

Extraordinary Opportunity:

Clinical Trials and Clinical Research of Critical Importance

The DRWG emphasized the importance of a substantial investment in clinical trials and clinical research to validate in humans fundamental observations made in test tubes, cells, and animals, and permit true testing of therapeutic strategies. While clinical research is essential for a comprehensive program for tackling major public health problems such as diabetes, the DRWG noted that a shortage of clinical investigators and the high costs, long-term nature, and complexity of clinical trials have limited clinical research in diabetes.

Since the issuance of the DRWG's Strategic Plan, the NIH has significantly expanded clinical research directed at advancing the prevention and care of diabetes. In particular, considerable work has been done to establish the clinical infrastructure needed to efficiently conduct large, long-term trials by creating national, multi-center research networks or consortia, as suggested by the DRWG. Many of these consortia provide opportunities for partnerships among the NIH, academia, and industry for collaboration and co-funding of clinical trials and for support of clinical research training in diabetes. They also provide for collection of biologic specimens for use in ancillary clinical research studies to address key questions of disease pathogenesis and mechanisms of response to therapies as well as opportunities for development and validation of surrogate markers that can be used to gauge the health of the patient before development of diabetes or its complications. The DRWG noted that such markers are particularly useful for prevention studies as they permit early detection of disease. The NIH has also been responsive to the DRWG's recommendation to achieve appropriate representation of high risk, but understudied, populations such as women and minority groups. This section of the report describes major new results achieved and new clinical research undertaken since issuance of the DRWG Strategic Plan, to address the prevention and treatment of diabetes and its many complications.

Major New Findings from Diabetes Clinical Research

PREVENTION OF TYPE 2 DIABETES IN PEOPLE AT HIGH RISK

The Diabetes Prevention Program (DPP) demonstrated that individuals at substantial risk of developing type 2 diabetes could prevent or delay disease onset and improve their blood sugar levels through modest improvements in diet and exercise. The DPP compared three approaches—lifestyle modification, treatment with metformin, and standard medical advice—in more than 3,200 individuals with pre-diabetes. On the advice of the DPP’s external data monitoring board, the trial ended a year early because the data had so clearly answered the main research questions. Importantly, the DPP, conducted at 27 centers nationwide, is the first major clinical trial to show that diet and exercise can effectively reduce diabetes in a diverse American population of overweight people with pre-diabetes. The lifestyle intervention, which targeted a 7 percent (or an approximate 15 pound) weight loss, and 150 minutes of walking or other moderate-intensity exercise per week, reduced the risk of getting type 2 diabetes by 58 percent compared to the control group, which received standard medical advice. The same study found that treatment with metformin also reduced diabetes risk, though by a less dramatic 31 percent, in people at high risk for type 2 diabetes. DPP participants ranged from age 25 to 85, with an average age of 51 years. Upon

entry to the study, all had pre-diabetes and were overweight. Minority groups who suffer disproportionately from type 2 diabetes—African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and Native Americans—made up 45 percent of those enrolled. The trial also recruited other groups known to be at higher risk for type 2 diabetes, including individuals age 60 and older, women with a history of gestational diabetes, and people with a first-degree relative with type 2 diabetes. Significantly, lifestyle modification worked equally well in men and women and in all the ethnic groups. It also worked particularly well in people age 60 and older, who have a nearly 20 percent prevalence of diabetes and who constituted 20 percent of the study population, reducing the development of diabetes by 71 percent in this subgroup.

In total, about 29 percent of the DPP standard group developed diabetes during the average follow-up period of three years. In contrast, 14 percent of the diet and exercise arm and 22 percent of the metformin arm developed diabetes. Long-term follow-up studies are under way to assess the durability of the DPP interventions in preventing or delaying diabetes and to determine whether the interventions reduce cardiovascular disease and atherosclerosis, major causes of death in people with type 2 diabetes. This approach will also provide important information on the clinical course of new-onset type 2 diabetes in this diverse study population.

An estimated 16 million Americans have pre-diabetes, putting them at increased risk for developing type 2 diabetes. The DPP findings, which establish that changes in diet and exercise can substantially reduce risk, represent a major step toward the goal of containing and ultimately reversing the epidemic of type 2 diabetes in this country. Moreover, every year that a person can live free of diabetes means an added year of life free of the burden of this disease and its associated micro- and macro-vascular complications.

► PREVENTION OF DIABETES COMPLICATIONS

The Epidemiology of Diabetes Interventions and Complications study (EDIC) is a ten-year, observational study that tracks participants of the landmark Diabetes Control and Complications Trial (DCCT) to determine the long-term outcome of intensive blood glucose control on micro- and macrovascular complications. The DCCT documented dramatic health benefits of intensive versus conventional treatment of blood glucose levels in 1,441 individuals with type 1 diabetes studied for an average of 6.5 years. In 1993, the DCCT was stopped early because of compelling evidence that intensive glycemic control significantly reduced the development and progression of diabetic eye, kidney, and nerve disease, and volunteers in the conventional treatment group were offered instruction in intensive treatment. Since then, glucose control has been very similar in the former intensive and conventional treatment groups. With participant retention at more than 90 percent, these volunteers are being followed to examine the continued effects

of a 6.5 year period of separation in glucose control on the development of diabetes complications. Strikingly, EDIC found that seven years after the end of the DCCT individuals who received intensive therapy during the trial continued to have a dramatically lower risk of complications than those who had been on conventional treatment. Taking as the new baseline state for EDIC the eye exams done at the end of the DCCT, researchers found that those in the former intensively treated group had a 62 percent reduction in progression of eye disease (retinopathy), seven years after intensive glycemic control was extended to the conventional group. These observations demonstrate that, not only is intensive management of blood glucose levels extremely effective in reducing the painful, debilitating, and costly complications of diabetes, but also that the benefits of intensive therapy persist for years.

► SUCCESS WITH ISLET TRANSPLANTATION

The dramatic findings of the DCCT/EDIC underscore the importance of near normalization of blood glucose in preventing the devastating complications of diabetes, such as blindness, kidney failure, amputation, and nerve damage. Yet, with the medicines and tools available, most patients with diabetes are not able to achieve this level of blood glucose control. Islet transplantation is one approach to achieving normal glucose control in diabetes, but for many years, fewer than 10 percent of patients receiving insulin-producing islets isolated from a donor pancreas became insulin independent.

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Recently, there has been tremendous progress with a modified approach to islet cell transplantation, developed by researchers in Edmonton, Canada. This approach has now been used in more than seventy people with poorly controlled type 1 diabetes and has improved control of diabetes in nearly all those studied and actually freed many from the need for insulin for as long as two years. This success has now been repeated at several centers, including the NIH, and is being tested in an international multi-center study to see if it can be more generally reproduced.

While tremendously exciting, these results do not yet represent the cure that everyone seeks for this disease. We do not know if complications will occur with long-term use of the immunosuppressive drugs needed to prevent rejection of

the islets, and, over time, some of the transplants have begun to fail. Also, should further studies be successful, we would not have enough islets for all the people who might benefit from this therapy, a problem being addressed through research discussed in the section of this progress report on “Autoimmunity and the Beta Cell.” Nonetheless, the encouraging initial clinical results have led to several initiatives to further develop this exciting therapeutic approach. These include new clinical trials involving alternate approaches to modulation of the immune system that may prevent rejection and recurrent autoimmunity with fewer side effects, development of a registry to track and compare results of trials undertaken at various sites, and support for pancreas collection and islet isolation centers to provide islets for future clinical trials.

Creation of Networks for Prevention and Treatment of Diabetes with a Focus on Children and Adolescents

Type 1 diabetes, formerly known as juvenile onset diabetes, is a devastating disease that can strike in early childhood, adolescence, or young adulthood. More recently, type 2 diabetes, traditionally viewed as a disease largely affecting older adults, has been reported with increasing frequency in children.

Data from many pediatric diabetes clinics suggest that type 2 diabetes has increased from less than 5 percent to 20 to 30 percent of childhood diabetes over the past decade, with particularly high rates among certain minority populations. The increase of type 2 diabetes in children and adolescents is

presumed to be a consequence of increased obesity and decreased physical activity. The NIH, together with the CDC, is conducting a major surveillance study in six representative areas of the country to determine the true incidence and prevalence of both types of diabetes in children.



Photo: NIDDK.

While serious at any age, the occurrence of diabetes in childhood is particularly troublesome because the complications of diabetes become more severe with the duration of the disease. Thus, adults who developed diabetes as children are at particularly high risk for the premature disability and mortality associated with diabetes. A study of Americans diagnosed with type 1 diabetes between 1950 and 1981 found death rates up to seven times higher than in the general population. New therapies have improved the prognosis for children with diabetes. One recent study found that death rates between 10 and 20 years after diagnosis for type 1 diabetes declined from 8.4 percent in those diagnosed between 1965 and 1969 to 3.5 percent in those diagnosed between 1975 and 1979. However, despite these improvements, new methods to treat and prevent childhood forms of diabetes are urgently needed.

▶ TYPE 1 DIABETES TRIALNET

A consortium of investigators, clinical recruitment centers, and core support facilities has been established to perform intervention studies to preserve pancreatic beta cell function in patients with new-onset type 1 diabetes and to prevent

type 1 diabetes in high risk individuals. TrialNet centers are completing the Diabetes Prevention Trial for Type 1 Diabetes, an ongoing clinical trial to determine if the use of oral insulin in non-diabetic relatives of persons with type 1 diabetes can delay the onset of diabetes. Furthermore, TrialNet will design and execute pilot and expanded studies of new agents to prevent or ameliorate type 1 diabetes as well as natural history and genetics studies in populations screened for or enrolled in these studies. Fourteen clinical centers and approximately 350 satellites and sites affiliated with these centers throughout the U.S. and Canada are participating in this consortium. The TrialNet will conduct studies in collaboration with the Immune Tolerance Network, a consortium of leading immunologists, that is focused on assessing methods to reprogram the immune system to reverse autoimmunity in a number of autoimmune disorders, including type 1 diabetes.

TrialNet will facilitate the rapid, preliminary testing of emerging therapeutic strategies for immunoprevention of type 1 diabetes; candidate agents will be evaluated to obtain safety and optimal dosage data. Those agents that prove most promising can then be quickly moved into larger-scale trials. To further leverage the resources supported by TrialNet, biological samples and other data collected from trial participants may be placed in repositories for use by many investigators. Importantly, TrialNet is formulating surrogate endpoints for diabetes and its complications. A surrogate marker is a reliable, easily measured biological event that can precede and predict the development of a disease or condition. The identification of informative markers could save time and costs in clinical trials of new treatments for diabetes.

ENVIRONMENTAL TRIGGERS OF TYPE 1 DIABETES

The NIH is creating a consortium of collaborating investigators to participate in the development and implementation of studies to identify infectious agents, dietary factors, or other environmental factors, which trigger type 1 diabetes in genetically susceptible individuals. Several independent population-based studies are under way to achieve this objective. Creation of the consortium will lead to a coordinated, multi-disciplinary approach to this complex problem, collection of information and samples in a standardized manner, and greater statistical power than can be achieved in smaller, independent studies. Clinical centers will recruit and enroll subjects, obtain genetic and other samples from newborns and parents, and prospectively follow selected newborns throughout childhood or until development of diabetes. The clinical research projects designed and implemented by this consortium will elucidate the environmental triggers and genetic interactions that initiate the autoimmune process and lead to diabetes.

With NIH support, American investigators are participating in an international “Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically-at-Risk” (TRIGR). This trial examines an intervention targeted at cows’ milk, one putative environmental trigger of type 1 diabetes. Newborns identified as being at high genetic risk for type 1 diabetes are being randomly assigned to receive either standard or modified cows’ milk formula. In the modified formula, the milk is treated to break its proteins into subcomponents in the hope that this will reduce the milk’s antigenicity. In addition to

testing whether modifying cows’ milk will reduce the development of diabetes, this trial will provide an opportunity for careful study of newborns at high risk for type 1 diabetes. It may generate important information about other factors that influence the development of diabetes with important implications for novel strategies to prevent type 1 diabetes.

NETWORK FOR TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS

The NIH has created a network of investigators to develop trials for treatment of type 2 diabetes in children and to develop and test interventions to reduce children’s risk of developing type 2 diabetes. The majority of children with type 2 diabetes are in the pre-adolescent or adolescent age range, a period that presents special challenges to health care providers and families when attempting to promote behavior and lifestyle changes. Prevention and treatment programs must also consider cultural differences among racial and ethnic groups that may influence acceptance of medical regimens. This is especially important for type 2 diabetes in children, which disproportionately affects minority populations.

In addition to those with frank diabetes, significant numbers of children may be at high risk of developing diabetes based on the presence of insulin resistance and blood glucose levels above normal but not as high as in diabetes. The Diabetes Prevention Program showed that lifestyle modification could reduce the development of diabetes in adults at high risk by 58 percent, but these results may not be directly applicable to

children. The Network for Type 2 Diabetes in Children and Adolescents is developing a prevention trial protocol that will focus on cost-effective, school-based interventions to decrease risk factors for type 2 diabetes and thus lower the incidence of this disease in children and adolescents. It is anticipated that the prevention strategies developed and tested will have the potential for broad, population-wide application.

To address its other major research goal, the Network will design trials to identify appropriate and effective treatment regimens for type 2 diabetes in children. The drugs currently available

for the treatment of this disease in adults have not been used widely in children. Treatment options, including lifestyle changes and pharmacologic therapy, need to be studied in this population to determine the most efficacious, safe, and cost-effective strategies to achieve and maintain near normal blood glucose levels in the pediatric age group. Such treatment strategies are essential for reducing the long-term progression to diabetic complications for those who were diagnosed with diabetes during childhood and are at particularly high risk due to early development, and therefore longer duration, of their disease.

New Trials Focus on Preventing Complications of Diabetes

While prevention of diabetes is a critical public health issue, prevention of the development of complications of diabetes in the 17 million Americans who already have diabetes is another compelling goal.

In addition to the seminal findings described previously about the reduction in eye, nerve and kidney complications that can be achieved with improved control of blood glucose, recent clinical trials have demonstrated other interventions, such as blood pressure and lipid lowering, to be highly effective in preventing onset or progression of complications. Notably, drugs that reduce the production or action of angiotensin, a hormone that acts on the blood vessels of the kidney, have been shown to dramatically reduce the rate of progression to kidney failure in people with the earliest signs of diabetic damage to the kidneys.

Two thirds of deaths in diabetes are due to premature cardiovascular disease, and rates of cardiovascular disease are elevated two- to four-fold in people with diabetes compared to the general population. While rates of cardiovascular disease are falling in the American population overall, this improvement is not seen in those with diabetes. Information on treatments that will reduce the increased risk of cardiovascular disease associated with diabetes is urgently needed and is the focus of several major new clinical trials supported by the NIH.

**LOOK AHEAD:
ACTION FOR HEALTH IN DIABETES**

We now know that weight loss can dramatically reduce the development of type 2 diabetes in those at high risk, but a benefit of weight loss in preventing complications in people with diabetes has not yet been established through clinical trials. Because support from health care providers for achievement of weight loss is costly, it is important to establish the benefits and the cost-effectiveness of weight loss in people with type 2 diabetes. To address this issue, the NIH is conducting the largest clinical trial to date to examine the long-term health effects of voluntary weight loss. This multi-center, randomized clinical trial will examine the consequences of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and increased exercise. Look AHEAD will focus on the disease most associated with overweight and obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease.

In June 2001, 16 Look AHEAD Clinical Centers and a Data Coordinating Center began the two and one-half year process of enrolling 5,000 obese patients with type 2 diabetes. Trial participants, who will be followed for up to 11.5 years, are randomly assigned to one of two protocols, the Lifestyle Intervention, which is designed to help participants achieve and maintain weight loss over the long term, or Diabetes Support and Education. Look AHEAD will primarily study the impact of these two interventions on major cardiovascular events: heart attack, stroke, and cardiovascular death. The trial also will investigate the effect of the interventions on other

cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include diabetes control and complications, fitness, general health, health-related quality of life and psychological outcomes. The cost and cost-effectiveness will be assessed for each of the two interventions.

**ACTION TO CONTROL CARDIOVASCULAR
RISK IN DIABETES (ACCORD)**

This randomized, multi-center trial is being undertaken by the NIH to study three key approaches to preventing major cardiovascular events in individuals with type 2 diabetes. The risk factors to be targeted in the ACCORD interventions are control of blood glucose, blood pressure, and lipid levels. Despite the two- to four-fold elevation of cardiovascular disease in the American population with type 2 diabetes, there is a lack of definitive data on the effects of intensive control of blood glucose on cardiovascular disease event rates in diabetic patients. ACCORD is designed to compare current practice guidelines with more intensive glycemic control in 10,000 individuals with type 2 diabetes, including those at especially high risk for cardiovascular disease events because of age, evidence of subclinical atherosclerosis, or existing clinical cardiovascular disease. More intensive control of blood pressure than is called for in current guidelines and a medication to reduce triglyceride levels and raise HDL (good) cholesterol levels will also be studied in subgroups of these 10,000 volunteers. Each treatment strategy will be accompanied by standard advice regarding lifestyle, including diet, physical activity, and smoking cessation, appropriate for diabetic individuals.

The primary outcome that ACCORD will measure is the first occurrence of a major cardiovascular disease event, specifically heart attack, stroke, or cardiovascular death. In addition, the study will investigate the impact of the treatment strategies on other cardiovascular outcomes, total mortality, limb amputation, eye, kidney, or nerve disease, health-related quality of life, and cost-effectiveness. Volunteers will be treated and followed for four to eight years at approximately 60 clinical sites associated with seven clinical center networks in the U.S. and Canada.

Although several clinical trials have examined optimal management of blood pressure in type 2 diabetes, this issue has not been examined through clinical trials in type 1 diabetes. Since different mechanisms may underlie the increased risk of cardiovascular disease in the two forms of diabetes, it is important to establish optimal practices for prevention of cardiovascular disease for each.

▶ **BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION IN TYPE 2 DIABETICS TRIAL (BARI 2D)**

This multi-center clinical trial will compare medical versus early surgical management of patients with type 2 diabetes who also have coronary artery disease and stable angina or ischemia. At the same time, BARI 2D will study the effect of two different strategies to control blood sugar—providing more insulin versus increasing the sensitivity of the body to insulin—on risk of cardiovascular mortality and morbidity.

A total of 2,800 patients, both men and women, are being entered into BARI 2D at 30 clinical centers. Upon enrollment, study volunteers are

randomized to receive medical therapy or either angioplasty or bypass surgery and, simultaneously, are randomly assigned to an insulin-providing or insulin-sensitizing strategy of blood glucose control. Patients in both groups will be followed for five years with aggressive management of risk factors. The primary trial outcome is total mortality; also, secondary outcomes such as cardiac mortality, heart attack, angina, and quality of life will be examined.

▶ **TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)**

NASH is a chronic liver disease involving fat accumulation (steatosis) and inflammation in the liver. The cause of NASH is unknown but it is associated with diabetes, obesity, and insulin resistance. Liver cirrhosis, which may progress to liver failure, ultimately requiring liver transplantation, occurs in 10 to 15 percent of patients with NASH and significant liver scarring in another 30 percent. Currently no effective treatment exists for patients with this disease. To accelerate research on this poorly understood disease, the NIH has created a NASH Clinical Research Network. This group will study the causes, contributing factors, natural history, complications, and therapies of NASH; develop common definitions, nomenclature and terms for the diagnosis and staging of NASH; and generate preliminary data for further investigator-initiated research. In a pilot clinical research study of patients with NASH, researchers will investigate the effectiveness of pioglitazone, a new diabetes medicine that increases sensitivity to insulin, on improving liver function. If pioglitazone therapy is safe and appears beneficial in improving liver disease in these patients, then a larger, controlled clinical trial will be planned.

TREATMENT OF DIABETIC EYE DISEASE

A clinical research consortium will examine new therapies for diabetic eye disease and conduct a pilot clinical trial in patients with diabetic macular edema, a common complication in patients with diabetes. The pilot study will compare two methods of laser therapy as well as the value of vitamin E and aggressive lipid lowering in preventing eye damage in the setting of laser therapy. In diabetic eye disease, blood vessels in the retina become leaky and the retina swells. The macula—the center part of the retina that is responsible for fine vision—may also swell and cause vision loss. Laser therapy reduces leaking from blood vessels in the retina and its value is well established in reducing vision loss in patients with diabetic retinopathy. However, traditional laser treatment causes scarring that can adversely impact vision, particularly in the critical macular area, despite its overall benefit in preserving vision. A different type of laser has been shown to have no such adverse effects in short-term studies but long-term effects of this treatment are unknown. In a pilot study, forty adult patients with either type 1 or type 2 diabetes and macular edema will be randomly assigned to receive one of the two laser treatments and either vitamin E or a placebo. Subjects with high cholesterol may also be randomized to either conventional or more aggressive treatment to lower these levels. This pilot study is an important first step in planning a large multi-center clinical trial to evaluate medical and laser approaches to improving the visual outcome for patients with diabetic retinopathy.



To detect diabetic eye disease, the doctor uses an ophthalmoscope to examine the light-sensitive tissue at the back of the eye called the retina. He looks for early signs of disease, such as: (1) leaking blood vessels, (2) swelling, (3) pale, fatty deposits on the retina—a sign of leaking blood vessels, (4) damaged nerve tissue, and (5) abnormal blood vessels.
Photo: National Eye Institute.

SLOWING OR PREVENTING DIABETIC NEPHROPATHY

Many patients with diabetes develop progressive renal disease even when they adequately manage their blood sugar and receive the most effective known therapy for diabetic nephropathy. Thus, new strategies to prevent and slow progression of diabetic nephropathy are desperately needed. Pilot clinical trials will test the ability of new agents or drug combinations to slow or prevent progressive kidney disease. These trials will use blockade of the renin-angiotensin system (RAS) as the current standard of care and examine either addition of alternate agents or incremental effects of RAS blockade. Recruitment will focus on patient populations in young- to mid-adulthood, with a strong representation of patients with type 1 diabetes. If successful in small-scale clinical trials, these therapies will then be tested in large phase III interventional trials.

Translating the Results of Clinical Research into Clinical Practice

The past few years have seen encouraging progress in development of effective new treatments for diabetes. Now, a key challenge is to ensure the American people benefit from what researchers have discovered.

One approach to this challenge is education—dissemination, to those at risk and their care providers, of information about measures proven effective for treating type 1 and type 2 diabetes and for preventing type 2 diabetes in individuals at high risk for this disease. However, providing information alone is not sufficient to translate what we know into practice. We need to develop

methods to take interventions that have been demonstrated to be beneficial in careful clinical investigations, and extend or adapt them to larger populations or other settings. There is also increasing recognition that behavioral factors play a major role in the increased prevalence of obesity and type 2 diabetes and in the management of diabetes and its complications.

▶ BEHAVIORAL RESEARCH—KEY TO PREVENTION AND TREATMENT OF DIABETES

Recent clinical trials have provided definitive evidence that type 2 diabetes can be prevented with lifestyle change and that rigorous control of blood glucose, blood pressure and lipid levels can delay or prevent diabetes complications. Yet, this control can be arduous—requiring adherence to a complex regimen of medications, diet and physical activity—and it is optimal in very few Americans with this disorder. The DRWG recognized the importance of understanding the health-related behaviors that contribute to the risk of diabetes and diabetes

complications and the critical need to apply this information to develop behavioral interventions that can produce sustained changes. In response to the DRWG's scientific recommendations, the NIH has acted to stimulate application of behavioral science to diabetes through multiple initiatives. One solicitation called for research related to sociocultural, environmental, and behavioral mechanisms that contribute to successful self-management of diabetes. A subsequent solicitation specifically addressed diabetes self-management in the minority populations who are disproportionately affected by diabetes

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and its complications. A broader NIH-wide solicitation addressed the clarification of disease-relevant social and cultural factors and the linking of behavioral research to practices for improved prevention and treatment. More targeted research has focused on the role of psychological disorders — such as depression and eating disorders — on the risk of developing diabetes and its complications. People with diabetes have twice the rates of depression seen in the general population; moreover, people with depression have increased prevalence of diabetes. An NIH conference focused on research issues in depression in diabetes and other selected chronic diseases; this was followed by a solicitation to increase research on the relationships among depression, eating disorders, diabetes and obesity, and to explore how treatment of psychological disorders may improve outcomes in diabetes.

▶ NATIONAL DIABETES EDUCATION PROGRAM (NDEP)

The National Diabetes Education Program (NDEP) is a collaborative initiative of the NIH and the CDC that uses over 200 public and private partnerships to promote, through education, routine clinical application of the therapies and other activities that have demonstrated value in the prevention of diabetes and its complications. A key feature of this program is the participation of individuals who represent communities such as African Americans, Hispanics/

Latinos, Native Americans/Alaska Natives, and Asian and Pacific Islanders who are disproportionately affected by diabetes. Among its many educational efforts, the NDEP is the primary mechanism for translating the striking results of the DPP into real health improvements for the public. The NDEP and its partners will promote clinical recommendations for health care providers and consumer information for people at risk of developing diabetes so that they will know what these findings mean to them and what steps they can take to reduce their risk. By mobilizing its partners at the national, state, and local levels, the NDEP will use the important, science-based diabetes prevention findings of the DPP to help reverse the rising tide of diabetes in this country.



Photo: NIDDK.

▶ NIH EDUCATION PROGRAMS TARGET DIABETES COMPLICATIONS

The NDEP also plays a central role in dissemination of information about prevention of complications. Its new campaign, “Get Smart About Your Heart: Know the ABC’s of Diabetes,” is focused on increasing awareness of evidence-based guidelines regarding targets for hemoglobin A1c (a measure of glycemic control), blood pressure, and cholesterol in patients with diabetes. Complementary campaigns of the National Cholesterol Education Program and the National High Blood Pressure Education Program also promulgate guidelines for patients with diabetes, based on data that people with diabetes and no known heart disease are at the same degree of risk for heart attack and other cardiovascular events as people without diabetes who have had a heart attack. We now know this risk can be reduced with aggressive management of risk factors but very few people with diabetes are taking all of the steps that have been proven effective in reducing their risk of cardiovascular disease. Because diabetes is the leading cause of kidney failure and blindness in the U.S., moving into practice therapies proven to reduce the risk of these diabetes complications is a major focus of the NIH’s new National Kidney Disease Education Program and the National Eye Health Education Program.

▶ TRANSLATIONAL RESEARCH FOR THE PREVENTION AND CONTROL OF DIABETES

Sadly, advances from “gold standard” clinical trials on therapy of diabetes and prevention of its complications have not been successfully incorporated into general health care practice. Underutilization of current knowledge was highlighted in a recent study of individuals with diabetes that demonstrated a low frequency of self-monitoring of blood glucose, good glycemic control, regular foot care, and ophthalmic examinations, all of which markedly reduce the development and progression of diabetic complications. With the demonstration that modest lifestyle changes can dramatically reduce the risk of developing type 2 diabetes in high risk individuals comes the imperative to develop both population-based and clinic-based strategies to establish cost-effective programs to identify individuals at high risk who could benefit from prevention programs and/or successfully promote lifestyle change. Additional research is also needed on improved methods of health care delivery to patients with diabetes and to compare the effectiveness and use of different clinical practices, interventions, and technologies in particular population subgroups. These opportunities are being explored through new Diabetes Prevention and Control projects.

Opportunities to Answer Important, Remaining Questions

The DRWG noted that, compared to other common diseases that impact dramatically on public health such as hypertension and cardiovascular disease, relatively few trials have been carried out in diabetes, where age-adjusted disease mortality has risen by epidemic proportions. Since the DRWG report was issued, there has been progress in expanding both the number of clinical trials and the infrastructure to conduct clinical research in diabetes. Already, we have garnered important new information from recently completed clinical trials. From newly begun studies, we anticipate a further expansion of knowledge that will greatly improve therapy for people with diabetes or at risk for this disease.

However, many important questions remain to be answered about prevention of diabetes and its optimal therapy. For example, trials comparing the various classes of drugs available for treating type 2 diabetes could define optimal initial glyce-mic therapy that might preserve the function of the insulin-producing beta cell and optimal glyce-mic therapy to prevent cardiovascular disease. Studies in multiple populations could determine how optimal therapy may differ for people with onset of type 2 diabetes in youth or older age, or in different racial and ethnic groups. Much could also be learned through the implementation of common outcome measures in medical studies across different cultures and environments. Many questions remain about optimal management of lipids and blood pressure and use of antioxidants and anti-inflammatory agents in people with diabetes, and how these may differ for those with type 1 or type 2 diabetes. The optimal glyce-mic target for type 1 diabetes in pre-pubertal children remains to be defined as does how to maximize implementation of intensive therapy for type 1 diabetes.

Evidence-based medicine from clinical trials needs to be translated into clinical practice in a rigorous, science-based manner across various models of health care delivery systems. Approaches to the study of improved outcomes in clinical settings might include trials in which physician groups or other care providers are randomized. A critical need is for development of low-cost ways to influence patient and provider behavior.

A key area of clinical research relates to the patho-physiology and natural history of obesity. We would like to understand how some people stay thin in an environment in which most Americans are over-weight and to know more about how and why body weight changes occur during particular times, such as puberty and menopause in women. Information is also needed on the relationship between risk of diabetes and particular patterns of weight gain or particular stage of life in which weight gain occurs. Weight loss maintenance strategies are critically important and should be developed in coordinated studies in which approaches can be evaluated with common endpoints.

New technologies will create major new oppor-tunities for clinical trials and clinical research. These include development of continuous and/or non- or minimally-invasive methods for measuring blood sugar; development of new approaches for gene therapy; development of new methods to grow, harvest, or encapsulate islets; development of new approaches to modulation of the immune system; development of new technologies for meta-bolic assessment; progress in the application of genomic, proteomic and other approaches to pheno-type and identify subgroups of patients who might benefit from particular therapeutic approaches; and development of reliable biomarkers of disease, imaging technologies, and surrogate markers reflecting clinical outcomes.

Story of Discovery

On the Road to a Cure: From Identification of Insulin to Islet Transplantation

A major milestone in the quest for a cure for type 1 diabetes is recent progress in the transplantation of pancreatic islets, the body's precious insulin-producing factories. While scientists have attempted islet transplantation for years with little success, a new, significantly-advanced procedure is showing promise in preliminary trials with a small number of patients. Following islet transplantation, many patients have remained free from the need for daily insulin injections to control their blood sugar for as long as two years — providing “proof-of-principle” that replacing lost or damaged islets may be sufficient to restore normal insulin-regulation of blood sugar levels in patients with diabetes. These encouraging results reflect a coalescing of scientific ideas and insights painstakingly accumulated over decades of basic and clinical biomedical research, from the initial discovery that type 1 diabetes results from a defect in pancreatic insulin production, to more recent advances in transplantation and modulating the immune system.

A major insight into the causes of diabetes came in 1889, when researchers who removed the pancreas of a dog found that the dog developed severe diabetes. Spurred by this finding, another group of scientists developed a way to extract from pancreatic tissue a substance that could treat diabetes — insulin. This research dramatically changed the lives of people with type 1 diabetes, for whom the onset of disease, generally in childhood, had once meant imminent death. Insulin could now be administered to patients to lower the dangerously high blood glucose (sugar) levels characteristic of this disease. For their discovery and purification of insulin, the scientists won the Nobel Prize.

Several decades later, recombinant DNA technology revolutionized biological science and led to significant improvements in the treatment of type 1 diabetes. Previously, cow- and pig-derived insulins were the only sources of this therapy. Although these animal insulins were highly effective, they sometimes produced side effects, such as allergic reactions. Now, with recombinant (genetically-engineered) human insulin, researchers could diminish these side effects. Subsequent research led to the development of insulin with improved characteristics. These include quick-acting formulations that can be taken with a meal to bring down blood sugar levels rapidly, and long-acting forms that give steady control over glucose levels throughout an entire day. Additional technological advances have also affected the lives of people with diabetes. A recent NIH-supported study found that improved long-term survival for patients with type 1 diabetes roughly correlated with the introduction of glucose self-monitoring devices, better methods of assessing glucose control, and advances in blood pressure therapy in the 1980s.

While insulin therapy has dramatically extended and improved the lives of patients, it is a treatment, not a cure, and its success requires both extreme vigilance in monitoring blood glucose levels and daily doses of insulin. The critical importance of intensive therapy, guided by frequent glucose monitoring, was demonstrated in the landmark Diabetes Control and Complications Trial, an NIH-supported study. This study showed that intensive glucose control dramatically reduces the risk of microvascular complications of diabetes, including diabetic retinopathy (eye disease),

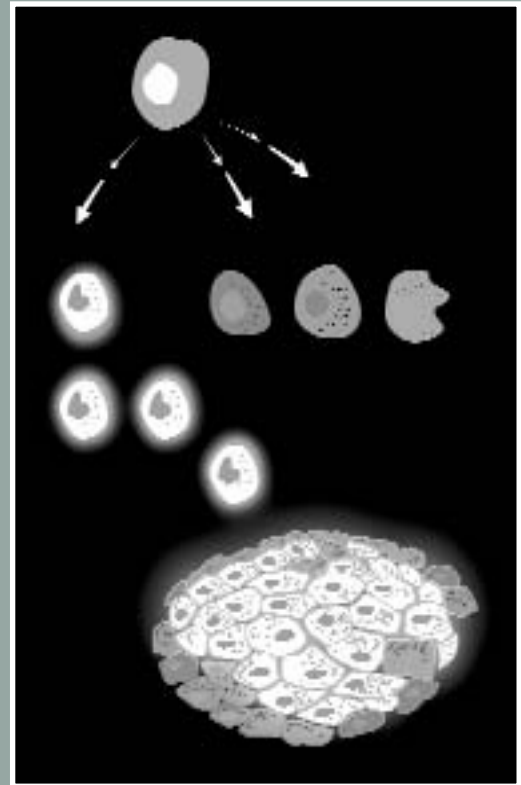
Story of Discovery

nephropathy (kidney disease), and neuropathy (disorders affecting nerve function). A follow-up study to the DCCT showed that the limited period of improved glucose control during the trial yielded benefits that persisted long after the trial ended, with dramatic reductions in complications of diabetes continuing for at least seven years. However, this intensive insulin therapy was also associated with an increased risk of severe hypoglycemia, dangerously low blood sugar. Because of the burden and difficulty of trying to maintain optimal blood glucose control with externally-supplied insulin, researchers have redoubled their efforts to search for a cure — a transplant that would allow people with diabetes to make their own insulin. This proved to be a far greater challenge than originally imagined.

As one method for trying to cure diabetes, doctors can transplant an entire pancreas into a diabetic patient. Since this procedure is technically demanding and poses significant risks to the patient, it is usually limited to people who are undergoing a simultaneous kidney transplant. The idea of transplanting only the islet cells of the pancreas, a potentially simpler procedure, arose a number of years ago. Islets are little clusters of cells that contain insulin-producing cells. In 1972, an NIH-supported scientist first reported that islet transplantation could cure diabetes in rats. Until recently, however, attempts at islet transplantation to help patients with diabetes fared poorly.

The success rate for islet transplantation has now improved dramatically. Drawing upon lessons learned from extensive, previous research, a group of scientists in Edmonton, Canada, devised a new procedure for islet transplantation and published very promising results. Research conducted and supported by the NIH, including the initial islet transplant studies in rats, as well as other important discoveries, had laid important groundwork for the Edmonton advance. For example, islets require very delicate handling, but after years of experimentation, researchers improved islet isolation techniques and ways to assess islet function. An NIH grantee refined the method for isolating islets from pancreatic tissue so that larger numbers of human islets could be obtained from donor pancreata.

Another avenue of research, the investigation of drugs that modulate the immune system, also contributed to the success in Edmonton. The body's immune system is designed to attack foreign invaders, such as viruses and bacteria. Unfortunately, however, the immune system can also perceive transplanted cells and organs from a donor as foreign,



The stem cell has the potential to develop into all the cell types that make up an islet, including the insulin-producing beta cells. Research to find ways to coax stem cells to become islets could remedy the current shortage of human islets for transplantation. Illustration: Donald Bliss, Medical Arts and Photography Branch, NIH.

On the Road to a Cure: From Identification of Insulin to Islet Transplantation

and attack these too. This problem has long plagued the field of transplantation research, because agents that suppress the immune system to prevent transplant rejection could also leave a patient more vulnerable to infection and other complications. An added layer of complexity exists in type 1 diabetes, as the underlying cause of the deficiency in insulin production is an immune system gone awry. The immune cells of people who develop this disease mistakenly attack and destroy the body's own insulin-producing beta cells in the islets. Many of the islet transplants attempted previously had used glucocorticoids as immunosuppressive agents, but research suggested these agents could be particularly problematic. The Edmonton researchers thus developed a glucocorticoid-free immunosuppressive strategy with several different immunosuppressive agents, including a substance called FK-506, now known as tacrolimus. An NIH-supported scientist, who is one of the world's premier liver transplant researchers, had pioneered the use of FK-506 years earlier to prevent immune rejection of transplants.

In the year 2000, 50 years after President Truman established the NIH Institute that encompassed diabetes research in its mission, scientists at the NIH replicated the Edmonton protocol, successfully transplanting islets into a patient suffering from type 1 diabetes. The procedure that had worked so well in Canada is now showing great promise in helping people in the U.S. with type 1 diabetes become free from the need for externally administered insulin.

While success has not been universally attained for every islet transplant patient, and only a small number of patients have as yet undergone this procedure, the results from the islet transplant trials are far better than had been achieved previously, with many patients remaining off insulin for more than a year thus far. Several others, while not completely insulin-independent, have gained more control over their disease. Based upon this evidence, researchers are cautiously optimistic that these patients may be able to maintain normal or near-normal insulin regulation of blood glucose levels for a prolonged period of time.

With the hope that ongoing and planned islet transplantation clinical trials will continue to show promise, scientists are exploring new ways to surmount additional challenges. Given the potential risks of long-term suppression of the immune system, scientists are investigating novel immunosuppression methods. Clinicians also continue to monitor patients carefully to evaluate other risks and side effects associated with the transplant procedure. Additionally, this procedure is currently being tested only in adults; it is not yet ready for trials in children. Finally, before islet transplantation could ever become standard clinical practice, a sufficient supply of pancreatic islets will need to be available. Currently, there is a severe shortage of donor pancreata. Further compounding this problem is that the Edmonton protocol requires more than one pancreas. Researchers are vigorously pursuing several strategies for increasing the supply of islets, including genetically-engineering other types of cells to produce insulin, and exploring the potential for coaxing adult and embryonic stem cells to become islet cells.

From the injections of insulin that provide a transient—but life saving—treatment for diabetes, to the infusions of islet cells that now show promise for becoming a cure, progress in diabetes research has been achieved through incremental advances in knowledge in a diversity of scientific fields. Both basic scientists and clinical investigators continue to intensify their efforts to improve the lives of people with diabetes, with the ultimate goal of curing this disease.

PATIENT PROFILE: Sigrun Schwendinger

ISLET TRANSPLANTATION HOLDS HOPE FOR TYPE 1 DIABETES PATIENTS

Sigrun Schwendinger lived with type 1 diabetes for 50 years. Diagnosed at age 7, she took insulin daily to keep her blood sugar levels within normal range—and to stay alive. Today, at age 59, Sigrun is insulin-free, thanks to a revolutionary new treatment originally developed by researchers at the University of Alberta in Edmonton, Canada, and now reproduced by a team at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institutes of Health (NIH) Clinical Center. Commonly referred to as the “Edmonton protocol,” the procedure centers on the infusion of insulin-producing beta cells found in clusters called “islets” within the pancreas. The islets are extracted from the pancreata of deceased donors and then transplanted into patients with type 1 diabetes, who then are treated with an experimental combination of immunosuppressive drugs. So far, only a few people worldwide have undergone this experimental yet promising new transplant technique. Because the approach is highly experimental, only adults with severe diabetes are currently eligible to participate in this research; the research protocols do not admit children.

Sigrun underwent the procedure at the NIH Clinical Center in December 2000 and is the first person in the U.S. to have been transplanted using the new protocol. Shortly after the procedure, Sigrun said, “I feel extremely fortunate that I qualified for this protocol, and that my prayers of years ago to be insulin-free have been answered.”



Sigrun Schwendinger was the first U.S. patient to receive an islet transplant based on a protocol pioneered by a team of scientists in Edmonton, Canada. Since February 2001, the transplanted islets are producing enough insulin to free her from daily insulin injections.

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Today, nearly two years after having her transplant, Sigrun remains insulin-free. However, she says she is experiencing negative side effects as a result of the anti-rejection drugs she takes. These side effects include higher blood pressure, anemia, low white blood count, swelling of her ankles, and a tremor of her hands, conditions that did not exist prior to her undergoing the procedure. The fact is, islet transplantation using the new protocol is still very much in its infancy, and no one knows what the outcomes will be five, ten, or twenty years from now for people who undergo the procedure today. But scientists both at the University of Alberta in Edmonton, Canada, and the NIH remain hopeful that the new islet cell research may eventually lead to more

effective treatments not only for type 1 diabetes patients, but for some type 2 diabetes patients, as well. They are also hopeful that researchers will develop better means to prevent the immune system's rejection of transplanted tissue, so that transplant recipients will not face a lifetime of harsh, immunosuppressive drugs.

An estimated one million Americans suffer from type 1 diabetes; an additional 16 million have type 2.

LIVING WITH DIABETES

Type 1 diabetes results when the body's immune system destroys the pancreatic insulin-secreting beta cells that control blood sugar (glucose) levels. As a result, people with type 1 diabetes fight a constant battle to keep their blood glucose levels from going too low or too high. People with type 1 diabetes must "manage" the disease by taking daily injections of insulin — sometimes as often as four or five times a day, depending on their glucose level — or by using an insulin pump, and by controlling their diet and physical activity.

Even those who "manage" their diabetes well are at high risk for heart disease, stroke, and nerve damage. Diabetes is also the leading cause of kidney failure, blindness (in adults), and non-traumatic amputations, and shortens average life expectancy by up to 15 years.

Unlike most with the disease, Sigrun, an admissions assistant at a private school, says diabetes did not hamper her lifestyle for many years. Until recently, she required only one shot of insulin a day. Even as a teenager, Sigrun says, "I never had a craving for sweets,

and when I did have something like pudding, I'd only take one spoonful, and no more." Also, she was fortunate in that she never suffered any early complications as a result of her diabetes. She married, gave birth to and raised three healthy, non-diabetic sons, and, for the most part, led a normal life — until her mid 40s.

"Everything was going well," Sigrun says. "After menopause, however, my blood sugar periodically would spike to 300 in a matter of hours" (a non-diabetic normal range is between 80 and 120 after a meal). Every couple of weeks she experienced rapid heart beat, excessive perspiration, and felt confused due to extremely low blood sugar levels. Although Sigrun never had serious kidney ailments, by her mid 40s she began manifesting symptoms of nerve and eye diseases associated with diabetes, and had cataracts removed from both of her eyes. After years of successfully living with diabetes, "I suddenly became more frightened of my situation," she says, "and its terrible side effects."

EDMONTON PROTOCOL

Islet-cell transplantation is not new. Over the past 25 years or so, more than 300 patients have undergone such transplants in medical centers around the world. But only a few were successful, and very few if any proved effective long-term (beyond one year). Most scientists believe that the poor long-term success rate has been due to the body's rejection of the transplanted cells.

The scientists in Edmonton, Alberta, Canada, developed a clinical protocol that uses a novel, steroid-free combination of three drugs. The drug combination appears to prevent rejection and halt autoimmune destruction

PATIENT PROFILE: Sigrun Schwendinger

of the islets, and is less damaging to transplanted islets than previous methods of immunosuppression. In this technique, islets are isolated from the pancreas of organ donors. Following isolation, the islets are injected into the portal vein, which supplies blood to the liver. The islets then migrate to the liver, where they flourish and produce exactly the amount of insulin required to maintain almost perfect blood sugar control. More of the patients who have been transplanted using this new protocol have remained insulin-free than in previous islet transplantation trials. As a result, the approach taken in the Edmonton protocol is now being tested in a larger number of patients.

RESEARCH TO INCREASE THE SUPPLY OF ISLETS

One of the limiting characteristics of the Edmonton protocol is that it usually requires two or more pancreata to yield sufficient islets for each patient. Should the protocol become more commonplace, the demand on an already short supply of donor organs will inevitably increase dramatically. Scientists at the NIH and elsewhere already are trying to induce islet cells to reproduce in laboratory cultures. They also are attempting to determine whether or not stem cells can be programmed to grow into islets.

BECOMING INSULIN-FREE

After going through an extremely rigorous screening process that included filling out a lengthy questionnaire and meeting with several physicians, Sigrun underwent a battery of tests, including EKGs, stress tests, and insulin tests. She was eventually placed among the NIH's list of 60 candidates for the procedure. "I was advised of all the risks involved," says Sigrun, including blood clots in the vein where the islets are placed, and side effects from a weakened immune system. Sigrun emphasized the fact that she was told repeatedly by her NIH research physician that she could leave the protocol at any time. But with the support of her husband and family, Sigrun decided to go through with the procedure, and as a result, played a part in the history of this new transplant technique.

Because the procedure is so new, researchers don't know what complications might arise over time. "Therefore, the biggest risk is the unknown," says David Harlan, MD, Chief of the Transplantation and Autoimmunity Branch of NIH, who attended to Sigrun during her transplant. He adds that, while Sigrun has benefited from her new-found and—hoped for—long-term independence from insulin, she also has contributed toward the development of a treatment that may one day legitimately be called a cure for type 1 diabetes. "Not only has she helped win a victory for humanity," he says. "Sigrun also afforded me the privilege I have long sought. That is, she was the first patient I was able to look in the eye and say, 'Congratulations, you no longer, at least for today, have diabetes.'"

As this document goes to press, it has been nearly two years since Sigrun underwent the two-stage islet transplant procedure — and she remains insulin free. NIH physicians monitor her condition on a regular basis, and she continues to take immunosuppressant drugs. She says the dosage of these drugs is based upon her need at the time.

Sigrun, who describes herself as an optimistic, confident, cheerful person, as well as a risk taker, admits that she had given up all hope years ago of being cured of diabetes. “As a result of this procedure, and the follow-up I am receiving at the NIH, I’m very hopeful for not only my future, but for the future of the millions of others who suffer with type 1 or type 2 diabetes.”

UNDERGOING ISLET TRANSPLANTATION

A single donor pancreas provides about 250,000 to 500,000 islets. Each recipient patient, however, needs about 800,000 cells before he or she is insulin-free. As a result, the patient normally needs two infusions of cells, from two donors.

In Sigrun’s case, after being called in for her first infusion, she was sent home because researchers were unable to isolate enough islets in the lab. A week later, another donor organ of her blood type was received and she was able to undergo the first infusion. It took a month and a half before a second suitable organ was found to complete her islet transplant. Between the first and second infusions her dosage of insulin was reduced by half. A day after the second infusion, she was insulin free.

Along with clinical trials to improve immune tolerance of transplanted islet cells, the NIH is supporting basic research studies aimed at improving scientists’ understanding of the underlying biology of the insulin-producing beta cells. The recently established Beta Cell Biology Consortium is using an interdisciplinary approach to investigate the development and function of beta cells, and to explore sources other than pancreatic islets for new supplies of these insulin-producing cells. With an increased knowledge base, researchers may be able to offer insights leading to improved strategies for replacing missing or malfunctioning beta cells.

Countering the Epidemic of Type 2 Diabetes: The Diabetes Prevention Program

The recently completed DPP clinical trial demonstrated that lifestyle modification can prevent or delay diabetes onset in those at highest risk.

The impetus for the Diabetes Prevention Program (DPP) clinical trial was the alarming rate at which type 2 diabetes was and is occurring in this country. There are now 16 million Americans with type 2 diabetes and about 800,000 new cases are reported each year. In addition, another 16 million people have a condition described as “pre-diabetes.” People with pre-diabetes have blood sugar levels above normal, which puts them at high risk for developing diabetes. Each year, up to ten percent of those with pre-diabetes develop full-blown diabetes. The DPP was conducted to determine whether the ever-increasing health and economic burdens of type 2 diabetes could be curtailed through prevention.

The frequency of diabetes increases with age, and is related to an individual’s family history and racial or ethnic background. An important characteristic of all of these risk factors is that they cannot be changed. However, other risk factors for the development of type 2 diabetes—such as obesity and a sedentary lifestyle—can be changed. This simple question formed the basis of the DPP: are there safe and effective strategies that can be used to prevent the development of type 2 diabetes in a susceptible population?

STUDY DESIGN

The DPP compared three approaches—standard medical advice, treatment with the drug metformin, and an intensive lifestyle modification—in over 3,000 overweight people with pre-diabetes, a condition in which blood glucose levels are higher than normal but not yet diabetic. Populations at greatest risk for developing diabetes were chosen for study. Forty-five percent of the study’s participants were recruited from among racial and ethnic minority groups, because epidemiologic research has shown that minority populations are disproportionately affected by type 2 diabetes. Efforts were made to ensure that individuals who entered the DPP study would be able to adhere to a long-term, intensive protocol. Those efforts were rewarded with a high level of retention of patients in the study and of adherence to the regimen of the study.

Patients in the placebo arm of the study received regular physical exams and standard medical advice to improve their diets, lose weight, and increase exercise. A second group of patients received the same advice and the drug metformin. Metformin helps the body respond more efficiently to the

insulin it makes naturally and it decreases the amount of sugar made in the liver. The current FDA-approved use of metformin is for the treatment of existing type 2 diabetes. Metformin is effective in lowering blood sugar and has a history of safety and tolerability with minimal side effects. Furthermore, it has an acceptable dosing regimen, and the potential for translation with regard to availability and cost, and for clinical application across the diverse study populations of the DPP. For these reasons, DPP investigators believed metformin might be able to block the progression of pre-diabetes to full-blown diabetes.

A third group of patients received intensive counseling to help them lose weight and increase their physical activity. The goals of the intervention were a 7 percent loss of body weight and at least 150 minutes per week of moderate intensity physical activity. To help participants achieve these goals, they were seen individually and received ongoing intervention throughout the trial. All individuals initially participated in a 16-session core curriculum that taught basic information about nutrition, physical activity and behavior change. A “tool box” of approaches was used to allow for individualization of the intervention. In addition, the investigators permitted flexibility in the delivery of the intervention for an ethnically diverse population. DPP centers offered three group courses—such as diet, exercise, resistance training and behavior—per year during the maintenance phase. Three to four motivational campaigns were conducted each year in which participants competed with others in the same center or across centers to see who could achieve the weight loss or exercise goals.

The DPP investigators viewed physical activity as an important component of achieving and maintaining weight loss. The strategy for achieving the physical activity goal was to stress brisk walking and other activities of similar intensity, such as aerobic dance or bicycling. Prior studies suggested that even short bouts of exercise—as little as ten minutes—could be very helpful in promoting weight loss and improving fitness. This concept was employed in the DPP.

The weight loss goal was achieved through lowering the amount of fat in the diet and restricting total calories, in combination with increased activity. Participants were given a dietary fat goal that reduced their fat intake to 25 percent of calories and were instructed to self-monitor their intake to help achieve the weight loss goal.

Dr. David Nathan, Chairman of the DPP study, Director of the Diabetes Center at Massachusetts General Hospital, and Professor of Medicine at Harvard Medical School, points out that much of the success of the DPP derives from the strong foundation provided by previous research. All aspects of the trial were grounded in knowledge gained from several decades of investment in basic behavioral intervention research and the translation of that research. Dr. Rena Wing, Professor of Psychiatry and Human Behavior at Brown Medical School-Miriam Hospital and the coordinator of the DPP’s intensive behavioral lifestyle intervention, concurs. “This intervention was based on prior studies suggesting that modest changes in weight or physical activity might reduce the risk of developing type 2 diabetes. Clinical trial data also existed that suggested that we could produce modest changes in weight and physical activity.”

STUDY RESULTS

The intensive lifestyle intervention arm of the DPP clinical trial yielded remarkable findings about how diet and physical activity can reduce the risk of developing type 2 diabetes in individuals who are prone to the disease. The trial participants assigned to the lifestyle intervention lost an average of five to seven percent of their body weight, performed at least 150 minutes of physical activity per week, and reduced their chance of developing diabetes by 58 percent over an average 2.8 year follow-up period. Metformin reduced the risk of developing diabetes by 31 percent.

The results of the lifestyle change were extremely consistent across diverse subgroups in the study. Both men and women and all ethnic groups benefited similarly from lifestyle intervention. Participants over 60 years of age had the best response to lifestyle with a 71 percent reduction in the development of diabetes. This result is particularly significant because type 2 diabetes is considerably more prevalent in those over age 60.

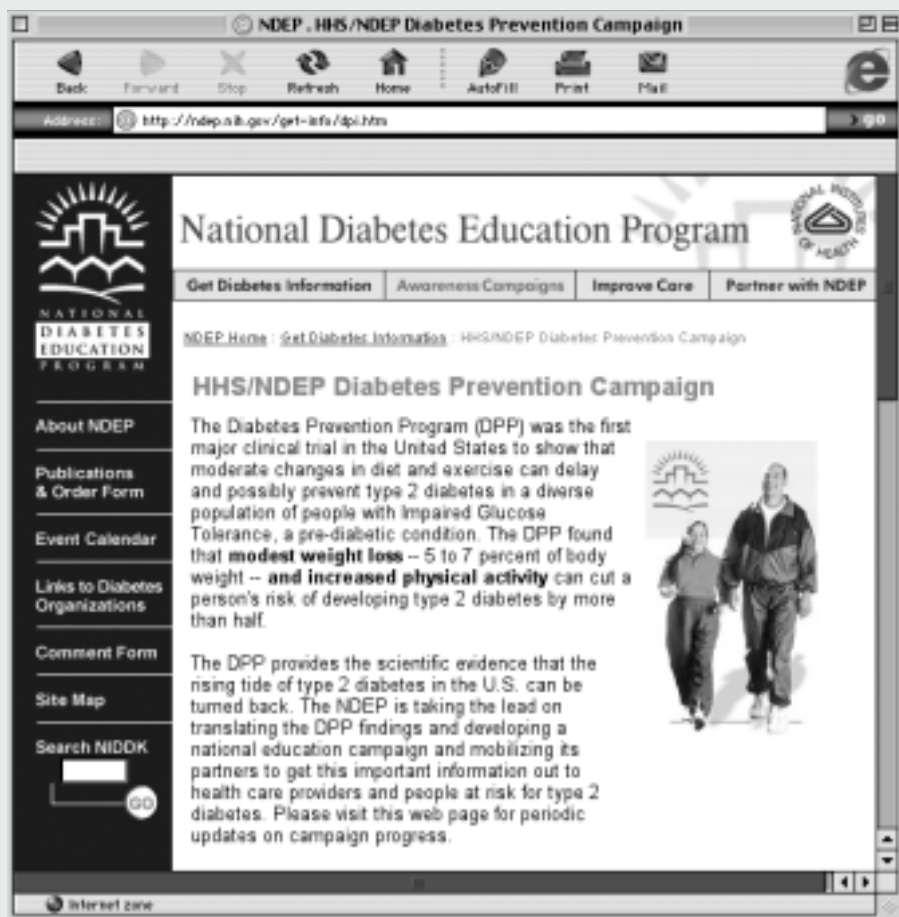
Rigorous, systematic, and controlled testing of the weight loss-physical activity hypothesis through the DPP provided definitive proof that prevention of type 2 diabetes is possible through lifestyle changes.

There are at least ten million Americans who resemble participants in the DPP with respect to their risk for developing type 2 diabetes; if they adopt lifestyle changes similar to those in the DPP, their disease risk can be reduced by over 50 percent.

Dr. Nathan notes that it is a well-accepted notion that if a person is overweight, losing weight is probably good for his or her health. However, prior to the DPP, the preventive effects of lifestyle changes in a diverse population at risk for type 2 diabetes had never been scientifically demonstrated. Dr. Nathan says, “For the first time, we have shown that people can actually modify lifestyle. The DPP is the first study to demonstrate in a diverse population—urban, rural, North, East, South, and West—that people who volunteered for this study could accomplish the change in lifestyle that we asked them to, and that a high proportion could take the metformin throughout the study period.” He notes, “It is not a question of *whether* the interventions will help them—particularly the intensive lifestyle intervention. We now have definitive evidence that lifestyle modification or metformin does reduce the development of diabetes, and that they work in men and women, and in all the ethnic and racial minorities we studied. So it’s not a question of guesswork any longer. We *know* that these interventions will decrease the development of diabetes.”

Dr. Wing points out, however, that the ability to implement the intensive lifestyle modification arm of the trial—as well as its success—was far from guaranteed. Because the DPP would be a long-term study, many of the investigators were concerned that, while initial changes in weight and physical activity could be achieved; these changes might not be sustained over time. Investigators were also concerned

about whether the intervention could be applied successfully to diverse populations. A third concern was that some of the 27 research centers participating in the trial had very little experience with weight control or physical activity interventions. In spite of these concerns, though, the intensive lifestyle modification was a success, both in terms of its implementation as well as its impact on health.



The NIH is actively promoting the translation of the message of the Diabetes Prevention Program into clinical practice. The National Diabetes Education Program, a collaborative effort among the NIH, the CDC, and over 200 private sector organizations, is being expanded so that it can broadly and effectively disseminate the results of the study to physicians and to the public through outreach programs and publications. Ancillary studies to the original DPP clinical trial are aimed at identifying the long-term benefits of lifestyle intervention and metformin on delaying diabetes and its complications. The NIH is also supporting efforts to promote exercise and other interventions for the treatment of obesity and diabetes.

Perspectives on the DPP

This research conveys a powerful message of hope to people at risk for type 2 diabetes, a painful, life-threatening disease that has been increasing in this country along with obesity. By adopting a moderate, consistent diet and exercise program, many people with one or more of the risk factors for type 2 diabetes can stop the disease before it becomes irreversible.

Tommy G. Thompson

Secretary

Department of Health and Human Services

Lifestyle intervention worked equally well in men and women and in all ethnic groups. It was most effective in people age 60 and older, who lowered their risk of developing diabetes by 71 percent. Metformin was also effective in both sexes and in all the ethnic groups. However, it was relatively ineffective in older volunteers and in those who were less overweight.

Dr. David Nathan

Massachusetts General Hospital

Chairman, Diabetes Prevention Program

Not only did changes in diet and physical activity prevent or delay the development of diabetes, they also actually restored normal glucose levels in many people who had impaired glucose tolerance. These findings bring us closer to the goal of containing and ultimately reversing the epidemic of type 2 diabetes in this country.

Dr. Allen Spiegel

Director, National Institute of Diabetes and Digestive and Kidney Diseases

Study participants from American Indian communities helped prove that type 2 diabetes can be delayed in many people at high risk. By adopting healthy diet and exercise habits, individuals can do a great deal to lower the risk of diabetes and add immeasurably to their overall health and quality of life.

Dr. William Knowler

Chief, Diabetes and Arthritis Epidemiology Section

National Institute of Diabetes and Digestive and Kidney Diseases

How Is the DPP Helping to Shape the Future Behavioral Research Agenda?

With completion of the DPP, Dr. Rena Wing, coordinator of the DPP's intensive lifestyle intervention, is turning her attention to the future and to ways to implement the lessons of this intervention to prevent type 2 diabetes. Dr. Wing notes that, "The DPP suggests certain areas of particular importance for future research. With the most intensive, best program we could develop, our lifestyle participants achieved their best weight losses at six months, maintained them through a year, and then gradually regained. They regained even though we were giving them intensive contact. This is the problem we have in the field. I think this is the number-one priority for our research, that is, to understand how we can help individuals maintain their weight loss long-term, and maintain other aspects of behavior change."

Dr. Wing believes there are three approaches to this maintenance of behavior change on which research should be encouraged. One is to study people who have successfully changed their behavior long-term. "We need to understand how they do it—how are they able to succeed?" she says. A second approach is to understand more fully why maintenance is so difficult. "What happens at six months or a year that makes people start to regain? Is it a physiological change or is it a behavioral problem that leads them to regain?" Lastly, Dr. Wing believes there is a need to encourage investigators to develop innovative strategies for long-term maintenance of behavior change. She notes that, "What we're doing isn't working as well as it should be and I think we need to encourage creativity and innovative approaches."

Dr. Wing also believes that, to apply the results of the DPP to the general population, it is important to disseminate the DPP message effectively. She is looking at the Internet as one means of disseminating treatments to a large number of people, observing that, "It's increasingly popular, it has no geographic limitations, is convenient to people, and is interactive, between a therapist and a participant. There are also opportunities for support among participants." Offering both educational materials and a structured behavioral program on the Internet, Dr. Wing and her colleagues recently reported that, at both the three-month and the six-month point, the Internet behavior therapy program was far more effective than the Internet educational program in changing participants' body weight. The researchers were able to produce a weight loss of about nine pounds through the behavior therapy program. They are now working to develop an even more effective behavioral program that includes initial weight loss and maintenance of weight loss. "Again, we need to be applying behavioral principles," Dr. Wing says, "carefully looking at how to change the cues and the consequences in the environment so as to maintain the behavior change. I also think we really need to be studying how to intervene on the whole environment, particularly the home, where most meals are eaten."

PATIENT PROFILE: Monica Boone

A PATIENT IN THE DIABETES PREVENTION PROGRAM

Monica Boone, a soft-spoken mother of two from Zuni, New Mexico, was haunted by a fear of diabetes. Like many other Native Americans, several members of her family — of the Zuni Indians in New Mexico — had been stricken by type 2 diabetes. It had killed her father, who died of a diabetes-induced heart attack at age 57, and one of his brothers. Another paternal uncle now struggles with the disease. She thought there was a good chance she was next in line. Three years ago, Monica, who is 5- feet 3- inches tall, weighed 173 pounds, had little energy, and didn't get much physical activity. So, she became interested in a diabetes research study that was just beginning in Zuni. She was permitted to participate in the study when her blood tests revealed that she had pre-diabetes, a condition just one step away from outright diabetes.

Pre-diabetes affects about 16 million people in the United States. Individuals with pre-diabetes have blood glucose levels that are higher than normal, but not yet in the range that indicates diabetes. Having pre-diabetes sharply increases the risk of developing type 2 diabetes and heart disease. Once a person develops type 2 diabetes, the risk of heart disease is even higher—two- to four-times that of people without diabetes.

“I was scared for myself and my family, but I still wanted to know where I stood,” she recalls. “When I found out about the study, I felt I was being given a second chance. I decided to take that chance. I wanted researchers to find out if this disease can be prevented.”



Monica Boone was a participant in the Diabetes Prevention Program (DPP) clinical trial. She helped demonstrate that improvements in diet, coupled with moderate exercise, can delay and possibly prevent type 2 diabetes in those at high risk for the disease.

Photo: Indian Health Service.

Like thousands of other adults across the country at high risk for type 2 diabetes, Ms. Boone joined a research study called the **Diabetes Prevention Program (DPP)**, a large, multi-center clinical trial sponsored by the National Institutes of Health (NIH). All of those enrolled in the study had pre-diabetes and were overweight. Participants were randomly assigned to one of three groups:

Lifestyle changes: Participants in this group aimed to lower their body weight by seven percent by reducing their intake of fat and calories, and by exercising 150 minutes a week with moderate intensity. Most chose walking an average of 30 minutes a day, five days a week.

Drug Treatment: Participants in this group took 850 milligrams of the oral diabetes drug metformin twice a day. This group also was given standard information on diet and exercise. Metformin lowers blood glucose mainly by decreasing the liver's production of glucose.

Placebo: Participants in this group took placebo pills in place of metformin. This group also received standard information on diet and exercise.

Ms. Boone was randomly assigned to the group focused on lifestyle changes. She worked to lose seven percent of her weight — about 12 pounds — by curbing fat and calories in her diet, and by exercising 150 minutes per week. She decided her exercise would be to walk. Her first time out was tough. “My heart was beating so fast,” she recalls. Slowly, she built up her endurance from one mile to four miles, at least five days a week. She gradually mixed in jogging with walking. She ate less “fast food”

and began cooking nutritious meals at home. Her weight started to drop. In time, she lost 20 pounds. Best of all, her blood glucose levels returned to normal.

Ms. Boone was one of over 3,200 DPP participants who helped demonstrate that improvements in diet coupled with moderate exercise can delay and possibly prevent type 2 diabetes. Specifically, diet and exercise resulting in a five to seven percent weight loss lowered the development of type 2 diabetes by 58 percent in this high-risk group. The study also found that metformin reduced the risk of developing type 2 diabetes by 31 percent. The drug was most effective in younger, heavier individuals.

The good news didn't end there. While both interventions lowered fasting blood glucose levels, diet and exercise were more effective at lowering glucose levels two hours after a standardized glucose drink — the “oral glucose tolerance test.” Also, about twice as many people in the lifestyle group, compared to those who received standard information, regained normal blood glucose levels, showing that diet and exercise can reverse the pre-diabetes that often leads to type 2 diabetes.

These findings show that people don't have to exercise excessively or starve themselves to lose weight in order to achieve the goal of preventing diabetes. Dr. Rena Wing, a Brown University professor who oversaw the lifestyle portion of the study, adds that, “We're not saying to people that they need to achieve ideal body weight. These are reasonable goals.” Indeed, the study participants lost, on average, a modest 15 pounds.

PATIENT PROFILE: Monica Boone

Extensive NIH-supported advances in clinical research on obesity, nutrition, and behavior converged in the design of this clinical trial, particularly the intensive lifestyle intervention arm. By employing counseling methods and information on diet and exercise that had previously proven most effective, the researchers were able to help participants achieve their weight-loss goals. This provided the researchers with a large enough pool of successful participants to satisfactorily answer the question, “Can diabetes be delayed or prevented through lifestyle changes?”

Researchers who conducted the DPP study announced their results in August 2001, at a press conference convened by Health and Human Services Secretary Tommy G. Thompson. They concluded that the findings of the study were so dramatic and had such great potential for stopping or delaying the onset of new cases of type 2 diabetes, that the study should be terminated a year sooner than planned. Their findings were reported on February 7, 2002, in the *New England Journal of Medicine*.

Other research has shown that diet and exercise can delay type 2 diabetes in at risk people. But the DPP, conducted at 27 centers nationwide, is the first major study to show that lifestyle changes can delay diabetes in a diverse population of overweight American adults with pre-diabetes. Nearly one-half of the DPP participants were from minority groups that suffer disproportionately from type 2 diabetes: American Indians, African Americans, Hispanic

Americans, Asian Americans, and Pacific Islanders. Diabetes has hit American Indians harder than any other ethnic group in the United States, taking an enormous toll in pain, disability, and loss of life. On average, American Indians and Alaska Natives are 2.6 times more likely to have diabetes than non-Hispanic Caucasians of similar age.

Can lifestyle changes or metformin treatment prevent diabetes completely? “We just don’t know how long diabetes onset can be delayed, beyond the three-year period studied,” says Dr. David Nathan, of the Massachusetts General Hospital—the Chairman of the DPP. “We hope to follow the DPP volunteers to learn how long the interventions are effective.” The researchers will analyze the data to determine whether the interventions reduced heart disease and atherosclerosis, major causes of death in people with type 2 diabetes.

Behind Monica Boone’s house are the trails she runs and has come to love, paths that wind through a valley surrounded by the stark beauty of Corn Mountain and the Bluebird Mesas. Since joining the DPP study, she has gone through 10 pairs of running shoes. “I look forward to my runs now,” she says. “I see small animals like rabbits and rodents and beautiful birds, even a golden eagle sometimes. I have more energy; I’m quicker in my movements; and I enjoy going here and there. I used to dread it. People say, ‘Is that you?’ They don’t recognize me,” she laughs.

The National Diabetes Education Program and Public Education Programs Relevant to Diabetes

The recent, impressive results of diabetes clinical trials underscore the need to quickly disseminate these findings to the general public. To this end, new public education efforts are being launched by the National Diabetes Education Program (NDEP)—a collaborative initiative of the NIH, the Centers for Disease Control and Prevention, and over 200 public and private partnerships which promotes early diagnosis and improved treatment and outcomes for individuals with diabetes. A key feature of the program's partnership is the participation of individuals who represent communities disproportionately affected by diabetes, including African Americans, Hispanics/Latinos, Native Americans/Alaska Natives, and Asian and Pacific Islanders.

The NDEP is the primary mechanism for translating the impressive results of the NIH's recently completed major clinical trial, the Diabetes Prevention Program (DPP), to the public and to health care practitioners. This multi-center trial



Public education materials for diabetes are developed by several institutes at the NIH. These publications help patients and their families manage daily life with diabetes and take steps to prevent diabetes and its cardiovascular, kidney, eye, and other complications. Some publications are available in Spanish and other languages and in easy-to-read versions. Photo: Bill Branson, Medical Arts and Photography Branch, NIH.

showed that a relatively modest exercise and weight loss program could significantly prevent or delay the onset of type 2 diabetes in those at risk for this disease. Importantly, these findings applied across all ages and ethnic/racial groups studied (individuals from minority groups who are disproportionately affected by type 2 diabetes represented approximately 45 percent of the DPP study population). Based on these scientific results, the NDEP is now being expanded so that this critically important prevention message can be broadly translated.

The National Diabetes Education Program...

The NDEP also conducts diabetes awareness campaigns using the theme, "Control Your Diabetes. For Life." This effort is built on landmark clinical trials, which showed the importance of blood glucose control in preventing diabetic complications. By reinforcing this theme, the NDEP encourages patients with diabetes to manage the disease closely in order to live healthier lives. The campaign targets both general audiences and populations disproportionately affected by diabetes through television, radio and print public service announcements, educational materials, and information kits for the media and communities. The program is currently developing campaigns to help health care providers work with their patients to improve glucose control and special efforts to improve awareness of effective diabetes care for children, older Americans, and minority populations.

In addition, the NDEP is joining forces with the American Diabetes Association to inform the public that good diabetes management is more than just lowering blood glucose. To communicate the importance of comprehensive care in simple language, the "ABC's of Diabetes" have been developed. The "A" stands for the hemoglobin A1c test, which reflects the average blood glucose over the previous three months. "B" is for blood pressure, and "C" is for cholesterol. This campaign was developed because most patients are not aware that heart disease and stroke are the leading killers of people with diabetes, and that lowering of blood pressure and cholesterol can markedly reduce this risk.

Important health information relevant to diabetes is disseminated through several other NIH education programs. These include:

The National High Blood Pressure Education Program

(NHBPEP): A cooperative effort among professional and voluntary health agencies, state health departments, and many community groups, this program has the goal of reducing death and disability related to high blood pressure through professional, patient, and public education. Both the NHBPEP and the NDEP emphasize the importance of blood pressure control in reducing the complications of diabetes.

The National Cholesterol Education Program:

This program seeks to reduce illness and death from coronary heart disease (CHD) in the U.S. by reducing the number of Americans with high blood cholesterol. Through educational efforts directed at health professionals and the public, the program aims to raise awareness and understanding about high blood cholesterol as a risk factor for coronary heart disease and the benefits of lowering cholesterol levels. Both the NCEP and the NDEP encourage rigorous control of LDL cholesterol based on evidence from clinical trials that this will reduce the risk of cardiovascular disease in patients with diabetes.

and Public Education Programs Relevant to Diabetes

The National Eye Health Education Program (NEHEP):

This program seeks to increase awareness and knowledge of diabetic eye disease and to encourage actions to prevent loss of vision. Diabetic eye disease is often asymptomatic until its later stages, after the optimal time for treatment has passed. Thus, early recognition of disease is critical in preventing loss of vision. To this end, this program collaborates in developing, testing, promoting, and distributing educational materials to patients, high-risk groups, and health care professionals.

The National Kidney Disease Education Program:

This new program will raise awareness of the seriousness of kidney disease and the importance of early diagnosis, and increasing implementation of the appropriate management and prevention strategies for the disease and its complications. The number of people with end-stage renal disease has doubled each decade for the last two decades. These increases appear to parallel the rising prevalence of diabetes, the leading cause of kidney disease. Clinical trials have shown that optimal management of diabetes and blood pressure can reduce onset and progression of kidney disease.

The risks for kidney disease run in my family.

Good thing awareness does, too.



African Americans with diabetes, high blood pressure or a family history of kidney disease are at high risk for developing irreversible kidney failure—end stage renal disease. The new National Kidney Disease Education Program (NKDEP) is conveying this important health information through educational messages.

Photo: NKDEP.