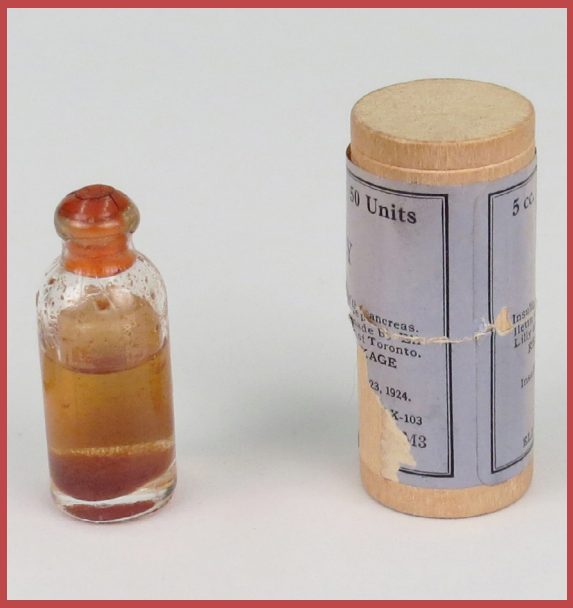

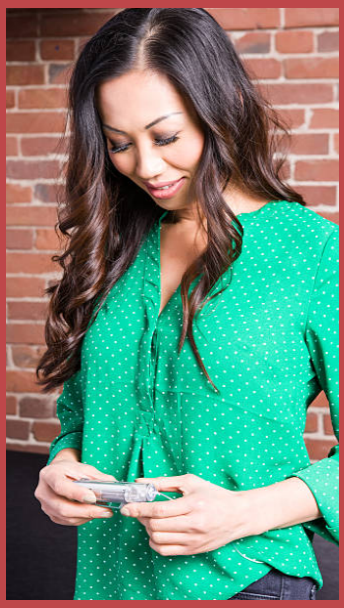

As described in this chapter, 2021 marks the 100th anniversary of the seminal discovery of the hormone insulin, which transformed type 1 diabetes from a fatal disease into a chronic one. The image on the left shows a commercial insulin vial from the 1930s. Although early insulin injections were lifesaving, there were many challenges to their use. Today, as a result of research supported by the NIDDK and others, people have improved formulations of insulin along with advances in technology that can more closely mimic normal physiologic delivery of insulin. These advances provide people with less burdensome disease management options that have led to a reduction in diabetes complications, and improved health, quality of life, and longevity. Examples of those options are represented by images on the right: insulin pen (boy), insulin pump (woman), and artificial pancreas technologies (drawing) that link blood glucose (sugar) sensing with insulin delivery. Although it is clear that type 1 diabetes treatment has come a long way since 1921, the NIDDK strives to continue its pursuit of research to build on advances and further improve people's health.

Image credits: Historic insulin vial—Division of Medicine and Science, National Museum of American History, Smithsonian Institution; boy—iStock.com/dmphoto; woman—iStock.com/MarkHatfield; artificial pancreas drawing—Fang-Mei Liu, The Scientific Consulting Group, Inc.

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] The NIDDK is vigorously pursuing research to combat diabetes and its associated health consequences.

Diabetes is a debilitating disease that affects an estimated 34.2 million people in the United States—or 10.5 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 U.S. adults 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, 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

[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, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2020.*
[3] *American Diabetes Association. Diabetes Care 41: 917-928, 2018.*

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, and body metabolism is significantly disrupted, resulting in a severely decompensated and catabolic (a breakdown of molecules such as proteins or lipids) state. 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, insulin-producing 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 further develop and enhance 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 reduction of insulin secretion, relative to the body's needs, results in elevated and abnormal blood glucose levels. Treatment approaches for managing glucose levels include lifestyle modification (*i.e.*, diet and exercise), and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 88 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

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

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 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.

ASSESSING DIABETES RATES IN YOUTH

Diabetes Continues To Rise Among American Youth: Scientists demonstrated that rates of both type 1 and type 2 diabetes continue to increase in people under the age of 20 in the United States, with higher rates of increase among racial/ethnic minority youth. Diabetes is a common chronic disease and results in increased risk for serious complications of the heart, kidneys, and eyes, among others. Efforts to understand the burden of this disease among different populations are essential to development of targeted public health efforts to help people at risk for or diagnosed with diabetes. The SEARCH for Diabetes in Youth study, a joint effort supported by the NIDDK and the Centers for Disease Control and Prevention, was established in 2000 to produce data on the scope of and trends in the disease. This research continues to highlight important and concerning information.

In this report, SEARCH researchers compared the rates of development (incidence) of type 1 and type 2 diabetes from 2002 to 2015 to determine whether the annual rates were changing. For type 1 diabetes, the scientists determined an overall rate of increase of 1.9 percent per year. They observed the steepest increases among racial/ethnic minority populations: Asian and Pacific Islanders (4.4 percent per year), Hispanics (4.0 percent per year), and Blacks (2.7 percent per year). In contrast, incidence among Whites rose 0.7 percent per year, and an increase was not observed among American Indians.

Among youth with type 2 diabetes, the annual rate of increase in incidence was determined to be 4.8 percent per year. Again, the researchers observed the highest increases among racial/ethnic minority populations: Asian and Pacific Islanders (7.7 percent), Hispanics (6.5 percent), Blacks (6.0 percent), and American Indians (3.7 percent). These trends are worrisome as research supported by the NIDDK has demonstrated that type 2 diabetes is more difficult to treat in youth than adults as youth may not respond as well to medications used in adults, and that many youth with type 2 diabetes develop complications early in their lives. These data highlight the continued need for research to prevent and treat both type 1 and type 2 diabetes.

Divers J, Mayer-Davis EJ, Lawrence JM,...Wagenknecht LE. Trends in incidence of type 1 and type 2 diabetes among youths—selected counties and Indian reservations, United States, 2002-2015. MMWR Morb Mortal Wkly Rep 69: 161-165, 2020.

RESEARCH ON TYPE 1 DIABETES

New Artificial Pancreas System Outperforms Sensor-augmented Pump Therapy for Managing Type 1 Diabetes: A clinical trial has found that a new artificial pancreas system is more effective than sensor-augmented pump (SAP) therapy at increasing the time people with type 1 diabetes spend with blood glucose (sugar) levels in a healthy range, knowledge that led to U.S. Food and Drug Administration (FDA) approval of the new system in 2019. Artificial pancreas technology, or a closed-loop system, aims to automate type 1 diabetes

management by measuring blood glucose levels using a continuous glucose monitor (CGM) and automatically delivering insulin when needed using an insulin pump. By contrast, SAP therapy—the control treatment used in the trial—couples CGM use with an insulin pump but does not adjust insulin levels automatically. Thus, by automating diabetes management, artificial pancreas technology holds promise to help people with type 1 diabetes achieve recommended blood glucose levels day and night, as well as alleviate the enormous burden associated with managing the disease. A first-generation closed-loop system was approved by the FDA in 2016, and researchers have continued working to develop new and improved systems.

Researchers in the NIDDK-supported, multi-center International Diabetes Closed-Loop (iDCL) Study enrolled 168 female and male participants ages 14 to 71 years with type 1 diabetes. Participants were randomly assigned to use either SAP therapy or an artificial pancreas system called Control-IQ™. Some unique features of the artificial pancreas system include a dedicated safety module to prevent hypoglycemia (dangerously low blood glucose levels), and gradually intensified blood glucose control overnight to target near-normal blood glucose levels every morning. During the 6-month trial, participants lived their normal day-to-day lives and only had contact with study staff every 2 to 4 weeks to download and review device data. Results showed that artificial pancreas users significantly increased the amount of time with their blood glucose levels in the recommended target range (percent increase in time in range) by an average of 2.6 hours per day, while the time in range in the control SAP group remained unchanged. Compared to the SAP group, artificial pancreas users also showed improvements in their average blood glucose control (HbA1c levels) and had less high and low blood glucose. There were no severe episodes of hypoglycemia in either group.

These positive trial data—showing that the artificial pancreas system outperformed SAP therapy—were used by the FDA to approve marketing of the Control-IQ technology. The Control-IQ technology itself was derived from a system originally developed with NIDDK support. This success story demonstrates how the sustained and long-term NIDDK investment in research—from technology development to supporting clinical trials testing the technology and the clinical trial demonstrating the efficacy of the system—culminated in a new commercially available device to improve type 1 diabetes management.

Brown SA, Kovatchev BP, Raghinaru D,...Beck RW; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 381: 1707-1717, 2019.

Researchers Develop First Functional, Lab-generated Islets That Evade Immune System Attack: Scientists have developed functional human islet-like organoids (HILOs) that can be shielded from immune system attack, an advance that allowed these HILOs to treat a mouse model of type 1 diabetes for weeks without immunosuppressive drugs. Pancreatic islet dysfunction can compromise the body's ability to maintain healthy blood glucose (sugar) levels. In type 1 diabetes, the immune system plays a key role in this dysfunction, destroying insulin-producing β (beta) cells in the islets. Transplanting healthy, insulin-producing islets into people with diabetes can help manage blood glucose levels without the need for insulin injections, but several major issues keep this procedure from being routinely used. One hurdle is that limited amounts of cadaveric islets of transplantable quality are available. Another issue is that immunosuppressant drugs that can cause serious side effects must be used to prevent transplant rejection. However, making human islet-like cell clusters in the lab that both mimic healthy islets and evade the immune system has proven to be challenging.

Now, a group of scientists has identified physical and biological factors needed to produce functional, immune-evading HILOs. Building on previous research, they grew β-like cells derived from human induced pluripotent stem cells in a gel-like, three-dimensional scaffold that more closely mimics the human pancreas. These growing conditions produced mature cell clusters that had many of the characteristics of healthy islets, including producing insulin in response to glucose and reducing blood glucose levels in a mouse model of type 1 diabetes. But how could these HILOs be protected from immune attack? Previous work had suggested that a protein called PD-L1 helps shield islets from the immune system. When the scientists treated HILOs to induce PD-L1 production, these HILOs were protected from immune attack when transplanted into a mouse model of type 1 diabetes. Even when

transplanted into a mouse model engineered to have a human-like immune system, the HILOs provided steady blood glucose control for over 50 days without the need for immunosuppression.

More research is needed to clarify how long the HILOs' immune protection can last and how long they can remain functional when transplanted. These issues and others are key to determining whether HILOs can be used to manage blood glucose levels in people with diabetes. Overall, these findings give hope that it may one day be possible to protect transplanted islets in the human body from immune attack. Such advances could lead to improved treatments that free people with type 1 diabetes from the need for insulin injections without incurring the risks of immunosuppression.

Yoshihara E, O'Connor C, Gasser E,...Evans RM. Immune-evasive human islet-like organoids ameliorate diabetes. Nature 586: 606-611, 2020.

Insights into the Autoimmune Process in Type 1 Diabetes: Using a systematic approach, researchers identified and characterized the protein fragments (peptides) associated with β (beta) cell autoimmunity, a misguided immune attack on the β cells of the pancreas that leads to type 1 diabetes. Normally, the immune system defends the body against foreign invaders or pathogens. Immune molecules known as major histocompatibility complex (MHC) molecules bind peptides from the pathogens and display them for recognition by immune cells called T cells. This prompts the T cells to "activate," leading them to attack the pathogen. In many people with type 1 diabetes, however, variants of class II MHC molecules (MHC-II) inappropriately bind and display peptides from the insulin-producing β cells. When this happens, the T cells can be activated by these peptides, leading them to target the β cells. While decades of research have added knowledge about this process, much remains unknown, including identification of all the peptides that drive the autoimmune process in type 1 diabetes. Understanding the molecular components involved in triggering the attack and its progression could lead to earlier and improved detection of the disease, a better understanding of disease progression, and new prevention and treatment approaches.

To understand further what triggers the autoimmune attack, researchers sought to catalog the "immunopeptidome" of β cell-derived peptides displayed by MHC-II in a mouse model of type 1 diabetes. By examining the β cells, pancreatic lymph nodes, and spleens of female mice, they found that the most prominent peptide families bound to MHC-II in those sites were those derived from insulin B-chain (InsB) and C-peptide (InsC). To determine whether these peptides induced an autoimmune response, the researchers characterized the peptides both on their ability to induce a reaction from a specific type of T cell and on how well they bound MHC-II. They confirmed that most of the T cell reactivity was directed to InsB and InsC. Further experiments allowed the researchers to determine additional features of these peptides that affect reactivity and enhance binding to MHC-II, such as chemical modifications and segments that were particularly immunogenic. These findings identified what parts of the insulin protein trigger the autoimmune attack on β cells in this mouse model of type 1 diabetes. Additional research will be necessary to determine whether these findings extend to humans.

Wan X, Vomund AN, Peterson OJ, Chervonsky AV, Lichti CF, and Unanue ER. The MHC-II peptidome of pancreatic islets identifies key features of autoimmune peptides. Nat Immunol 21: 455-463, 2020.

Identification of Risk Factors for Heart Disease in Type 1 Diabetes: Researchers determined that blood glucose (sugar) levels and age are the strongest risk factors for total cardiovascular disease (heart disease and stroke) burden in people with type 1 diabetes. Cardiovascular disease remains a leading cause of death for people with type 1 diabetes, despite improvements in the control of blood glucose, blood pressure, and lipid (fat) levels. Insights into type 1 diabetes and cardiovascular health previously came from the NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. DCCT/EDIC demonstrated that higher levels of hemoglobin A1c (HbA1c; a measure of average blood glucose levels over 3 months) were a strong risk factor for cardiovascular disease. These findings, however, were limited to analyzing the risk of a first cardiovascular event. Because subsequent cardiovascular events are associated with significant morbidity and mortality, understanding their risk factors could improve prevention strategies.

To extend their previous analyses, the researchers evaluated potential risk factors for their association

with first and subsequent cardiovascular events after 29 years of follow-up of DCCT/EDIC participants. They found that older age was associated with an increased risk of cardiovascular death and with other first and subsequent events including heart attack, stroke, and congestive heart failure. Additionally, they found that higher levels of HbA1c were associated with increased risk of both the first and subsequent events. These findings confirm the importance of intensive glucose control to reduce the risk of a first cardiovascular event. They also suggest that after the first event, it is still important for people with type 1 diabetes to practice intensive blood glucose control to reduce their risk of a subsequent event. Importantly, blood glucose levels can be managed for many people with technologies like continuous glucose monitors and improved insulin delivery devices, making intensive blood glucose control more achievable. Continued research is needed to understand how blood glucose levels affect cardiovascular disease toward improved detection, prevention, and treatment in people with type 1 diabetes.

With these new findings, it is clear that the long-term dedication of the DCCT/EDIC volunteers and the investigators continues to generate a treasure trove of data about type 1 diabetes and its complications that is identifying ways to improve the health of people with this disease.

Bebu I, Schade D, Braffett B,...Lachin JM; DCCT/EDIC Research Group. Risk factors for first and subsequent CVD events in type 1 diabetes: The DCCT/EDIC Study. Diabetes Care 43: 867-874, 2020.

RESEARCH ON TYPE 2 DIABETES

Community-based Approach To Screen Black Men for Type 2 Diabetes: Researchers have found that community barbershops are promising venues for screening Black men for type 2 diabetes and identifying those with undiagnosed disease, so treatment could begin earlier. Many people with type 2 diabetes do not know they have it, and minority groups have disproportionately high rates of undiagnosed diabetes. Timely diagnosis is important so that people with the disease receive appropriate treatment to control their blood glucose (sugar) levels and prevent life-threatening complications. Black men with diabetes have high rates of diabetes complications and are less likely to live into their seventies than men from other racial/ethnic groups. However, type 2 diabetes diagnosis is often delayed, particularly in Black men who do not receive regular primary care and thus may not ever be screened or tested for the disease. Thus, it is important to identify approaches for timely diagnosis of type 2 diabetes in this population to improve their health.

In a recent study, researchers examined whether a community-based approach using barbershops owned by Black individuals could identify Black men with undiagnosed type 2 diabetes. The researchers asked 895 Black men at 8 different barbershops in Brooklyn, New York, if they would be willing to be screened for type 2 diabetes using a type of hemoglobin A1c (HbA1c) test that can be administered onsite and that gives results in 5 minutes. About one-third of the men agreed to be screened and 290 were successfully tested. Testing showed that 26 men (9 percent) had undiagnosed type 2 diabetes and 82 (28 percent) had prediabetes—a condition of intermediate blood glucose levels that is a known risk factor for later developing type 2 diabetes. The researchers gave the men with diabetes or prediabetes follow-up information, including the names of local primary care clinics. The most common reason participants gave for declining screening was because they already knew their health status or were under a doctor's care. Some limitations of the study include the fact that it took place in only one city, so it is unknown if similar participation rates would be observed in other areas of the country. In addition, although the point-of-care HbA1c test used is very convenient and fairly accurate, follow-up laboratory tests, which were not included in the study, would be needed to confirm the initial diagnoses.

Community-based approaches at barbershops have been used successfully for addressing other health conditions, such as identifying and treating Black men with high blood pressure. Therefore, adopting strategies like the one in this study to help identify people with undiagnosed type 2 diabetes who would benefit from treatment—particularly if paired with approaches for lowering other barriers to obtaining proven therapies—hold promise to yield progress toward U.S. health equity.

Osorio M, Ravenell JE, Sevick MA,...Lee DC. Community-based hemoglobin A1c testing in barbershops to identify Black men with undiagnosed diabetes. JAMA Intern Med 180: 596-597, 2020.

Rare Genetic Variants Protect Against Type 2 Diabetes by Promoting Insulin Processing and Secretion: Studying rare variations in the gene *SLC30A8* that were previously found to protect against type 2 diabetes, researchers have now discovered that these variations promote release of insulin in response to a rise of blood glucose (sugar) levels, potentially by increasing the proportion of insulin that is ready for release relative to a precursor form of the hormone. A previous genetic study of thousands of people from several parts of the world showed that very rare variants of *SLC30A8*—found in about 1 in 5,000 people—significantly reduce the risk of type 2 diabetes. The gene encodes a protein called ZnT8 that helps package insulin in a form that is compact yet can be quickly released from insulin-producing β (beta) cells when blood glucose levels rise, such as after a meal. Thus, ZnT8 plays an apparently key role in controlling blood glucose levels.

Results from this new study may therefore seem surprising: people with the type 2 diabetes-protective gene variant have less ZnT8 protein in their cells than people with the more common form of the gene, yet their insulin response to rising glucose levels was both faster and more robust. This super-charged insulin response is likely to be responsible for the unusual resistance to type 2 diabetes resulting from the rare mutation, raising the possibility that a medical intervention to reduce the activity of ZnT8 in β cells might help prevent type 2 diabetes in people at risk, or be a useful method to treat the disease in those that have developed it. Experiments in isolated human β cells are consistent with that idea: the scientists utilized an experimental approach to lower the amount of ZnT8 protein produced in these cells and found that this resulted in a higher rate of insulin secretion even at normal glucose levels. Notably, the procedure shifted the ratio of mature insulin relative to a precursor form of the hormone: compared to normal β cells, those with less ZnT8 had a higher proportion of mature, ready-to-secrete insulin. This suggests that by helping β cells store large quantities of tightly packed insulin precursor protein, ZnT8 might simultaneously be slowing the production and release of the mature, active hormone in times of caloric excess, when its rapid release is a higher priority. If so, and if medications can be developed that safely lower ZnT8 activity in β cells, such medicines may one day be clinically valuable for treating or preventing type 2 diabetes.

Dwivedi OP, Lehtovirta M, Hastoy B,...Groop L. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. Nat Genet 51: 1596-1606, 2019.

Combined Analysis of Studies with East Asian Participants Yields a Dramatic Increase in Knowledge of Type 2 Diabetes Genetics: Bringing together information from multiple genetic studies of type 2 diabetes in people of East Asian descent has yielded a wealth of new information about the disease that may one day help improve its treatment and prevention for people whether or not they have East Asian genetic heritage. Understanding genetic risk for type 2 diabetes has grown in importance in recent decades as lifestyle changes have interacted with genetic traits that might have been benign in prior generations, but now predispose a person to type 2 diabetes. This dynamic is helping fuel a worrisome rise in diabetes prevalence around the world, and East Asian countries are seeing some of the largest increases. Researchers have identified over 240 different genetic regions—mostly within the last 15 years—where variations appear to have a measurable influence on susceptibility to type 2 diabetes. Most of these advances came from genome-wide association (GWA) studies, in which scientists look for genetic features that are either more or less common in people with a disease than in people without it. By themselves, most of the known diabetes risk genes have only small effects on a person's likelihood of getting the disease, and early GWA studies often required genomic analysis of thousands of participants in order to detect them. As the field progressed, even larger studies were required to find genes with still smaller effects, or for which the variants of interest were rarer. Eventually, the only practical way to obtain a large enough sample size was to combine results from several previous studies so that hundreds of thousands of research participants were effectively included. The great majority of type 2 diabetes susceptibility genes found in this manner, however, were identified by combining GWA studies whose participants were primarily of European ancestry. As a result, less is known about unique genetic risk factors for the disease in people of East Asian and other non-White backgrounds.

Researchers have now completed a pooled analysis of numerous previous GWA studies conducted in Japan, China, Korea, and other East Asian countries, yielding a cumulative total of 433,540 participants, 77,418 of whom had type 2 diabetes. In this way they identified 183 different parts of the genome where genetic features influence predisposition to type 2 diabetes in people with ancestry from this part of the world. Most of these genetic regions had been identified in previous studies as affecting the risk for type 2 diabetes, confirming and bolstering what was known about the relationship of those gene regions to the disease. However, a remarkably large number—61—could be clearly distinguished from previously detected type 2 diabetes genetic risk factors, and were therefore new discoveries. Some of the gene regions newly linked to type 2 diabetes risk were notable for affecting susceptibility to the disease even in participants considered to have a healthy body weight. These findings may help explain an intriguing scientific mystery: although overweight and obesity are risk factors for type 2 diabetes throughout the world, people with East Asian ancestry are more likely than those from other backgrounds to develop type 2 diabetes at lower body weight. Increasing the number of known genetic risk factors for type 2 diabetes by about 25 percent, this study sheds light on aspects of type 2 diabetes genetics that are unique to those of East Asian descent and may someday make it possible to tailor diabetes prevention or care for a large fraction of the world's population. The findings have also reinforced and clarified previous discoveries in participants from other parts of the world and yielded information that could eventually lead to new therapeutic approaches with potential to benefit anyone with type 2 diabetes, regardless of where his or her ancestors come from.

Spracklen CN, Horikoshi M, Kim YJ,...Sim X. Identification of type 2 diabetes loci in 433,540 East Asian individuals. Nature 582: 240-245, 2020.

METABOLIC REGULATORS OF HEALTH AND DISEASE

Fat Cell Signaling Molecules Identified as Critical for Regulating Metabolic Health in Mice:

Researchers have identified new ways that adipocyte (fat cell) signaling can disrupt glucose (sugar) regulation in mice, with metabolic consequences throughout the body. Adipocytes are known to mediate obesity-related disruptions in glucose metabolism, and knowing how these cells "talk" with other cells and organs in the body could lead to new targets for diabetes treatments. One major group of signaling molecules in animals is the "G proteins," which transmit crucial information about a cell's environment to its interior and thus inform the cell's behavior. Some G proteins help to regulate adipocyte function and blood glucose levels, but the specific role of the G_i family proteins in adipocytes was unclear.

To determine G_i proteins' function in fat cells, researchers created a mouse model that lacks functional G_i proteins in adipocytes. Compared to normal male mice, male mice lacking G_i proteins in their adipocytes displayed many signs of poor metabolic health. The lack of G_i proteins in their adipocytes impaired the mice's ability to regulate their blood glucose levels. The mice also showed signs of reduced insulin sensitivity in various organs, including the liver and muscle, particularly when given a high-fat diet. Scientists found that mice on a high-fat diet that lacked G_i proteins in their adipocytes had increased fatty acid concentrations in the blood, increased fat in the liver, increased markers of inflammation in fat tissue and blood, and impaired insulin receptor signaling compared to normal mice on the same diet. The researchers then demonstrated that functional G_i proteins in adipocytes were required to prevent these poor health outcomes and to maintain metabolic health. Furthermore, work with a different mouse model showed that selectively activating G_i signaling in adipocytes improved both glucose metabolism and insulin sensitivity regardless of diet. Enhancing G_i protein signaling for longer periods of time also helped improve various aspects of metabolic health while on a high-fat diet.

Though these findings will need to be confirmed in humans, they suggest that the G_i family of proteins in adipocytes is critical to maintaining healthy glucose regulation in mice and is particularly important when the mice are given a high-fat diet. Selectively activating these proteins may also be a novel way to combat the symptoms of metabolic disorders, such as diabetes, in humans.

Wang L, Pydi SP, Zhu L,...Wess J. Adipocyte G_i signaling is essential for maintaining whole-body glucose homeostasis and insulin sensitivity. Nat Commun 11: 2995, 2020.

A Factor in Fat Tissue That Helps Preserve Insulin-producing Beta Cells in Mice: Studies of a protein involved in maintaining fat tissue and regulating metabolism have led to new discoveries about β (beta) cell health in mice, with possible implications for treating diabetes. During type 2 diabetes, the body becomes resistant to insulin's effects and gradually loses insulin-producing β cells in the pancreas. Currently, there are no therapies to stop this loss of functional β cells, leading researchers to study what factors are involved in maintaining β cell health.

Adipsin is a protein secreted by fat cells that was known to increase insulin production in the body in response to glucose (sugar), but its role in diabetes was unclear. Scientists hypothesized that adipsin might be important somehow in maintaining β cell numbers or β cell health. Researchers investigated this possibility by testing a treatment that caused increased adipsin production in a mouse model of type 2 diabetes. They saw improvements over 6 months: blood glucose levels were lower, insulin levels were higher, and fewer β cells had been lost in the mice that were making extra adipsin than in mice that had not received the treatment. Further experiments showed that adipsin's positive effects on β cell health and function stemmed at least in part from its ability to inhibit production of a protein made in β cells called DUSP26. The researchers found that, in a mouse model of type 2 diabetes, over-production of DUSP26 reduced insulin levels in the blood, whereas reducing DUSP26 levels improved the mice's blood glucose control. Inhibiting DUSP26 also helped preserve the health of human β cells in the laboratory. Taken together, these results suggested that changes in DUSP26 levels might contribute to development of type 2 diabetes by increasing susceptibility to β cell loss. To explore if the adipsin made by fat cells could potentially protect people from diabetes, scientists studied blood samples and body fat imaging data from a large cohort of men and women. They found that higher adipsin levels in the blood correlated with a lower risk of future diabetes in middle-aged adults with obesity. The researchers also explored the conundrum that although obesity is a risk factor for type 2 diabetes, adipsin—which is made by fat cells—seems protective. Examining different body fat tissues in people with imaging technology, they found that adipsin in the blood was associated with fat tissue mass under the skin, but not with fat tissue deeper in the body around internal organs (visceral fat), which is linked to metabolic problems.

More research is needed to fully understand the roles adipsin and DUSP26 play in human health and disease, but these new findings suggest that boosting the effects of adipsin or inhibiting those of DUSP26 could be promising targets for future diabetes treatments.

Gómez-Banoy N, Guseh JS, Li G,...Lo JC. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. Nat Med 25: 1739-1747, 2019.

New Tools and Surprising Results Pave the Way to More Comprehensive Understanding of Melatonin and Circadian Rhythm: In an important new study, scientists have combined computer modeling, chemical synthesis and refinement, and validation in animal models to identify novel compounds modulating melatonin receptor activity—advancing our ability to develop therapeutics that could help address health problems related to sleep and metabolism. Normally, the body uses a complex biological system, called the circadian rhythm or "body clock," to help govern many physiological functions throughout the day and night. For this to work, the internal circadian rhythm needs to be synchronized to external day-night (light-dark) cycles. The hormone melatonin is key to this synchrony. In response to changing light levels, the brain produces more melatonin at night, which in people induces physiological changes that promote sleep, and less during the day, which stimulates wakefulness. Disruptions to normal circadian rhythm contribute to metabolic diseases such as diabetes and obesity, along with sleep disorders and other conditions, such as depression and increasing incidence of cardiovascular diseases. Thus, a better understanding of circadian biology and improved therapeutics are needed—and melatonin activity is a key target. Two cellular receptors for melatonin, MT_1 and MT_2, are known, but it has been unclear whether these might have different functions when bound to melatonin, or whether drugs designed to target one or the other might have different effects.

To gain further insights, researchers decided to synthesize molecules that actively and selectively bind one or the other of these melatonin receptors. To do this, the research team used a virtual jigsaw puzzle piece approach. As a first step, they took

the known three-dimensional structure of human MT_1 and, using computer modeling, screened over 150 million virtual molecules to find ones predicted to fit well into MT_1's melatonin binding site. Based on the results, they synthesized a subset of compounds to test in the laboratory, focusing on compounds with high selectivity at a very low concentration. After synthesizing and testing 38 compounds, the scientists found 15 new chemical structures that interacted well with either MT_1, the very similar MT_2, or both. As a key goal was to find molecules that could selectively engage with the subtypes of melatonin receptors and thereby enable probing of each receptor's biological activities in animal models, the researchers chemically tweaked some of the 15 chemical structures and studied 3 of the resulting compounds. Two of these interacted selectively with MT_1, and one interacted selectively with MT_2. Among the exciting and unexpected results from circadian rhythm experiments in two different mouse models, the scientists found that the MT_1-selective molecules could either block or mimic melatonin's effects, depending upon the experiment—providing new insight into how melatonin works through its receptors. For example, the researchers found that administration of the MT_1-selective molecules at experimentally defined "dusk" caused the mice to change their normal behaviors in ways similar to the effect of administering melatonin itself. The study validates a powerful approach to finding novel, valuable compounds for investigating circadian biology and for potential development as therapeutics for diseases influenced by circadian rhythm—an approach that can be extended to other areas of investigation as well.

Stein RM, Kang HJ, McCorvy JD,...Dubocovich ML. Virtual discovery of melatonin receptor ligands to modulate circadian rhythms. Nature 579: 609-614, 2020.

STRIDES IN THE TREATMENT OF CYSTIC FIBROSIS

Therapies To Treat the Molecular Cause of Cystic Fibrosis Now Approved for Ninety Percent of People with the Disease: Researchers recently found that a combination of three drugs for cystic fibrosis (CF) has substantial benefit in people for whom previous medical treatments did not work. CF, a rare disease resulting in childhood fatality if left untreated, is caused by mutations in the *CFTR* gene. This gene encodes the CFTR protein, a key cellular channel for chloride ions (one of the two chemical components of table salt). Everyone receives one version of *CFTR* from each parent, and if either of those copies is normal that person does not get the disease. But if neither copy produces a functional form of the CFTR protein, he or she will develop CF. There are many disease-causing variants of the *CFTR* gene known, but by far the most common is one designated *Phe508del*: 90 percent of people with CF have at least one copy of this variant, and about half received this version of the gene from both parents. Researchers previously developed a medication, ivacaftor, that restores some function to certain disease-causing forms of CFTR, so the protein can act as a channel for chloride. This was life-changing for the small number of people who have these particular variant forms of CFTR. Unfortunately, the Phe508del form not only lacks channel function but is also unstable and is quickly degraded by the cell. In 2018, the U.S. Food and Drug Administration (FDA) approved two different two-drug combinations of ivacaftor, the channel opening drug, along with either of two CFTR stabilizing drugs, tezacaftor or lumacaftor. These combinations made a real clinical difference for people with either two copies of *Phe508del* or one copy along with a milder *CFTR* mutation. However, even though they provided some clinical benefit, CFTR function remained too low in people with two copies of *Phe508del*. Moreover, the existing two-drug combinations were ineffective in people who have one copy of *Phe508del* plus a "minimally functioning" (*MF*) *CFTR*—one that effectively produces either no CFTR protein at all or a form of the protein that does not respond to any of the previously developed medications.

Scientists reasoned that an additional CFTR-stabilizing medicine might be added to one of the approved two-drug combinations to have greater benefit. In 2019, scientists found that such a three-drug combination was significantly more effective than the approved two-drug therapies at improving CFTR function in people with two copies of *Phe508del*. In a new industry-led clinical trial, with additional support from the NIDDK and others, researchers tested that three-drug combination

of tezacaftor, ivacaftor, and a newer medication—elexacaftor—in a study with 403 participants who have one *Phe508del* variant and one *MF* variant. The treatment dramatically improved lung function and quality of life while reducing serious CF complications during the 24-week study. The FDA has now approved this triple combination therapy for people ages 12 and over with CF and at least one copy of *Phe508del*. That the root cause of CF can now be treated in roughly 90 percent of those with the disease is a tremendous achievement, yet further research will be important to develop effective therapies for those whose disease cannot be treated by any of these new methods—and to develop a cure for this life-long disease.

Middleton PG, Mall MA, Dřevínek P,...Jain R; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del *allele. N Engl J Med 381: 1809-1819, 2019.*

Celebrating the Discovery and Development of Insulin

This year marks the 100th anniversary of the discovery, in 1921, of insulin, a hormone required for the body to absorb glucose (sugar), the main cellular fuel. The loss of insulin is the hallmark of type 1 diabetes, and, in individuals with type 2 diabetes, there is a relative lack of insulin compared to the body's needs. Without insulin the body is not able to maintain normal metabolism, resulting in high blood glucose levels and a severe catabolic (a breakdown of molecules such as proteins or lipids) state. The discovery of insulin led to its production as a commercially available lifesaving treatment for people with type 1 diabetes. Continued research to understand the insulin molecule—its structure and function—has led to new formulations and technologies that have improved the lives of people with the disease.

DISCOVERY OF INSULIN

The discovery of insulin was built on decades of research around the world enabling scientists at the University of Toronto to extract the molecule from animal pancreata and, by injecting it into a dog model of diabetes, demonstrate its importance in the disease. More research was required, though, before the discovery could help people with type 1 diabetes; researchers needed to figure out how to purify the insulin and, eventually, how to produce sufficient quantities for the demand. It was not long, however, before this discovery would change the lives of people with type 1 diabetes, extending life expectancy considerably and improving quality of life.

In 1923, the first commercial insulin product was produced. Though this insulin was life-saving, it was far from perfect. It was extracted from animal pancreata and thus was not human insulin, was difficult to purify and produce, was unstable, and did not last long in the body. Scientists continued to study insulin to develop solutions to these problems. For example, a decade later, they discovered that the addition of the molecules protamine and zinc produced a long-acting animal insulin that required fewer injections throughout the day.

DEVELOPMENT OF INSULIN ANALOGS

NIDDK support of research on insulin has spanned decades and made possible many advances to move the field forward. Another key milestone in insulin research occurred in the late 1970s when researchers developed the ability to produce so-called "recombinant" human insulin. Identifying and sequencing the gene that encodes insulin and determining the structure of the insulin protein were critical research feats that laid the groundwork for this improvement. Thus, based on knowledge of the human insulin gene, this recombinant insulin could be produced in large quantities in bacteria in the laboratory. This breakthrough increased production of insulin, improved purification, and eliminated the dependence on animal-derived insulin and the accompanying allergic reaction that some people had to it.

Despite its life-saving ability, insulin therapy remained a considerable burden for people with type 1 diabetes. For example, its dose needed to be calculated carefully and injected by syringe into fat in the body, limiting how quickly the body would respond. A miscalculation of too much insulin could lead to dangerously low blood glucose levels (hypoglycemia) with serious consequences, and a delay in insulin injection could lead to higher blood glucose levels (hyperglycemia) after meals. Without adequate control of blood glucose levels over time, the risk for diabetic complications increases significantly.

Armed with knowledge of the sequence and structure of insulin, scientists experimented further, modifying single amino acids (the building blocks of proteins) of the insulin protein and studying whether these modifications altered insulin's action or stability. Such studies led to the development of analogs—synthetic forms of insulin that have minor structural changes but perform the same action in the human body. Today there are many analogs on the market that provide different advantages. For example, fast-acting insulin is absorbed quickly into

the blood stream and can be used to correct high blood glucose levels and at mealtimes when blood glucose levels rise because of food intake. Long-acting insulin is absorbed more slowly, lasts longer, and is used to control blood glucose both during the day between meals and overnight. Additionally, the development of insulin pumps—small, computerized devices worn on the body that deliver insulin—have aided diabetes management. These technologies can provide people with type 1 diabetes more reliable blood glucose control, though challenges to their use remain.

THE FUTURE OF INSULIN AND DIABETES MANAGEMENT TECHNOLOGIES

NIDDK-supported scientists continue to study insulin with the goal of improving its usability. On the horizon are insulins that are ultra-rapid acting or highly concentrated that could be delivered by a patch rather than a bulky insulin pump. These insulins would also improve diabetes management technologies developed with NIDDK support such as artificial pancreas technologies, which combine a continuous glucose monitor with an insulin pump and a computer algorithm to automatically control blood glucose levels. Scientists are also trying to develop thermostable formulations of insulin so that refrigeration is not required. Not only would this generally make insulin easier to use, especially where access to refrigeration is an issue, but it would also enhance its use in technologies like the artificial pancreas. Efforts are also under way to develop a glucose-responsive insulin—an insulin that remains inactive in the body until activated in response to rising blood glucose levels—to more closely mimic the body's own regulation.

NIDDK-supported research aims to improve the technologies available, including insulin, as well as develop and test next-generation diabetes management devices that are smaller, easier to use, and could be available to all people with this disease. This could allow people with type 1 diabetes the ability to choose which device and insulin fits their needs—personalizing this treatment while reducing burden, controlling blood glucose levels, reducing risk for diabetic complications, enhancing quality of life, and improving health. One hundred years ago, a diagnosis of type 1 diabetes meant a significantly decreased life span. Today, people with type 1 diabetes are living longer and healthier lives enabled by research on insulin. Future strategies to make disease management easier for everyone will continue to improve lives and provide hope as researchers work toward the goal of a cure for type 1 diabetes.

Seeing the Whole Picture: Two NIDDK Workshops Aim To Advance Pancreatic Imaging

The pancreas plays essential roles in converting the food we eat into fuel our cells can use. In its "exocrine" role, the pancreas makes and secretes digestive enzymes that break down the proteins, carbohydrates, fats, and other components in food. The pancreas also has "endocrine" functions, producing hormones such as insulin and glucagon that help regulate blood glucose (sugar) levels. A healthy pancreas expertly coordinates release of these enzymes and hormones with the body's needs, while pancreatic dysfunction can lead to a variety of health problems, including diabetes, pancreatitis, and pancreatic cancer.

Detailed assessments of pancreatic function can be crucial to diagnosing pancreatic diseases, but examining a living pancreas inside the body can be challenging. The pancreas is surrounded by the stomach, small intestine, liver, and spleen, and this crowded environment limits clinicians' ability to access the pancreas. The pancreas is also structurally delicate, and the digestive enzymes it produces can cause additional problems if the pancreas is damaged. For these reasons, inspecting the pancreas and removing and analyzing tissue samples (obtaining a biopsy) can be difficult. Thus, pancreatic imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) are especially valuable tools in monitoring pancreatic health and diagnosing issues.

In early 2020, the NIDDK held two workshops on using cutting-edge imaging tools to explore the pancreas and pancreatic diseases. These workshops brought together researchers from the endocrine and exocrine pancreas fields to identify challenges and emerging opportunities in pancreatic imaging as a whole. The presentations and panel discussions from these workshops demonstrated that though significant challenges remain, recent technological advances in pancreatic imaging are paving the way toward new methods to diagnose, monitor, and/or guide treatment of various pancreatic diseases and conditions.

Imaging the Pancreas in Diabetes, and Benign and Malignant Exocrine Pancreatic Disease, January 13-14, 2020: Clinicians have observed numerous connections between the exocrine pancreas and the pathogenesis of diabetes, which is considered an endocrine disease. Substantial changes in the size and probably the architecture of the exocrine pancreas can precede the onset of diabetes, for example, and both type 1 and type 2 diabetes can coincide with various exocrine pancreatic diseases. Furthermore, there are likely shared causes for some endocrine and exocrine pancreatic diseases, and their treatment could potentially have favorable or adverse effects on the function of the entire pancreas. However, the pancreas' exocrine and endocrine functions tend to be studied by different research communities, and as such, endocrine and exocrine pancreatic diseases are generally treated by different medical specialists. There is thus a great opportunity for researchers in these different disciplines of pancreatic research to inform each other, and imaging serves as a major nexus where advances can further both the endocrine and exocrine pancreas fields.

The goal of this symposium was to showcase the use of pancreatic imaging to detect and explore the pathogenesis of diabetes, pancreatitis, pancreatic cancers, and other pancreatic diseases, with an emphasis on information that could inform various pancreatic fields. Topics included the use of clinical imaging in cancerous and non-cancerous pancreatic disease, imaging pancreatic physiology both in health and disease, and imaging's role in examining the architecture, development, physiology, and function of pancreatic islets, structures that play a key role in diabetes. Scientific poster sessions and panel

discussions offered opportunities for attendees to share knowledge, discuss emerging technologies, and identify promising research opportunities.

Strategies for Clinical Imaging in Diabetes, January 15, 2020: The ability to noninvasively image the numbers and function of different cell types in the pancreatic islet (particularly the insulin-producing β [beta] cells) would allow researchers and clinicians to better track the development and progression of diabetes. Current data on the fate of human β cells comes largely from data "snapshots" gathered from donated cadaver pancreases or from studies of β cells cultured in the laboratory, but neither of these approaches can give a full picture of how β cells develop and change in living people or of how diabetes develops. Therefore, methods for real-time pancreatic imaging are needed and could have significant implications for diabetes research, diagnosis, and treatment.

At the time of this workshop, several promising imaging agents were at various stages of development and validation. The workshop was designed to stimulate discussion about the current state of imaging of the pancreatic islet's β cells and their function in people. Attendees presented data on promising imaging agents and techniques, and discussed how such advances could be used to inform diabetes clinical care in the future. A roundtable at the end of the workshop focused on how to move the field forward, including identifying studies needed to promote development of experimental β cell imaging techniques into tools that could one day be used in the clinic.

STORY OF DISCOVERY

How Different Medications for Diabetes and Obesity Emerged from Basic Research on One Pancreatic Hormone

Basic research to understand and characterize the hormones controlling blood glucose (sugar) levels, including the discovery of the glucagon gene, ultimately led to two very important therapeutics with very different purposes. One of these therapies helps people with type 2 diabetes lower their blood glucose while reducing their risk of cardiovascular disease and also helps people with obesity lose weight; the other helps raise blood glucose levels in people with type 1 or type 2 diabetes if they develop hypoglycemia. Remarkable advances along the way came from studies in a variety of model organisms including not only typical lab animals like mice and rats, but also organisms like the deep-sea anglerfish and the desert-living Gila lizard.

GLUCAGON: INSULIN'S HORMONAL OPPOSITE IS ALSO ITS ESSENTIAL PARTNER

In healthy individuals, the pancreatic "islets"—small, densely packed groups of several different types of cells—have a central role in maintaining optimal glucose levels in the body. One islet cell type, designated β (beta), responds to elevated blood glucose levels by releasing insulin, the hormone that induces cells to absorb sugar. When blood glucose levels are too low, another type of islet cells—α (alpha) cells—release a hormone called glucagon, which signals the liver to release glucose into the blood. These two critical hormones also regulate one another—rising insulin levels help inactivate lingering glucagon, and vice versa—to ensure agile transitions between periods of fasting and of caloric plenty. The net effect is to provide precise regulation of glucose levels within a narrow range that supports the optimal function and the long-term health of the body's cells and organs. In diabetes, this perfectly choreographed regulatory dance is disturbed either by loss of the insulin-producing β cells (type 1 diabetes) or by inadequate amounts of insulin to compensate for a weakened response to the hormone by other cell types (type 2 diabetes).

The 1921 discovery that purified insulin could be used to treat diabetes meant that for the first time in history, children diagnosed with what we now call type 1 diabetes could live to adulthood. However, the dangers of over-treating diabetes soon became clear: depending on severity, hypoglycemia—low blood glucose levels—can cause symptoms ranging from clumsiness, irritability, or confusion, to lost consciousness, seizures, and even death. In contrast, high glucose levels may not cause acute symptoms until they are well above normal. Over time, however, high blood glucose levels have been shown to lead to the chronic complications of diabetes. The landmark NIDDK-supported Diabetes Control and Complications Trial (DCCT) changed this by showing that keeping blood glucose control close to normal is vital to slowing development and progression of long-term diabetes complications that can lead to disability and death. Researchers have long been vigorously searching for better ways to control blood glucose levels both safely and effectively.

STORY OF DISCOVERY

Treating mild cases of low blood glucose levels is sometimes as simple as consuming a source of glucose, so schools, as well as individuals with diabetes who take insulin or certain other drugs that can cause excessive release of the hormone, often keep glucose tablets on hand for use in such situations. But one of the greatest concerns for people with type 1 diabetes, and those who love and care for them, is a drop in blood glucose levels that goes unnoticed because it occurs during sleep, and therefore can become extremely dangerous. Glucose tablets are only helpful, of course, when hypoglycemia is recognized and when it occurs in someone who is conscious and able to eat or drink, so more severe episodes of hypoglycemia can be deadly. In a hospital setting, intravenous delivery of glucose can be a life saver if hypoglycemia is noted. Similar interventions can sometimes be necessary for children with diabetes if they refuse to eat, or if another disease like the flu prevents someone with diabetes from keeping food down. In schools and homes, however, there have been few practical options. Moreover, the danger of hypoglycemia is a major source of anxiety not only for people with diabetes but also for their caregivers and is a serious obstacle to achieving optimal glucose levels for long-term health. Furthermore, repeated episodes of hypoglycemia can lead to a weaker compensatory glucagon release from α cells and also cause people to lose the ability to recognize hypoglycemic symptoms, increasing the risk for severe episodes. As a result, scientists have long recognized the potential of glucagon as an emergency medical treatment to combat dangerously low blood glucose levels.

Why did nearly 100 years pass after insulin came into widespread use to treat diabetes for its vital opposing partner in controlling glucose levels to start becoming more widely available and convenient to use? The factors that long frustrated therapeutic development of glucagon, and the innovations that are overcoming those problems, are part of a remarkable scientific story.

FISHING FOR GLUCAGON

In fact, researchers developed a process for isolating glucagon from an animal pancreas in 1923, just 2 years after the landmark purification of insulin. Indeed, a preparation of glucagon was approved by the U.S. Food and Drug Administration (FDA) in 1960 for the emergency treatment of hypoglycemia, but two characteristics limited the product's therapeutic potential: the hormone rapidly forms insoluble, injection-clogging fibrils in water; and it quickly degrades if not kept frozen. Because it would be impractical to keep frozen, dissolved glucagon on hand at all times, the FDA approved the drug as a dried powder. Unfortunately, dissolving the hormone with sterile water and administering it in time and at the correct dose posed logistical challenges for non-medical professionals that limited its usefulness.

The first step to understanding and overcoming these problems was to find the glucagon-encoding gene; and the first glucagon gene to be identified came from what might seem a very unlikely source: the deep-sea-dwelling Atlantic anglerfish. These animals hide on the ocean floor, waiting for prey to come along, and glucagon is essential to maintain their glucose levels when that wait is a long one. But there was also a practical reason to study the hormone in anglerfish: their islets are encapsulated in easily identified and isolated structures, rather than hidden within the pancreas. Thus, anglerfish α cells proved to be a convenient source for the NIDDK-supported scientists who first identified the glucagon gene in 1982. Having the anglerfish version in hand facilitated the search for corresponding mammalian glucagon genes, so researchers soon identified rodent and human versions as well.

These advances made it possible to put the gene into laboratory bacteria to produce significant quantities of the human glucagon protein—called "recombinant" glucagon—so that producing the hormone became more efficient, and the preparations more easily purified. However, it was

not until 1998, 5 years after publication of results from the DCCT establishing the importance of keeping blood glucose levels close to normal, that two different pharmaceutical companies developed recombinant glucagon as a commercial product and received approval from the FDA to make and market it for emergency treatment of severe hypoglycemia. Unfortunately, the recombinant hormone was just as likely as glucagon from other sources to form fibrils and degrade in water, so the barriers to its widespread use remained in place.

NEW APPROACHES FOR GLUCAGON DELIVERY—AND NEW NEEDS

Two significant innovations facilitating use of glucagon were FDA approved for use in 2019. The first of these is a new method of delivering the hormone: by simply spraying the dried powder into the nose. This eliminates the need to dissolve it in water or inject it and therefore makes the prospect of giving the drug much less intimidating to untrained bystanders. The second, developed with NIDDK small-business grant support, takes the approach of dissolving the hormone in a non-toxic liquid called dimethylsulfoxide (DMSO), instead of water. Glucagon remains stable for months in room-temperature DMSO without forming fibrils. The DMSO-dissolved hormone is distributed in easy-to-use injector "pens" that automatically deliver an appropriate dose to raise glucose levels.

A need for smaller, non-emergency doses of glucagon is now arising as a result of another major advance in medical care for type 1 diabetes: development of "artificial pancreas" devices. In their simplest form, these devices continuously measure a person's blood glucose levels and automatically administer an appropriate amount of insulin, if needed, to bring glucose levels down to healthful levels. This approach reduces the chances of developing hypoglycemia due to an accidental overdose of insulin. However, if glucose levels fall too low for any other reason—as a result of fasting, exercise, or illness, for example—the inability of such an insulin-only device to react by providing glucagon is a major limitation compared to a healthy pancreas. A "bi-hormonal" artificial pancreas—one that can respond like a functioning biological pancreas by lowering glucose with insulin or supplying a low dose of glucagon to raise glucose levels, if necessary—might therefore be a great boon to patients, adjusting blood glucose to optimum levels before they get into a range that would cause the wearer to experience symptoms or suffer any negative long-term health consequences. Today, several companies, often with vital NIDDK academic and small-business grant support, are developing and testing methods for delivering low-dose glucagon, using some of the same methods that are either approved or in development for use with emergency glucagon pens. In the future, such formulations may improve on already beneficial artificial pancreas products, leading to better, simpler care with lower risk of hypoglycemia for people who require long-term treatment with insulin.

AN UNEXPECTED BONUS HORMONE IDENTIFIED DURING THE HUNT FOR THE GLUCAGON GENE

The complementary effects of α and β cells and their signature hormones would seem to offer a simple, tidy explanation of the way the body controls blood glucose levels; but that explanation turns out to be incomplete in fascinating ways. In the 1960s, researchers were surprised to discover that the pancreas releases more insulin when a given amount of glucose is absorbed through the digestive system than if it is injected directly into the blood. The underlying reasons were a mystery, but the scientists speculated that the presence of glucose or other food in the gut might prompt the release of some different, unknown hormone that signals the pancreas to prepare for an increase in glucose levels by readying its supply of insulin. The scientists referred to such hypothetical insulin production-promoting hormones as "incretins," but decades passed before work in other laboratories proved that this idea was correct.

STORY OF DISCOVERY

In fact, the next clue to the incretin mystery was uncovered during the 1982 discovery of the anglerfish glucagon gene: an adjacent gene turned out to encode a protein that is notably similar to glucagon, yet clearly different from it. The researchers therefore called it a "glucagon-like peptide," or GLP. Further work showed that, in contrast to fish, mammals do not have just two similar genes next to one another—they have three: the gene for glucagon, plus genes that came to be designated *GLP-1* and *GLP-2*. Additional NIDDK-supported research later demonstrated that a truncated form of the product of one of these genes may be able to act as an incretin: pancreatic β cells release more insulin in response to elevated glucose if they are first stimulated with part of the GLP-1 protein. Thus, surprisingly, GLP-1 turns out to work somewhat in opposition to the very similar glucagon, helping to lower glucose levels by boosting the release of insulin. In another contrast with glucagon, experiments demonstrated that GLP-1 is produced not in the pancreas but by intestinal cells close to the stomach—and only when stimulated by the presence of food—helping establish that it is, in fact, an incretin. Experiments also demonstrated that GLP-1 has at least one other important effect on the body: it briefly slows stomach emptying, delaying digestion for a few minutes so that insulin will be ready for release before glucose levels have risen significantly.

DEVELOPMENT OF AN ENTIRELY NEW CLASS OF DIABETES MEDICATION

The effects of GLP-1 sound very much like properties one might like to have in a treatment for type 2 diabetes: by boosting insulin secretion in response to food, GLP-1 might bolster the natural insulin response of a person with the disease and thereby help keep glucose at healthier levels, while slowing digestion to allow this to happen. Unfortunately, scientists soon discovered a problem with the idea: GLP-1 only lasts a few minutes in the blood stream before it is degraded by other proteins. A therapeutically useful form of the hormone would therefore need to be much more stable in order to be a practical treatment for type 2 diabetes.

As it happens, scientists discovered a solution to this problem in what may seem like the unlikeliest of animals—a venomous lizard that lives in a habitat that could hardly be more different from that of the anglerfish, the U.S. Desert Southwest and Northwest Mexico. At about the same time that the glucagon-like peptides were being discovered by NIDDK grantees, NIDDK intramural scientists working with the lizard, called a "Gila monster," discovered that mingling with the venom in the lizard's saliva were proteins that appeared to "jump-start" its digestive system after the months of fasting that normally occur between its meals. Isolated from this protein mixture was a hormone they designated exendin-4 that was notably similar to glucagon, and even more akin to GLP-1. Scientists showed that exendin-4 and GLP-1 are both capable of stimulating gastric secretions in guinea pigs, though exendin-4 is the more potent of the two. They went on to show that both proteins work by stimulating the same cellular receptor, and that exendin-4 is a potent incretin. Importantly, a small but significant difference between the GLP-1 and exendin-4 structures protects the latter from digestion in the blood, where GLP-1 disappears within a few minutes, yet exendin-4 persists for about 12 hours.

Based upon these critical, NIDDK-supported basic science discoveries, pharmaceutical companies developed "exenatide," a synthetically produced but chemically identical form of exendin-4, as a medication for people with type 2 diabetes. Because "exenatide" cannot be absorbed in pill form, a pharmaceutical company developed an easy-to-use injection "pen" (not unlike the one later approved for administering emergency glucagon) that patients could use to give themselves the correct dose of the drug. In industry-supported randomized controlled clinical trials, this approach proved highly beneficial in participants with type 2 diabetes whose blood glucose was inadequately controlled. At the conclusion of the studies, participants who had received exenatide were found to have maintained

significantly healthier blood glucose levels than those who had received a placebo; and those receiving a higher dose of exenatide had achieved better blood glucose control than those who received a lower dose. Because it does not directly increase insulin levels, but rather signals β cells to be ready to produce a robust insulin response if it is needed, those taking it did not tend to experience hypoglycemia. The drug therefore also proved to be a relatively safe method for improving blood glucose control. As a result, the FDA approved exenatide in 2005 as a supplementary treatment for type 2 diabetes in patients whose blood glucose is not otherwise well controlled.

NEW BENEFITS AND A NEW INDICATION FOR THE NEW CLASS OF MEDICINES

Subsequent FDA approvals went to even longer-lived forms of GLP-1, like liraglutide, which lasts 24 hours, and semaglutide, which lasts an entire week. Together, these medications constitute a distinct and entirely new class of medications for type 2 diabetes called "GLP-1 receptor agonists." Because the FDA wanted to be sure that these drugs help people to control their blood glucose levels without incurring risks that might worsen cardiovascular disease, the diabetes complication most likely to result in death, the agency ordered post-approval research of long-term outcomes in people taking them. As a result, we now know that the medicines in this class significantly reduce the risk for heart attacks and other cardiovascular complications that are the leading killers of people with diabetes.

Another exciting finding from randomized clinical trials of these therapeutics is that people taking these medications typically lose a significant amount of weight. This "side effect," of course, is quite valuable, because type 2 diabetes is associated with overweight and obesity. These findings spurred interest in testing GLP-1 receptor agonists for another purpose: treating obesity. Indeed, clinical trials have indicated that they are remarkably effective as weight-loss medications. Depending on the dose, for example, weekly semaglutide treatment led to an average weight loss of about 16 percent within 1 year in people with obesity who did not have diabetes, while being relatively safe for many people and fairly well tolerated.

Thus, basic research on the hormonal control of blood glucose levels, studies in animals as different as deep-sea fish and desert-dwelling lizards, and creative innovations in drug stabilization and delivery have helped lead to the development and FDA approval of two new classes of medication—glucagon and GLP-1 receptor agonists. These medications have very different effects, but together they are improving care and health for millions of people: reducing the risk of hypoglycemia in people with type 1 diabetes, improving blood glucose control in people with type 2 diabetes, and yielding weight loss for people with obesity.

Testing a New Artificial Pancreas System for Managing Type 1 Diabetes

Type 1 diabetes is a condition in which there is an absolute deficiency of insulin that is required to maintain normal blood sugar (glucose) levels. As such, it is a very burdensome disease to manage. Every day, people with the disease must use insulin to mimic the job that the pancreas should be doing: specifically, deliver the hormone insulin in response to blood sugar levels. NIDDK-supported research has focused on developing technologies that make it easier for people to manage their type 1 diabetes, such as artificial pancreas devices. Recent exciting progress includes findings from a clinical trial that has led to a U.S. Food and Drug Administration (FDA)-approved artificial pancreas device, the Control-IQ™ system. Research advances such as these have relied on the contributions of countless volunteers with type 1 diabetes participating in artificial pancreas trials. (See inset for the story of a participant in the recent Control-IQ clinical trial.)

ABOUT TYPE 1 DIABETES

In type 1 diabetes, the insulin-producing beta cells of the pancreas are destroyed by the immune system. Therefore, people with the disease must measure blood sugar levels throughout the day and night and administer insulin when needed via injections or an insulin pump. While insulin therapy helps keep blood sugar from climbing too high, it brings with it the risk of potentially life-threatening episodes of hypoglycemia (dangerously low blood sugar). The risk of hypoglycemia greatly limits people's ability to achieve the recommended level of blood sugar control that reduces the risk of long-term complications such as blindness and heart, kidney, and nerve disease.

Thus, a major goal of NIDDK-supported research has been to improve devices to help people keep their blood sugar levels in a healthy range.

DEVELOPING ARTIFICIAL PANCREAS TECHNOLOGIES

An artificial pancreas, or closed-loop system, consists of a continuous glucose monitor (CGM) that measures blood sugar levels, an insulin pump, and a computer that calculates the amount of insulin needed based on the CGM's data. Artificial pancreas technology could help people with type 1 diabetes achieve recommended blood sugar levels while preventing hypoglycemia, which could alleviate the enormous burden associated with managing the disease and improve people's health and quality of life.

A first-generation closed-loop system was approved by the FDA in 2016, and many other systems are under development. The Control-IQ system was first developed at the University of Virginia with support from the NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program), which the NIDDK administers. In the Control-IQ system, the insulin pump is programmed with advanced control algorithms based on a mathematical model that uses glucose monitoring information to automatically adjust and administer the needed insulin dose. It also has a dedicated safety module to prevent hypoglycemia and gradually intensifies blood sugar control overnight to target near-normal blood sugar levels every morning.

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TESTING CONTROL-IQ IN A MULTI-CENTER CLINICAL TRIAL

After developing, refining, and testing the Control-IQ technology over many years, scientists were ready to test it in a larger and longer trial. That trial was the multi-center International Diabetes Closed-Loop (iDCL) Study, which was funded by the NIDDK through the Special Diabetes Program. The iDCL Study enrolled 168 women and men ages 14 to 71 years with type 1 diabetes at 7 sites throughout the country. Participants were randomly assigned to use either the Control-IQ artificial pancreas system or a comparator treatment called sensor-augmented pump (SAP) therapy, which couples a CGM and insulin pump but does not automatically calculate and administer insulin doses. During the 6-month trial, participants lived their normal day-to-day lives and only had contact with study staff every 2 to 4 weeks to download and review device data. The participants were not monitored remotely so that the study would reflect real-world use.

Trial results showed that Control-IQ users significantly increased the amount of time with their blood sugar levels in the recommended target range (percent increase in time in range) by an average of 2.6 hours per day, while the time in range in the SAP group remained unchanged. Control-IQ users also showed improvements in their average blood sugar control (HbA1c levels) and had less high and low blood sugar levels. An improved HbA1c level over time has been shown to correspond with fewer diabetes complications. No severe hypoglycemia events occurred in either group.

Overall, the trial demonstrated that Control-IQ outperformed SAP therapy. Trial data were used by the FDA to authorize marketing of the Control-IQ technology, making it commercially available for type 1 diabetes management. This success story demonstrates the fruits of the sustained and long-term support of NIDDK artificial pancreas research from technology development to testing to commercial product.

HOPE THROUGH RESEARCH

The NIDDK continues to support research to improve and test artificial pancreas technologies to develop next-generation devices, with a focus on testing artificial pancreas use in groups for which blood sugar control is particularly challenging, such as children, adolescents, older adults, pregnant women, and people who have frequent, severe episodes of hypoglycemia. Continued research could give people with type 1 diabetes a range of available devices so they can choose one that best fits their needs.

ELENA'S STORY

Elena, pictured, participated in an NIDDK-supported clinical trial testing a new artificial pancreas device

Elena was diagnosed with type 1 diabetes 6 years ago at the age of 40. "It was a total shock," she recalls, not only for her, but also for her husband, Justin, and daughters Adeline and Laurel, who were teenagers at the time. However, little did Elena know that she would personally have a profound impact on advancing treatment approaches for herself and other people with type 1 diabetes. That impact

comes from her dedication to participating in clinical trials testing new technologies for type 1 diabetes management, including the NIDDK's International Diabetes Closed-Loop (iDCL) Study. "I honestly have lost count," she says, but "I have been in the neighborhood of 10 to 12 trials."

Says Elena of clinical study participation: "I would absolutely recommend anyone who is interested in a trial to take a look at what's available in your area."

Elena's journey to participating in clinical trials began soon after her diagnosis when she did research on the Internet to figure out what diabetes management devices might work best for her. She decided to start using a continuous glucose monitor (CGM), which she liked because it let her see changes in her blood sugar levels in real time so that she knew when she needed to administer insulin. Even with the CGM, managing her type 1 diabetes was a lot of work. "It required constant attention," she says, "I really had to stay on top of it all the time." Through the Internet, Elena also heard about a peer support conference where people with diabetes got together to share experiences. That conference gave her needed perspective that she was not alone in trying to figure out how to manage her disease, and it was "where I first heard of the idea of getting involved in a clinical trial," she recalls.

Elena discovered that Sansum Diabetes Research Institute (SDRI) in Santa Barbara, California, was not too far from her home, and they were conducting trials testing new artificial pancreas technologies. Such trials were particularly appealing to Elena because she would be testing devices that could potentially manage her diabetes better than she could with less burden, so it did not take long for her to sign up for her first trial. Since then, Elena has personally witnessed the evolution of artificial pancreas clinical trials—from early trials when she stayed overnight at SDRI and study staff monitored her constantly to ensure that early prototype systems did not cause a medical emergency, to the iDCL trial when device safety had advanced so far that she could do the trial at home without any remote monitoring.

When she first heard about it in August 2018, Elena was very excited about the iDCL trial and about possibly using the Control-IQ artificial pancreas system, so she signed up through SDRI—one of seven participating sites. Participants were randomly assigned to either the Control-IQ group or to the trial's control (or comparison) group—that is, the group who did not use the advanced system. This group used sensor-augmented pump (SAP) therapy, which includes a CGM and an insulin pump, but not the technology that automatically calculates and administers insulin doses. When Elena heard that she was assigned to the SAP group, "I felt really disappointed," she admits. However, she quickly realized, "Somebody has to be in the control group because … there has to be some kind of comparison to show that the [artificial pancreas device] works and is effective."

After 6 months, participants in the SAP group, including Elena, were switched to the Control-IQ system as part of a trial extension phase. The timing for switching to the Control-IQ system could not have been better for Elena—it helped ease her diabetes management burden during some challenging personal times. When she received the Control-IQ system, her younger daughter had recently gotten engaged, so Elena was very busy helping with wedding planning. Even though she was extremely happy for her daughter, she was also soon facing an empty nest, as her older daughter was already married and out of the house. That would be a difficult transition for Elena, particularly because her daughters had been homeschooled and she was used to having them home all the time. After the wedding, she and her husband drove to the Midwest to help the recently married couple move. Between the wedding and the move, it was a chaotic time. "I felt like I had so many things to think about…. I just didn't have as much

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mental energy to spare on diabetes," she remembers. She was happy that she did not have to put nearly as much work into managing her type 1 diabetes as usual—she relied on the Control-IQ system to do it for her. "I really felt like that [Control-IQ] study pump was fantastic," she states.

Elena and her husband returned home to California from the Midwest, thinking that things would finally calm down. However, just a few days later, the morning of Independence Day 2019 brought more upheaval: a major earthquake. "Everything in my house sounded like it was going to fall down on the ground," Elena describes. She and her husband spent their holiday cleaning up and feeling fortunate that they were not injured. Then on July 5: another earthquake. "It hit hard," Elena states, "I could tell this was worse than the one we just had." All Elena and her husband could do was try to survive while watching their belongings crash to the ground and parts of their house fall apart. Thankfully, they were not hurt, and again she felt grateful to have the Control-IQ system. As she explains, "I didn't have a single spare second to think about diabetes."

While using an artificial pancreas system in a clinical trial, Elena says, "I definitely feel like my mental health improved…. I'm not having to babysit my blood sugar 24/7."

From these experiences, Elena realizes that the benefits of the artificial pancreas system for her were not measured by her traditional diabetes health numbers, such as HbA1c levels, which were already in the recommended range and improved modestly while on the system. Rather, "I definitely feel like my mental health improved…. I'm not having to babysit my blood sugar 24/7, and yet I'm getting as good or slightly better results [managing blood sugar levels] as I was doing on my own." She also says that the device was a huge help at night. "Prior to using the closed-loop system, I was waking up every night because of diabetes," she recalls. With the closed-loop system, "I didn't wake up anymore for high or low blood sugars. I could just sleep as much as I could sleep because the pump was able to handle it…. I woke up every morning with a clean slate."

Elena also says that a big benefit to using an artificial pancreas system is that a computer, unlike a person, "is unemotional…. It can take care of your blood sugar better than you can because it doesn't get tired or frustrated or annoyed." During the trial, the computer was unfazed by serious personal stress—whether it be the happy stress of a wedding or the life-threatening stress of earthquakes. The system managed her diabetes through challenging times when Elena would have had difficulty doing so herself.

As for her clinical trial experiences, "I cannot say enough good things about the study team at SDRI," Elena says. "I have always felt that they have been encouraging, helpful, and respectful." She quickly adds: "I would absolutely recommend anyone who is interested in a trial to take a look at what's available in your area."

Elena is also happy that her steadfast participation in clinical trials has contributed to the availability of new type 1 diabetes management devices. When she sees people get excited about a new device that she helped test and talk about how it works great for them or their children, she thinks to herself: "That's really neat. I had something to do with that." It is only through the generous contributions of Elena and other clinical trial participants that new artificial pancreas devices and other type 1 diabetes management technologies have come to fruition.

Contributing to Type 2 Diabetes Prevention Research

Type 2 diabetes is the most common type of diabetes and develops when the body can no longer overcome "insulin resistance" to keep blood sugar (glucose) levels from getting too high. Our bodies extract energy from the foods we eat, converting it into the form of blood sugar that is the main fuel used by our body's cells. The hormone insulin is made by the pancreas and acts in the tissues of the body (*e.g.*, muscle) to promote absorption of sugar from the blood. In some people, their bodies can become resistant to insulin, requiring the pancreas to produce more of the hormone to keep blood sugar at a healthy level. Type 2 diabetes develops when the pancreas loses its capacity to produce enough insulin to compensate for the body's insulin resistance. More than 100 million Americans have type 2 diabetes or are at risk of developing the disease, which increases risk of cardiovascular disease, kidney disease, blindness, and numerous other serious complications. The good news is that thanks to years of research, we now know steps we can take to prevent or delay its development. With the help of thousands of research participants from around the country, NIDDK-supported scientists embarked upon a decades-long journey to demonstrate that type 2 diabetes is preventable as demonstrated in the highly successful, landmark Diabetes Prevention Program (DPP) clinical trial. (See inset for the story of a DPP participant.)

A LANDMARK STUDY IS LAUNCHED

In the early 1990s, the prevalence of type 2 diabetes was increasing at an alarming rate, and evidence from observational and interventional studies suggested that lifestyle factors might be the cause. In 1996, the NIDDK launched the DPP—a randomized, controlled clinical trial conducted at 27 clinical centers—to assess whether a lifestyle intervention or the drug metformin (a safe, generic medicine used to treat type 2 diabetes) could prevent or delay the disease. The DPP was also co-sponsored by others. The trial enrolled 3,234 participants who were at high risk of developing type 2 diabetes. Among the participants, 55 percent were Caucasian, and 45 percent were from racial/ethnic minority groups at disproportionately high risk for the disease. Many of the participants were over 60 years old, were women who had developed gestational diabetes during pregnancy, or had a family history of type 2 diabetes—all factors associated with higher risk for the disease. Participants were then randomly assigned to 1 of 3 groups: (1) a lifestyle intervention group that received intensive training and coaching to help participants lose a minimum of 7 percent of their body weight and maintain that weight loss through diet and enhanced physical activity (defined as moderate exercising at least 150 minutes per week); (2) a metformin group in which participants took metformin twice a day and received standard advice about diet and physical activity; and (3) a placebo group that received pills with no therapeutic effect, rather than metformin, along with the same standard advice about diet and physical activity. The metformin and placebo study components were "blinded," meaning that neither the participants nor the study scientists who worked with them knew which people were in group 2 or group 3.

SUCCESS IS ACHIEVED

After 3 years, the DPP showed that participants assigned to the lifestyle intervention lowered their chances of developing type 2 diabetes by 58 percent compared with participants who took a placebo. The intervention was effective for all participating racial

and ethnic groups and in both men and women. It worked particularly well for participants ages 60 and older, lowering their chances of developing the disease by 71 percent.

Taking metformin was also found to prevent the disease, though to a lesser degree overall. Participants who took metformin lowered their chances of developing type 2 diabetes by 31 percent, compared with those who took a placebo pill. Metformin was effective for all participating racial and ethnic groups and both men and women. It was most effective in women with a history of gestational diabetes, in people who were between the ages of 25 and 44 when they began taking the medication, and in people with obesity who had a body mass index of 35 or higher.

Because the results were so compelling, the trial ended early in 2001. Soon thereafter, all participants were provided a modified, group-based version of the DPP's lifestyle intervention.

BUILDING UPON THE SUCCESS

Beginning in 2002, the DPP Outcomes Study (DPPOS) began monitoring most of the participants initially enrolled in the DPP to determine if the lifestyle intervention or metformin continued to delay the development of type 2 diabetes over time, whether they affected other measures of health and well-being, and whether they were cost-effective. There were some changes made to the groups: while each group was offered lifestyle-change classes, the original lifestyle intervention group received more intensive coaching to reinforce self-management behaviors for weight loss; and the metformin group continued to take metformin, but not in a blinded fashion. (The original placebo group no longer took a placebo pill.)

After 10 years, the DPPOS found that participants enrolled in the intensive lifestyle intervention continued to have a lower rate of disease development by 34 percent compared to the original placebo group, and those who were 60 years or older when first enrolled in the DPP continued to have an even lower rate of disease by 49 percent with the intensive lifestyle intervention compared to placebo. Those who were in the metformin group had a lower rate of disease by 18 percent compared to placebo. Participants from all three groups improved their risk factors for cardiovascular disease, but those in the lifestyle intervention group required fewer medications to do so than those in the other groups. In addition, the lifestyle intervention was shown to be cost-effective, and metformin was shown to be cost-saving. At the 15-year follow-up, participants enrolled in the lifestyle intervention continued to experience a 27 percent lower rate of disease onset, while participants taking metformin had an 18 percent lower rate of disease development.

The NIDDK continued to build upon the success of the DPP/DPPOS findings by funding research to develop cost-effective adaptations of the lifestyle intervention that could be delivered efficiently to millions of Americans who would stand to benefit. The Centers for Disease Control and Prevention also scaled up related, national efforts, calling it the National Diabetes Prevention Program. And in 2018, the Centers for Medicare & Medicaid Services began coverage of certain lifestyle change program providers for Medicare beneficiaries with prediabetes.

The current phase of the DPPOS aims to determine the effects of metformin on the prevention of cancer, cardiovascular disease, and other age-related health issues and continues to assess diabetes prevention.

The NIDDK-supported DPP/DPPOS is one of the largest and longest ongoing prevention studies of its kind. Its results demonstrate that prevention or delay of type 2 diabetes is possible and can yield other important health benefits. The long-term durability of the response to lifestyle intervention and metformin in preventing or delaying development of diabetes, still persisting many years after participants entered the program, is a testament to the power of the interventions and their value in reducing disease. The success of this program will continue to depend upon the thousands of participants that contribute their time and efforts to advancing this important research effort.

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PAMELA'S STORY

Pamela, pictured, participated in an NIDDK-supported clinical trial to prevent or delay type 2 diabetes

Pamela, a 72-year-old communications specialist who lives in the Washington, D.C., area and has written for both *Reader's Digest* and *McCall's Magazine*, had always lived an active lifestyle, having been an avid runner and even a member of a ski team. It's not surprising she takes her health seriously since her mother, who had type 1 diabetes, always taught Pamela and her five siblings from a young age to value their health and made sure they recognized the importance of maintaining a healthy lifestyle. So, in the summer of 1997 when Pamela received a postcard in the mail that invited her to be tested to see if she qualified for participation in a new research study on possible ways to delay or prevent the development of type 2 diabetes, she jumped at the chance. "I went in, got tested, and found out I had prediabetes, which qualified me for the study … so I signed up right away." She was randomized to the Diabetes Prevention Program (DPP) lifestyle intervention group on October 1, 1997, and so her journey of participating in a clinical trial began.

After several months of diet and exercise with support from DPP clinicians, Pamela achieved her initial goals and even surpassed her 7 percent weight-loss target. She does admit, though, that it was not always easy. In the beginning, she did not quite care for documenting everything she ate, though she appreciated the study coordinators. As she puts it, "I was judging myself … but the study coordinators had no judgment. They were data-driven and incredibly supportive and encouraging to all of the participants." She says the intervention changed the way she approached her daily activities—it forced her to pay close attention to exercise consistency, portion sizes, and reading nutrition labels.

After those initial months of the lifestyle intervention, the good results for Pamela just kept coming. She put in the effort and learned that, with the support of her DPP doctor and study coordinators, she had the power to change the course of disease. Part of that support included the fact that the DPP team organized group events, such as holiday dinners and baseball games, so that participants could meet and inspire each other. The study team even encouraged them to bring along friends, which turned out to be helpful to Pamela. "If I bring a friend to an outing, maybe the next day I recruit them for a run. It's easier to exercise with a friend."

"Historically," Pamela says, "it has been difficult to get African Americans to participate in any research study. I realized if I don't participate [in the Diabetes Prevention Program/ Outcomes Study], scientists won't have the critical data they need…. Diseases manifest differently in different races and sexes … it's so important."

Soon after the DPP came to an end, and the DPPOS was beginning, Pamela knew she would remain a participant. She had worked hard and had seen the fruits of her labor—losing weight and preventing her prediabetes from progressing to

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type 2 diabetes—but that wasn't the only reason. She was also motivated by her mother's fight with her illness, and she realized the significance of her participation in clinical research. "Historically," she says, "it has been difficult to get African Americans to participate in any research study. I realized if I don't participate, scientists won't have the critical data they need.... Diseases manifest differently in different races and sexes ... it's so important."

Beyond the recommended goals of weight loss and exercise, Pamela also noticed the DPP lifestyle program provided her with other health benefits like better stress management. Life has a way of handing you challenges, and it certainly did for Pamela. Throughout her years in DPP, she drove her mother to medical appointments because her job afforded her more flexibility than her siblings, and she helped her mother deal with many of the complications common to both major forms of diabetes. In 2002, Pamela's region was rocked by a frightening development—a sniper began terrorizing the area at random. This effectively halted her outdoor runs. And, in 2008 the economic recession hit, which negatively impacted Pamela's consulting job as a writer. But she looked to the knowledge she had gained about lifestyle change from being a DPP participant and was able to minimize her stress through breathing techniques, in addition to keeping her diet and exercise routine as healthy as possible when each change in circumstances arose.

Pamela has now been a participant in DPP/DPPOS for more than 23 years, a remarkable contribution to scientific research—and also to her own health. Today, not only has she prevented the development of type 2 diabetes, but she no longer has prediabetes and has achieved and maintained an impressive 12 percent weight loss—a testament to her incredible dedication to maintaining a healthy lifestyle as a DPP/DPPOS participant. When discussing her appreciation and respect for the DPP doctors and nurses, she goes so far as to say if she had to do it all over again, she would choose a career in science or medicine. "This is one of the best things to ever happen to me, to have had this opportunity to be part of this program.... Self-management is a discipline. It's not always easy, but it's something we need to strive for. It's a journey, and DPP was the catalyst for me."

Talking about her experiences in the Diabetes Prevention Program clinical trial, Pamela says: "This is one of the best things to ever happen to me, to have had this opportunity to be part of this program."

Pamela is proud to have contributed to the DPP's success, and when asked what she would tell someone considering participating in a similar clinical trial she doesn't hesitate: "I'd tell them to do it! And, I'd even go with them!" Without Pamela and her fellow DPP/DPPOS participants, there might still be no proven way to prevent type 2 diabetes. Thanks to their efforts, a healthier world has become possible.