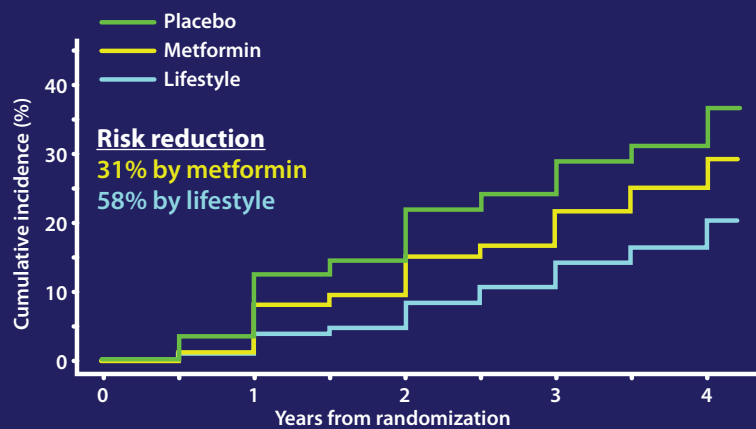


Incidence of Diabetes



The landmark Diabetes Prevention Program demonstrated for the first time that type 2 diabetes could be prevented or delayed in a diverse group of people at high risk, through lifestyle intervention—diet and exercise—or through use of the diabetes medication metformin. Now, people with pre-diabetes have hope that they may stave off diabetes and its complications. Going forward, clinical research and clinical trials should help open the door to new strategies to help people prevent or manage diabetes. (Image credits: Left image: The DPP Research Group, NEJM 346: 393-403, 2002. Right image: © iStockphoto.com/azndc)

CLINICAL RESEARCH AND CLINICAL TRIALS

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INTRODUCTION

Diabetes is a major independent risk factor for premature morbidity and mortality and a host of serious chronic disorders, including cardiovascular disease (CVD), eye and kidney disease, neuropathy, chronic pain, erectile dysfunction, cirrhosis, cognitive decline, bone fractures, and even cancer. To combat the burden of diabetes, a robust program of clinical research and clinical trials is necessary to identify new approaches to the treatment or prevention of diabetes and its complications, and to translate fundamental research advances into effective, practical, and sustainable therapies for use in clinical care.

Major advances in the past decade have identified the means to improve the care of people with diabetes, to prevent or delay onset or progression of disease, to ameliorate long-term complications, and to improve long-term health and quality of life. For example, the Diabetes Prevention Program and other clinical prevention trials have demonstrated that onset of type 2 diabetes—a disease which has reached epidemic proportions, accounting for the majority of the estimated 1.9 million new cases of diagnosed diabetes per year in the United States (1)—can be prevented or delayed. Major challenges now are to extend the period of time that individuals at risk of developing type 2 diabetes keep their blood glucose levels in the normal, healthy range, to improve translation of these findings into cost effective and sustainable clinical treatment strategies, and to make preventive measures as widely accessible and practical as possible. Similarly, while there is currently no way to completely prevent type 1 diabetes, recent clinical studies have demonstrated that the progression of new-onset type 1 diabetes may be slowed

by treatments that modulate the immune system and reduce inflammation.

During the past decade, new treatments have been developed for both type 1 and type 2 diabetes. For example, technical advances have led to devices for continuous glucose monitoring, and researchers are progressing toward development of a biomechanical “artificial pancreas” system that can maintain glucose levels in a healthy range with reduced risk of hypoglycemia. Recent advances in islet transplantation and the identification of drugs that enhance beta cell mass in animals raise hope for expanding human islet cell mass and restoring normal glucose control through cell replacement strategies. New drugs and new strategies for their use may improve the capability of achieving and maintaining an optimal range of blood glucose levels for longer periods after onset of type 2 diabetes. (These and other examples are described throughout this research plan.) Despite this progress, optimal initial therapy for diabetes is not known and comparative studies are needed to determine the relative efficacy of different approaches.

Diabetes is a heterogeneous disorder in its etiology, rate of progression, and propensity to develop complications. In the past several years, advances in genetics and genomics have identified regions of the genome associated with both type 1 and type 2 diabetes. Improved understanding of the genetic, physiologic, and environmental factors that underlie diabetes clinical heterogeneity may lead to more individualized treatment of people with the disease. Already the identification of specific mutations causing monogenic neonatal diabetes

has allowed affected infants to switch from insulin to oral medication with improved diabetes control. Better understanding of the pathogenesis of type 1 and type 2 diabetes could facilitate and enable the development of new medications and ways to prevent or postpone onset of diabetes. Novel discoveries about complex gene-environment interactions, including apparent modification of diabetes risk *in utero* and possibly during the early neonatal period, provide additional new opportunities for diabetes prevention, particularly for type 2 diabetes.

The past 15 years have also seen considerable progress in reducing both the acute and chronic complications associated with diabetes. Clinical studies, such as the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) and the United Kingdom Prospective Diabetes Study (UKPDS), have revealed that good glucose control is clearly of major importance in reducing the risk of microvascular complications. Assiduous glucose control also appears to be highly effective in reducing macrovascular complications in type 1 diabetes. Treatments to reduce hypertension, dyslipidemia, and other risk factors associated with macrovascular disease have been very effective in people with type 2 diabetes. Over several decades, these interventions have been shown to substantially reduce macrovascular complications, similar to results seen in people without diabetes. Unfortunately, even with these relative improvements, the pathogenesis of micro- and macrovascular complications remains poorly understood (see the chapter on “Diabetes Complications”). Moreover, people with diabetes remain at substantially higher risk for premature morbidity and mortality from cardiovascular disease.

While much has been learned about causes, prevention, treatment, and complications of diabetes, new clinical

research studies and clinical trials are necessary to gain more knowledge of the pathogenesis of diabetes and its complications—a key step in developing new ways to treat and possibly prevent diabetes and its related health problems. Already, following up on the landmark findings of the DCCT/EDIC and other advances, a major program of clinical studies is under way to prevent type 1 diabetes or improve its treatment in patients. A group of large clinical studies has been developed for this purpose as part of the research conducted with support from the *Special Statutory Funding Program for Type 1 Diabetes Research*. One of these efforts is the Type 1 Diabetes TrialNet, a collaborative, multi-center clinical research network established by NIH that is identifying individuals recently-diagnosed with type 1 diabetes or at high risk of developing the disease, and testing immunologic interventions to prevent diabetes or slow its progression. Improved understanding of the autoimmune process that destroys beta cells and causes type 1 diabetes to develop has led to the identification of drugs that selectively suppress the self-destructive immune response. Several early studies have been conducted in people with new-onset diabetes to assess the ability of selective immune modulation to preserve a patient’s own pancreatic insulin secretion. Early prevention studies are also under way. In the future, combination therapies aimed at suppressing multiple steps of the toxic immune response will hopefully produce clinically significant delay in onset and, ultimately, prevention of type 1 diabetes.

Because of the extensive ongoing, collaborative efforts of TrialNet and another NIH-supported effort, the Immune Tolerance Network, to prevent or ameliorate type 1 diabetes, many of the clinical research opportunities described here will focus on type 2 diabetes. However, this chapter will also identify future opportunities to test interventions for preventing

cardiovascular complications in people with type 1 diabetes. More work is needed to understand the unique components of CVD risk in these patients, and this topic is not addressed by the ongoing type 1 diabetes research program. Other clinical studies related to the treatment of type 1 diabetes are covered primarily in the chapters on “Type 1 Diabetes and Autoimmunity” and “Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia.”



Clinical research in diabetes can lead to new interventions to improve the public health. (Photo credit: Brand X Pictures/Getty Images.)

Encouragingly, the insights generated from studies in one form of diabetes may be applicable to improving treatment in the other major form of the disease. For example, efforts to understand and prevent glucose-induced damage to beta cells or to reduce micro- and macrovascular complications may lead to knowledge applicable to both type 1 and type 2 diabetes. Other efforts where research may benefit both of the major known types of diabetes include clinical studies of stimulating islet cell proliferation, preserving or restoring beta cell function, and intervening to reduce inflammation.

RECENT RESEARCH ADVANCES

In just the past decade, clinical investigators have made great progress in diabetes prevention and treatment, understanding disease etiology, and addressing diabetes complications. The following are some major examples of this research.

Type 2 Diabetes Can Be Prevented or Delayed:

Prevention of type 2 diabetes has been a research goal for decades, and diabetes investigators have made tremendous progress on this front. In the last 10 years,

randomized controlled trials of varying size have shown that application of a variety of interventions for approximately 3 years of time can reduce the short-to-intermediate-term incidence of diabetes by 30 to 60 percent. In the United States, the Diabetes Prevention Program (DPP) tested strategies to prevent or delay the development of type 2 diabetes in individuals at high risk. Lifestyle intervention, leading to moderate weight loss and increased physical activity levels, reduced

diabetes incidence by 58 percent and treatment with the drug metformin decreased the incidence by 31 percent, compared with placebo. The effects were similar for men and women and for all ethnic and racial groups. Of note, participants aged 60 years and older had a particularly robust benefit with lifestyle intervention, with 71 percent reduction in diabetes development. Other studies have shown that type 2 diabetes can also be prevented or postponed by treatment with medications, including acarbose, rosiglitazone, and pioglitazone. Some studies have shown that interventions that reduce diabetes development also have beneficial effects on CVD risk factors. Finally, several intervention studies have demonstrated regression or remission of impaired glucose tolerance to normal control of blood glucose levels in patients, raising the possibility that there may be some repair of beta cell damage in response to these interventions. It appears that these prevention interventions are also cost effective, at least in initial years. Collectively, these studies represent an important breakthrough that has made possible a new era of type 2 diabetes prevention.

Interventions Alter the Course of Gestational Diabetes: Gestational diabetes confers a very high risk of postpartum development of type 2 diabetes. Recent studies have shown that both intensive lifestyle and drug therapy reduce the short- and intermediate-term risk of progression to type 2 diabetes by about 50 percent. In pregnancy, diabetes and hyperglycemia at levels lower than those diagnostic for diabetes in the non-pregnant state often lead to serious obstetrical complications to the mother and infant. In addition, it has recently been recognized that gestational diabetes may have long-term adverse effects on the offspring of these pregnancies, including obesity during childhood and early onset of type 2 diabetes and other metabolic abnormalities. The adverse effects on the children have been most evident

among American Indians, who develop type 2 diabetes at younger ages, often during the child-bearing years. The incidence of gestational diabetes, however, is increasing in most ethnic groups, and the increased risk for type 2 diabetes in children is now also being seen in ethnic groups other than American Indians. Not only is the incidence of type 2 diabetes increasing in the United States, but so are rates of obesity among American women of childbearing age. Obesity predisposes to type 2 diabetes, including during pregnancy, and current trends will lead to more gestational diabetes if treatments are not found to prevent this condition and its consequences. This new understanding of the short- and long-term consequences of gestational diabetes offers special opportunities for intervention that may improve the health of both mothers and their offspring. A better understanding of the effects of short-term intrauterine exposure to hyperglycemia on risk of short- and long-term metabolic changes in the offspring will be a critical part of developing new, effective interventions.

Clinical Studies Reveal Potential Link Between Bariatric Surgery and Remission of Type 2

Diabetes: Small clinical trials suggest that bariatric surgery—surgery performed on the digestive tract to induce weight loss—may be an effective treatment for type 2 diabetes, at least in the short term. Studies have suggested that alterations in gut hormone physiology may contribute to these diabetes remissions independent of weight loss. While additional, larger, and longer-duration clinical studies with good follow-up rates are needed to clarify the long-term effects of bariatric surgery on diabetes, these findings have opened up a potential new avenue for therapy.

Understanding the gut hormone alterations following such surgery may lead to new insights into the etiology and treatment of type 2 diabetes and may enable

development of non-surgical treatments that achieve similar results.

Reducing Diabetes Complications: Clinical trials have identified treatments that can substantially reduce both micro- and macrovascular complications of type 1 and type 2 diabetes. The DCCT showed that near-normal glucose control through intensive insulin therapy significantly reduces or delays onset of microvascular complications in people with type 1 diabetes, when compared with then-conventional therapy. Similarly, the UKPDS demonstrated that therapies that lowered

be effective, laser photocoagulation has substantially reduced rates of blindness. Improved control of hypertension further reduces rates of microangiopathy. More recently, intriguing long-term benefits of early intensive glycemic control have been identified. The long-term follow-up of DCCT participants, the EDIC study, has shown a durable beneficial effect of initial intensified treatment on rates of both micro- and macrovascular complications. Of great interest is the observation that people in the intensively treated arm continue to have a lower rate of diabetes complications compared with people who were conventionally treated, despite the fact that the hemoglobin A1c (HbA1c) levels of both groups have converged following the end of the active treatment phase of the study. In addition, the 20 year follow-up of UKPDS participants has found a significant reduction in cardiovascular complications as well as preservation of the benefits on microvascular complications. These studies have had a profound effect on clinical care for people with diabetes.

Intensive Blood Glucose Control and Cardiovascular Complications of Diabetes:

Although there have been improvements in therapies to prevent and treat CVD, resulting in improved outcomes, people with diabetes continue to suffer worse outcomes than non-diabetic individuals. Moreover, diabetes accounts for a steadily increasing proportion of CVD burden both in the United States and worldwide. Thus, research has been aiming to identify the best ways to treat people with diabetes to prevent this life-threatening complication. Results from three recent large clinical trials attempting to prevent cardiovascular complications did not demonstrate a benefit of intensified glucose control (versus standard treatment strategies and blood glucose targets) on clinical CVD events in people with type 2 diabetes who generally had the disease for at least 5 to 10 years and had moderate to



Studying diabetes and its risk factors across generations, across the lifespan, and among diverse populations is important to finding ways to combat this disease and its complications. (Photo credit: © iStockphoto.com/digitalskillet)

average glycemia reduced microvascular complication rates in people with type 2 diabetes. In people with more advanced disease, where glycemic control may no longer

high risk for developing CVD. One of the studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, indicated that, in people with this particular clinical profile, standard treatment actually yielded lower mortality than more aggressive control aimed at lowering blood glucose levels to near normal levels. Of note, the incidence of CVD events was lower than anticipated in the conventional treatment arm, indicating that these studies may not have been able to detect additional cardiovascular benefit in an era in which lipid-lowering, blood pressure, and anti-platelet therapies already confer a substantial measure of protection.

The recent studies were conducted in people with moderate- to long-term diabetes duration who often had a substantial risk for—or a history of—CVD. These late prevention or secondary intervention studies could not address whether earlier interventions would be more effective. In support of this notion, the long-term follow-up of participants in the UKPDS trial suggests that good glucose control during the initial years after diagnosis of diabetes may have beneficial effects on CVD risk 20 or more years later. When results of several studies are combined, analysis of recent type 2 diabetes clinical trials suggests a moderate benefit of improved glycemic control on coronary heart disease, while subgroup analyses suggest greater benefits in primary prevention and recent-onset disease. Together, these findings have stimulated interest in investigating the benefits of early, more aggressive therapy at onset of hyperglycemia.

Potential Contributors to Diabetes Detected in the Human Genome: Genome-wide association (GWA) studies are playing an important role in the search for genetic contributors to complex diseases. In type 2 diabetes, five high-density GWA studies in populations of European origin, a follow-up meta-analysis, and several lower-density GWA studies in

multiple populations have been published recently. Many of the identified loci are associated with beta cell function or development, rather than with insulin sensitivity or resistance. The pace is comparable in type 1 diabetes, where many loci implicated in immune regulation have been associated with the disease. Genotype scores have been developed for prediction, risk stratification in clinical trials, and initial evaluation of pharmacogenetic approaches. The application of these new genetic tools and knowledge in clinical diabetes studies can provide new insights into the origins, progression, and treatment of disease. (See also the chapter on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications.”)



Clinical research and clinical trials are uncovering new ways to identify, prevent, and treat diabetes and pre-diabetes in the United States and around the world. Samples from large, federally-supported clinical trials are stored in repositories and made available to the broad research community to understand how and in whom interventions may have been effective. (Photo credit: National Institutes of Health.)

Treatment of Diabetes Comorbidities Through Control of Blood Pressure and Cholesterol: Many studies have demonstrated the importance of treating CVD risk factors in individuals with diabetes. Statin therapy to lower LDL-cholesterol reduces CVD in individuals with type 2 diabetes, as it does in those without diabetes. Improving control of hypertension

has beneficial effects on both micro- and macrovascular complications in individuals with either type 1 or type 2 diabetes. Most recently, the ACCORD Trial demonstrated that further reduction in blood pressure beyond current guidelines and targeting near-normal systolic blood pressure does not reduce cardiovascular events, sparing patients unnecessarily aggressive therapy. Data from the Framingham Heart Study indicate that the major reductions in CVD mortality seen in the general population over the past 5 decades have also been seen in people with type 2 diabetes. However, an analysis of data from more recent years

indicates that the benefits may be less in men with diabetes and may be deteriorating in women. Multiple rigorous studies demonstrate that substantial reductions in the risk of CVD can be achieved in people with diabetes using currently available clinical therapies. Clinical practice guidelines based on this compelling research have already led to improved outcomes in Americans with diabetes. Improved implementation of these research-proven therapies can yield further substantial reductions in morbidity and mortality associated with diabetes (see the chapter on “Clinical Research to Practice: Translational Research”).

KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the importance of clinical trials and observational studies in understanding and improving treatment of the numerous severe health problems caused by diabetes and its complications. In the intervening years, significant progress has been made in answering several key clinical questions, while others still pose major challenges. Despite reductions in risk, diabetes remains a leading cause of blindness and end-stage renal disease, and adults with diabetes still have a greater than 2-fold increased risk of cardiovascular complications than adults without diabetes (1). Projected increases in the number of older men and women and in the prevalence of obesity augur an even greater number of people living with pre-diabetes and diabetes in the coming decades. Without improved prevention strategies or treatments, diabetes will be responsible for a larger proportion of eye, kidney, and heart diseases in the U.S. population. At the same time, new opportunities to enhance clinical investigations, such as those offered by advances in genetics and genomics, as well as new drugs and new treatment strategies, have opened up. Because recent clinical trials have made it clear that proven benefits of diabetes interventions cannot always be simply extrapolated from one group of patients to another, there are also important ethical considerations in testing new treatments or treatment strategies for diabetes control that will need to be addressed in the design of new trials. Described below are research questions and opportunities to pursue in the next several years to reach the goal of improving clinical outcomes for individuals at risk for or living with diabetes. Clinical studies related to the treatment of type 1 diabetes are

covered primarily in the chapters on “Type 1 Diabetes and Autoimmunity” and “Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia.”

Preventing Type 2 Diabetes

The identification of clinically effective type 2 diabetes prevention strategies in the past several years has yielded both hope and a new set of challenges. The major challenge for prevention of type 2 diabetes is to translate the results from clinical trials into interventions that are cost effective and can be implemented and sustained in public health programs and in clinical care settings. Efforts to apply what has been learned are under way, but much more needs to be done to adapt, disseminate, and evaluate type 2 diabetes prevention programs widely in the United States, especially among high-risk populations, including minority populations and obese children and adults. To sustain such efforts successfully, it is important to understand how to change patient and health care provider attitudes and behaviors, as well as to develop improved understanding of type 2 diabetes pathophysiology, new drugs, and improved treatment strategies. Given the sustained participant effort required to achieve and maintain the lifestyle changes necessary to prevent type 2 diabetes and to treat it effectively, understanding patient behavior and motivating change will remain important for the foreseeable future.

Additional opportunities for study include interventions in pregnancy and early childhood to reduce or prevent environmental exposures that increase the risk of developing type 2 diabetes for the mother and her

offspring. Women with gestational diabetes are at greatly increased risk for the subsequent development of type 2 diabetes. In addition to the increased risk for the mother, it is now appreciated that exposure to the hyperglycemic intrauterine environment has adverse effects on the developing fetus, including an increased risk of obesity, type 2 diabetes, and other metabolic disturbances later in life. Preventing and treating gestational diabetes may be critical to break the vicious cycle of trans-generational diabetes transmission that has emerged.

Key Questions

- **How can strategies to prevent type 2 diabetes be effectively translated into practice, especially among high-risk populations?**
- **What are the optimal approaches for controlling glucose in women with gestational diabetes, to decrease their risk for subsequent development of type 2 diabetes and to improve pregnancy outcomes?**
- **Which approaches to glucose control in women with diabetes who are pregnant will prevent or reduce the risk of long-term metabolic consequences in the offspring of hyperglycemic pregnancies?**
- **Can improved understanding of pathophysiology from advances in genetics and of environmental risk factors for the development of type 2 diabetes over the lifespan be harnessed to develop more effective prevention programs?**

Future Directions

- **Conduct studies to understand better how to disseminate the results of clinical trials and promote diabetes prevention.**

A major obstacle to maximizing the benefits of what is already known about effective type 2 diabetes prevention is the lack of a “prevention culture” in society. Currently, most health care systems in the United States do not provide a reward structure to develop public-health-based diabetes prevention and complication reduction programs, and greater focus is needed on prevention efforts aimed at targets such as obesity. Projects demonstrating the feasibility and sustainability of prevention projects are essential, especially in high-risk populations. Research also is needed on how to tailor recommendations for diet and physical activity changes for individuals. To optimize translating what is already known, there need to be changes in public behavior, health care delivery, and the general environment. This goal is discussed in more detail in the chapter on “Clinical Research to Practice: Translational Research.”

- **Conduct clinical trials to test treatments to prevent or treat gestational diabetes.**

Although insulin has been the treatment of choice for women with gestational diabetes, small studies suggest that some oral hypoglycemic agents may be safe and efficacious. Larger studies are needed to evaluate the safety and efficacy of oral hypoglycemic agents in achieving normal control of glucose levels during pregnancy and whether any particular pharmacologic treatment is more efficacious in delaying or preventing the subsequent risks of type 2 diabetes in mothers

and offspring. In addition, studies are needed to understand whether behavioral interventions starting early in pregnancy to control pregnancy weight gain to recommended levels reduce the incidence of gestational diabetes or worsening hyperglycemia in the mother.

- **Conduct long-term studies to determine whether achieving good glycemic control in pregnant women with diabetes will prevent long-term metabolic sequelae in the offspring.**

Long-term studies are needed in well-characterized cohorts of pregnant women to understand weight and glycemic control targets (and how best to achieve them) that will prevent or reduce the development of obesity and type 2 diabetes in the offspring of women with diabetes.

- **Conduct epidemiologic studies to identify and characterize environmental determinants of diabetes over the lifespan.**

Diabetes clearly develops as a result of interactions between the environment and the genetic risk of the individual. Many of the characteristics of the environment that may increase the risk of developing diabetes are only poorly understood, including those that affect the developing fetus. Further studies expanding this epidemiologic approach do not fall in any one research area but require trans-disciplinary collaborations and would be very useful both to clarify risk factors and to monitor the current global diabetes epidemic.

- **Conduct studies to improve understanding of the special needs of older patients with diabetes.**

While many characteristics of diabetes are similar across the lifespan, the high frequency of serious co-

morbidities and the metabolic changes associated with aging may require modification of treatment plans in elderly patients with diabetes. More information is needed to determine whether high-risk subgroups can be identified so that more specific guidance can be provided for individualizing therapy. Additional clinical research studies needed for older adults with diabetes are described in the chapter on “Special Needs for Special Populations.”

Treatment

In addition to preventing or delaying the devastating complications of diabetes (see the chapter on “Diabetes Complications”), optimal treatment of diabetes will slow the loss of insulin production that is the hallmark of diabetes. Proof that intensified glucose control produces major reductions in microvascular complications of diabetes has stimulated the development of new drugs and treatment strategies for people with diabetes. However, these advances also highlight the importance of determining the optimal initial treatment of people with type 2 diabetes. Head-to-head comparisons of the newer agents are sparse and not of sufficient duration to provide guidance regarding optimal initial treatment. Moreover, existing studies have limited mechanistic data that might shed light on how to optimize therapy for any individual patient. In addition, to improve patient outcomes, studies are needed to understand how to improve patient adherence to treatment regimens, particularly in the context of a lifelong condition.

Evidence that both lifestyle and pharmacologic interventions can slow and even reverse the progressive rise of glucose levels in people at high risk for developing type 2 diabetes strongly suggests that such a benefit may also accrue to people with recently-diagnosed diabetes. Given the high incidence of type 2 diabetes, the lifelong burden of this disease, and the importance of cumulative

exposure to hyperglycemia in developing long-term complications, any intervention that slowed or reversed this disease once it was diagnosed could have a major impact on morbidity and mortality rates. In addition, among individuals with new-onset type 1 diabetes, preservation of limited residual insulin secretion appears to make long-term control of hyperglycemia less difficult to attain, reduces the risk of hypoglycemia, and reduces the development of long-term complications.

Key Questions

- **Are there approaches to the initial treatment of type 2 diabetes that will reverse or slow the decline in beta cell function that has been shown to occur over time?**
- **What is the optimal timing for diabetes interventions? Do specific treatments have maximum benefit at different stages of the disease?**
- **What genetic factors or other patient characteristics influence the choice of initial therapy for individuals?**
- **How can adherence to diabetes treatments be improved?**

Future Directions

- **Conduct studies to preserve endogenous insulin secretion or induce “remissions” of diabetes.**

The large prevention studies mentioned previously and numerous small studies in people with recent-onset diabetes suggest that it may be possible to preserve beta cell function during pre-diabetes and early in the course of type 2 diabetes. Whether and to what extent beta cell recovery is possible later in the course

of diabetes is unknown. Definitive studies of remission and prevention and delay of insulin secretory failure are needed. Mechanistic studies are necessary to understand why beta cells lose their ability to secrete insulin, as well as the physiology underlying recovery and preservation of endogenous insulin secretion, and to identify the most promising strategies to ameliorate the decline in secretion. The optimal timing of interventions needs to be established. If patients studied are at early stages of the disease process, it will take more patients/longer time to be able to evaluate success of interventions. Timing may be important, however, because limited data suggest that longer-duration patients may be less responsive due to more advanced beta cell dysfunction, perhaps secondary to deficits in cell mass. Studies will need to be done to determine whether preserving beta cell function translates into improved clinical care (e.g., improved ability to achieve target glucose levels or reduce the need for complex drug regimens) that can be sustained long enough to be clinically relevant. Finally, novel treatments are under development to stimulate islet neogenesis with potential to improve beta cell mass and function. Though promising, whether such therapies translate into clinically meaningful improvements in health outcomes is completely unknown and will require ongoing study.

In addition to their relevance to initial treatment of type 2 diabetes, studies of reversible insulin secretion defects may also be applicable in the treatment of people with type 1 diabetes and in islet transplantation, as they may identify ways to prevent or reduce hyperglycemia-related damage to beta cells and glucose sensing/insulin secretion control mechanisms. Additional studies are also needed to understand whether preserving residual insulin secretion in people with type 1 diabetes will reduce the risk of severe hypoglycemia and make it easier for them to achieve good glucose control.

► **Determine whether preventing or delaying diabetes can also delay or prevent the chronic complications of the disease.**

Given the relationship between glycemic exposure and the development of long-term complications, it seems intuitive that preventing or delaying diabetes could prevent or delay chronic complications; however, this relationship requires empirical demonstration. Answering this question will require long-term studies; therefore, ongoing clinical studies should be leveraged to examine this question. For example, long-term follow-up of the DPP cohort is focusing not only on glycemic outcomes, but on assessing both micro- and macrovascular complications, in order to answer this question. Similar opportunities should be explored in other large diabetes trials.

► **Evaluate the effect of bariatric surgery procedures on obesity, diabetes, and underlying pathophysiology.**

Rigorous comprehensive assessments of both the short- and long-term effects of bariatric surgery procedures on type 2 diabetes are needed to compare results across various surgical procedures and to determine the persistence of the reported benefits and whether they differ from results that can be achieved by medical interventions. In addition, such studies will provide opportunities for mechanistic explorations to improve understanding of the contributions of gut hormones to the pathogenesis of type 2 diabetes, and potentially lead to new treatment strategies.

► **Evaluate early effects and duration of action of commonly used anti-diabetic drugs for the initial treatment of early type 2 diabetes.**

Numerous drugs are available for the treatment of type 2 diabetes and all are generally effective in the short-

term. However, it is not known whether certain drugs or drug combinations will have more durable effects, particularly with respect to the maintenance of glycemic control. Comparative effectiveness studies employing direct head-to-head comparisons of drugs and treatment strategies will provide important information for assessing the health benefits as well as cost effectiveness of different treatments. A primary goal of such studies should be to design trials that will yield results that are easily translatable into sustainable clinical care.

► **Identify biomarkers.**

Identification of biomarkers (genetic or metabolic) that predict the likelihood of preserving insulin secretion will be important because the limited existing studies suggest there is considerable variability in responsiveness to treatments among individual patients. Studies also should employ new tools, such as *in vivo* imaging of beta cell mass, as they become available. Further development of measures that directly measure beta cell mass are particularly important because current methods to estimate beta cell mass *in vivo* are all linked to beta cell function, which appears to have both reversible and irreversible components.

► **Design well-powered, comprehensive clinical trials aimed at individualizing therapy of type 2 diabetes.**

Current clinical practice, as implemented in the recommendations of diabetes professional societies, uses a “one-size-fits-all” algorithm in which the choice of medications is generally based on duration of diabetes and level of glucose control. However, as noted, not all individuals respond to all drugs in the same way. The degree to which demographic, physiologic, or genetic variations alter individual responses to specific treatments is largely unknown. Clinical

trials should include pharmacogenetic studies to understand the importance of genetic variants and their interaction with other factors that influence response to therapy. Such studies will enable the development of more individualized therapies. (The role of genetic investigations is discussed in more detail in the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter.)

- ▶ **Examine the causes of and means of improving poor adherence to diabetes treatment regimens.**

The effective treatments of diabetes and its complications are complex, demanding, and expensive. Good long-term outcomes require a high level of adherence to lifestyle changes and medication regimens that is a challenge to most patients. Behavioral research to determine how adherence can be improved should complement studies aimed at simplifying treatment.

- ▶ **Describe the epidemiology of hypoglycemia.**

With efforts to intensify glucose control, hypoglycemia is an inevitable consequence and is often a treatment-limiting factor in trying to achieve glycemic levels known to decrease long-term complications. Data on frequency, severity, and consequences of hypoglycemic episodes occurring in clinical settings would enable estimation of trends and identification of ways to reduce the risks. Information is needed on whether new medications and treatment strategies are altering the risk. In addition, studies are needed to delineate the cardiovascular effects of hypoglycemia, particularly whether and how hypoglycemia may contribute to CVD events or sudden death.

- ▶ **Determine whether hypoglycemia unawareness can be prevented or reversed.**

The recognition that hypoglycemia unawareness increases the risk of severe hypoglycemic episodes highlights the need to develop strategies to recognize and to prevent or treat this condition.

Etiology of Diabetes and Its Complications

Diabetes is commonly described as a heterogeneous disorder that may have multiple causal factors. To date, however, other than the distinction between type 1 and type 2 diabetes and several relatively rare causes of hyperglycemia, distinct underlying causes have eluded discovery. There is also considerable heterogeneity in the course of the disease as it evolves from mild glucose intolerance to overt diabetes of increasing duration. Both genetic and environmental factors likely interact to cause the development and progression of hyperglycemia. Similarly, the course and development of long-term complications cannot be solely explained by the duration of exposure to hyperglycemia. Adding to the complexity of diabetes is the recognition that some individuals seem to have characteristics of both type 1 and type 2 diabetes. There may be some pathophysiologic processes common to both main types of the disease. Alternatively, the coincidence of autoimmune diabetes and the common genetic and environmental factors that underlie type 2 diabetes may lead to a clinical form of diabetes that is unique. The fundamental roles of inflammation and other processes that lead to beta cell dysfunction and destruction in both type 1 and type 2 diabetes need to be better understood and are discussed in the “Type 1 Diabetes and Autoimmunity” and “The Beta Cell” chapters. Similarly, further research is needed to identify diabetes genes and elucidate their role at a molecular level (see the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter). Clinical

studies on a number of fronts—particularly genetics, but also metabolism, effect of environment, and the interactions between these multiple elements—will be needed to fully elucidate the origins, development, and heterogeneity of diabetes and its complications.

Key Questions

- **Can genetic information improve disease prediction over currently available clinical markers?**
- **Can genetic information predict response to lifestyle or pharmacological interventions in disease prevention or treatment?**
- **Can genetic information predict the development of diabetic complications? For instance, do genetic predictors of hyperglycemia also influence risk of coronary heart disease?**
- **What are the etiologic factors that explain clinical heterogeneity and provide a rational molecular basis for disease taxonomy, particularly in type 2 diabetes?**
- **What are the mechanisms underlying the impact of intrauterine exposures or diet and exercise on the risk of developing type 2 diabetes?**
- **What is the impact of environmental exposures on the risk of developing type 1 diabetes?**
- **What is the role of sleep disturbances in increasing the risk of type 2 diabetes? What is the effect of treating obstructive sleep apnea in the prevention and therapy of type 2 diabetes?**

Future Directions

- **Continue to expand knowledge of the genetic basis for type 1 and type 2 diabetes.**
- **Continue to incorporate newly-discovered variants into genetic prediction models using existing prospective population cohorts.**

Several clinical prediction rules can be used to discriminate future risk of type 2 diabetes in an individual. These prediction rules have been derived and validated in various prospective population cohorts, such as the Framingham Heart Study, the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), and others. Many of these studies have collected DNA samples. Emerging genetic information should be applied to these cohorts as new type 2 diabetes-associated variants are discovered, to evaluate whether a genetic score can provide additional predictive information beyond that furnished by clinical risk factors. Similarly, these cohorts may be able to shed light on the particular stage of pathophysiologic progression (normal glucose tolerance ⇒ subdiabetic hyperglycemia ⇒ type 2 diabetes) at which each specific variant exerts its effect. Because of the modest effect sizes and relatively low number of incident cases, such studies are most likely to be productive via integration and collaboration.

- **Conduct studies to assess how environmental and genetic factors interact to produce type 2 diabetes and affect responses to interventions.**

Preliminary evidence suggests that the lifestyle intervention implemented in the DPP was equally effective in carriers of the risk genotype at each of two type 2 diabetes-associated loci as it was in individuals without these risk genes. Studies should be conducted to determine if this extremely hopeful message, by which one may overcome his/her inherited predisposition to this metabolic disease through healthy behaviors, can be extended to other genetic variants associated with type 2 diabetes. This can be done by integrating information from recent and current lifestyle intervention trials (e.g., DPP, Look AHEAD, and TODAY). Identifying the subset of patients for whom this intervention may be particularly effective, or those particularly resistant to weight loss, should help target preventive measures to the segments of the population most likely to benefit.

➤ **Identify factors that influence the evolution of type 1 diabetes.**

Although all individuals with type 1 diabetes have beta cell destruction and are dependent upon insulin treatment, there is considerable heterogeneity in the degree of residual beta cell function, prevalence of severe hypoglycemia, and the development of chronic complications. Research advances have made it possible to identify individuals who are genetically at high risk for developing type 1 diabetes prior to the onset of hyperglycemia. Long-term studies characterizing at-risk individuals in the pre-diabetic state (e.g., The Environmental Determinants of Diabetes in the Young (TEDDY) and the Trial to Reduce IDDM in the Genetically at Risk (TRIGR)) should be done to identify genetic, immunologic, and environmental factors that may influence the long-term clinical course of the disease (see also the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” and the “Type 1 Diabetes and Autoimmunity” chapters).

➤ **Harness genetic information to characterize individual susceptibility to diabetic complications.**

Data from prospective population cohorts (e.g., Framingham Heart Study, CHS, ARIC, Coronary Artery Risk Development in Young Adults (CARDIA) Study, and the Jackson Heart Study) and clinical trials (e.g., DCCT/EDIC, DPP, Look AHEAD, TODAY, and the ACCORD Trial) could be integrated to: 1) compile (or obtain *de novo*) phenotypes relevant to diabetic complications (e.g., with fundus photography and measurement of urinary albumin excretion, glomerular filtration rate (GFR), and cardiovascular outcomes); 2) evaluate whether current genetic predictors of hyperglycemia or diabetes are associated with specific phenotypes; and 3) discover novel genetic variants that underlie the pathophysiologic cascade leading to micro- and/or macrovascular complications.

➤ **Conduct studies to improve understanding of both the relative importance and the mechanism(s) by which sleep disturbances increase the risk of type 2 diabetes.**

➤ **Evaluate whether treating obstructive sleep apnea has an effect on the prevention and treatment of type 2 diabetes.**

The mechanism(s) underlying the relationship between sleep deprivation or disturbance and diabetes are not well understood. Sleep disturbances may contribute to difficulties in controlling hyperglycemia. The sleep disorder obstructive sleep apnea, in which there are momentary collapses or blockages of the airway during sleep, appears to be common in obese people with type 2 diabetes, and studies have shown that treating this condition with continuous positive airway pressure

(CPAP) improves both glucose control and blood pressure in these individuals. However, the direct role of sleep disturbances on risk of and control of hyperglycemia and the effects of treating sleep disorders need further study to separate sleep disorders from associated causes known to cause or worsen control of diabetes.

Complications

The past 2 decades have produced a major expansion of knowledge of the causes of the chronic complications associated with both type 1 and type 2 diabetes. A person with diabetes receiving optimal treatment today has a substantially better chance of postponing or avoiding chronic micro- and macrovascular complications than his/her counterpart of 20 years ago. Despite this substantial progress, however, the intensively treated patient with diabetes still has an increased risk of premature morbidity and mortality, and diabetes remains a leading cause of end-stage renal disease, vision loss in working age adults, and non-traumatic lower leg amputations in the United States (1). In addition, the attributable risk of diabetes as a cause of cardiovascular disease is increasing. More effective, safe, acceptable, and cost effective means of controlling the myriad risk factors for long-term complications must be developed and implemented in order to improve the health of persons with diabetes.

Key Questions

- **How does the pathophysiology of atherosclerosis differ in people with type 1 diabetes, in people with type 2 diabetes, and in non-diabetic populations?**
- **How important is insulin resistance in the development of macrovascular complications in people with type 1 diabetes?**

- **What are the principal mediators of atherosclerosis in people with type 2 diabetes and can specific targeted interventions be developed?**
- **How important is aggressive and sustained blood pressure and lipid lowering in reducing the risks of micro- and macrovascular complications in people with type 1 diabetes, and when should they be implemented in the course of the disease?**
- **What is the mechanism of the adverse impact of renal disease on CVD in individuals with type 1 and type 2 diabetes?**
- **Can reliable biomarkers of disease, including the long-term microvascular and cardiovascular complications, be identified to make clinical trials more efficient and guide therapy?**

Future Directions

- **Define optimal treatment to reduce CVD risk in people with type 1 diabetes.**

Studies are needed to determine whether the same CVD risk factors are operative in both type 1 and type 2 diabetes patients, and/or whether the relative importance of these risk factors may be different. A better understanding of risk factor attributable risks could change the optimal intervention strategy to reduce cardiovascular complications in people with type 1 diabetes. Such studies would examine the role of glycemia, as well as the contributions of insulin resistance, dyslipidemia, and hypertension, and determine optimal treatment targets for these comorbidities.

- **Assess the rate of development of atherosclerosis in people with type 1 diabetes and investigate which interventions will have the most salutary effects and when they should be applied.**

Studies are needed to understand the role, timing, and goals of interventions to lower lipids and blood pressure. For example, research is needed to determine whether statins should be used aggressively in all individuals with type 1 diabetes or in subgroups, and when therapy should be initiated. Current recommendations suggest that statins should not be used routinely in people with type 1 diabetes until age 40, and only then when additional risk factors are present. Many people with type 1 diabetes will have had diabetes for 25 or more years at that point. Studies are needed to determine if earlier therapy can prevent CVD or even microvascular complications. Similar questions exist regarding intervention for blood pressure elevations.

- **Examine the role of coagulation abnormalities as risk factors for CVD in type 1 and type 2 diabetes patients.**

Clot formation in blood vessels, or thrombosis, is a major factor in the development of clinical cardiovascular disease. In addition to its common association with well-known CVD risk factors, diabetes is often associated with hemostatic abnormalities, including elevated levels of certain factors (plasminogen activator inhibitor-1 and fibrinogen), which contribute to acute thrombotic events. Other, unidentified risk factors may contribute to CVD events, and the search for biomarkers of increased risk related to coagulation abnormalities remains essential. In type 1 diabetes, a somewhat different pattern of coagulation abnormalities may occur with a less certain effect upon CVD risk. Further assessment of the role of coagulation factor abnormalities in the pathogenesis

of CVD events is needed. This is particularly needed if measures of subclinical disease are planned to assess atherosclerosis in people with diabetes because differences within diabetic types and between diabetic and non-diabetic patients could alter the power of subclinical disease measurements in people with diabetes to predict clinical vascular events.

- **Assess how neuropathy contributes to unique CVD risk in people with diabetes.**

Studies have demonstrated that autonomic neuropathy can affect cardiac function and may be associated with serious cardiac arrhythmias. Studies are needed to understand better how diabetic neuropathy may contribute to morbidity and mortality in people with diabetes.

- **Examine the role of nephropathy in contributing to CVD in people with diabetes.**

Renal disease is a major risk factor for CVD and a major contributor to CVD morbidity and mortality in people with diabetes. Most people with end-stage renal disease (irreversible kidney failure) die of cardiovascular diseases, including myocardial infarction, congestive heart failure, and arrhythmias, with rates exceeding 10 times those of the general population. The risk is only partially explained by levels of traditional CVD risk factors, and studies to date have failed to demonstrate a benefit to statin therapy. Studies to improve understanding of the factors responsible for this major cause of death in people with type 1 and type 2 diabetes are necessary.

- **Develop surrogate end points and biomarkers that can be used in studying interventions to decrease vascular complications in diabetes.**

Given the lower incidence of type 1 diabetes and the cost and difficulty of following long-term clinical outcomes of interventions in this generally younger group, alternates to a hard end point clinical trial should be considered. Reliable biomarkers and surrogate outcomes will make clinical trials much more efficient. Studies are needed to validate such measures, because subclinical disease end points and biomarkers, while attractive, may be misleading if the results of interventions using surrogates diverge from results using hard CVD outcomes. Encouragingly, evidence of change in carotid intima-media thickness and the results of coronary calcification studies in the EDIC observational follow-up to the DCCT paralleled CVD outcome results in that patient group—suggesting that intervention studies using subclinical disease end points such as these could provide useful information on development

and progression of atherosclerosis and the relative importance of conventional and diabetes-related risk factors in people with type 1 diabetes.

► **Study the effect of glycemia and insulin resistance on cognitive function.**

Both hypo- and hyperglycemia have been associated with cognitive decline. Susceptibility to adverse cognitive effects may vary depending upon diabetes type, treatment, age, duration of diabetes, and many other factors. Identifying appropriate and efficient tools to measure cognitive function in people with diabetes will be essential to assess the magnitude of the problem and to identify ways to minimize cognitive decline. Collaborations between psychometric, imaging, and metabolic researchers should be encouraged.

IMPORTANCE OF RESEARCH GOALS AND STRATEGIES: HOW TRANSLATING RESEARCH OUTCOMES MAY LEAD TO IMPROVEMENTS IN HEALTH

Clinical research is both a testing ground and a wellspring for new discoveries that can improve the lives of people with diabetes. Determining the broad efficacy of diabetes treatments expands the options that clinicians can offer to people. At the same time, identifying specific therapies that are relatively more effective in identifiable subgroups of patients will make therapy more cost effective. Determining how and why diabetes progresses and takes its toll could open up new avenues for fundamental study and clinical pursuit. Results from prevention studies could help generate strategies to reduce the burden of diabetes and

its complications on future generations of Americans. Enlisting powerful new and emerging tools in genetics, bioinformatics, and other fields, clinical researchers and study participants can together work to overcome the multifaceted problem of diabetes and improve treatment, care, and prevention of this disease and its complications. Given the complexity of diabetes care now and in the foreseeable future, improved understanding of how to amplify adherence to effective treatments and prevention strategies is critical to realize maximal health benefits.

