and their families. Furthermore, we now know that type 1 diabetes diagnoses are on the rise, and that the disease is occurring in children at younger ages than before, often appearing during infancy.

IMPROVING THE OUTLOOK FOR PEOPLE WITH TYPE 1 DIABETES

Research in type 1 diabetes has made a tremendous impact on the health and quality of life of people with the disease. NIDDK's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive blood glucose control, beginning as soon as possible after diagnosis, can prevent or delay diabetic complications of the eyes, kidneys, nerves, and heart. The DCCT concluded in 1993, but its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continued to follow participants to determine the long-term effects of prior intensive versus conventional blood glucose control. In a recent report, the researchers compared overall rates of eye, kidney, and cardiovascular complications in DCCT/EDIC participants. After an average of 30 years with type 1 diabetes, participants in the DCCT/EDIC intensive control group had lower complication rates than participants in the conventional control group. Improved control over a 6 year average study time yielded health benefits that last for decades. Since the study began in 1983, the prognosis for people with longstanding type 1 diabetes has greatly improved due to major improvements in glucose monitoring and insulin delivery. This progress has accelerated in the past decade. For example, several continuous glucose monitoring devices now approved by the FDA give real-time information for tracking and trending of glucose levels, helping people with type 1 diabetes supplement the management of their blood glucose to help control their disease. Because of these insights and improvements in diabetes care and therapy, people with type 1 diabetes are

living longer, healthier lives than ever before and experiencing lower rates of disease complications. For example, only about 70% of people diagnosed with type 1 diabetes in the 1950's survived for 25 years with the disease compared to about 95% for those diagnosed in the 1970's. Indeed, the Joslin Diabetes Center in Boston, Massachusetts, has a Medalist Program that recognizes individuals who have lived with type 1 diabetes for 25, 50, and 75 years with a special award to commemorate their dedication to lifelong diabetes management. Just last month Joslin awarded one of these medals to a man on his 90th birthday—the first American known to live 85 years or longer with type 1 diabetes. These inspiring accomplishments don't stop with a medal; many of the 50-year medalists have volunteered to participate in an NIDDK-funded study to identify factors that protect from the development of eye and kidney disease. It's exciting to report that through research, the outlook for people with type 1 diabetes continues to improve.

Still, the burden of living with diabetes is enormous, so it is critical to build on research progress to find ways to prevent and cure the disease. For example, advances in research have led to blood tests that can now predict the risk of developing the disease in relatives of people with type 1 diabetes. Building on this knowledge, we are now able to launch clinical trials to test new prevention strategies. Until prevention and cure are possible, improved outcomes will depend on improving devices to monitor and control blood glucose levels. Advances in continuous glucose monitoring are expected to help people of all ages. To build on these developments, research on how to best help people use new technologies is key toward moving this treatment strategy into practical use.

Pursuit of the research goals to prevent, treat, and cure the disease involves partnerships among scientists—with diverse backgrounds and expertise from many academic institutions— as well as partnerships among many of the Institutes and Centers of the NIH, the FDA, the CDC,

following newborns until they are 15 years of age, and recently completed enrollment of over 8,600 after screening over 425,000 newborns to identify infants at high genetic risk to develop type 1 diabetes. For a decade and a half, investigators—aided by devoted parents—will regularly collect information about the child's diet, illnesses, vaccinations, allergies, and other life experiences. Biological samples are being collected as well and will be used for studies to identify early markers of the disease. Importantly, children enrolled in the study are now developing autoimmunity and type 1 diabetes at the predicted rates, indicating that the study is on track and poised to make a major contribution to type 1 diabetes research.

This achievement represents tremendous progress toward amassing the largest set of data and samples in the world on newborns at risk for autoimmunity and type 1 diabetes. To ensure that we learn as much as possible from these samples and maximize our investment in TEDDY, samples from the study will be made widely available to researchers. Already TEDDY investigators are using newly developed technologies emerging from the NIH Human Microbiome Project to study the microbiomes of these children to determine whether viral or bacterial-based treatments could be used to prevent the disease. Importantly, the benefits of TEDDY are expected to extend more broadly to include people with celiac disease, a digestive disorder caused by autoimmunity directed at gluten proteins in wheat and other grains. Celiac disease and type 1 diabetes share some genetic susceptibility factors, and many people have both diseases.

While TEDDY is a prospective, long-term investment to find the environmental causes of type 1 diabetes, scientists in The Trial to Reduce IDDM [insulin dependent diabetes mellitus] in the Genetically at Risk (TRIGR), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), are testing whether a dietary intervention can reduce

the risk of diabetes-associated autoimmunity or type 1 diabetes. A small pilot study, conducted by the Finnish arm of this trial, recently reported the promising finding that children who received the intervention had fewer diabetes-associated autoantibodies than children who did not receive it. Prevention strategies will also be informed by knowledge of who is developing diabetes. The CDC-led Search for Diabetes in Youth (SEARCH) is providing important information on the number of U.S. children in certain areas with diabetes, the rates of development of childhood diabetes, and whether these rates and the clinical course of diabetes in children and youth are changing over time. By building on critical SEARCH findings, researchers may be able to design interventions that can prevent or delay disease onset in at-risk individuals and interventions to reduce risk for complications of diabetes.

TESTING STRATEGIES TO STOP T4 Tc 0.004 Tw 28.35 0 Td [0(as)-5( )]T [(P)]TJ 0.003 Tc -0

In addition to preventing the disease, it is important to identify ways to halt or reverse disease progression after onset. This could result in preservation or restoration of a person's insulin-producing capacity. Results from clinical trials have suggested that preserving remaining beta cell function in people with type 1 diabetes can have dramatic, long-term health benefits. Toward this goal, TrialNet also conducts trials testing therapies in newly diagnosed patients, frequently in collaboration with the National Institute of Allergy and Infectious Diseases' (NIAID) Immune Tolerance Network (ITN). Several agents have now been proven effective in slowing the progress of type 1 diabetes and preserving beta cell function, but these effects wane over time. The next step will be trials of combinations of agents that are individually effective to determine if the beta cell preservation can be extended when the agents are used concurrently. Collectively, TrialNet and ITN have 8 ongoing trials testing therapies in newly diagnosed people. One trial, a collaboration between TrialNet and the NICHD-led Diabetes Research in Children Network, is testing whether intensive blood glucose control upon diagnosis can preserve the ability of a person's pancreas to produce some of its own insulin. This trial employs a "closed-loop" system—a continuous glucose monitor linked to an insulin pump—in the hospital within a week of diagnosis. Patients are then sent home with an insulin pump and a continuous glucose monitor to use as part of the trial for the next 2 years, and investigators will determine whether this approach is able to delay progression of the disease.

DEVELOPING AN ARTIFICAL PANCREAS

components: a continuous blood glucose sensor, an insulin delivery system, and a way to link the two in a loop. Such a system would automatically turn the measurement of blood glucose levels into a practical, precise, and "real-time" insulin-dosing system. Importantly, artificial pancreas technology could help people safely achieve the tight blood glucose control associated with preventing or delaying life-threatening disease complications. Thus, this technology has high potential to have a positive impact on patients' health and quality of life, alleviate an enormous amount of patient burden, and improve long-term health outcomes. Working closely with our partners at FDA, we are pursuing research to develop the artificial pancreas and ensure that these technologies are safe and effective for people with type 1 diabetes. I'm pleased to share with you some of the progress that has been recently made in this area.

diabetes following two different real-life scenarios. In one, people had an “eating in” meal that mimicked a night of eating a medium-sized meal at home. In the other scenario, people had an “eating out” meal—a larger meal at a later hour. In both scenarios, a closed-loop system was able to improve glucose control and reduce the risk of dangerous drops in blood glucose levels overnight. Testing the closed-loop system technology in real situations that people find themselves in daily is critical to its development, and this advance marks a step toward moving closed-loop systems outside the clinic. This study used continuous glucose monitors that were derived from an NIDDK grant to a small business, highlighting the importance of fostering small business innovation in this field.

Our partners in industry are critical to the growing momentum toward an artificial pancreas. In addition to NIDDK small business grants that laid the groundwork for continuous glucose monitors, another company, SmartCells, Inc., who also received support from NIDDK small business grants, made substantial progress in preclinical development of a new formulation of insulin in which insulin release is automatically responsive to

recruit more bioengineers into diabetes research and create many more success stories in the future.

RESTORING BETA CELL FUNCTION

Although insulin therapy is life-saving, it is not a cure. Therefore, a major goal of type 1 diabetes research is to vigorously investigate ways to replace beta cells destroyed by the disease and restore beta cell function

field closer to this goal. It is through studies in the BCBC that a key factor necessary for making the insulin-producing beta cells—a factor called Rfx6—was identified. Researchers now know that they will have to ensure that Rfx6 is present in order to successfully generate beta cells from precursor cell types in the laboratory. Another group of BCBC investigators discovered that by increasing the levels of a protein called Pax4 they could coax established alpha cells—another pancreatic cell type—into becoming beta cells in mice. Other BCBC scientists observed spontaneous conversion of alpha cells to beta cells in adult mice that were engineered to lack beta cells. These discoveries—of a critical factor for beta cell development, and that adult pancreatic cells have the potential to convert to beta cells—generate a fuller picture of pancreatic development and plasticity and may pave the way toward new cell-based therapies for diabetes.

PREVENTING, ARRESTING, AND REVERSING COMPLICATIONS

Persistent elevation of blood glucose levels, despite insulin therapy, slowly damages the body's organs and can lead to life-threatening diabetes complications. Until prevention or cure of type 1 diabetes is possible, intensified research toward preventing and treating the complications of the disease is critically important. Diabetes has multiple effects on blood vessels. While a paucity of small blood vessels contributes to poor wound healing in people with diabetes, in the eye, diabetes leads to excessive new blood vessel formation. Basic research on the growth of new blood vessels led to the discovery of a key regulator of blood vessel growth. Because tumors require a blood supply for growth, a drug that inhibits this regulator, and thus new blood vessel growth, emerged from research on cancer and is now an FDA-approved

glucose control is important for personalizing therapy to provide the optimal care to each individual.

Cardiovascular disease is increased up to 10-fold in people with type 1 diabetes and

childhood diabetes received such training and career development. I'm pleased to report that a recent evaluation of this program showed that, of the 28 pediatric endocrinologists who received training under the program, 27 of them—96 percent—remain in academic science. Many of them have also successfully competed for independent funding to conduct research. The success of this program led NIDDK to recently issue a solicitation announcement for the next round of the program, and also plan to develop similar programs in other fields, such as

of type 1 diabetes research. Research supported by the *Program* has resulted in important scien