFTR function. That was an important achievement, but it remained critical to further increase the amount of the mutant protein on the cell surface in order to improve clinical outcomes. A pharmaceutical company therefore developed new ΔF508-stabilizing drugs that work by different mechanisms from tezacaftor and lumcaftor. They identified two such agents and designated them VX-445 and VX-659. In new research led by the pharmaceutical company but with additional support from the NIDDK, they tested the ability of each of these to supplement tezacaftor-ivacaftor. In lab-cultured human airway cells producing only ΔF508-CFTR or ΔF508-CFTR along with a rarer, minimally functional mutant CFTR protein, both of the tested three-drug combinations significantly increased the net amount of the protein through improved biosynthesis, stability, or both, and increased the flow of chloride ions through the cell membrane compared to the two-drug combinations.

The researchers also reported clinical trial results of these triple combination therapies in men and women with CF who had at least one copy of Δ*F508-CFTR*. The two 4-week trials involved similar numbers of participants—122 for VX-445 and 117 for VX-659—and yielded very similar results. The resulting triple combination therapies significantly boosted CFTR function, based on improvements in measures of respiratory function and quality of life, among other tests. For example, in people with two copies of Δ*F508-CFTR* who had been taking a combination of tezacaftor and ivacaftor at the beginning of the trial, a measure of respiratory function improved 9.7 percent with the addition of VX-659, and 11 percent when VX-445 was the third added drug. People with one copy of Δ*F508-CFTR* and one copy of a different minimally functioning CF mutation—none of whom had been taking tezacaftor-ivacaftor to begin with—had an average improvement of 13.3 percent or 13.8 percent in the same test when they began taking the VX-659 or VX-445 triple combination therapies, respectively. Although these improvements may appear small, their expected health benefit is potentially significant. Importantly, neither of the three-drug combinations appears to have caused serious side effects. Based in part on these results, the FDA approved the VX-445-tezacaftor-ivacaftor triple combination for treating CF in people ages 12 and over with at least one copy of the Δ*F508-CFTR* variant. Further research will be needed to determine the long-term impact of this therapy on patient health, but the findings described here suggest it will provide a significant improvement in health for the majority of people with CF.

Davies JC, Moskowitz SM, Brown C,...Rowe SM; VX16-659-101 Study Group. VX-659-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del *alleles. N Engl J Med 379: 1599-1611, 2018.*

Keating D, Marigowda G, Burr L,...Taylor-Cousar JL; VX16-445-001 Study Group. VX-445-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del *alleles. N Engl J Med 379: 1612-1620, 2018.*

Improving Combination Therapy for Cystic Fibrosis: Researchers have developed new candidate medications that correct distinct structural defects of Δ*F508-CFTR*, the most common CF-causing mutation, an approach that could potentially lead to improved therapies for the great majority of people with the disease. Like many proteins, CFTR contains multiple functional elements, called "domains." Two such CFTR domains bind to a key, channel-activating cofactor called a nucleotide, so these structural elements are referred to as nucleotide-binding domains 1 and 2 (NBD1 and NBD2). Two other structural elements are the parts of the protein that cross the cell membrane (where CFTR must be located to allow the flow of chloride ions) and are thus called membrane spanning domains 1 and 2 (MSD1 and MSD2). The Δ*F508-CFTR* mutation, while located in NBD1, not only destabilizes that key structural element, it also destabilizes NBD2 and the interactions of both NBDs with the MSDs. The two FDA-approved CFTR-corrector drugs, lumacaftor and tezacaftor, both work by similar means, stabilizing the interactions of NBD1 with MSD1 and MSD2. The researchers considered the possibility that restoring full or nearly full function of ΔF508-CFTR would also require stabilizing the NBDs themselves, as well as the interactions of NBD2 with the MSDs.

The scientists screened 600,000 different chemical compounds in human cell lines and employed a variety of techniques to identify new CFTR correctors that would act on different parts of the

protein than do the existing FDA-approved agents. For example, they determined which of them allowed more of the protein to accumulate in the cell membrane of cells expressing ΔF508-CFTR that were already being treated with lumacaftor: the idea is that if the candidate drug works by a different mechanism from lumacaftor, the actions of the two together would be expected to yield significantly greater stabilization of CFTR than will either medicine by itself. They followed up with tests to determine which of the key domains of CFTR these compounds bound to, in order to separate them into groups that act on distinct portions of the protein. With such approaches, they provisionally assigned them into three classes: I, compounds like lumacaftor that stabilize the interactions of NBD1 with the MSDs; II, compounds that stabilize NBD2 or its interactions with the MSDs; and III, compounds that specifically stabilize NBD1.

While each of these compounds on its own stabilized ΔF508-CFTR just a little bit, when they combined correctors of different classes the researchers observed a synergistic increase in stability of the mutant protein. For example, if a class I and a class II corrector each improved stability by 5 percent on its own, combining them together yielded substantially more than 10 percent improvement. And indeed, by treating cells simultaneously with all three classes of corrector, the scientists were able to make ΔF508-CFTR roughly as stable as normal, healthy forms of CFTR. Importantly, even without addition of a potentiator like ivacaftor, these new triple corrector combinations also yielded near-normal CFTR function in cultured cells, and restored chloride channel function in mice that have Δ*F508-CFTR* in place of their normal *CFTR* gene. Further, the triple correctors also appeared to be effective in treating a variety of other, rarer CF-causing mutations. Clinical trials would be needed to determine whether any of these combinations is safe and effective in people with CF. If one or more of them is, it could lead to a dramatic improvement in health for people with the disease.

Veit G, Xu H, Dreano E,...Lukacs GL. Structure-guided combination therapy to potently improve the function of mutant CFTRs. Nat Med 24: 1732-1742, 2018.

Pregnancy, Metabolism, and the Short- and Long-term Health of Women and Their Children

Pregnancy can be a time of great joy, but also acts as a stress test on a woman's body. Important physical changes that occur to support pregnancy can also unmask or exacerbate risk of metabolic problems and other conditions in the mother. These, in turn, can have lasting adverse impacts both on a woman's own health and the health of her offspring. For example, one set of changes affects how women are able to metabolize glucose (sugar), the body's major source of energy. In some women, these changes can cause their blood glucose levels to rise to such a degree that they are diagnosed with and treated for a condition called gestational diabetes (GDM), a form of diabetes that is diagnosed during pregnancy and is not clearly identified as either preexisting type 1 or type 2 diabetes. GDM is known to confer short- and long-term health risks to mothers and children. Now, through a long-term study involving thousands of women and children, researchers have found that elevated maternal blood glucose levels even below those meeting traditional GDM diagnostic criteria increase the risk of future type 2 diabetes in mothers and impaired glucose metabolism and greater excess fat in children ages 10 to 14 years post-delivery. These and other findings have prompted new NIDDK-supported research efforts with the ultimate goal of promoting healthier outcomes for women and their children both during and post-pregnancy.

GESTATIONAL DIABETES

GDM is typically diagnosed just before or during the third trimester of pregnancy; approximately 7 percent of U.S. pregnancies are affected. GDM increases near-term health risks for mothers and babies, including high birth weight babies and delivery complications. Controlling maternal blood glucose levels through lifestyle change (modifications to diet and exercise) and/or with injections of the hormone insulin, if needed, can mitigate some of these risks.

Traditional approaches to diagnosing GDM in the United States include a screening test 24 to 28 weeks into pregnancy, during which women are given a sugary drink and then tested for blood glucose levels to see if they are at risk. Women identified as at-risk then go through further testing to see if their blood glucose levels exceed certain threshold values for diabetes. GDM, as diagnosed using these traditional criteria, is not only associated with near-term health risks, but also with longer-term health problems. For the mother, GDM confers a greater risk of developing type 2 diabetes post-pregnancy. For the children of an affected pregnancy, GDM increases the likelihood of developing obesity or type 2 diabetes.

RISKS FROM ELEVATED GLUCOSE DURING PREGNANCY EVEN BELOW TRADITIONALLY DEFINED GDM LEVELS

In 2008, the landmark NIH-funded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported findings of health problems associated with glucose levels during pregnancy that were above normal (hyperglycemia), but not high enough to be considered diabetes. Studying a racially and ethnically diverse international cohort of over 23,000 pregnant women and their babies, the HAPO researchers found that elevated maternal blood glucose levels below those diagnostic of GDM were associated with increased risk of multiple adverse outcomes for the mother and child. These included high birth weight, low blood glucose in the baby at birth, and need for caesarean delivery. Strikingly, the HAPO researchers observed that even modestly elevated maternal blood glucose levels were associated with risks, which increased with maternal blood glucose levels in a linear fashion for most outcomes. Because HAPO only included women whose glucose levels were not high enough for a diagnosis of GDM at the time, they were not considered to have this disease and thus were not treated for it.

Primarily as a result of HAPO, alternative criteria for diagnosing GDM were proposed and adopted by a number of organizations around the world; these criteria include lower blood glucose level threshold values for a GDM diagnosis. However, these criteria are not widely used in the United States, largely due to findings from an expert panel NIH convened in 2013 regarding GDM diagnosis. The findings pointed out gaps in knowledge about how best to treat women diagnosed with the alternative criteria, and the absence of evidence about long-term outcomes and benefits for these women with or without treatment—as well as the potential for short-term harms, such as the additional stress a woman can experience when diagnosed with GDM. Thus, a critical question regarding maternal blood glucose levels that are elevated but do not meet the traditionally defined criteria for GDM is this: what are the long-term impacts on the health of women and their children?

FINDINGS FROM THE HAPO FOLLOW-UP STUDY

Researchers with the HAPO Follow-up Study (HAPO FUS) sought to address this question. Recognizing the enormously valuable information that could be gained from further study of HAPO participants, HAPO FUS researchers, with funding from NIDDK and additional support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, recruited a subset of the original HAPO mother-child pairs and performed comprehensive metabolic tests 10 to 14 years post-delivery to help answer questions about the long-term impacts of these maternal glucose levels. Participating mothers were tested for type 2 diabetes and prediabetes and were also asked to fill out health-related questionnaires. The researchers measured the children's height, weight, waist circumference, and body fat (adiposity), and also tested them for blood glucose levels and other measures related to diabetes. A total of 4,967 women and 4,832 children participated in HAPO FUS.

The HAPO FUS researchers recently published several major study results. They first studied participating mothers whose pregnancies during HAPO met, in retrospect, the alternate criteria for GDM, although they did not meet the traditional criteria for GDM. This group included about 14 percent of the women. Over half of these women developed type 2 diabetes or prediabetes in the 10 to 14 years post-delivery, versus only 20.1 percent of the women who had lower glucose levels. Moreover, even after adjusting for many known risk factors for type 2 diabetes, women who retrospectively met the alternative criteria for GDM were over five times more likely to develop diabetes than women who had lower glucose levels.

When the researchers examined participating children, they found that the likelihood of having any excess weight, at the level of either overweight or obesity, did not differ significantly between the children of mothers whose glucose levels met the alternate GDM criteria and the other children. However, narrowing their focus to just higher levels of excess weight in the children, they found that the likelihood of having obesity was significantly greater among children of affected pregnancies. (For these analyses, the researchers also took into account each mother's body mass index, BMI—a measure of weight relative to height—during pregnancy, as that, too, can influence the risk of excess weight in her offspring.) Furthermore, the researchers found evidence that children from pregnancies meeting the alternate GDM criteria were more likely than the other children to have developed insulin resistance, another risk factor for type 2 diabetes. No difference was seen between girls and boys in this regard.

Having examined the impact of maternal glucose levels meeting the alternative GDM criteria on risk for metabolic problems in the children, the HAPO FUS researchers then asked whether there was a direct correlation between maternal blood glucose levels—including those below levels meeting the alternative GDM criteria—and measures of childhood adiposity years later. After taking into account maternal BMI during pregnancy, they observed increasing risk of childhood adiposity with increasing maternal glucose levels during pregnancy. The overall outcome was largely similar for boys and girls.

FUTURE DIRECTIONS

The HAPO FUS findings are important as they demonstrate that elevated maternal blood glucose levels below those traditionally used to diagnose GDM are associated with long-term health risks for mothers and children. However, large gaps in knowledge remain—for example, how maternal blood glucose levels change across the entire course of pregnancy is unknown. It is also unclear whether screening for GDM earlier in pregnancy than the late second to third trimester, treating GDM at an earlier stage of pregnancy, or providing treatment for lower (but still elevated) maternal blood glucose levels would result in health benefits for mothers and children. As other NIDDK-supported studies have demonstrated the devastating impact of type 2 diabetes in youth, closing these knowledge gaps could have critical ramifications for the health of future generations.

To begin to address these questions that are so important to both diabetes care and prevention, the NIDDK is cultivating new research in this area, starting with a newly funded pregnancy research consortium. This clinical consortium will employ cutting-edge technology to ascertain the "profile" of blood glucose levels in women across the span of pregnancy, beginning in the first trimester. Such information could help lay the foundation for future clinical studies and trials evaluating new approaches to GDM screening, diagnosis, and intervention, with the ultimate goal of improving the health of women and their children.

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Lowe WL Jr, Scholtens DM, Lowe LP,...Metzger BE; HAPO Follow-up Study Cooperative Research Group. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. JAMA 320: 1005-1016, 2018.

NIDDK Director Testifies on Type 1 Diabetes Research

On July 10, 2019, NIDDK Director Dr. Griffin P. Rodgers testified about progress and future directions in type 1 diabetes research before the Senate Special Committee on Aging, which is led by Chairman Susan Collins (R-Maine) and Ranking Member Bob Casey (D-Pennsylvania). The hearing, entitled "Redefining Reality: How the Special Diabetes Program Is Changing the Lives of Americans with Type 1 Diabetes," was held in conjunction with the Children's Congress, an event sponsored every 2 years by JDRF to highlight the value and progress of type 1 diabetes research for children and adults living with this disease. Testifying with Dr. Rodgers were Dr. Aaron Kowalski, JDRF President and CEO; actor Mr. Victor Garber; and JDRF Children's Congress delegates Ruby Anderson, age 9, and Adriana Richard, age 16.

In his testimony, Dr. Rodgers described research made possible by the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), which the NIDDK administers on behalf of the Secretary of the Department of Health and Human Services. Examples of research progress include:

- Findings from a clinical trial conducted by NIDDK's Type 1 Diabetes TrialNet showing that treatment with a drug targeting the immune system can prevent onset of clinical type 1 diabetes in high-risk individuals for at least 2 years (see advance in this chapter);
- Progress toward the development of new diabetes management technologies, including artificial pancreas devices that automate blood glucose (sugar) sensing and insulin administration;
- Results reported by the NIDDK's Human Islet Research Network using novel technologies to visualize—at the same time—individual insulin-producing beta cells and other pancreatic cell types, as well as immune cells involved in the type 1 diabetes autoimmune attack (see advance in this chapter); and
- Findings from NIDDK's The Environmental Determinants of Diabetes in the Young (TEDDY) study that are providing new insights on childhood health and development, as well as environmental factors that may contribute to type 1 diabetes in children (see advance in this chapter).

To solicit input on new, emerging, and innovative research for the treatment and prevention of type 1 diabetes and its complications that could be supported by the Special Diabetes Program, the NIDDK convened a planning meeting in May 2019, held under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee. At

Shown at the dais (left to right): Sen. Kyrsten Sinema (D-AZ), Sen. Jeanne Shaheen (D-NH), Sen. Bob Casey (D-PA, Ranking Member), and Sen. Susan Collins (R-ME, Committee Chair). Photo credit: Camera1@nycphoto.com

NIDDK Director Dr. Griffin P. Rodgers testifying before the Senate Special Committee on Aging. Also shown at the table (left to right): JDRF President and CEO Dr. Aaron Kowalski, actor Victor Garber, and Children's Congress delegates Ruby Anderson and Adriana Richard. Photo credit: Camera1@nycphoto.com

the meeting, a panel of external scientific experts and a lay representative provided input on potential new research initiatives proposed by the NIDDK, other institutes at NIH, and the Centers for Disease Control and Prevention; they also provided input on the continuations of ongoing programs.

Guided by that input, diabetes research strategic plans, and input that the NIDDK receives at venues such as scientific conferences and workshops, the Institute is identifying the most compelling areas of current research opportunity to pursue with Special Diabetes Program funds, to continue the Program's exceptional track record of supporting cutting-edge research to improve the health and well-being of people with type 1 diabetes and its complications.

STORY OF DISCOVERY

Progress on the Pathway to Prevention of Type 1 Diabetes

Type 1 diabetes is a devastating illness where the body's ability to produce the pancreas-derived hormone insulin is lost, requiring people with the disease to administer insulin daily for survival. Even with this burdensome treatment, people with type 1 diabetes are at risk for life-threatening complications. Research shows that the incidence of type 1 diabetes is on the rise in the United States, so identifying ways to prevent type 1 diabetes in those at risk is critical, in parallel with efforts to cure the disease in those who have been diagnosed.

The story of type 1 diabetes—which is still being written as key questions and challenges remain—involves geneticists, epidemiologists, molecular and cellular biologists, immunologists, endocrinologists, bioengineers, researchers in other fields, and patient participants. This multifaceted and collaborative approach has resulted in valuable new knowledge that is moving us closer to a long-standing goal of type 1 diabetes prevention.

IDENTIFYING THOSE AT RISK TO DEVELOP TYPE 1 DIABETES

Preventing type 1 diabetes requires not only a successful therapy, but also the ability to identify those who are at risk of developing the disease. But answering the deceptively simple question of "who is at risk?" required a multi-pronged research approach.

One of the first steps was to understand the disease better. Early on, scientists searched for a toxin or infectious agent that caused type 1 diabetes. However, some observed that people with type 1 diabetes sometimes had other disorders related to abnormal hormone levels or function (endocrine disorders), particularly those associated with autoimmunity, leading scientists, after decades of studying the disease, to hypothesize that type 1 diabetes was an autoimmune disease. Autoimmune diseases result when a person's immune system does not properly distinguish between "self" and "non-self" and inappropriately targets and attacks the body's own organs, tissues, and cells. One component of an immune attack is antibodies, produced by an immune cell type called B lymphocytes. Self-directed antibodies are called "autoantibodies," and their presence in the blood can indicate an autoimmune process.

In the early 1970s, researchers found that, by using blood from people with multiple autoimmune endocrine disorders, including type 1 diabetes, they could detect a specific autoantibody response to insulin-producing pancreatic islet tissue. Later research demonstrated that antibodies that react with islet cells could be found in the majority of people with newly diagnosed type 1 diabetes. Further research has identified more than four different autoantibodies specifically enriched in people with type 1 diabetes. One of the earliest autoantibodies to appear, most commonly in younger children, is directed against insulin.

Early studies of families with type 1 diabetes in the 1970s led to the observation that the disease often appeared in siblings, indicating that there could be a genetic component to the disease. NIDDK-supported scientists and others soon discovered that human leukocyte antigen (HLA) gene alleles (variant forms of a gene required for the function of another immune cell type—T cells) were associated with type 1 diabetes. With the use of modern tools for genetic analysis, we now know that HLA accounts for approximately 50 percent of the heritability of type 1 diabetes. Additionally, NIDDK-supported researchers and others have since identified more than 50 other genetic loci that contribute to type 1 diabetes susceptibility, accounting for nearly 90 percent of genetic risk

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in the Caucasian population, which is most affected by type 1 diabetes. Many of these genes are known to be involved in the immune response, further strengthening the understanding of type 1 diabetes as an autoimmune disease. These exciting findings set the stage for efforts to identify those at risk to develop type 1 diabetes and to test immune-modulating therapies to prevent the disease.

A WINDOW OF OPPORTUNITY TO PREVENT TYPE 1 DIABETES

Until the discovery of autoantibodies, it was generally assumed that type 1 diabetes had an acute onset whose first clinical symptoms were the sudden appearance of metabolic abnormalities as a result of the loss of insulin in previously healthy people. Prevention would be difficult in such a disease, as there would be no warning before the clinical appearance of the disease and identifying at-risk individuals would not be possible. Not only did the revelation that type 1 diabetes was an autoimmune disease mean that autoantibodies could possibly be used to identify those at risk before the manifestation of clinical symptoms, but it also suggested that a window of opportunity for prevention might exist. Destruction of the insulin-producing β (beta) cells (which are in the pancreatic islet cell clusters) by an errant immune attack might happen over time, rather than immediately, and perhaps this destruction could be delayed or stopped altogether, preserving the precious remaining β cells.

NIDDK-supported scientists and others spent the 1980s studying cohorts of people that had these autoantibodies in their blood but had not been clinically diagnosed with diabetes to determine whether the appearance of autoantibodies preceded loss of insulin and if they indicated the early stages of type 1 diabetes. In one study, NIDDK-supported investigators followed a set of triplets and a set of twins, each with one person with type 1 diabetes. These people were studied for nearly 2 decades. Over that time, one triplet and one twin—neither of whom had diabetes at the start of the study—first developed autoantibodies and then onset of clinically overt disease, allowing scientists to document the slow, progressive loss of insulin before the onset of clinical diabetes.

In another study, NIDDK-supported scientists screened over 1,700 first-degree relatives (parents, siblings, and offspring) of people with type 1 diabetes for the presence of islet-cell autoantibodies. Only 16 of those screened had the autoantibodies, but 2 of those developed type 1 diabetes in the next 2 years, compared to 1 of the 1,700 without antibodies. In addition, the researchers examined the insulin response in 12 of the relatives with autoantibodies and found that 6 of these individuals had low insulin responses, an indicator of diminished β cell function. Results from these and similar studies contributed to the growing body of evidence that islet-cell autoantibodies were predictors of type 1 diabetes and that β cell destruction was not an immediate event. These studies also provided key information on how screening programs could be designed to identify people and assess their risk, setting the stage for trials to prevent type 1 diabetes.

SETTING THE STAGE FOR A LARGE-SCALE PREVENTION TRIAL

For a first test of type 1 diabetes prevention, researchers turned to a familiar candidate: insulin. Studies in animal models, as well as small pilot studies in humans, suggested that insulin could delay type 1 diabetes development. It was thought that administering low-dose insulin to an at-risk person before the disease progressed could induce protective immunity that might slow or prevent the immune system's attack. In 1994, the NIDDK-supported Diabetes Prevention Trial-Type 1 Diabetes (DPT-1) began screening first- and second-degree relatives to identify eligible participants for a clinical trial to test this hypothesis. More than 84,000 people were screened; about 340 were found positive for autoantibodies, had more than an estimated 50 percent chance to develop

type 1 diabetes in the next 5 years, and elected to participate in a study testing injectable insulin for prevention of type 1 diabetes. Participants were studied for an average of about 3.5 years, and this clinical trial concluded in 2001. DPT-1 also tested the effect of orally administered insulin in relatives who had an estimated 26 to 50 percent chance of developing type 1 diabetes in the next 5 years. Over 370 participants were studied for an average of 4.3 years in that trial, which concluded in 2003. Although both injectable and oral insulin were very safe, with negligible side effects, neither was found to delay or prevent type 1 diabetes.

Despite the negative results, the DPT-1 was a success in other ways. DPT-1 researchers estimated participant risk using the presence of islet-cell antibodies, insulin response to glucose tests, and the presence or absence of specific HLA alleles, validating these predictive tools and demonstrating that it was possible to identify a cohort of people at high risk for type 1 diabetes. DPT-1 also demonstrated that large type 1 diabetes prevention trials were feasible in at-risk family members of individuals with type 1 diabetes, establishing a path for future prevention trials, just in time for the emergence of new agents that would require testing.

CREATING A NETWORK FOR PREVENTION TRIALS: TYPE 1 DIABETES TRIALNET

As the DPT-1 was concluding, the continued need for a network of investigators and sites to conduct trials of promising therapies to prevent type 1 diabetes became evident. These trials would require screening of large numbers of people to identify those who would be eligible to participate. Additionally, a coordinated and collaborative effort would accelerate progress in this field. Thus, in 2001, NIDDK launched Type 1 Diabetes TrialNet. Since its start nearly 2 decades ago, TrialNet has become an international network of clinical research centers, affiliate sites, a hub, and a coordinating center that involves hundreds of scientists and staff and, most importantly, thousands of participants. TrialNet has conducted multiple studies of agents to delay progression of type 1 diabetes in people with and at risk for the disease, as well as contributed key insights into understanding the type 1 diabetes disease process.

REFINING RISK AND STAGING PROGRESSION OF TYPE 1 DIABETES

The ability to accurately assess those at risk for type 1 diabetes is critical to identify participants for prevention trials and to ensure that as many people as possible can benefit, if and when new prevention strategies are proven effective. To refine and quantify type 1 diabetes risk, NIDDK-supported researchers pooled data from multiple studies and, in 2013, reported that the majority of children who had multiple islet autoantibodies in their blood progressed to the disease over the next 15 years, suggesting that prevention studies focus on this high-risk population.

Data from DPT-1, TrialNet, and other studies revealed that progression to clinical type 1 diabetes proceeds through distinct stages prior to onset of symptoms. This formed the basis for a recommendation from TrialNet, JDRF, the Endocrine Society, and the American Diabetes Association for a type 1 diabetes staging classification in at-risk individuals. This staging provides a framework for the research and development of preventive therapies (see Figure 1): stage 1 is defined as the presence of two or more different types of islet autoantibodies with normal blood glucose (sugar) levels and is considered early type 1 diabetes; stage 2 diabetes is the presence of two or more autoantibodies but with abnormal blood glucose levels without symptoms; and stage 3 is when clinical diagnosis has been reached and symptoms of type 1 diabetes are usually present. TrialNet's prevention trials enroll individuals with pre-clinical (stage 1 and 2) type 1 diabetes, and TrialNet's new-onset trials enroll participants in early stage 3 diabetes.

STORY OF DISCOVERY

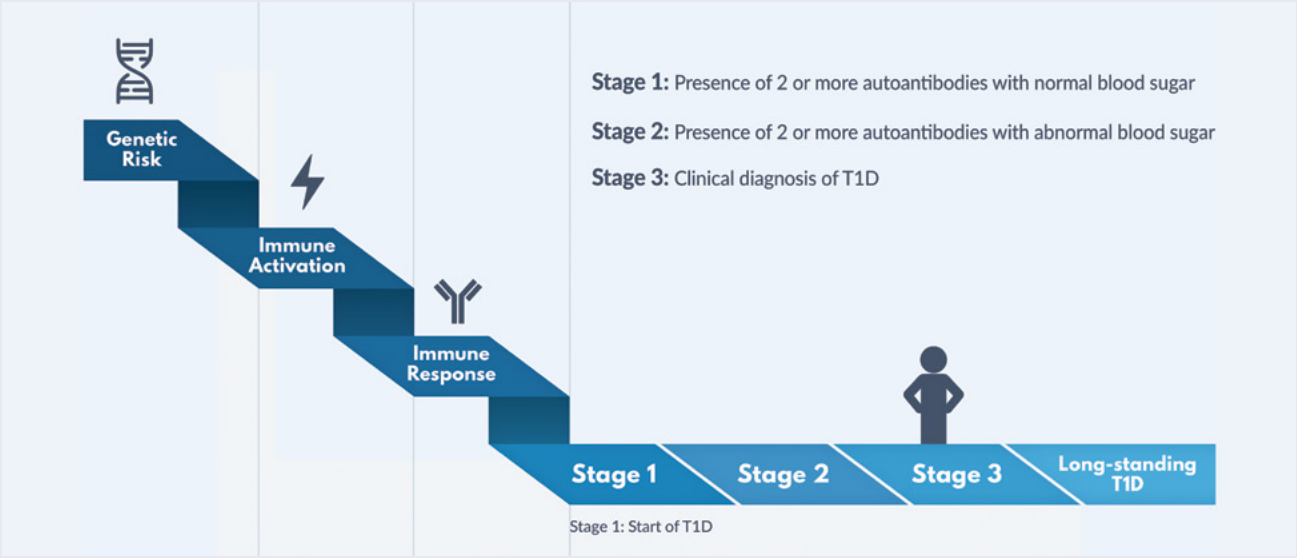

Figure 1: Windows for Prevention of Type 1 Diabetes (T1D): *This graphic illustrates how type 1 diabetes progresses. Genetic risk, combined with an unknown environmental trigger(s), is followed by inappropriate activation of the immune system to attack the insulin-producing β cells. The appearance of more than one islet-cell autoantibody in a person's blood indicates that the immune system has been activated and the person has a high risk of development of type 1 diabetes. Stages 1 and 2 are considered the start of type 1 diabetes, even before the appearance of clinical symptoms and before the clinical diagnosis of diabetes is made—a window of opportunity for strategies to prevent onset of clinical disease. Research by Type 1 Diabetes TrialNet contributed to this new knowledge of type 1 diabetes staging, and TrialNet's goal is to test agents to prevent or delay the disease at all stages. (Graphic courtesy of Type 1 Diabetes TrialNet.)*

The combination of these efforts led to the following understanding of type 1 diabetes disease risk: 35 percent of people in stage 1 and 70 percent of people in stage 2 will progress to clinical diabetes within 3 to 5 years of identification. The lifetime risk for developing clinical type 1 diabetes from stage 1 or 2 nears 100 percent. In the future, risk assessment could take into account an individual's genetic makeup and their environmental exposures to determine risk even before autoantibodies appear.

Of note, most new cases of type 1 diabetes occur in people who have no affected relatives. There is currently no way to identify these people other than by conducting population-wide genetic screening, which is not currently feasible. Therefore, for now, research has demonstrated that the most efficient way to identify people at risk for type 1 diabetes is to screen first- and second-degree relatives of people with the disease due to their 15-fold increased risk for developing the disease compared to the general population. To date, TrialNet has screened more than 200,000 relatives and screens more than 15,000 annually to identify at-risk individuals for enrollment in trials. More than 7,000 people have enrolled in TrialNet's Pathway to Prevention Study (an observational study for relatives with autoantibodies) and/or have participated in a TrialNet trial.

IDENTIFYING CANDIDATE THERAPIES TO TEST

One of the challenges of clinical trials is balancing the potential benefits against the risks. There is risk associated with introducing an agent, particularly one that modulates the immune system and may have serious side effects, into a healthy person—albeit one who will eventually develop clinical diabetes but has not yet done so—especially when the participants are children. Therefore, careful consideration is paramount in deciding which agents

are the most promising and should be tested in prevention trials. With that in mind, TrialNet looks for agents that have been tested for safety in animal models, in pilot studies in people, or have been tested (or even approved for use) in people with other autoimmune diseases or conditions before a larger prevention trial is considered.

One of the first agents to emerge as a possible candidate for therapy was an antibody known as anti-CD3, which modifies the function of T cells, but does not dramatically deplete them. In studies of mouse models of type 1 diabetes, anti-CD3 agents have consistently reversed diabetes at the onset of symptoms. In a small clinical trial funded by NIDDK and reported in 2002, scientists found that an anti-CD3 agent, teplizumab, preserved some insulin production after 1 year with no severe side effects in people recently diagnosed with type 1 diabetes. Following these results, multiple larger and longer studies confirmed that teplizumab treatment delayed the loss of insulin production, including one done by the National Institute of Allergy and Infectious Diseases' Immune Tolerance Network, an important TrialNet partner.

To continue to make progress towards a more effective, durable and safe therapy for type 1 diabetes, TrialNet has tested additional immune-modifying agents in people newly diagnosed with type 1 diabetes. For example, in 2009, TrialNet reported that rituximab, which is approved as a cancer therapy and destroys B lymphocytes, slowed disease progression for 6 to 9 months. Another TrialNet trial tested the drug abatacept, which acts on T cells and is an approved therapy for rheumatoid arthritis. The results showed that participants who received abatacept had higher insulin production than those who received placebo after 2 years. In 2018, TrialNet reported that another immune system suppressant, low-dose anti-thymocyte globulin (ATG), delayed the loss of insulin production and improved blood glucose control for up to 2 years. All of these drugs can have significant side effects and each had only temporary benefit, likely due in part to immune cell regeneration when the treatments ended. However, these positive results showed that many immune-modulating therapies could slow the disease, indicating that these agents could be tested in prevention trials, where their effects could be more beneficial.

DEMONSTRATION THAT TYPE 1 DIABETES CAN BE PREVENTED

Teplizumab, with several positive trials in people with newly diagnosed type 1 diabetes, was chosen by TrialNet as the first agent to test for disease prevention. TrialNet began a trial in 2011 and, in 2019, reported that teplizumab delayed onset of clinical type 1 diabetes in people at high risk (stage 2) for an average of 2 years (see advance and Patient Profile in this chapter). This exciting discovery provides the first evidence that the onset of clinical type 1 diabetes can be delayed with early preventive treatment. Participants are being followed to determine the durability of the effect, but these results have important implications for people, particularly youth. Treatment with teplizumab could give at-risk individuals 2 years free of type 1 diabetes and insulin administration; 2 years that they do not have to check blood glucose levels; and 2 more years of good health towards preventing or delaying diabetes complications. Based on TrialNet's results, the U.S. Food and Drug Administration gave teplizumab "Breakthrough Therapy Designation" to expedite its development and review.

THE FUTURE FOR PREVENTION TRIALS OF TYPE 1 DIABETES

Much remains to be explored about teplizumab and other immune-modifying drugs so that more effective treatments can be designed. First and foremost, we need to understand more about the mechanisms of autoimmune pathogenesis and how individual people respond to therapies. From the beginning, TrialNet has engaged in mechanistic research, collecting blood samples from people

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enrolled in trials and analyzing them for the specific mechanistic effects of treatment. Building on these data, TrialNet has designed a new prevention trial that will combine two agents that showed benefit to newly diagnosed participants in previous trials and that affect complementary immune pathways. Alternative dosing regimens, testing agents even earlier in at-risk people (*i.e.*, stage 1), and other types of combination trials all present exciting opportunities to build on this advance. Additionally, TrialNet currently has two other single-agent prevention studies under way: one testing abatacept (see earlier) and one testing the drug hydroxychloroquine, both of which are already used to reduce symptoms and progression of other autoimmune diseases. There are also many other promising therapies in TrialNet's pipeline, with even more expected in the future as new knowledge is uncovered by TrialNet's mechanistic work and through other NIDDK-supported research efforts focused on the underlying mechanisms of type 1 diabetes development.

With continued research, the goal of preventing type 1 diabetes—permanently and in anyone who could develop the disease—now seems possible after decades of contributions from countless scientists and, most importantly, the trial participants who never gave up hope.

SCIENTIFIC PRESENTATION

Dr. Jeff Pessin—The Link Between Body Fat Production, Feeding, and Fasting

Jeff Pessin, Ph.D., is a Professor in both the Department of Medicine and the Department of Molecular Pharmacology at Albert Einstein College of Medicine. He is the Judy R. and Alfred A. Rosenberg Professorial Chair in Diabetes Research, and Director of the Diabetes Research Center at Albert Einstein College of Medicine. Dr. Pessin's research interests focus on three areas: the molecular mechanism of adipose (fat) tissue inflammation leading to fibrosis and programmed cell death; the regulation of insulin and nutrient signaling and the regulation of glucose and fat production in the liver; and the dysregulation of such signaling in states of insulin resistance. At the January 2019 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Pessin presented results of his research.

The body stores much of the excess energy (calories) from our diet as fat—usually in fat tissue, but also in the liver—and it synthesizes this body fat via a process called lipogenesis. Excessive lipogenesis can lead to fatty liver disease, which in turn can lead to more serious liver problems, and in some cases even to liver failure. Thus, it is important to understand the factors controlling this process.

The body increases lipogenesis when we consume more calories from food than we need, so the excess calories can be stored for later use; conversely, lipogenesis is inhibited during fasting, when the body must liberate energy from its storage depots rather than adding to them. Like many other processes in the body, lipogenesis begins with an increase in the quantities of the proteins that produce these fats within cells, and lipogenesis is turned off when cells reduce the amounts of those same proteins. Dr. Pessin described research on the molecular mechanisms that link these lipogenic (fat-generating) protein levels to the body's nutritional state—in this case, the amount of dietary energy available in the body.

A cell's first step in making more of any needed protein is to increase the "expression" of the gene that encodes that protein. That is, the cell makes temporary copies of the gene, called transcripts, which are effectively instructions for assembling the protein. The signal to make these transcripts is the arrival of a protein called a transcription factor at the gene. Expression of the lipogenic genes is activated by arrival of the transcription factor SREBP-1c.

However, as is often the case with transcription factors, SREBP-1c does not scan the genome to locate the lipogenic genes on its own. A large group of proteins called the "mediator complex" must first bind to a nearby region of DNA. The mediator complex then binds SREBP-1c, bringing it close to the lipogenic genes and promoting their expression. During fasting, when lipogenesis is no longer needed, a component of the mediator complex called CDK8 modifies SREBP-1c in such a way that it is targeted for degradation. The effect is not to eliminate lipogenic proteins directly, but rather to reduce expression of their genes, so that more of these proteins are not made unnecessarily.

But what is the molecular link between nutritional state and CDK8 activity? Dr. Pessin presented recent research from his laboratory addressing that question. Working with mice, he and his colleagues found that feeding activates a group of proteins called mTORC1, which then tags CDK8 for destruction. Without CDK8 around, SREBP-1c can promote the expression of lipogenic genes and thus the production of body fat. During fasting, the process is reversed: mTORC1 is turned off, so CDK8 is available to target SREBP-1c for destruction… so lipogenesis is off during fasting. Dr. Pessin showed that inhibiting mTORC1 with a drug mimics fasting: even when the animal is feeding, lipogenic genes are not expressed.

In additional studies, Dr. Pessin showed that mTORC1 activity—and thus nutritional state—likely determines not only whether CDK8 is targeted for destruction, but also whether any remaining CDK8

continues to be associated with other proteins that comprise the large mediator complex. Thus, nutritional state affects lipogenic gene expression by determining not only how much CDK8 there is, but also whether it is close enough to SREBP-1c to affect its activity.

These findings extend our knowledge of how body fat production is controlled, which may one day lead to improved treatment for diseases such as fatty liver disease, in which control of lipogenesis goes awry.

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Claire: A Lifetime of Contributing to the Science of Type 1 Diabetes Prevention

Left to right: Randall (father), Claire, Correne (mother), and Henry (brother)

For Claire and her mother, Correne, type 1 diabetes has always been a part of their lives, even though neither has been diagnosed. Several of their close relatives have the disease, and when Claire was 4 years old, she and her family received the sobering news that she was at risk of developing type 1 diabetes as well. However, that knowledge has also enabled Claire, now age 13, to spend most of her life participating in clinical research, including a clinical trial aiming to halt type 1 diabetes before symptoms can occur.

"I think it's really important to contribute to science," Claire says, when asked what she'd tell others thinking of participating in a clinical trial. "Even though there are challenges … they are all definitely worth it."

LIVING IN THE SHADOW OF TYPE 1 DIABETES

Family members on both sides of Claire's family tree live with type 1 diabetes. "We just grew up with type 1 [diabetes] in our family," Correne says. At family gatherings, everyone knows what to do if someone with the disease has an episode of dangerously low blood glucose (sugar). For Correne, a pediatrician, type 1 diabetes also affects her professional life: she diagnoses patients with the disease in her own practice. One New Year's Day, she even noticed that a visiting family member was abnormally thirsty at breakfast—an observation that led to a type 1 diabetes diagnosis. "Type 1 diabetes is so personal for our family because it just has had a huge impact on our lives," Correne says.

It was also family that brought Correne and Claire to NIDDK's Type 1 Diabetes TrialNet, an international clinical research network aimed at discovering ways to delay or prevent type 1 diabetes. When a family member was dropping her daughter off at diabetes camp, she noticed that TrialNet was recruiting participants from families of people with type 1 diabetes. She asked Correne if her family would be interested in enrolling. Correne's response was, "Sure! Anything we can do."

So began the summer tradition of what the family called "pokey parties," where Claire, her brother Henry, and other young children in their extended family would visit the diabetes camp to have their blood drawn so they could be screened for risk of type 1 diabetes. The "poke" was not popular with Claire, who was not a fan of needles, but there were prizes afterwards, and since the kids did it together, the sense of camaraderie helped.

The risk of developing type 1 diabetes can be determined through blood tests, like those Claire and Henry volunteered for. In particular, their blood samples were tested for the presence of diabetes autoantibodies. These autoantibodies are proteins produced by the body that indicate the immune system is attacking the insulin-producing beta cells of the pancreas, and their appearance in the blood means that the person has an increased risk of developing type 1 diabetes in the future. That risk

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rises as the number of different types of diabetes autoantibodies rises.

When Claire was 4 years old, they got a phone call from TrialNet study staff. Claire had tested positive for one of the autoantibodies. With this sobering news, though, came a new opportunity: would they be interested in participating in a bit more testing and surveillance of Claire's health?

The family agreed, and so from age 4 until age 9, in addition to blood draws, every 6 months Claire took an oral glucose tolerance test that measured her body's ability to metabolize the sugar glucose. Claire dreaded these tests, because they required more needles: an intravenous (IV) line (or "straw shot" as she and her family took to calling it) in her arm. Participating in TrialNet, though, gave her and her family a front-row seat to how Claire's health was changing. By the time she was 9, Claire's blood tests indicated that she had four different diabetes autoantibodies, a sign that the autoimmune attack on her pancreas was well underway, and the results of her oral glucose tolerance tests indicated that her body's ability to manage her blood sugar was fluctuating.

"Type 1 diabetes is so personal for our family because it just has had a huge impact on our lives," says Correne, whose daughter Claire participates in type 1 diabetes research.

Claire remembers, when she first joined TrialNet, her mother telling her that she had "special blood" and that she might help find a cure for type 1 diabetes someday. As the number of diabetes autoantibodies in her blood rose, Claire says, "I didn't really understand what the antibodies were doing, but I knew that somehow it was related to the possibility that I would get this disease." Once she developed the fourth antibody, the possibility that she might be diagnosed with type 1 diabetes became more real to her.

Meanwhile, Claire's parents could only watch from the sidelines, because there weren't any treatments known to prevent type 1 diabetes or halt its progression. Once Claire had four autoantibodies in her blood, her risk of developing symptoms of type 1 diabetes in the next year or two was very high. Correne says, "At that point we had kind of resigned ourselves … it's coming."

Then, her family received another call from TrialNet staff. TrialNet was recruiting for a clinical trial, and Claire might be eligible to enroll. Would the family be interested in learning more about a prevention trial? "Yes," Correne answered. "Absolutely."

DISCUSSING RISKS AND HOPING FOR REWARDS

The prevention trial, Claire and her family learned, would be testing a drug called teplizumab (also known as "anti-CD3"). Teplizumab targets the immune system and had been shown previously to slow the loss of beta cells in people recently diagnosed with type 1 diabetes. Now researchers wanted to test whether the treatment could prevent clinical onset of type 1 diabetes. To investigate this, they were recruiting relatives of people with type 1 diabetes who did not yet have the disease themselves but who were at high risk of developing it…like Claire.

Taking part in the trial would be a big commitment. The study site at Yale University was hours away from their home, and the trial would involve an IV infusion daily for 14 days and additional trips for follow up. Also, there was a risk that the drug could cause short- or long-term side effects. Finally, due to the trial design (which would randomly assign participants to either inactive placebo or teplizumab treatment so the two could be compared), Claire might not receive the drug if she was in the placebo arm of the trial, something she and the research staff would not know until the end of the study. Claire

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hoped she'd receive the treatment, and that it would help prevent type 1 diabetes, but there was no guarantee that either would be the case.

Whether or not to participate was a family decision. Claire's parents discussed the pros and cons from all angles. They and their extended family also gave then-9-year-old Claire information about the study, its goals, and its importance. "It was a really tough conversation, to kind of come to a consensus that we wanted to do this," Correne says. "We were excited that they were doing a prevention trial, but there was a lot of thought that went into making that decision [to enroll]."

In the end, the family agreed to participate. Correne explains, "We need randomized trials. We need good data … to make sure that we're moving in the right direction for patients." Also, she says, "From a mom standpoint … you'll do anything, you know? If you think that it may help."

TAKING PART IN THE UPS AND DOWNS OF CLINICAL RESEARCH

In December of 2015, Correne and Claire traveled to New Haven, Connecticut, where they would stay for 2 weeks. Each day, Claire and Correne headed to the research hospital early in the morning, and the staff performed preliminary blood tests to ensure that Claire's organs were functioning normally and that she was still eligible for the trial. Then she received an infusion over an hour or two, and by lunch they were done for the day. Claire generally felt fine after the infusions, and they would often spend the rest of the day exploring New Haven. As time passed, Claire got used to the routine.

Correne praised the TrialNet research staff and nurses that they interacted with. "They were phenomenal. They were just outstanding." The nurses were both efficient and caring, always trying to accommodate the trial participants' preferences, answering any questions they had, and even suggesting things to do around town. "They went above and beyond to take care of Claire and meet her needs," Correne says.

Despite the support, Correne says that accompanying Claire during the trial was an emotional experience. "It was just overwhelming … you're sitting there, and you're just watching stuff go through this [IV] tube, and just worrying, you know? 'Am I doing the right thing?'"

Then, around day 11, Claire began feeling unwell. On day 13, after her morning blood tests, the TrialNet staff informed Claire that her liver function, though not alarming, was no longer within the range needed to continue in the trial. Though this change was not necessarily related to the experimental treatment she was receiving, she was not eligible to receive the final two planned infusions.

Claire, a volunteer in the Type 1 Diabetes TrialNet network, encourages others to participate in clinical research. "Even if it doesn't end up benefitting them, it'll benefit others, and will definitely contribute to science."

Correne and Claire were disappointed, and as they headed home, they wondered: had Claire been in the group receiving the experimental treatment after all? If so, did she get enough of the drug to have an effect?

WAITING, AND HOPING FOR GOOD NEWS

Life resumed for Claire and Correne, and TrialNet study personnel continued to monitor Claire's health via regular blood tests and oral glucose tolerance tests. As the years passed and the trial's follow-up continued, no news was good news: despite her still having the diabetes autoantibodies that statistically give her a high chance of developing the disease, Claire did not show clinical symptoms of type 1 diabetes.

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In the above images, Claire, then age 9, dramatized how she imagined her immune system attacking her pancreas (in red) and how the drug teplizumab (in green) would come to its rescue. Claire drew these images during her participation in a Type 1 Diabetes TrialNet study testing whether teplizumab could prevent clinical onset of type 1 diabetes. Images used with permission.

Then, the day that the teplizumab trial's results were published in June of 2019, Claire's family received the good news they had been waiting for: the study Claire had participated in had demonstrated that teplizumab could delay diagnosis of clinical type 1 diabetes by 2 or more years among people who were at high risk. Furthermore, Claire was part of the 57 percent of trial participants who received teplizumab and had not developed type 1 diabetes by the time the trial's results were analyzed. In comparison, only 28 percent of those who received placebo had not developed type 1 diabetes at the same timepoint. These results provided the very first evidence that clinical type 1 diabetes can be delayed with early preventive treatment. This breakthrough was only possible because of the dedication of clinical trial participants such as Claire. Their willingness to be randomly assigned to groups receiving either placebo or teplizumab treatment was critical, since participants in both groups were key to the trial's success.

The family was excited by these results and also by the confirmation that Claire had received teplizumab. Claire was happy that the results had been so positive: "I was just glad it worked." She believes that it's important to help move the science forward and feels that her participation in the teplizumab trial was a great way to do that. "All I had to do was get poked by needles," she says, a smile in her voice.

Claire has also signed up for a TrialNet follow-up study that will continue to monitor her health and the effects of the teplizumab treatment, including how long its effects last. She encourages others to participate in clinical research as well. "Even if it doesn't end up benefitting them, it'll benefit others, and will definitely contribute to science." Correne agrees: "I would do it again. And I would do more studies, or whatever they ask because … there's such value in it."

Despite her daughter Claire being still at risk for developing type 1 diabetes even after her participation in a Type 1 Diabetes TrialNet network study, Correne says, "Every day without diabetes? It's a gift."

Both of them also continue to think about the future, and about others with type 1 diabetes. "It kills me when I have to make a new diagnosis of diabetes for my patients," Correne says. Given her family history, helping to find a new treatment or even a way to eliminate the disease would be a huge personal victory. Claire also looks forward to new ways to delay, prevent, and cure the disease, especially when she sees family members treating their type 1 diabetes.

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CHANGING WHAT YOU CAN

Correne and Claire understand, though, that even with the successes of the teplizumab trial, their struggle with type 1 diabetes may not be over. When they were interviewed for this article, 42 months from Claire's first teplizumab infusion, Claire was still type 1 diabetes-free. However, it's not clear if the treatment Claire received can halt type 1 diabetes progression permanently or if it has only delayed onset of the disease. To this day, when Claire sees family members injecting insulin or managing their insulin pumps, she says, her thoughts turn to the possibility that she might have to do the same, one day.

That, Correne and Claire say, was something they understood from the beginning: that there were no guarantees. When asked how they feel about how Claire might—despite the needles, travel, and other worries of the trial—still be diagnosed with type 1 diabetes, Correne takes a deep breath. "Every day without diabetes? It's a gift." She thinks back to when Claire was 9, and they were expecting her to develop type 1 diabetes in the next year or two. "Where she's at now, and the childhood that she's gotten to enjoy…. It's just a gift."

Claire is now in eighth grade, her spare time often taken up by dancing, musical theater, and oil painting. She is thinking about studying anthropology and medical illustration in college, and she would like to attend Yale.

Her participation in TrialNet has made Claire a little more positive about things that she can't change. "I can't change the fact that I might get [type 1] diabetes," she says, but "even a prevention that might wear off in a few years is still great." And despite all the things she can't change, Claire continues to change what she can, for others and for herself. She and other clinical research volunteers make type 1 diabetes prevention trials possible, and through their efforts our understanding of how to prevent this disease is changing, one day at a time.

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Valentina: Overcoming Pancreatitis and Diabetes, All with a Positive Attitude

Valentina (2nd from left), her mother Sonia, her father Juan Pablo, and her sister Nicole

Seventeen-year-old Valentina is an extremely talented high school senior living in southern Florida. She has many interests and would like to attend a university in Florida to major in international studies. She is currently participating on the school cheerleading team, student government, and National Honor Society, and she volunteers for Relay for Life (American Cancer Society) and Best Buddies. However, since the fall of 2017, she has faced—and overcome—life-threatening medical issues related to chronic pancreatitis and its associated treatments, including a major surgery called total pancreatectomy-islet cell autotransplantation, or TP-IAT. "I was always positive," Valentina states. "I never really focused on the bad things. I just kept pushing through. I think that's one of the biggest things that helped me get better." Her proud mother, Sonia, states simply: "It was just amazing how she overcame her disease!"

AN OVERHEARD CONVERSATION LEADS TO A DIAGNOSIS

Valentina started having pancreatitis symptoms in second grade, but she, her mother, father Juan Pablo, and younger sister Nicole, now 13 years old, did not know it was pancreatitis at the time. "I would just have a lot of stomach aches," Valentina remembers, "I would feel really sick occasionally. It got to the point where we would have to go to the hospital and they would just tell us that I had gastritis or that I was constipated." Gastritis is a condition in which the stomach lining is inflamed, or swollen, and is often managed by reducing dietary acid intake. Valentina was told to follow a low-acid diet, which helped her. She remembers having flare-ups on rare occasion, but nothing too bad.

That all changed in October 2017 when she was in 10th grade and had a major flare-up. "We thought it was just going to pass away as it always does," Valentina recalls, "but the flare-up lasted for a week, and it got to the point where I was vomiting blood. That's when we were like 'ok, we need to go to the hospital.'" At the hospital, the staff asked Valentina for her family history to help pinpoint the cause of her illness. By a stroke of luck, she had recently overheard her parents saying that her father may have pancreatitis based on a chance finding from a medical examination, although Valentina did not realize at the time that he had not been diagnosed, and he did not have symptoms. Thus, when asked about her family history, "I told them that my dad had pancreatitis," she states. "Because of that reason … they tested me for it and it came out positive." The doctors told the family that they typically do not test children for pancreatitis because it is so rare, so it was fortunate that this conversation Valentina overheard—and decided to mention to the doctors—led to an accurate diagnosis of her illness so quickly after her severe symptoms started.

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ABOUT PANCREATITIS

The pancreas is an organ located behind the stomach that has many important functions. Tiny clusters of cells in the pancreas, called islets, produce hormones such as insulin that regulate blood sugar (glucose) levels. The pancreas also produces fluid that is released through ducts into the intestine and contains enzymes that are necessary for digestion of food. Usually, these powerful digestive enzymes are inactive until they exit the pancreas and enter the small intestine. In cases of pancreatitis, however, digestive enzymes are activated prematurely while still inside the pancreas, resulting in damage and inflammation, and symptoms of abdominal pain, nausea, and vomiting. As Valentina explains, "My pancreas is actually digesting itself." Chronic pancreatitis is rare in children and is often associated with a genetic mutation. People with genetic forms of pancreatitis have a higher risk of developing pancreatic cancer later in life.

After she was diagnosed, Valentina was admitted to the hospital for 5 days and then went home, but she was not there long. "She got very, very sick again, so we had to take her back to the hospital," says her mom. At that time, the gastrointestinal doctor was on vacation, so there was no specialist available to help them. Sonia, speaking through tears, remembers how terrifying the experience was. "I couldn't do anything for her. I was so worried because she couldn't eat," she says. "It was awful.... She was dying in the hospital. She was so, so sick, with a lot of pain."

Not knowing what else to do, Sonia spent her nights searching the internet for a doctor who had expertise in pancreatitis and could help her daughter. She found a pancreatitis specialist at University of Florida (UF) Health, but the doctor was about 6 hours away and only treated adult patients. However, Sonia was adamant that Valentina desperately needed this doctor's help, and her persistence paid off: the doctor made an exception and agreed to see Valentina very quickly. Reflecting on that experience, Sonia has an important message for other parents: "Be your own advocate."

Sonia finding that doctor at UF Health changed the entire course of Valentina's illness. It was there, in late November, about a month after her diagnosis, that Valentina underwent her first surgery to treat her pancreatitis: "Endoscopic retrograde cholangio-pancreatography, or ERCP," she explains. "What they did was remove what was blocking the pancreatic ducts, and placed stents to keep the ducts open and allow the enzymes to flow to the small intestine." After that surgery, she was feeling better, and was even able to eat a little bit.

It was also there that Valentina found out that she had a genetic form of pancreatitis. She explained that the genetic mutation is in a gene called *PRSS1*. Because of the increased cancer risk associated with her form of pancreatitis, their doctor at UF Health recommended that Valentina have her pancreas removed via TP-IAT, and their doctor also suggested that Valentina be treated by TP-IAT experts at the Medical University of South Carolina (MUSC).

UNDERGOING TP-IAT SURGERY

In the first stage of the TP-IAT procedure, the pancreas is surgically removed and the gastrointestinal tract is reconstructed. Removing the pancreas would result in lifelong diabetes because the organ contains the only source of insulin-producing beta cells in the body; without insulin, the body cannot regulate blood sugar levels, so the patient would become insulin dependent. However, in the second stage of TP-IAT—islet autotransplantation—the islets that contain the beta cells are collected from the patient's pancreas and infused back into the portal vein of the liver. The islets then become lodged in blood vessels of the liver where they settle, grow, and begin producing insulin. Thus, the TP-IAT surgery serves the dual purpose of removing the source of severe pain and also eliminating the increased cancer risk while preserving some insulin production, reducing the risk of developing diabetes.

Additionally, because the islets are from the patient's own pancreas, the body does not recognize them

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as "foreign" and mount an immune response to them. Thus, people undergoing TP-IAT do not need to take immune-suppressing medicines, which can have serious side effects. This is in contrast to islet transplantation alone, which is an experimental procedure that uses islets from deceased organ donors to treat some people with type 1 diabetes. Notably, people undergoing TP-IAT do require lifelong supplements to replace their pancreatic digestive enzymes.

When hearing about the possible TP-IAT surgery, Valentina didn't have any reservations: "I immediately felt that this was something that I had to do…. I surprisingly wasn't afraid." Her parents, on the other hand, were not thrilled at the thought of their daughter undergoing major surgery to remove a vital organ. As Sonia explains, "Valentina was doing better with the stent. She was able to eat more, so we were kind of more relaxed." Valentina remembers that her parents were also worried about the prospect that she could have diabetes for the rest of her life, so Sonia and her husband thought about waiting a year before considering the surgery. "But then Valentina started getting sick again, even with the stent, and we had to take her back to the hospital," Sonia remembers. Because Valentina was barely able to eat, she lost 50 pounds during the course of her illness—weighing only 82 pounds at her lowest. She also had to stay in bed nearly all the time because she was so sick and weak. As a result of Valentina's worsening health, the family decided to move forward with the TP-IAT evaluation to determine by the MUSC's doctors if she was a candidate for this type of surgery.

For the evaluation, Valentina underwent 3 days of intensive testing and meetings with various doctors at MUSC. For example, "we had a meeting with an endocrinologist, a psychologist, and a nutritionist and they explained to us how a diabetes life would work," recalls Valentina. Even though the hope was that the islet autotransplantation component of the surgery would reduce her risk of developing diabetes, there was still a possibility that her own transplanted islets would not function properly, or not make enough insulin to regulate her blood sugar levels. Thus, it was possible that, after her surgery, she would have to manage diabetes by counting carbohydrates when she ate, monitoring her blood sugar levels, and administering insulin.

After the evaluation, the family returned to their home in Florida and soon found out that Valentina was a candidate for TP-IAT. The surgery was scheduled for January 2018—only 3 months after she was diagnosed with pancreatitis. Now the family was faced with the fact that they had to separate, as Valentina's surgery was far from their home and her sister and father couldn't come with her due to school and work. Her mom was able to obtain permission from work to take time off for Valentina's surgery and for her recovery in South Carolina. Her father took care of her younger sister and provided all the financial support. The family rented a house near MUSC so that they could be near Valentina for the surgery and during the 1 month of recovery period.

When hearing about the possible total pancreatectomy-islet cell autotransplantation (TP-IAT) surgery for pancreatitis, Valentina didn't have any reservations: "I immediately felt that this was something that I had to do…. I surprisingly wasn't afraid."

"The day of my surgery, I remember waking up very early. Honestly, it was very peaceful…. In the car ride there [to the hospital], I prayed the whole ride. It was kind of me saying I had an understanding that if it was time to go, that I was OK with it," Valentina recalls, even though she was only 16 years old at the time. Her surgery lasted a total of 12 hours. During the first 6 hours, the surgeons removed her pancreas, along with nearby organs such as her spleen and gallbladder. After that, it took another 4 hours to isolate the pancreatic islets and 2 hours to transplant them

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into her liver. Throughout the procedure, Valentina was in excellent medical hands—both she and her mother raved about the MUSC doctors and nurses, who they said were outstanding, explained everything, and made Valentina feel comfortable.

LEARNING TO MANAGE DIABETES

After the surgery, Valentina spent a few days in the intensive care unit before being transferred to another floor of the hospital. It was a difficult time. She was hooked up to numerous machines and had to take medicine to manage her severe post-operative pain. Even talking was difficult. Also, because it could take several months or longer to know whether Valentina's own transplanted islets were going to function properly, she had to be treated for diabetes. The nurses checked her blood sugar levels around the clock and administered insulin. However, Valentina's positive attitude shined through even under these most challenging circumstances: "She walked the second day after her surgery," beams her proud mother. "She did so great, walking with pain every single day, three or four times per day to recover fast to leave the hospital."

"I am pain-free ever since recovering from my surgery," Valentina says.

After Valentina was released from the hospital, the family stayed in South Carolina for a month to be close to the MUSC doctors. During that time, Valentina remembers that, "It was hard getting used to everything, especially the diabetes part. In the beginning, we were so lost … with the counting carbs [carbohydrates] and understanding that a certain amount of carbs meant a certain amount of insulin." She said things only got harder over time. "At first it wasn't too hard," she states, "because after such a big surgery I wasn't eating very much. But … when my appetite started going up, that's when we had the most difficulties."

ACHIEVING INSULIN INDEPENDENCE

Coming home after a month in South Carolina, Valentina was still recovering from her surgery and managing her diabetes. Sonia had to return to work after taking 4 months off to care for her daughter, so the family hired a nurse to help Valentina during her long and challenging recovery. Valentina returned to school that summer, after missing nearly an entire school year. That transition was also difficult because she was not fully recovered from her surgery, got tired easily, and had to learn how to manage her diabetes while at school.

However, as time progressed, she made a welcome discovery: "We started noticing that my blood sugars were getting lower and lower every day." During one of her regular endocrinologist check-ups, the doctor told Valentina not to take insulin if her blood sugars were within a healthy range. "It got to the point that I didn't need any insulin," she states happily. As of November 2018, Valentina has been insulin independent. "Now, I only check my blood sugar when I'm feeling sick," she explains, which is roughly once every couple of weeks. If her blood sugar levels are elevated, she lays down or drinks water and that helps her levels come down without needing insulin. "We don't have insulin in the house anymore," says Sonia.

As Valentina notes, "My diabetes was obviously very different from most diabetes," since it resulted from the removal of her pancreas. Therefore, TP-IAT is not an option for treating other forms of diabetes, like type 1 or type 2 diabetes, because the underlying cause of the disease is different.

LIVING A PAIN-FREE AND DIABETES-FREE LIFE

Her successful surgery and recovery have enabled Valentina to look toward the future, with her plan to pursue international studies or law when she begins college next year. At the time she was interviewed for this profile, it had been 1½ years since she

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underwent her TP-IAT surgery. "I am pain-free ever since recovering from my surgery," she says. She has also recently been able to be more active, including cheerleading for her school, playing tennis and volleyball, and doing a lot of volunteer work.

Valentina says that before her total pancreatectomy-islet cell autotransplantation (TP-IAT) surgery, which could cause diabetes, the doctors "told us there was a possibility that I wouldn't be dependent on insulin, but I don't think I really had high hopes for that…. For me to get past my expectations of where I was going to end up after the surgery is just mind-blowing."

One of the complications after her surgery is that her body cannot adequately absorb iron, so she has to get intravenous iron infusions. She also has to spend a lot of time keeping track of her diet to figure out what foods make her feel good and which ones make her feel unwell, and she takes enzyme replacement supplements at each meal, something she will continue to do for the rest of her life. And, even though she's feeling much better physically, the entire experience has taken a mental toll on her. "I don't really feel normal," she explains. "Thinking about it mentally, I feel like a year of my life has been stolen from me, where I've been forced to become more mature and aware of everything." However, Valentina's positive attitude is still apparent: "But I think I'm appreciative of that, of what I know and what I've yet to learn."

Additionally, Valentina says that before her TP-IAT surgery, the doctors "told us there was a possibility that I wouldn't be dependent on insulin, but I don't think I really had high hopes for that…. For me to get past my expectations of where I was going to end up after the surgery is just mind-blowing." Valentina is grateful for the islet autotransplantation portion of her TP-IAT surgery—the extra 6 hours it took to isolate and transplant her own islets has given her freedom from diabetes.

HOPE THROUGH RESEARCH

NIDDK has supported much of the clinical research on use of TP-IAT for treating chronic pancreatitis in adults and children, and currently supports research to improve outcomes after TP-IAT surgery, including at MUSC and other sites. For example, MUSC researchers are testing a strategy to enhance survival and function of the transplanted islets in adults with chronic pancreatitis undergoing TP-IAT to further reduce the risk that people will develop diabetes after surgery.

NIDDK has also supported other research related to pancreatitis conducted by individual investigator-led teams, as well as larger, multi-center studies, such as the North American Pancreatic Study Group and, more recently, the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, that have led to important discoveries of genetic risk factors and other advances in understanding and managing pancreatitis in children and adults.

"If we didn't have this research, Valentina wouldn't be here today," her mother, Sonia, exclaims.

Valentina and her mother value and appreciate the role of NIDDK-supported research in Valentina's improved health. "If we didn't have this research, Valentina wouldn't be here today," Sonia exclaims. "I'm so thankful to the Lord Jesus for the technology, the doctors, the researchers." Valentina adds about the research progress: "I think it's incredible." Also incredible is the fact that Valentina, at such a young age, has faced formidable health issues with tremendous maturity and positivity—there is no question that her future is bright.