# INTRODUCTION

## OVERVIEW, BURDEN, AND IMPACT OF DISEASE

This Strategic Plan focuses on type 1 diabetes—the form of the disease in which the body's immune system destroys the cells that produce insulin, a hormone that regulates the amount of glucose (sugar) in the blood and is essential for life. Because patients with type 1 diabetes no longer produce insulin, which is necessary for survival, they require daily insulin administration, either through injections or an insulin pump. In the other major form of diabetes—type 2 diabetes—loss of effective insulin action is due to a combination of defects, both in normal insulin action (insulin resistance) and in the ability of pancreatic beta cells to overcome this insulin resistance by secreting sufficient amounts of additional insulin. Both forms of the disease share the same possible complications, which include blindness, kidney failure, nerve damage, lower limb amputations, heart disease, and stroke.

Type 1 diabetes can be more serious and costly for patients because it tends to strike earlier in life. For example, while type 2 diabetes increases the risk of heart disease 2- to 4-fold (1), heart disease risk is increased by up to 10-fold in patients with type 1 diabetes compared to the general age-matched population (2, 3). Importantly, the longer a person has diabetic complications, the more severe, difficult-to-treat, and costly they can become. Thus, an early diagnosis of type 1 diabetes can set the stage for a lifetime of living with and medically managing the disease complications. Few chronic medical conditions rival type 1 diabetes in terms of the extent to which maintenance of acceptable health is so heavily dependent on the capacity of patients and families to make and execute effective self-management decisions while simultaneously addressing many other complex priorities.

With respect to quality of life, dreaded complications can diminish the vitality of childhood and adolescence, as well as the prime productivity of young adulthood. Patients and their parents often wait anxiously to receive test results of their eye and kidney function. A broken blood vessel in the retina, or the finding of protein in the urine, can be the first sign that a relentless complication of the disease has emerged, and that grueling and costly treatments are in the near future. Even with recent advances in treatment, type 1 diabetes is estimated to lower average life expectancy by 15 years (4). For childhood-onset cases, greater than 15 percent of patients with type 1 diabetes will die by age 40 (4). Thus, early onset type 1 diabetes has major adverse impacts on patients and on society because of its extremely high personal and economic costs.

Type 1 diabetes has much in common with type 2 diabetes despite key differences in the mechanisms underlying development of the two forms of diabetes. Both involve malfunctions in the body's system for maintaining appropriate blood glucose levels due to defects in insulin production. Thus, research to understand the intricacies of insulin-producing beta cells, and to find ways to preserve and restore beta cell function, would benefit all diabetes patients. Similarly, the mechanisms of hypoglycemia (dangerous episodes of low blood sugar that can lead to coma and death) are also common to both forms of the disease and limit the ability to deliver therapy proven to prevent or slow complications. Therefore, research to understand and counteract hypoglycemia's effects on the brain would help those with both forms of diabetes. In the same way, all diabetes patients would gain from research directed toward understanding, treating, and preventing the eye, nerve, kidney, heart, and other complications that type 1 and type 2 diabetes share. Alarmingly, both forms of the disease are being increasingly diagnosed at a younger age,

**1901**

"Diabetes Mellitus" defined as "destruction of the islands of Langerhans."

**1915**

"Rainbow test," glucose monitoring with Benedict's Solution, provided an inexpensive way to roughly measure sugar levels in urine.

**1921**

Frederick Banting and Charles Best "discover" insulin, successfully treating a diabetic dog.

**1922**

First diabetes patient successfully treated with insulin.

**1935**

Doctors recognized distinction between type 1 and type 2 diabetes based on "insulin sensitivity."

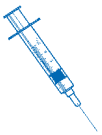
when the disease is more difficult to control; earlier onset increases diabetes' toll in lost health and productivity. Research aimed at diabetes in pediatric populations may help to shed light on and combat this trend. Furthermore, researchers are increasingly recognizing that many patients may have "hybrid" forms of diabetes. Careful characterization of patients considered to have type 2 diabetes reveals that a subset also have markers of type 1 diabetes known as autoantibodies. Interestingly, some patients with type 1 diabetes have the "insulin resistance" that was previously considered a hallmark of type 2 diabetes. Over the past 10 years, evidence has mounted to show that, in type 1 diabetes, high blood glucose levels themselves eventually cause secondary insulin resistance in nearly all patients. These observations are further blurring the line that has historically separated the two forms of the disease. They underscore how research progress on one form of the disease can have enormous benefits for the other form as well.

The interdependence and synergism of research on the two forms of diabetes have been clearly demonstrated, and research on type 1 diabetes has already contributed greatly to improved management of both forms of the disease. For example, a landmark clinical trial in type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), proved that intensive glucose control can prevent or delay damage to the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). The findings of this trial paved the way to studies that replicated these impressive results in patients with type 2 diabetes. Most recently, the DCCT findings were extended to show that intensive control reduces heart attacks and strokes (macrovascular complications), the major cause of death in both forms of diabetes. Because of this pioneering research in type 1 diabetes, close control of blood glucose levels is now a cornerstone of the medical management of both forms of the disease. Moreover, this landmark trial in type 1 diabetes also established the value of hemoglobin A1c (HbA1c) levels—a measurement of blood glucose levels over time—as an outcome measure for future clinical trials in both type 1 and type 2 diabetes, dramatically shortening the cost and duration of clinical trials of new therapies and encouraging development of new therapies for diabetes. The use of HbA1c as an outcome measure was the basis for Food and Drug Administration (FDA) approval of improved forms of injected insulin, inhaled insulin, and several new classes of oral drugs for type 2 diabetes, which when used in combination can delay the need for insulin therapy.

Unfortunately, most national data on the incidence, prevalence, and burden of diabetes do not distinguish between type 1 and type 2 diabetes—although ongoing studies may help to address this problem. Within the context of available data, it is generally estimated that type 1 diabetes accounts for 5 to 10 percent of all diagnosed cases of diabetes in the U.S. (5). However, the burden of type 1 diabetes is disproportionate to its prevalence because complications and loss of quality life years are much greater when diabetes strikes at younger ages. Collectively, both type 1 and type 2 diabetes constitute an enormous public health challenge in the United States. Although this Strategic Plan is focused on type 1 diabetes, the following indicators of the overall burden of diabetes are presented because the best available epidemiological data are reported for diabetes as a whole.

- Patients with diabetes have an increased risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurological problems, limb amputation, chronic wounds and skin ulcers, periodontal disease, depression, and pregnancy-related problems.
- In the past 25 years, the number of people with diabetes has more than doubled to 20.8 million (5, 6), or 7 percent of the total U.S. population (5). Evidence now suggests that one in three Americans born in 2000 will develop diabetes during his or her lifetime (6). It is generally believed that these trends are largely attributable to type 2 diabetes, and related to increases in obesity, a known risk factor for type 2 diabetes, as well as to changes in demographics, such as increases in the elderly and minority populations of the United States who are prone to developing type 2 diabetes. Rates of type 1 diabetes are increasing in some European countries where reliable data are available.

**1944**



Standard insulin syringe is developed, helping to make diabetes management more uniform.

**1948**

Development of delayed action insulin reduced the number of daily insulin injections.

**1950**

National Institute of Diabetes & Digestive & Kidney Diseases

Medical Research Act established national research institute for diabetes, which later became NIDDK.

**1950**

Discovery that insulin promotes glucose transport.

**1955**

Ile-Val-Glu-Gln-Cys-Cys-Ala-Ser-Val-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Try-Cys-Asn

Amino acid sequence of insulin protein determined.

More limited data suggest that rates of type 1 diabetes are increasing in very young children and infants in the U.S. Baseline national data on diabetes in children have recently been collected in the U.S., and the next phase of this study will provide definitive information on whether type 1 diabetes rates in children are stable or changing.

- Diabetes is the sixth leading cause of death in the United States, resulting in more than 73,000 deaths in 2002 (7). More than 224,000 people die annually from diabetes-related complications common to both type 1 and type 2 diabetes. This number is considered to be significantly underreported (5).
- The problem of diabetes extends globally. The World Health Organization estimated that 1,125,000 people worldwide would die from diabetes in 2005 (8). Overall, the risk of death for individuals with diabetes is approximately double that of people without diabetes of similar age (5).

The burden of both forms of diabetes extends far beyond mortality. In the United States each year, 12,000 to 24,000 people become blind as a result of diabetic eye disease and approximately 82,000 people undergo diabetes-related amputations (5). Encouragingly, declines in the incidence of end-stage renal disease (ESRD) due to diabetes are being noted for the U.S. population, in reports from the United States Renal Data System. These improvements are most noteworthy in patients under age 30 with diabetes (most of whom have type 1 diabetes) and have been observed in Caucasians, but not in African Americans (9). However, ESRD remains a major public health problem. In 2003, 45,330 Americans with diabetes began treatment for irreversible kidney failure (ESRD), and 165,113 people with failed kidneys needed chronic dialysis or a kidney transplant to remain alive (9).

The financial burden of diabetes is tremendous. The direct and indirect costs associated with both forms of diabetes in the United States during 2002 were estimated to be $132 billion (5). The average annual health care costs for a person with diabetes are $13,243, which is 2.4 times greater than those for an individual without diabetes (10). In 2002, 11 percent of national health care expenditures were directed to diabetes care (10). The costs of treating the complications of diabetes, which both forms of the disease share in common, account for much of the health care costs associated with the disease. Although estimates of the rates of diabetes have increased since 2002, the associated cost estimates have not yet been revised; hence, the economic data given here are conservative. Clearly, the economic and societal burden of diabetes has a profound impact on the Nation.

## Incidence and Prevalence of Type 1 Diabetes

In the United States, it is estimated that approximately 1 in every 400 to 600 children and adolescents has type 1 diabetes (5). There is evidence that the incidence (the number of new cases) and prevalence (the total number of cases) of the disease are increasing in Europe. In the United States, the incidence and prevalence of type 1 diabetes are not precisely known because of the lack of uniform national data on the rates of childhood diabetes and how the rates are changing over time. This gap in knowledge is being addressed by the Search for Diabetes in Youth Study (SEARCH), which is determining the prevalence and incidence of diabetes in children and youth less than 20 years of age. Emerging data from the SEARCH study (11) suggest that the incidence of type 1 diabetes in American children may be higher than an earlier estimate of 13,000 per year (12). In total, about 30,000 people (children and adults) are diagnosed with type 1 diabetes annually (12).

## Key Features of Type 1 Diabetes

Type 1 diabetes is an autoimmune disease in which the body's own immune system attacks and destroys specialized cells of the pancreas called beta cells. Beta cells are found within tiny clusters called islets and produce the hormone insulin. Insulin is required for survival; it sends signals to the body's cells and tissues, telling them to absorb glucose to use as a fuel. Without this vital hormone, the cells and tissues do not absorb glucose and patients can starve to death, despite having high levels of glucose in their bloodstream. An interplay of

**1956**

Development of the "dip-and-read" urine test allowed instant monitoring of glucose levels.

**1959**

Immunoassay allowed researchers to measure insulin in blood. This assay showed that patients with type 1 diabetes produced no insulin, but patients early in the course of type 2 diabetes had more insulin than normal.

**1960**

Self-monitoring of blood sugar with the "wet" method using glucose oxidase strips.

**1964**

First kidney transplants in patients with diabetes.

**1966**

First successful pancreas transplant performed.

genetic and environmental factors is responsible for the onset of type 1 diabetes (as well as type 2 diabetes). Having a family member with the disease puts one at higher risk for developing type 1 diabetes.

Type 1 diabetes differs from type 2 diabetes—which is more commonly diagnosed in adulthood, is strongly associated with overweight and obesity, and disproportionately affects minority populations. Although patients with type 1 diabetes require externally administered insulin to survive, type 2 diabetes patients may be treated with medications that make their tissues more sensitive to insulin or enhance insulin production or, in some cases, may be treated with insulin itself.

## Treatment Options and Challenges

The treatment of patients with type 1 diabetes was revolutionized in 1921 with the discovery of insulin by a group of researchers at the University of Toronto. To this day, insulin therapy continues to save the lives of patients with type 1 diabetes by replacing the essential hormone that their bodies no longer adequately produce. However, insulin therapy, whether through injections or via a pump, is not a cure and it cannot prevent complications. To manage the disease, patients must carefully monitor their food intake and physical activity. They must perform painful finger sticks multiple times a day to draw blood and test their glucose levels. Based on this monitoring, patients often give themselves several shots of insulin a day, or calculate the correct amount of insulin to administer through their insulin delivery pumps. This regimen is not just "once in a while;" it is every day of their lives. As many patients and their parents say: "There is never a day off from diabetes." Moreover, no matter how vigilant patients are at regulating their blood glucose levels, they can never achieve the fine-tuned regulation provided by a healthy pancreas, which exquisitely senses and responds to insulin needs with precise timing.

Because of the inadequacies of insulin treatment, patients with type 1 diabetes are susceptible to harmful fluctuations in their blood glucose levels—abnormally high blood glucose (hyperglycemia) or dangerously low blood glucose (hypoglycemia). Both of these conditions can be life threatening in extreme cases. In the case of a very young type 1 diabetes patient who cannot self-monitor, parents must assume the role that is no longer performed by the pancreas. The psychosocial impact on families is enormous. Parents often forego restful sleep because they are "on watch" to ensure that their child's blood glucose levels do not fall dangerously low in the middle of the night. They are also dependent on an extended team of caregivers when their child is not in their immediate care, such as school personnel, childcare providers, friends, and parents of their child's friends.

## Approaches for Preventing or Reversing the Disease

Currently, there are no known methods to prevent type 1 diabetes. However, recent clinical trials suggest that it may be possible to reverse or slow the rate of loss of the insulin-producing beta cells in newly diagnosed patients. While the environmental factors that may play a role in triggering type 1 diabetes remain to be defined, several key genes that increase the risk of type 1 diabetes have been identified. Genetic tests in combination with blood tests to detect antibodies directed against the insulin-producing beta cells can predict development of type 1 diabetes, allowing new strategies for prevention to be tested. Key strategies for preventing much of the burden of the disease include early detection, improved methods and delivery of care, and new interventions.

With the number of individuals with diabetes increasing, the associated societal and economic burdens will continue to rise. Yet, there are many positive developments, including reports showing that life expectancy for patients with type 1 diabetes is increasing (13). A key finding of NIH-supported research is that intensive control of blood glucose levels can dramatically prevent or delay the development of disease complications. Now, it is essential to find more effective ways to achieve blood glucose control. Progress being made in

**1967**

Laser treatment revolutionized the care of diabetic retinopathy.

**1969**

Determination of the three-dimensional protein structure of insulin.

**1971**

NIH scientists discover the insulin receptor: a protein on the cell surface that mediates effects of insulin in cells.

**1974**

Evidence that type 1 diabetes is an autoimmune disease provided by discovery of antibodies to insulin-producing cells in newly diagnosed patients and by genetic studies showing the association of type 1 diabetes with the HLA genes that control the immune system.

**1977**

Introduction of insulin pumps for continuous delivery of insulin.

the area of cell-based research could lead to ways to replace or restore a patient's insulin-producing capacity. Increased knowledge about the underlying mechanisms of beta cell development and function could potentially be used to develop therapeutic approaches to reverse the disease by promoting formation of new beta cells in the pancreas.

With continued, vigorous research, new strategies may be developed to prevent type 1 diabetes in those at risk, restore insulin independence in patients already diagnosed, and prevent the development of disease complications. Through research in these and other avenues, the burden of type 1 diabetes on people and the Nation can be lifted.

## GOALS OF TYPE 1 DIABETES RESEARCH

The promise of a cure for type 1 diabetes can only be realized through the vigorous support of scientific research. Type 1 diabetes research supported by the NIH is focused around six overarching research Goals listed below. Pursuit of research toward attaining each of these broad, scientific Goals can help achieve real progress in the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. The Goals are interdependent in that research on one Goal will inform research on others. Therefore, to maximize research progress, research toward achieving the Goals requires well-coordinated and integrated efforts, as described in this Strategic Plan.

**Six Overarching Goals of NIH-Supported Type 1 Diabetes Research**

- **Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes**
- **Goal II: Prevent or Reverse Type 1 Diabetes**
- **Goal III: Develop Cell Replacement Therapy**
- **Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes**
- **Goal V: Prevent or Reduce the Complications of Type 1 Diabetes**
- **Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

### Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes has a strong genetic basis that is modified by environmental factors. It is a "polygenic" disease, which means that it arises from the interaction of variations in multiple genes. Research has already identified some genes that are important in the development of type 1 diabetes. However, researchers have not yet found all of the genes that can play a role in disease development. Identification of key genes will not only help to predict who will develop the disease, but will also aid in the development of new prevention strategies. In addition to genes, the environment has also been found to play an important role in the development of type 1 diabetes. Potential environmental triggers are thought to include viruses, dietary factors, environmental toxins, and psychological stress. To date, no single trigger has been conclusively identified. Research to identify the key environmental trigger(s) could be used to prevent the disease in genetically susceptible people.

### Goal II: Prevent or Reverse Type 1 Diabetes

One obvious way to attack type 1 diabetes is to stop it before it starts. Preventing the disease means that patients would not require insulin administration or develop life-threatening disease complications. While recent clinical trials have suggested that further loss of insulin production can be slowed

**1978**

Development of glycosylated hemoglobin (HbA1c) test permitted monitoring average blood glucose control over a 90-day period.

**1978**

Insulin gene becomes first human therapeutic protein to be cloned and synthesized by genetic engineering.

**1980**

Development of first animal model of type 1 diabetes that could be used to test drugs for type 1 diabetes: non-obese diabetic (NOD) mouse.

**1983**

Introduction of the first biosynthetic human insulin.

**1983**

Clinical studies showed that preconception care of women with diabetes dramatically reduced congenital malformations in their babies.

in patients with newly diagnosed type 1 diabetes, research has not yet identified an effective disease prevention strategy. However, the ability to identify at-risk individuals permits promising strategies for prevention to be tested in rigorously designed clinical trials. Further research and increasing knowledge about what goes wrong with the immune system will facilitate the discovery of novel ways to prevent autoimmunity, and thus prevent disease onset.

In addition to preventing the disease before beta cell destruction starts, it is important to conduct research to prevent further beta cell destruction in newly diagnosed patients. Research has shown that, after patients are diagnosed with the disease, they still have some beta cell function and can produce C-peptide, a by-product of insulin production which is co-secreted from the beta cell with insulin and is a useful measure of endogenous insulin production. Furthermore, clinical studies have demonstrated major benefits of residual beta cell function in patients with type 1 diabetes, even though the patients require insulin therapy. For example, the DCCT demonstrated that higher and sustained levels of C-peptide were associated with reduced incidence of long-term disease complications of the kidneys and the eyes, as well as reduced hypoglycemia. This evidence suggests that preserving patients' remaining beta cell function could have dramatic, long-term health benefits. Already one agent has been shown to preserve beta cell function in new onset type 1 diabetes. To prevent or reverse beta cell destruction in newly diagnosed patients, further research efforts are required to identify and test additional strategies that may provide more durable benefits and few side effects.

## Goal III: Develop Cell Replacement Therapy

Patients with type 1 diabetes require insulin therapy because their immune systems have destroyed their pancreatic beta cells. A real "cure" for this disease could be achieved by replacing those missing cells, and scientists are aggressively pursuing this avenue of research. A major breakthrough occurred in 2000 when researchers at the University of Alberta in Edmonton, Canada, reported that patients with type 1 diabetes achieved insulin independence after transplantation with islets from two to four donor pancreata and treatment with a novel immunosuppressive regimen that omitted the widely used glucocorticoid drugs that are toxic to islets. A major barrier limiting the widespread use of islet transplantation is the shortage of islets available for transplantation. The diabetes research community believes that there is significant potential in the use of human embryonic[1] and tissue-specific adult multipotent progenitor cells in deriving a host of differentiated cell types, including insulin-producing beta cells. Understanding the underlying molecular mechanisms of beta cell biology, and how mature beta cells are formed from stem/progenitor cells, could help to overcome this barrier. Furthermore, as noted previously, recent research has shown that patients with type 1 diabetes have some remaining functional beta cells. Therefore, research on the mechanisms controlling islet cell growth and regeneration could lead to novel therapies designed to stimulate beta cell growth *in vivo*.

Another major barrier that prevents islet transplantation from being a widespread treatment option for patients with type 1 diabetes is the need for lifelong immunosuppressive drug treatments that are currently required to prevent rejection of transplanted islets. Research to identify ways to overcome the need for immunosuppressive treatment, or to identify less toxic immunosuppressives, can help to make islet transplantation a reality for greater numbers of patients with type 1 diabetes.

## Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Hypoglycemia is perhaps the most distressing acute complication of type 1 diabetes. Hypoglycemia can occur with missed meals, during exercise, or when too much insulin is in the body, which causes glucose to fall to dangerously low levels. Too little glucose means that the body—and particularly the brain—cannot function at its normal capacity. The immediate effects of hypoglycemia can include changes in cardiovascular and nervous system function, cognitive

[1] The NIH supports human embryonic stem cell research consistent with federal funding policies.

**1984**

Identification of early kidney disease marker—microalbuminuria—permitted doctors to intervene to prevent or delay kidney failure.

**1987**

Diabetic foot ulcers treated by total contact casting.

**1990**

First successful transplant of human islet cells reversed insulin dependency in patients.

**1993**

Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy delays the progression of long-term complications of the eyes, kidneys, and nerves.

**1993**

Collaborative study of diabetic nephropathy showed that ACE inhibitors reduce need for kidney dialysis and transplantation, and cut heart disease mortality.

impairment, increased risk for unintentional injury, coma, and sometimes death. In some cases, patients are not aware that their blood glucose level is dangerously low. This syndrome is called "hypoglycemia unawareness." It is characterized by the loss of the warning symptoms that alert patients that it is time to eat before their blood glucose level falls too low. In addition, episodes of hypoglycemia impair defenses against future hypoglycemia, resulting in a vicious cycle of recurrent episodes.

A severe limitation to the practice of intensive glucose control to prevent disease complications is the potential for acute episodes of hypoglycemia. It is estimated that patients on intensive treatment have two hypoglycemic episodes a week versus one episode if they are treated less intensively (14). Because intensive glucose control dramatically reduces the risk of long-term disease complications, it is imperative to pursue research to overcome this major obstacle to achieving tight glucose control. The risk of severe hypoglycemia may be related to a variety of behavioral and psychological variables, and behavioral interventions may reduce these risks. Strategies to meld technological, behavioral, and educational advances are key to this goal. Devices for minimally invasive continuous glucose monitoring, developed with NIH support and recently approved by the FDA, may represent a major advance in this regard. Further research is needed to improve glucose monitoring, to link monitoring devices to insulin delivery, and to empower patients and care providers to maximize the benefits of these devices. By reducing hypoglycemic episodes, improving glycemic control, and lessening the burdens of diabetes self-management, this research can also have a major impact on patients' quality of life until cell replacement therapy becomes a viable option for patients with type 1 diabetes.

## Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

Nearly every organ in the body is adversely affected by type 1 diabetes. Throughout the course of a patient's life, the persistent elevation in blood glucose levels despite insulin therapy damages vital organs, including the heart and kidneys. The longer a person has the disease, the more likely it is that he or she will develop these severe complications. Because patients with type 1 diabetes are often diagnosed in childhood and adolescence, they may develop complications at a young age.

The DCCT reported good news regarding preventing or delaying the onset of complications. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of disease complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered to continue to be followed in the Epidemiology of Diabetes Interventions and Complications Study (EDIC), which began in 1994. The DCCT/EDIC researchers continue to report remarkable long-term benefits of intensive blood glucose control in preventing or delaying complications of the eyes, kidneys, and the heart. However, given the limitations and difficulties of current therapies and technologies for achieving good glucose control, even most participants in the EDIC study cannot achieve the levels of control associated with reduced complications. Thus, other approaches are needed to prevent and delay progression of complications. New insights into the underlying molecular mechanisms of diabetes complications are imperative in order to develop new therapeutic approaches.

## Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

Research on type 1 diabetes spans a broad range of scientific disciplines, including endocrinology and metabolism; immunology; genetics; epidemiology; clinical trials; neuroscience; behavioral science; cell, developmental, and vascular biology; and the physiology of the heart, eyes, kidneys, and urologic tract, and the central and peripheral nervous systems. Propelling research progress on the understanding, prevention, and cure of type 1 diabetes requires a cadre of scientists with

| 1998 | 2000 | 2000 | 2002 | 2002 | 2003 |
|---|---|---|---|---|---|
|  First year of *Special Statutory Funding Program for Type 1 Diabetes Research.* | "Edmonton" Protocol improved success rate of islet transplantation from less than 5 percent to 90 percent. | Long-term follow-up of patients from DCCT suggested that the benefits of tight glucose control have a sustained effect on diabetes complications, a phenomenon called "metabolic memory." | The Diabetes Prevention Trial-Type 1 (DPT-1) demonstrated the feasibility of accurate assessment of risk for type 1 diabetes. | Research demonstrated that treating new onset type 1 diabetes patients with a monoclonal antibody preserves residual beta cell function. | The rate of kidney failure has stabilized in part due to improved management of diabetes. |

diverse research training and expertise. Furthermore, it is critical for basic scientists and clinical researchers to work together to translate research findings from the bench to the bedside, and from the bedside to clinical practice, in order to achieve real improvements in patients' health and quality of life.

Powerful new technologies that have emerged over the past few years make this an exciting time to be involved in scientific research and have quickened the pace of discovery. Application of these new and emerging technologies to type 1 diabetes research provides unprecedented opportunities to solve key problems. For example, "proteomics" involves the use of novel, integrated technologies to identify and quantitate proteins and study their interactions. Identifying how protein expression changes over the course of type 1 diabetes onset and progression can help researchers understand the underlying disease processes, develop biomarkers of disease onset and progression, and propose and test novel prevention and treatment strategies. Type 1 diabetes research stands to benefit greatly from the application of proteomics and many other new and emerging technologies.

## NIH TYPE 1 DIABETES RESEARCH PORTFOLIO

The NIH vigorously pursues and supports research on the understanding, prevention, and cure of type 1 diabetes. Current efforts span diverse areas, such as genetics, genomics, proteomics, immunology, developmental biology, imaging, bioengineering, glucose sensing, and insulin delivery. NIH-supported clinical trials are testing promising agents for type 1 diabetes and its complications. Type 1 diabetes research at the NIH is largely supported by regularly appropriated funds that the Department of Health and Human Services (HHS) receives for diabetes research through the Labor-HHS-Education appropriations subcommittees. In addition, it is supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which the NIDDK administers on behalf of the Secretary and in collaboration with multiple NIH Institutes and Centers, as well as the CDC.

Critical to the national effort to combat type 1 diabetes are studies funded through investigator-initiated research grants (primarily R01 grants). The NIH vigorously supports investigator-initiated research projects, and also fosters development of research efforts in areas of particular importance and opportunity through solicitations for grant applications and research contract proposals. This type of research has provided remarkable insights about type 1 diabetes and has laid the foundation for the development of improved treatment approaches and possible prevention strategies. Much of the positive impact of NIH-supported research comes from creative, hypothesis-driven endeavors undertaken by outstanding investigators working in laboratories across the country, funded through a peer-reviewed, highly competitive process. In addition, type 1 diabetes research has benefited from the results of other major cross-cutting NIH efforts such as the wealth of genetic information flowing from the Human Genome Project and the expanded knowledge base NIH research has fueled regarding developmental and cell biology, autoimmunity, and transplantation biology.

Complementing and extending this research base, the *Special Funding Program* has furthered the creation of unique, collaborative, and innovative research consortia and clinical trials networks to increase understanding about the prevention, treatment, and cure of type 1 diabetes. Initiatives supported by this program differ in size, scope, duration, and nature from other type 1 diabetes efforts supported through regular NIH appropriations. The *Special Funding Program* enabled the initiation of most of these large-scale, high-impact efforts, at a scientifically optimal scale of operation. Importantly, the research efforts that have been supported to date have

**2005**

DAISY study found that genetically vulnerable newborns can be identified and followed prospectively to prevent diabetic ketoacidosis, the leading cause of diabetes-related morbidity and mortality in infants.

**2005**

Long-term follow-up of patients from the DCCT demonstrated that intensive therapy reduces cardiovascular complications.

**2006**

FDA approved the first inhaled version of insulin.

**2006**

First generation of FDA-approved continuous glucose monitors paired with insulin pumps pave the way for developing an artificial pancreas and closing the feedback loop between glucose levels and insulin delivery.

spurred numerous future opportunities that could dramatically improve the lives of patients with type 1 diabetes. The following are highlights of some of the major collaborative research efforts and innovative approaches that are supported by the *Special Funding Program*. These research efforts are illustrative examples and not a comprehensive overview of the entire NIH type 1 diabetes research portfolio.

## Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

***Search for Diabetes in Youth (SEARCH)*:** There are no comprehensive population-based estimates of diabetes burden among American youth. SEARCH will define the prevalence and incidence of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. This study will help increase understanding of how type 1 diabetes strikes and unfolds.

***The Environmental Determinants of Diabetes in the Young (TEDDY)*:** The goal of TEDDY is to identify environmental causes of type 1 diabetes in genetically susceptible individuals. This long-term study is enrolling at-risk newborns and then following them until they are 15 years of age. The study is crucial to helping researchers understand the environmental triggers that play a role in type 1 diabetes disease onset and development.

***Type 1 Diabetes Genetics Consortium (T1DGC)*:** T1DGC is organizing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. This Consortium is currently recruiting 2,800 families who have two or more siblings with type 1 diabetes in order to identify genes that increase susceptibility. Finding these genes will not only increase understanding of the underlying molecular mechanisms of disease development, but also aid in the discovery of novel prevention strategies and identification of patients who could benefit from these approaches.

## Goal II: Prevent or Reverse Type 1 Diabetes

***Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)*:** The mission of the Prevention Centers is to engage in scientific discovery that significantly advances knowledge about the prevention and regulation of autoimmune diseases, including type 1 diabetes. Pre-clinical research conducted by the Prevention Centers is key to the development of strategies for modulating the immune system so that they can be tested in human clinical trials.

***Immune Tolerance Network (ITN)*:** Immune tolerance is the process by which the immune system accepts a protein or other molecule as "self" and does not attempt to destroy cells or tissues containing that protein. Tolerance induction can block the autoimmune process underlying type 1 diabetes or enable the body to accept transplanted islets without the need to globally suppress the immune system. Research conducted through the ITN is evaluating new treatments to induce tolerance in type 1 diabetes, as well as other disease areas. The ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. Research on tolerance is critical both for developing therapies to slow or reverse type 1 diabetes, as well as for improved approaches to islet transplantation.

***Standardization Programs*:** Standardized assessment of key measures for type 1 diabetes research is extremely important to ensure consistency across laboratories and clinical trial networks, so that data can be compared and combined. Efforts are ongoing to improve and standardize the measurement of autoantibodies (used to identify initiation of autoimmunity), C-peptide (a measure of beta cell mass and function), and HbA1c (a measure of long-term blood glucose control).

***Trial To Reduce IDDM in the Genetically At Risk (TRIGR)*:** This multicenter, international study is comparing the development of type 1 diabetes in genetically susceptible infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, versus standard cow's milk formula. TRIGR, which is currently in the patient recruitment phase, could have a major impact on disease prevention if differences are observed between the two types of formulas.

***Type 1 Diabetes TrialNet (TrialNet)*:** TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new onset patients and to prevent the disease in at-risk patients. TrialNet has launched several studies that are recruiting patients and is currently evaluating several other therapeutic agents to test in the network. This type of collaborative network infrastructure is

critical for facilitating clinical trials in type 1 diabetes, as well as for making real improvements in patients' health by identifying new therapeutic agents.

### Goal III: Develop Cell Replacement Therapy

***Beta Cell Biology Consortium (BCBC)*:** The mission of this Consortium is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to diabetic patients. Working toward this goal, the BCBC has created and distributed important reagents that will serve the scientific community at large. Research pursued through the BCBC can ultimately help to overcome a major barrier to islet transplantation—the shortage of islets.

***Clinical Islet Transplantation Consortium (CIT)*:** The purpose of this Consortium is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this Consortium aims to make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

***Collaborative Islet Transplant Registry (CITR)*:** The mission of the CITR is to expedite progress and promote safety in islet transplantation through the collection, analysis, and communication of comprehensive, current data on all islet transplants performed in North America. The CITR prepares an annual report with data on recipient and donor characteristics, pancreas procurement and islet processing, immunosuppressive medications, function of the donated islets, patients' lab results, and adverse events. This information will help to define the overall risks and benefits of islet transplantation as a treatment option for patients with type 1 diabetes.

***Immunobiology of Xenotransplantation Cooperative Research Program*:** This multi-institution Program is developing and evaluating pre-clinical porcine to non-human primate models of xenotransplantation (solid organ, tissue, or cell transplantation between species). The Program supports pre-clinical research to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts. The long-term goal is to develop novel and efficacious strategies for broad clinical application of xenotransplantation.

***Islet Cell Resource Centers (ICRs)*:** The ICRs serve as regional centers that provide clinical grade human islets to investigators engaged in islet transplantation protocols throughout the country; optimize the procedures used to obtain such islets; and distribute human pancreatic islets to investigators for use in laboratory-based research studies. This resource provides high-quality islets for use in human islet transplantation research and allows researchers to continue to investigate islets in basic research studies.

***Non-human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)*:** This multi-institution Study Group was established to evaluate the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of kidney and islet transplantation. The Group also supports research on immune tolerance. Pre-clinical research conducted by this Group will help scientists move promising therapeutic agents from the laboratory into human clinical trials.

### Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

***Diabetes Research in Children Network (DirecNet)*:** The focus of DirecNet is to investigate the use of technological advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia. The Network's goals include assessing the accuracy, efficacy, and effectiveness of continuous glucose monitoring in children with type 1 diabetes, and determining the extent to which exercise contributes to the risk of hypoglycemia. Until cell replacement therapy is a viable treatment option for children with type 1 diabetes, research on glucose sensing and insulin delivery is crucial to improving quality of life and decreasing the number of hypoglycemic episodes.

### Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

***Animal Models of Diabetic Complications Consortium (AMDCC)*:** The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The Consortium has already developed a number of

promising models for complications involving the heart, kidneys, and nervous system. Development of animal models is essential for pre-clinical drug development.

***Diabetic Retinopathy Clinical Research Network (DRCR.net)*:** Type 1 diabetes causes damage to the eyes and may lead to blindness. The DRCR.net conducts multicenter clinical research studies to test promising therapeutic agents for the treatment of two forms of diabetic eye disease—diabetic retinopathy and diabetic macular edema—and associated conditions. Because blindness is such a severe and debilitating disease complication, research pursued through this network could dramatically improve patients' quality of life.

***Epidemiology of Diabetes Interventions and Complications Study (EDIC)*:** The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the DCCT. The DCCT/EDIC research group has observed dramatic long-term benefits of intensive glucose control in preventing and delaying complications of the eyes, kidneys, nerves, and heart. These results have had a major impact on the clinical care of diabetes patients.

***Family Investigation of Nephropathy and Diabetes (FIND)*:** The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease in patients with diabetes, as well as genetic susceptibility to retinopathy in diabetic patients. A family-based study recruited more than 2,500 affected and discordant pairs of siblings. A separate case control study is completing recruitment of more than 3,000 individuals. These studies will help researchers understand the genetic underpinnings of the kidney and eye complications of diabetes, which can, in turn, inform prevention and treatment strategies.

***Genetics of Kidneys in Diabetes Study (GoKinD)*:** GoKinD was established to study the genetics of kidney disease in patients with type 1 diabetes. The study group has collected and is distributing DNA and other biological samples from more than 1,700 adults with type 1 diabetes in the United States and Canada. Scientists will use these samples to identify genes that are important in the development of, or resistance to, diabetic kidney disease.

### Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

***Research Training and Career Development in Pediatric Diabetes*:** This program provides support of research training and career development in pediatric diabetes at institutions that have environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric diabetes. The awards, through the T32 (institutional research training) and K12 (clinical scientist career development program) grant mechanisms of the NIH, are intended to provide an opportunity for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator. These integrated programs are designed to prepare pediatricians, selected by the institution, for careers in pediatric endocrinology research related to diabetes.

***Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)*:** The T1D-RAID program provides resources for manufacture and pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. The goal of T1D-RAID is to facilitate the translation of promising therapeutic agents from the bench to the bedside, in order to more rapidly impact patients' health.

> For more information on these and other type 1 diabetes research efforts, please visit a Web site dedicated to research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*: www.T1Diabetes.nih.gov.

## Collaborative Planning Process

The NIDDK is the lead Institute at the NIH for pursuing type 1 diabetes research. Because this research involves diverse scientific disciplines, the NIDDK collaborates extensively with other NIH Institutes and Centers, as well as other government agencies. Type 1 diabetes research involves nearly every Institute and Center of the NIH, including the National Center for Research Resources (NCRR), National Eye Institute (NEI), National Human Genome Research Institute

(NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Child Health and Human Development (NICHD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Environmental Health Sciences (NIEHS), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Library of Medicine (NLM), and other NIH Institutes and Centers that are represented on the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). The NIH also works closely with the CDC, the FDA, the Centers for Medicare & Medicaid Services (CMS), and other governmental agencies represented on the DMICC. Also contributing to program planning are the two major diabetes voluntary organizations, the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA).

## DEVELOPMENT OF THE STRATEGIC PLAN

### Origin and Purpose of the Plan

In January 2005, the NIDDK convened an *ad hoc* planning and evaluation meeting of external scientific and lay experts in type 1 diabetes. The purpose of the meeting was to perform a mid-course assessment of many currently funded type 1 diabetes research programs, and to identify future research opportunities within this context. The meeting focused on research consortia and clinical trials networks supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*. A detailed summary of the meeting can be accessed on the NIDDK Web site at: www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-FINAL.pdf.

One of the recommendations emanating from this meeting was to initiate a much broader review of the entire state-of-the-science with respect to type 1 diabetes, including recent research advances and emerging opportunities. Such a review would be far more encompassing and future-oriented than the assessment performed at the January 2005 meeting, which was largely focused on existing programs. In response to this recommendation, the NIDDK Director announced in March 2005, that the Institute would spearhead a new strategic planning effort in type 1 diabetes research under the auspices of the statutory DMICC, chaired by the NIDDK. The membership of this Committee includes all NIH components involved in diabetes research, as well as other relevant Federal agencies.

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

### Collaborative Planning Process

The Strategic Plan was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing type 1 diabetes research (please see Appendix A). Participants included representatives from the NIH and other Federal agencies represented on the DMICC, scientists external to the NIH, lay people representing patients' interests, and representatives from diabetes voluntary organizations.

The Strategic Plan was organized around the six overarching goals of type 1 diabetes research. To formulate the Plan, Working Groups were convened to address each of the first five goals. The sixth goal, "Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes," is an overarching goal that is relevant to all of type 1 diabetes research. Therefore, this goal was addressed by each of the five Working Groups. Each Working Group was chaired by a scientist external to the NIH and was composed of other external scientific experts, a lay representative, a representative of a diabetes voluntary organization, at least one member of the DMICC, and other senior scientific Government representatives. The Working Group members were asked to survey the state-of-the-science and develop a summary of progress and opportunities relevant to each goal.

In addition to the Working Groups, the Strategic Plan was informed by insights provided by an overarching Executive Committee, composed of the chairs of the five Working Groups and representatives from the government and from

diabetes voluntary organizations. The Executive Committee met on September 28, 2005, to ensure that in aggregate the components developed by the Working Groups were comprehensive and addressed the most compelling opportunities for the prevention, therapy, and cure of type 1 diabetes and its complications. The Executive Committee provided guidance on integrating the products of each Working Group into a final Strategic Plan that will serve the purpose of informing future priority-setting in type 1 diabetes research.

To solicit broad public input into the strategic planning process, a draft document was posted on the Strategic Plan's Web site (accessed at: www.T1Diabetes.nih.gov/plan) for a month-long period of public comment. Scientists with expertise relevant to type 1 diabetes and its complications and members of voluntary and professional health advocacy organizations were invited to comment. A broad range of expertise was represented among the individuals and organizations providing vigorous input on the draft Strategic Plan.

## Organization of the Strategic Plan

Based on the same general content, two versions of this Plan have been developed for: (1) patients with type 1 diabetes, their family members, and the public, and (2) the scientific research community. Both versions contain a summary of major research objectives.

The version of the Plan for patients and the public describes how achieving the goals will directly benefit the health and quality of life of patients with type 1 diabetes and their family members. Each Goal includes the following sections:

- *Why the Goal Is Important:* This section highlights the clinical relevance of the goal and describes how research progress can have a direct and dramatic impact on the lives of patients with type 1 diabetes and their family members.
- *Profiles of Patients or Scientists:* This section describes the impact of type 1 diabetes on the lives of patients with type 1 diabetes and family members, or the experiences of researchers studying the disease.

The technical version of the Plan provides greater detail regarding specific research directions that can be pursued to achieve the overarching goals of type 1 diabetes research. Under each Goal, the following sections are included:

- *Introduction and Background:* A brief description of the current state-of-the-science, and an overview of the importance of the goal in propelling research progress in type 1 diabetes.
- *Recent Scientific Advances:* Examples of major achievements in type 1 diabetes research that have made a significant impact on the research field or patients' health, particularly in the last 5 to 7 years.
- *Research Objectives and Strategies To Achieve Goals:* The objectives are specific research directions that can be pursued to realize the goal of the chapter. The objectives were identified by Working Group members as being critically important for overcoming current barriers and achieving progress in type 1 diabetes research relative to the chapter's overarching goal over the next 10 years. This section also describes some immediate steps that can be taken to achieve the research objectives.

## Implementation of the Strategic Plan

Successful implementation of the research objectives outlined in this Strategic Plan requires the collaboration of the multiple Institutes and Centers of the NIH, other government agencies represented on the DMICC, industry, and the diabetes research and voluntary communities. It is only through the involvement and collaboration of these different entities that research progress will be realized.

Although this document, which reflects current research advances and objectives, is necessarily "static," the strategic planning process is dynamic. Novel findings and new technologies can dramatically and positively change the course of planned research. Therefore, to be successful, this Strategic Plan must be periodically assessed by scientific experts in the type 1 diabetes research field, so that new and emerging opportunities can be identified. The DMICC will continue to serve an important role by assessing progress toward attaining the goals and objectives described in this Strategic Plan. The NIH will also continue to solicit input from the external scientific community through forums such as scientific workshops, conferences, and planning and evaluation meetings. This input will continue to be a valuable and necessary component of the NIH's strategic planning process for type 1 diabetes research.

## LOOKING FORWARD: FUTURE TYPE 1 DIABETES RESEARCH

Research efforts over the past several decades have led to tremendous improvements in the health and quality of life of patients with type 1 diabetes. The prognosis for newly diagnosed patients has dramatically improved compared to just a decade ago. While these improvements are positive, one thing remains certain: we are not there yet. People with type 1 diabetes still check their blood glucose levels, administer insulin, and develop life-threatening complications. It is imperative to build upon the strong existing research base to not only improve current treatment strategies, but also identify ways to prevent and cure the disease. Because of new and emerging technologies in areas such as genomics, imaging, and systems biology, there is great potential to make significant and dramatic improvements in the health of patients with type 1 diabetes in the near future. Thus, it is important to harness these technologies for type 1 diabetes research and to sustain and intensify the momentum that currently exists in the field. Achieving the specific objectives and making progress toward the overarching research goals outlined in this Strategic Plan will have an enormous impact on patients with type 1 diabetes, as well as on patients with other forms of diabetes and other autoimmune diseases.