Conquering DIABETES

A STRATEGIC PLAN FOR THE 21ST CENTURY

A Report of the Congressionally–Established
Diabetes Research Working Group
1999

This Strategic Research Plan for diabetes research funded by the National Institutes of Health has been developed by an independent, congressionally-established Diabetes Research Working Group, with input from diabetes investigators, diabetes patients, and other members of the broad diabetes research community. The Working Group is composed of scientific and lay experts external to the National Institutes of Health, as well as leaders of major diabetes voluntary organizations. The views, conclusions, and recommendations expressed in this document are solely those of the members of the Diabetes Research Working Group and do not necessarily reflect the positions or judgments of the National Institutes of Health, the Department of Health and Human Services, or the Administration, which must weigh the competing requirements of multiple programs and activities.

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TRANSMITTAL TO THE CONGRESS

In accordance with directives from the House and Senate Appropriations Committees, I am pleased to transmit to the Congress the Strategic Research Plan for NIH-funded diabetes research developed by the congressionally-established Diabetes Research Working Group.* As specified by the Congress, this Research Plan includes recommendations for future diabetes research directions and corresponding overall budget estimates for implementing the proposed new research initiatives.

The Diabetes Research Working Group is an independent panel composed of twelve scientific experts in diabetes and four representatives from the lay diabetes community. In developing its Strategic Research Plan, the Working Group held plenary meetings and subcommittee discussions, analyzed the existing NIH diabetes research portfolio, sought the expertise of *ad hoc* scientists, and enlisted public commentary. The Diabetes Research Working Group believes that the culmination of this year-long, in-depth planning process is a set of recommendations that will be of value to the Congress and to the NIH.

Clearly, the congressional action calling for the establishment of the Diabetes Research Working Group and the development of its Research Plan reflects the strong and continuing commitment of the Congress to conquering diabetes. The implementation of the research initiatives recommended in this Strategic Research Plan is the next vital step toward attaining that objective.

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Chairman
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*Note: The congressional directives calling for the establishment of the Diabetes Research Working Group and the development of its Strategic Research Plan can be found in Senate Report 105-58 (1998, p. 76, p. 110), House Report 105-205 (1998 , p. 69, p. 98) and House Report 105-635 (1999, p. 69). The charge to the Diabetes Research Working Group called for the development of a comprehensive plan for all NIH-funded diabetes research efforts, including the recommendation of future diabetes research initiatives and directions. Congressional language specifically asked the Working Group to include overall cost estimates to accomplish its recommendations in the final research plan.

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Summary of the Report and Recommendations of the Diabetes Research Working Group

Sixteen million people in the United States have diabetes mellitus. In both human and economic terms, it is one of our nation's most costly diseases. Diabetes is the leading cause of kidney failure, blindness in adults, and amputations. It is a major risk factor for heart disease, stroke, and birth defects, shortens average life expectancy by up to 15 years, and costs the nation in excess of $100 billion annually in health-related expenditures. At present, more than one of every ten health-care dollars and about one of every four Medicare dollars are spent on people with diabetes. Over the next decade these numbers will grow as the number of people afflicted by diabetes continues to increase at an accelerating rate. At present, there is no method to prevent or cure diabetes, and available treatments have only limited success in controlling its devastating consequences.

This problem is made more complex by the fact that diabetes mellitus is not a single disease, but occurs in several forms, and has complications that affect virtually every system of the body. The most common forms are Type 1 (insulin-dependent) diabetes, which usually starts in childhood or adolescence, and Type 2 (non-insulin dependent) diabetes, which typically affects adults and increases dramatically with age and obesity.

Congress has clearly recognized the gravity of diabetes through the establishment of a bipartisan Diabetes Caucus and has concluded that the only way to reduce the tremendous burden of this disease is through intensified biomedical research. Over the past three years, Congress has emphasized diabetes research in funding increases provided to the NIH and through other special initiatives. Realizing the critical need to build upon these important steps, the Congress directed the establishment of the Diabetes Research Working Group (DRWG) and charged it with developing a comprehensive plan for diabetes research. This plan is intended to help increase the effectiveness of NIH-funded diabetes research and find solutions to the extremely serious problems posed by this disease. During 1998, the DRWG and its subcommittees held a series of meetings, consulted with a wide range of experts in the field, and heard public commentary. It evaluated all aspects of the diabetes problem in an effort to develop a comprehensive plan for submission to the Congress. This document provides the Strategic Research Plan of the Diabetes Research Working Group.

Based on its extensive review and deliberations, the DRWG recognizes both great urgency and unprecedented opportunities in diabetes research. The seriousness of the disease and the widespread problems associated with it demand accelerated and expanded research programs, not only to discover the means to prevent and cure diabetes, but also to develop better and more effective treatment strategies. Meeting these challenges requires a well-thought-out and continuously updated research plan; a cadre of talented researchers and physician-scientists; a supportive infrastructure; and appropriate budgetary resources. The DRWG is convinced that taking action now to significantly increase NIH support of diabetes research will save many thousands of men, women and children from the severe consequences of a dangerous, often disabling and potentially fatal illness, and will also save the nation many billions of dollars in medical care and lost productivity. From both human and scientific perspectives, now is the time for the United States to move swiftly and decisively to begin to ensure a future for America without diabetes.

Magnitude of the Problem

The magnitude of the problem created by diabetes is clearly defined by a few simple facts:

- **Diabetes currently affects an estimated 16 million Americans, and about 800,000 new cases are diagnosed each year.**
- **Diabetes spares no group—attacking men, women, children, the elderly and people from every racial background.**
  - African, Hispanic, Native and Asian Americans, some of the fastest growing segments of the U.S. population, are particularly vulnerable to diabetes and its most severe complications.
  - Diabetes strikes both ends of the age continuum. Children and young adults with Type 1 diabetes face a lifetime of daily insulin injections and the possibility of early complications whose severity will likely increase with duration. Elderly diabetics are frequently debilitated by multiple complications.
- **Diabetes affects virtually every tissue of the body with long term and severe damage.**
  - Diabetic eye disease (retinopathy) is the most common cause of blindness in working age adults.
  - Diabetic kidney disease (nephropathy) accounts for 42 percent of new cases of end-stage renal disease, and is the fastest growing cause of kidney dialysis and transplantation (over 100,000 cases per year).
  - Nervous system damage (neuropathy) affects over 60 percent of diabetics, causing impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, impotence, and other problems.
  - More than half of lower limb amputations in the United States occur among people with diabetes. From 1993 to 1995, about 80,000 amputations were performed each year on people with diabetes.
  - Heart disease death rates in adults with diabetes are about 2 to 4 times those of people without diabetes. Premenopausal women lose their protection from heart disease and have even more markedly increased risk.
  - High blood pressure affects over 60 percent of people with diabetes. As a result of the combination of hypertension and diabetes the risk of stroke is increased 2 to 4 times.
  - Pregnancy related problems confront diabetic women. The rate of major congenital malformations and death of the fetus and newborn are increased 3 to 4 times.
  - Higher rates of infection, periodontal disease, and many other problems occur in people with diabetes.
- **Diabetes is the sixth leading cause of death due to disease in the U.S. and the third leading cause in some minority groups.**
  - Since 1980, the age-adjusted death rate due to diabetes has increased by 30 percent while the death rate has fallen for other common multifactorial diseases, such as cardiovascular disease and stroke.
  - Life expectancy of people with diabetes averages 10 to 15 years less than that in the general population.
- **The economic impact of diabetes is staggering.**
  - The cost of diabetes to the nation is over $105 billion annually.
  - More than one of every ten U.S. health care dollars is spent for diabetes.
  - One of about four Medicare dollars pays for health care of people with diabetes.

The Federal Investment in Diabetes Research

Reducing the tremendous health and human burden of diabetes and its enormous economic toll depends upon identifying the factors responsible for the disease and developing new methods for treatment and prevention. These advances can only occur through increased biomedical research. Although Federal support for diabetes research has produced a number of major advances in the past two decades, many scientific opportunities are not being pursued due to insufficient funding, lack of appropriate mechanisms, and a shortage of trained researchers. Improvements in technology and the general growth in scientific knowledge offer unprecedented opportunities for advances that might lead to better treatments, prevention and possibly cure. Unfortunately, the current funding, level of effort, and scope of diabetes research fall far short of what is needed to capitalize on these opportunities.

The U.S. Government, through the National Institutes of Health (NIH), will spend an estimated $443 million in FY 1999 on diabetes-related research. While this amount has steadily increased since 1981, there is unanimous agreement in the DRWG that this funding level is far short of what is required to make progress on this complex and difficult problem. In fact, the current federal budget for diabetes research represents less than one-half of one percent (0.5 percent) of the annual cost of diabetes to the U.S. economy. When compared with the 5 to 15 percent budgets for research and development in other high-technology sectors, the investment in diabetes research is trivial.

Meeting the challenges posed by diabetes requires investment of additional resources to conduct the needed research and a well-conceived, comprehensive research plan for its effective use. This Plan by the DRWG is the first step in this direction.

The Federal Investment in Diabetes Research

- **Represents about 3 cents out of each dollar, that is about 3 percent of the NIH research budget. Although there is no accepted method for determining appropriate levels of research funding, this is clearly a small investment for a disease that affects 6 to 7 percent of the population and accounts for more than 10 percent of all health care dollars.**
- **The proportion devoted to diabetes research, relative to the whole NIH budget, has decreased by more than 30 percent since 1981, at a time when the death rate due to diabetes has increased by 30 percent.**
- **Represents only about $30 per person affected with diabetes per year--less than two people might spend for a movie and a pizza.**

The Research Plan

The DRWG is convinced that a significant investment in research today will greatly speed progress in understanding and conquering this disease and its complications. The Strategic Research Plan set forth has two overarching goals:

- Understand the causes and define approaches to prevent the development of Type 1 and Type 2 diabetes and their complications.
- Develop methods for optimal management, treatment and ultimate cure of diabetes and its complications.

The DRWG has divided this Research Plan into the following three major components, and provided specific recommendations concerning the types of efforts, budgetary requirements and program mechanisms that should be pursued to realize compelling research goals:

- **Extraordinary Opportunities:** Rapidly expanding, crosscutting areas in which increased investment or development of new mechanisms will significantly speed research.
- **Special Needs for Special Problems:** Equally important, but more focused research areas targeted to specific populations, complications, and methodological approaches.
- **Resource and Infrastructural Needs:** A bold plan for increasing research manpower, technology and other infrastructure elements for diabetes-related research.

Extraordinary Opportunities

Exciting and rapid research advances in recent years have opened the door to a new understanding of diabetes. The next decade offers important research opportunities that, if seized now, can vastly improve the lives of people with or at risk for diabetes. The DRWG has identified five areas that offer extraordinary opportunities

for making genuine and significant progress toward understanding, more effectively treating, and ultimately preventing and curing diabetes. They are: the genetics of diabetes and its complications; autoimmunity and the beta cell; cell signaling and cell regulation; obesity; and clinical research and clinical trials of critical importance.

Genetics of Diabetes

Because Type 1 and Type 2 diabetes and their complications have strong genetic determinants, defining the specific genes involved is essential to prevention and could lead to new and better therapies. Defining the genes for diabetes and its complications will also help isolate the environmental factors involved in the disease and may identify genetic factors that contribute to variations in response to medications. Thus, a major goal for the coming decade must be to identify these predisposing genes.

Although most of the basic tools for genetic studies are in place and much progress has been made, current approaches are inadequate to tackle the vital genetics questions in a reasonable time frame. Three major impediments are inadequate resources; the lack of an appropriate mechanism to bring together the groups of researchers and patient samples to conduct the necessary studies; and fragmented genetic repositories.

Recommendations:

➤ **Establish a National Consortium for the Study of the Genetics of Diabetes to create a strong, coordinated effort for analysis of the role of genetics in diabetes and its complications.**

➤ **Enhance research in laboratory animals and humans to discover the biochemical mechanisms by which diabetes genes function to create susceptibility to diabetes and its complications.**

Autoimmunity and the Beta Cell

Type 1 diabetes is an "autoimmune" disease in which the body's own defense system mistakenly attacks and destroys insulin-producing beta cells of the pancreas. Important discoveries and concepts have emerged during the past decade from research in basic immunology, cell biology, and autoimmune diseases, including Type 1 diabetes. Based on this solid research foundation, the DRWG believes that aggressive pursuit of three scientific areas over the next decade could lead to dramatic improvements in diabetes therapy and prevention.

Recommendations:

➤ **Define the immunological basis of Type 1 diabetes and develop methods for prevention of the disease.**

- Intensify research to understand the immunological basis of Type 1 diabetes.
- Complete mapping of T cell specificity of autoimmune responses to major pancreatic islet cell proteins and identify optimal strategies for immunotherapy.
- Expand the scope of efforts to identify immune response markers that reliably detect individuals predisposed to Type 1 diabetes in the population at large.
- Conduct additional clinical trials of immunoprevention of Type 1 diabetes using antigen-specific, cytokine- or antibody-based immunotherapy.

➤ **Advance research on islet cell transplantation for treatment of diabetes.**

- Establish Centers for Islet Transplantation with appropriate funding to undertake immediate clinical trials of islet transplantation in patients with Type 1 diabetes and to evaluate various methods of immune intervention.
- Support an expanded system for national collection of human pancreas for isolation and distribution of islets for clinical studies, trials, and basic research, and establish a Task Force to make recommendations on approaches to enhance this process.

➤ **Develop methods to stimulate beta cell growth and regeneration.**

- Increase basic research on the control and regulation of islet cell differentiation, growth and development, and devise methods for stimulating growth or regeneration of islet cells.
- Create Interdisciplinary Centers for Beta Cell Biology to expand current efforts and bring new investigators into the field. These Centers should be applicable to research efforts on both Type 1 and Type 2 diabetes.

Cell Signaling and Cell Regulation

Intracellular and intercellular communication is the basic mechanism for the regulation of all cells. Disturbances in cell signaling are central to disturbances in insulin secretion and action, which lead to diabetes and to

both micro- and macrovascular complications. Basic research in this area is not only essential to understanding diabetes, but is also critical to understanding many diabetes-related complications. Most importantly, this type of "discovery" research can identify important targets for new treatments. It would also complement the important new information about the genetic underpinnings of disease.

Recent progress in research on signaling systems and in the ability to use genetic methods to study these pathways has created an extraordinary opportunity to determine the exact mechanisms of signal communication and its alterations in diabetes. A parallel opportunity exists to identify the molecular events responsible for the insulin resistance characteristic of Type 2 diabetes.

The DRWG has identified five areas of opportunity in cell signaling and regulation that warrant increased research. These are: dissection of insulin and hormone signaling pathways; understanding and countering insulin resistance; defining mechanisms regulating beta cell function; metabolic staging of diabetes; and defining alterations in signaling pathways that lead to development of diabetes complications.

Recommendations:

➤ **Complete the dissection of hormone signaling pathways, particularly the pathways of insulin action, and define their alterations in diabetes, including insulin resistance.**

- Significantly increase research in the fundamental science of cellular signaling as it relates to diabetes and its complications.
- Remove the limits currently present on research project (RO1) and program project (PO1) grants, such as budget caps, limitations on growth of programs, and considerations of average grant size, to maximize the opportunity for effective research teams to be formed.
- Establish research centers to focus on development of methods to study cellular signaling at the molecular and genetic level in humans with diabetes to allow correlation between the physiological defects and the molecular alterations.
- Expand research to identify the underlying genetic and biochemical basis of insulin resistance, and to develop interventions to prevent, reverse and ameliorate it in Type 2 diabetes and obesity.

➤ **Define mechanisms regulating beta cell function and their alterations in Type 2 diabetes.**

- Increase research on signaling pathways involved in the regulation of normal beta cell function and their derangements in diabetes.
- Use the proposed Interdisciplinary Centers for Beta Cell Biology to study the alterations in signaling in Type 2 diabetes.

➤ **Allow metabolic staging of diabetes and identify the mechanisms of complications.**

- Develop a program of research to allow metabolic staging of Type 2 diabetes, and to detect individuals at high risk for this form of the disease and its complications.
- Expand support of interdisciplinary research to identify the mechanisms of the complications of diabetes, including interactive mechanisms and program project grants, which bring together investigators with different areas of expertise.

Obesity–Critical in Diabetes and a Major Problem of Its Own

Obesity is a major risk factor for the development of Type 2 diabetes and insulin resistance, as well as a major cause of morbidity and mortality in the U.S. One of every two Americans is overweight, and the prevalence has increased 30 percent in the past decade alone. Obesity disproportionately affects minorities. Over 60 percent of African American, Mexican American, and Native American women meet the criteria for being overweight and between 33 and 37 percent are obese. Moreover, obesity in children and adolescents is increasing at alarming rates, leading to the occurrence of Type 2 diabetes in these groups.

Obesity results from an imbalance between energy intake and energy expenditure. The recent discovery of the fat cell hormone, leptin, and other appetite-regulating hormones has demonstrated that certain types of obesity are not simply due to overeating, but are the result of misregulated pathways that control the balance between appetite and energy expenditure. These new discoveries have provided a revolutionary understanding of obesity at the molecular level, thus leading to extraordinary opportunities in biomedical and behavioral research.

Recommendations:

➤ **Increase the size, scope, number and funding level of NIH sponsored Obesity Research Centers to meet appropriately the severity of this problem in the U.S.**

➤ **Significantly increase research in the basic sciences underlying obesity to capitalize on recent advances in hormonal control of appetite, energy regulation, metabolism, and adipocyte development.**

➤ **Develop stronger industry-NIH relationships to support obesity-related research.**

➤ **Enhance behavioral research in obesity.**

Clinical Research and Clinical Trials of Critical Importance

Translation of basic research into human therapies depends on an active and vigorous clinical research program. Studies in test tubes, cells and animals can answer questions of fundamental importance, and often provide the basis for development and initial testing of potential interventions. However, it is clinical studies in patients with diabetes that are essential for validating these observations and their relevance to human disease. In addition, clinical studies give key insights into the genetic, immune, hormonal, metabolic and environmental factors involved in the disease, and allow true testing of therapeutic strategies. Several prevailing forces, however, have significantly hampered clinical research and clinical trials in diabetes. Investigator-initiated clinical research is decreasing as a result of decreasing numbers of clinical investigators, limitations on funding of clinical research, the high cost of clinical research, and the complexity of clinical challenges. A major factor hampering clinical trials is the lack of infrastructure to organize and support them.

For diabetes, the long-term nature of the complications adds to the complexity of clinical trials. In most clinical studies, it is difficult to have adequate representation of high-risk minority groups due to the *ad hoc* nature of the organization of clinical trials. For robust and effective clinical research, additional well-trained clinical investigators and increased funding of meritorious clinical studies are required. Also needed are efficient systems for clinical research to provide the necessary numbers of patients and the stability of operations for long-term studies, and opportunities to include sufficient numbers of appropriate minority groups.

A comprehensive program for tackling a major public health problem such as diabetes requires a major investment, not only in basic research, but also in clinical research and clinical trials. The latter are particularly needed to document the safety and efficacy of various therapeutic strategies and generate the knowledge base for "evidence based medicine" that will lead to better treatment of diseases. There are two major needs to achieve these goals. The first is creation of an infrastructure to facilitate clinical trials—both improving efficiency and lowering cost. This need is especially apparent in diabetes where clinical trials to "hard endpoints" may take many years and even decades. The second need is a commitment to using clinical trials as a mechanism to develop the proper base of knowledge and to assure steady improvement in the care of people with diabetes.

Recommendations:

➤ **Establish a national diabetes trial network (Diabetes TrialNet) of cooperative clinical research groups to create the stable, high-quality infrastructure necessary for the conduct of effective and efficient clinical trials in diabetes.**

In addition, the DRWG recommends that NIH:

- Increase funding of meritorious clinical trials of emerging new therapies for diabetes and its complications.
- Support critical trials on how to most effectively apply the current methods of therapy and identify new, more generally applicable methods for achieving tight blood glucose control without hypoglycemia.
- Support clinical trials on the prevention of microvascular and macrovascular disease, the major causes of morbidity and death in people with diabetes.
- Develop effective partnerships among the NIH, academia and industry for collaboration and co-funding of clinical trials in diabetes and to provide training in the science of clinical trials.

➤ **Increase funding of meritorious clinical research for physiological studies and development of new technologies for metabolic assessment. These should include efforts to:**

- Initiate clinical studies of promising new therapies for diabetes, such as gene therapy, or tissue-specific approaches to microvascular complications.
- Initiate studies to determine the reasons that women and some minority populations with diabetes have higher risks for diabetic complications.
- Increase opportunities for and support of clinical research training in diabetes.
- Perform clinical studies to establish and validate surrogate endpoints for the complications of diabetes to be used in clinical research and clinical trials.

Micro- and Macrovascular Complications

The different types of diabetes and the array of complications they present offer a wide range of specific research needs unique to each. The micro- and macrovascular complications of diabetes are responsible for most of the morbidity and mortality in both Type 1 and Type 2 diabetes. Their prevention and reversal will greatly reduce the burden of this disease on individuals and on the nation. Understanding and combating the complications of diabetes will require significantly expanded research in mechanisms involved in the development and progression of the complications of diabetes. Several promising research avenues must be pursued through intensified basic and clinical research. This will require an increased effort from the existing community of scientists working in diabetes, as well as important new input from scientists in immunology, genetics, neurology, atherosclerosis, obesity and maternal and child health.

Recommendations for Microvascular Complications:

- **Expand support of research to identify the mechanisms of the microvascular complications of diabetes.**
- **Enhance clinical research and clinical trials.**
- **Develop valid surrogate markers for disease staging.**
- **Establish centers dedicated to the study of microvascular complications.**
- **Recruit scientists from outside the field to enrich research on diabetic complications.**

Recommendations on Diabetic Kidney Disease:

- **Increase the study of the basic mechanisms involved in diabetic nephropathy, including studies of extracellular matrix, growth factors, cytokines and genetic factors, and develop strategies to prevent and reverse this process.**
- **Initiate clinical studies to establish and validate additional markers for staging of disease and use in clinical trials on diabetic nephropathy, including functional imaging and other minimally invasive approaches.**
- **Establish multidisciplinary centers for the study of diabetic nephropathy in order to expand basic and clinical research studies and identify leads for prevention and treatment.**

Recommendations on Diabetic Eye Disease:

- **Increase basic and clinical research on the role of hormones, growth factors and other molecules in the development and progression of diabetic retinopathy.**
- **Increase research into the potential for tissue-specific gene therapy and drug delivery, including approaches for regeneration and rescue of retinal function.**
- **Increase basic and clinical research to develop and improve prosthetics and transplantation technology for diabetic retinopathy.**

Recommendations on Diabetic Nerve Disease:

- **Significantly increase the investment in fundamental research to determine the mechanisms of the nerve damage in diabetes, to expand research on nerve regeneration and rescue, and to evaluate methods to enhance peripheral and autonomic function.**
- **Initiate clinical studies to establish and validate surrogate markers for use in clinical trials on diabetic neuropathy, including new technologies that will aid in the measurement and evaluation of nerve function in people with diabetes.**
- **Establish new multidisciplinary centers for the study of metabolic nerve diseases, with an emphasis on diabetic neuropathy, to develop leads for prevention and treatment.**

Recommendations on Macrovascular Complications:

- **Increase research on the mechanisms by which diabetes and insulin resistance enhance the atherosclerotic process and on the mechanisms of angiogenesis and its use in the treatment and prevention of macrovascular disease.**
- **Increase research to determine the mechanisms responsible for the loss of the vascular-protective effect in premenopausal women.**
- **Increase basic and clinical research to study myocardial function and the cardiac and micrometabolic environment in diabetic heart disease in order to identify the mechanisms that lead to the high mortality in the peri-infarction period and in patients undergoing surgery, and**

to develop effective preventive interventions.

- **Support research to develop appropriate animal models of diabetes and atherosclerosis.**

- **Support further analysis of existing studies and new clinical research to identify the presence, predict the progression, and assess the response to therapy of macrovascular complications in patients with diabetes.**

- **Create multidisciplinary Centers for Diabetes and Vascular Disease.**

Methods to Optimize Glucose Control

Despite the findings of clinical trials and other studies that have demonstrated the importance of tight glucose control to minimize the risk of long-term complications, many patients continue to have far less than optimal control. This is due in part to the risk of hypoglycemia, which increases with intensified therapy, and in part to the difficulty of obtaining optimal control in a general clinical setting. The DRWG believes that identification of methods that promote implementation of these standards of treatment should be a high priority of current clinical research.

Recommendations:

- **Increase basic and clinical research to discover novel approaches for controlling hyperglycemia in diabetes. These approaches should include designing small, orally bioavailable molecules mimicking insulin action; overcoming insulin resistance or stimulating insulin secretion in a physiologic manner; and developing technologies that enable administration of insulin by routes other than injection. This research could involve enhanced collaboration with the pharmaceutical and biotechnology industry.**

- **Develop a focused, multi-disciplinary research program on hypoglycemia and hypoglycemic unawareness. This research should include the neuroendocrine and neuroscience mechanisms that underlie these problems, and increased clinical research to find simple, reliable techniques to identify patients at greatest risk for severe hypoglycemia.**

- **Initiate immediate review of the research program to develop mechanical approaches to insulin replacement by the Diabetes Technology Taskforce (see "Resource and Infrastructural Needs").**

Diabetes and the Environment

The environment appears to play important roles in Type 1 diabetes as a trigger for the autoimmune response and in Type 2 diabetes as a modifier of pre-existing genetic risk. While the latter influence is partly understood, but difficult to control, the former influence has been difficult to define in any specific way. Identification of these environmental factors would provide important information for any preventive strategies for either form of diabetes.

Recommendations:

- **Hold a series of conferences or workshops to explore new methods to search for the environmental triggers of Type 1 diabetes and other autoimmune diseases.**

- **Perform epidemiologic analysis of suspected triggering factors, such as latent or endogenous viruses (including retroviruses) or other substances, whose activation may initiate the autoimmune process.**

- **Explore with the Centers for Disease Control and Prevention the possibility of a national registry for Type 1 diabetes as a mechanism to enhance epidemiologic research.**

- **Support research to develop and apply new technologies to provide accurate, affordable, quantitative measures in normal, living humans of individual-specific energy expenditure, energy intake and macronutrient composition, which contribute to obesity and Type 2 diabetes.**

- **Initiate new epidemiological studies taking into account genetic susceptibility to help identify additional environmental risk factors for Type 2 diabetes, such as stress levels and bacterial/viral infectious agents.**

- **Study environmental factors responsible for the increase in Type 2 diabetes in children and ways to modify them.**

Diabetes in Women, Children and the Elderly

Diabetes mellitus presents additional problems to women with its impact on reproductive health and vascular complications. Children and the elderly present special problems in management and may have additional physiological variables that must be addressed through specific research.

Recommendations:

- **Increase basic and clinical research to identify the mechanisms by which the intrauterine environment, including the diabetic environment, affects the immediate and long-term health outcomes for children and their risks of diabetes and obesity.**

- **Support research to determine the impact of Type 1 and Type 2 diabetes on women, including their reproductive health; risk of cardiovascular disease; the relationship of insulin resistance syndrome and polycystic ovarian disease; and the risk of diabetes following gestational diabetes mellitus.**

- **Increase studies about specific psychosocial issues that face women, children and the elderly with diabetes, including eating disorders, impact of school settings on diabetes, and the management of diabetes in assisted-living situations.**

- **Increase studies of how to implement effectively the principles of the Diabetes Control and Complications Trial (DCCT) in children with Type 1 diabetes in an effort to improve glucose control and reduce the complications of disease.**

- **Increase studies on age-related changes in the development of Type 2 diabetes, and the effects of these changes on responses to treatment and prevention strategies in older persons.**

Diabetes in Minority Populations

Minority populations, including African Americans, Hispanics, Native Americans, and Asians, have the highest incidence of diabetes and the highest rates of complications of the disease. Current research has only begun to address the reasons for this in a very limited way. These groups are rapidly growing segments of the population and specific research must address the reasons for the disproportionate impact of diabetes they bear.

Recommendations:

- **Increase efforts in genetic studies in minority populations as part of the proposed National Consortium for the Study of Genetics of Diabetes.**

- **Support research to identify physiologic and environmental determinants for development of Type 2 diabetes and its complications in minority populations, including in children and adolescents.**

- **Support research to identify risk factors, co-morbidities, and primary and secondary prevention strategies for micro- and macrovascular complications of diabetes in minority populations.**

- **Initiate research to develop culturally sensitive, preventive and therapeutic approaches utilizing appropriate, innovative communication and education techniques applicable in relevant, "real world" settings, for example, rural clinics, county clinics, and urban health centers.**

- **Design and conduct studies in partnership with minority communities to understand more fully the cultural, familial, and other factors that influence adoption of health-promotion, and to change high risk behaviors in those with or at risk for Type 2 diabetes.**

Genetic Engineering

The ability to modify the function of cells through genetic engineering opens up tremendous opportunities for new therapeutic approaches to diabetes and its complications. The DRWG recommends that several applications of this technology be explored.

Recommendations:

- **Increase research to explore the possible use of genetic engineering as a strategy for beta-cell replacement and immunomodulation of transplanted cell lines.**

- **Expand research to explore the potential for gene therapy for Type 2 diabetes.**

- **Bolster research to explore unique applications of gene therapy for tissue-specific approaches to micro- and macrovascular complications.**

Behavioral and Health Services Research

Lifestyle variables, such as dietary intake and physical activity, represent important risk factors for Type 2 diabetes. Type 1 diabetes management can also be influenced by behavioral patterns and can greatly influence personal, family and social dynamics.

Recommendations:

- **Intensify clinical behavioral research to develop interventions to improve patients' adherence to diabetes treatment and their quality of life, and promote sustained improvements in lifestyle behaviors, particularly diet and exercise, which will effectively prevent and reduce the risk for diabetes.**

- **Extend research and development of valid methodologies to measure psychosocial and behavioral factors in diabetes.**

- **Integrate behavioral and pharmacological approaches to reduction of risk factors for diabetes and its complications.**

- **Develop interdisciplinary research teams and training programs to bring together individuals who have training in behavioral sciences with those who have training in diabetes, nutrition, and exercise physiology.**

- **Study the effectiveness of different clinical practices, interventions and technologies; and identify deficiencies in access to care for diabetic patients.**

- **Support research to address lifestyle risk factors and behavioral modification/counseling programs, including obesity, unhealthful dietary preferences, and smoking cessation.**

Oral Complications of Diabetes

Oral complications of diabetes include periodontal diseases, mucosal infections, salivary gland dysfunction, and neurological disorders. These complications are extremely common, as well as problematic. In addition, they are difficult to treat and greatly interfere with essential daily tasks such as eating and speaking.

Recommendations:

- **Establish multidisciplinary Centers for Oral Complications of Diabetes and identify means for prevention and treatment.**

- **Increase studies of the oral complications of diabetes, particularly with respect to the chronic destruction of gingival tissues, the immune response to oral bacteria, salivary dysfunction, healing of oral wounds, and oral neuropathies.**

Resource and Infrastructural Needs

An effective program of diabetes research can exist only if there is a supportive infrastructure. New and expanded initiatives are required to address issues of human resources, clinical research, special needs for animal research, high-cost technology, and other components of infrastructure. Also essential are mechanisms for ongoing review, evaluation, and advice regarding implementation of all of the recommendations in the Strategic Research Plan set forth by the DRWG.

Recommendations:

For Strengthening Human Resources for Research

- **Create new mechanisms and significantly modify existing programs to maximize recruitment, research training, and research career development of diabetes investigators, including special initiatives to promote clinical research and to attract investigators from other disciplines.**

For Enhancement of the Diabetes Research Centers

- **Create new Comprehensive Diabetes Research Centers (CDRCs) to provide enhanced infrastructure support, and enhance the effectiveness of existing Diabetes Centers (DERCs and DRTCs) by significantly increasing their funding levels and expanding their mission.**

For Developing and Harnessing New Technologies

- **Create a National Diabetes Technology Task Force.**

- **Create new regional centers with advanced technologies required for metabolic and functional imaging studies, such as nuclear magnetic resonance (NMR), positron emission tomography (PET), and related technologies, which are required for contemporary diabetes research, and provide ongoing support for their operation.**

For Animal Models for Study of Diabetes

- **Establish regional Centers for Animal Models of Diabetes and Related Disorders.**

- **Support mechanisms to develop and characterize larger animal models of Types 1 and 2 diabetes and their complications, and distribute these models for enhanced approaches to genetic and metabolic studies and the full range of diabetes complications.**

For Human Materials for Diabetes Research

- **Expand support of national programs for procurement of human tissues and organs in order to serve cutting-edge diabetes research; to provide adequate numbers of pancreases for islet cell clinical trials and research; to obtain appropriate tissues for study of diabetes complications and genetic research; and to ensure availability of a range of human tissues required to establish DNA and RNA libraries.**

For NIH–Pharmaceutical and Biotechnology Interactions

- **Establish an NIH–Industry–Academia Task Force to foster interactive research initiatives.**

For the Intramural Programs of the NIH

- **Create an advisory panel, established by the Director of the National Institutes of Health, to review and make recommendations concerning intramural NIH diabetes research efforts in all Institutes and Centers.**

For Extramural Research and Ongoing Strategic Planning

- **Create a Task Force on Strategic Planning in Diabetes Research that would report biennially to the Congress and the Directors of NIH and NIDDK.**

SUMMARY OF BUDGET RECOMMENDATIONS

The DRWG has conducted a careful review of NIH-funded diabetes research and believes that this enterprise is a strong and valuable component of U.S. biomedical research efforts. However, the nation is far from achieving its maximal potential with this difficult problem. Limitations are created in part by under-funding of diabetes research, and by the design of existing research mechanisms and infrastructure. The DRWG believes that progress over the past decade—coupled with the explosion of information in science—makes this an appropriate time to increase significantly the nation's investment to conquer this disease. To implement its recommendations, the DRWG calls upon the Congress and the American people to increase research funding through new appropriations to NIDDK and other Institutes and Centers of NIH.

The budgetary recommendations are summarized on pages 117-125. They call for stepwise expansion of funding for diabetes research providing an increment of $384.5 million for FY2000 rising to an increment of $1.166 billion by FY2004. Built on a base of diabetes research funding for FY1999 of $442.8 million, this proposed budget increment would result in an approximate four-fold increase in overall NIH funding for diabetes research over the coming five-year period. The DRWG believes that such a budget increase is necessary for implementation of the programs presented in this Research Plan, consistent with the rising impact of diabetes on the U.S. in both human and economic terms, and that the proposed budget is more in line with the levels of research funding for other major disease areas. Most importantly, the DRWG believes that such an investment has the potential to reduce dramatically the personal, societal and economic burden of diabetes for the American people in the 21st century.

The Challenge

In both human and economic terms, diabetes is one of the nation's most costly diseases. Diabetes is the leading cause of kidney failure, blindness in adults, and amputations. It is a major risk factor for heart disease, stroke, and birth defects. Diabetes shortens average life expectancy by up to 15 years, and costs our nation in excess of $100 billion annually in health-related expenditures – more than any other single chronic disease. Diabetes spares no group, affecting young and old, all races and ethnic groups, the rich and the poor. The discoveries of insulin in 1921 and subsequently oral agents have provided some methods for treatment, but neither treatment offers adequate levels of metabolic control or protection from the devastating long-term complications of the disease, let alone a cure. Over the past two decades, researchers have been searching for critical new insights that will provide better ways to treat, prevent, and eventually cure diabetes.

The Diabetes Research Working Group (DRWG) is composed of nationally recognized experts in the field brought together by NIH upon the request of Congress. The DRWG has concluded that the current explosion of discoveries and technological advances being made in the field of diabetes, and in biomedical research in general, present extraordinary opportunities to conquer many of the problems of diabetes. In this report, the DRWG puts forward its recommendations and describes how intensified efforts now could have a very significant impact on this disorder in the very near future.

Sixteen million people in the United States have Diabetes Mellitus.

What is Diabetes?

One reason that diabetes has been such a challenge to researchers is that it is not a single disease, but a cluster of disorders that share certain common features, the most characteristic of which is elevated levels of the sugar glucose in the blood. Under normal conditions, the body, and specifically the beta cells in the pancreas, respond to an increase in blood glucose by releasing the hormone insulin. Insulin stimulates the storage and metabolism (break down) of glucose, helping to return glucose levels toward normal. The two most common forms of the disease are referred to simply as Type 1 and Type 2 diabetes.

Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM) is caused by autoimmune destruction of insulin-producing beta cells in the Islets of Langerhans in the pancreas. Immune factors turn against and destroy the beta cells. This process leads to a deficiency of insulin; as a result, individuals with Type 1 diabetes require daily injections of insulin to survive.

Type 1 diabetes usually begins in childhood or early adulthood, and thus was formerly called juvenile–onset diabetes, but recent research has indicated that it can occur at any age. Both genetic and environmental factors contribute to its development. Unlike some childhood diseases, such as cystic fibrosis, which are due to defects in single genes, the predisposition to Type 1 diabetes results from normal variations (alleles) that occur in a number of genes, particularly those of the immune response system. These genes interact with each other and the environment to increase the risk of the disease and the rate of beta cell destruction.

Over 13,000 new cases of Type 1 diabetes are diagnosed each year in the U.S. in children and young adults under age 20, representing about 1 in 300 or 0.3 percent of this population. These young people affected with Type 1 diabetes suffer most, since they have a lifetime of disease and all of the problems it creates.

Type 2 diabetes (formerly known as non-insulin-dependent diabetes or NIDDM) is by far the most common type of this disease and, thus, has the largest public health impact. The prevalence of Type 2 diabetes is increasing at an alarming rate worldwide. It is approaching epidemic proportions due in part to increasing longevity, increasing obesity, and a more sedentary lifestyle. This form of the disease classically was thought to begin after the age of 40 and was formerly called adult-onset diabetes, but it is now increasingly common in childhood, especially in minority populations. Type 2 diabetes is closely linked to obesity and atherosclerosis, thus creating a major challenge to global public health.

In Type 2 diabetes, defects exist in both insulin action and secretion. The former is characterized by an inability of the cells of the body to respond to insulin. This insulin resistance usually develops in middle-aged or elderly persons, especially in those who are overweight. The pancreatic beta cells try to compensate but are unable to deliver insulin in a normal, precisely regulated pattern or in sufficient quantity to overcome the insulin resistance.

As in Type 1 diabetes, both genetic and environmental factors contribute to the development of Type 2 diabetes. It appears likely that many different genetic types of Type 2 diabetes exist, that is, the disease is genetically heterogeneous. In addition, the most common form of Type 2 diabetes appears to be polygenic, that is, more than one genetic alteration is necessary for its development. Thus, in most persons with Type 2 diabetes, it is likely a combination of normally occurring gene variations (alleles) that increases susceptibility to the disease. In Type 2 diabetes, however, the genes are clearly different from those involved in Type 1 disease and may also vary considerably from patient to patient, from family to family, and among ethnic groups.

Obesity and reduced physical activity, two major problems in the U.S. population today, are significant risk factors and causal determinants for the development of Type 2 diabetes in genetically susceptible individuals. It is estimated that over 97 million American adults (approximately 55 percent of all adults) are overweight, i.e. have a body mass index (BMI) of 25 kg per square meter or more and 22 percent are obese (have a body mass index of 30 or above). The problem is even greater among African Americans, Hispanics and Native Americans, in whom up to 66 percent of adults are overweight. Furthermore, obesity is now also a significant problem among children, especially in minority populations, leading to a progressively increasing incidence of Type 2 diabetes in young people. Obesity contributes to insulin resistance and thus is a major risk factor not only for Type 2 diabetes, but also for hypertension, increased blood lipids, and accelerated atherosclerosis. It has been estimated that obesity costs the U.S. in excess of $99 billion per year in associated illness, physician visits, and lost productivity. Obesity is the second most common correctable cause of premature death. About 80-90 percent of Type 2 diabetics are overweight, and in this group, control of body weight would significantly reduce the need for drug therapy.

There are also many other forms of diabetes. Gestational diabetes mellitus (GDM) occurs in 2 to 5 percent of pregnant women, mainly as a result of resistance to the action of insulin created by the hormones produced

during pregnancy. Up to 50 percent of these women will go on to develop Type 2 diabetes later in life. In addition, diabetes can develop as part of the pattern created by other hormonal diseases, specific genetic defects, or as a secondary effect of various stresses, including infection, surgery, or drugs.

All of these different types of diabetes can produce similar dire consequences. The metabolic abnormalities of diabetes, and especially the excess glucose in the blood, cause acute metabolic complications that can lead to death, such as diabetic ketoacidosis and hyperosmolar coma. Chronically elevated levels of blood glucose also damage tissues throughout the body and create many long-term complications. The major target of this damage is blood vessels—from the tiny blood vessels at the back of the eye, in the kidney, and in nerves (microvascular disease) to the large arteries that nourish the heart, brain, and extremities (macrovascular disease). Over time, this process results in permanent damage to the tissues supplied by these blood vessels. Eventually, this causes complications as diverse as blindness, kidney failure, changes in the ability of the nerves to function normally (leading to pain, loss of sensation, limb amputation, gastric disturbances, impotence, and cardiac arrhythmias), heart attacks, strokes, peripheral vascular insufficiency, and even peridontal disease and tooth loss. Thus, diabetic microvascular disease is the most common cause of blindness in working-age Americans; accounts for about 42 percent of all patients with end-stage renal failure; and is the most common cause of limb amputations. Diabetic macrovascular disease causes excessively high rates of heart attacks, heart failure, strokes, and peripheral vascular insufficiency. It is a major factor in about 29 percent of all individuals with cardiovascular disease. Diabetes in pregnant women can cause excess perinatal mortality and severe birth defects. These complications of diabetes exact an enormous toll in terms of personal debilitation and national health care costs.

The Diabetes Control and Complications Trial (DCCT) showed clearly that intensive therapy to maintain blood glucose levels as close to normal as possible slows the onset or progression of eye, kidney, and nerve disease in people with Type 1 diabetes. The recently completed United Kingdom Prospective Diabetes Study (UKPDS) and a study in Japan found similar results in patients with Type 2 diabetes. These studies indicate that control of blood glucose is the first step toward reducing the risk of diabetic complications. However, achieving tight control of blood glucose requires a daily regimen that is difficult to follow by even the most highly motivated patients, and is often nearly impossible with current therapeutic methods in some individuals. Hence, many individuals continue to develop the long-term complications of the disease and to suffer shortened lifespans. Moreover, patients who strive for tight control of blood glucose are at increased risk for hypoglycemic (low blood sugar) episodes, which are not only unpleasant, but can lead to dangerous repercussions, such as coma, seizures, and irrational behavior, as well as other complications such as weight gain. Clearly, more effective therapies and prevention strategies must be developed for the 21st century.

Magnitude of the Problem

Diabetes currently affects between 6 and 7 percent of the American population or about 16 million people. Of these,

Magnitude of Diabetes in the United States

- **Diabetes affects 16 million Americans.**
- **The prevalence of diabetes is increasing at alarming rates in all age groups from children to the elderly.**
- **Diabetes affects all groups in the U.S. population, with especially high rates in African Americans, Hispanic Americans, Native Americans, and Asian Americans.**
- **Diabetes is the sixth leading cause of death due to disease in the United States.**
- **Average life expectancy for diabetic patients is up to 15 years less than for non-diabetics.**
- **Diabetes costs the U.S. economy an estimated $105 billion annually.**
- **More than one of every ten U.S. health care dollars and about one of every four Medicare dollars are spent for care of people with diabetes.**
- **About 3 percent of the NIH budget is spent on diabetes-related research.**

one-third do not even know they have the disease. The number of individuals diagnosed with diabetes continues to grow by nearly 800,000 persons per year and will reach 23 million in just 10 years unless drastic changes occur.

Diabetes spares no group. It attacks men, women, children, the elderly, and people from every ethnic and racial background. Unfortunately, some of the fastest growing segments of the U.S. population, including individuals over age 60 and minority populations, are among the groups most at risk for developing diabetes and suffering the most severe complications of the disease. African Americans, Hispanic Americans, Native Americans, and Asian Americans are particularly vulnerable to diabetes. In most populations, risk factors such as family history, obesity, decreased physical activity, and "westernization" of lifestyle are clearly associated with the development of diabetes, suggesting that a combination of genes, the environment, and lifestyle factors increases susceptibility to the disease.

At a time when medical research is having a major impact in reducing death rates due to cardiovascular disease and stroke, the age-adjusted death rate due to diabetes has increased 30 percent (see Figure, page 2, Summary).

Thus, even with the accomplishments of diabetes research and medical care, life expectancy averages up to 15 years less in people with diabetes than in those without it. According to the most recent figures, in 1997, diabetes and its complications killed over 193,000 Americans, depriving them of 2 million years of life (CDC National Diabetes Fact Sheet, Nov. 1, 1998). Diabetes is the sixth leading cause of death by disease in the United States. These figures underestimate the true toll, however, because many deaths in which diabetes is a paramount factor are ascribed to other causes, especially cardiovascular disease, the major killer of persons with diabetes.

Costs of Diabetes

The economic costs of the disease to the Nation are staggering and continue to grow. Given the number of people affected and the range and seriousness of diabetes-related complications, it is not surprising that diabetes is one of the most costly diseases facing the country. In 1997, conservative estimates placed the cost of diabetes to the United States at $98.2 billion annually ("Economic Consequences of Diabetes Mellitus in the U.S. in 1997," Diabetes Care, Vol. 21, Feb. 1998). Based on even modest inflation and the growing number of people affected, this number now certainly exceeds $105 billion. About half of this total is the cost of treating the disease, but equally important is the other half—the lost productivity resulting from early death and/or disability. Indeed, it is estimated that more than one of every ten U.S. health care dollars and about one of every four Medicare dollars is spent for the care of people with diabetes. In stark contrast, about 3 percent of the NIH budget is spent on research directed toward diabetes and its complications, and this percentage has actually declined by almost one-third over the past 20 years.

Consequences of Diabetes

These costs of diabetes reflect the realities faced by people with diabetes and their families every day of their lives and occur in many forms.

Diabetic Eye Disease

One of the most common long-term complications of diabetes is its effects on the blood vessels and other tissues of the eye (retinopathy). In the United States, diabetic retinopathy is the leading cause of new blindness in people aged 20 to 74 years, resulting in 12,000 to 24,000 new cases each year. People with diabetes also have increased rates of cataract and macular degeneration, both of which can lead to severe visual loss.

Diabetic Kidney Disease

Diabetic kidney disease (nephropathy) accounts for more than 42 percent of all new cases of end-stage renal disease. Diabetic patients represent the fastest growing group of renal dialysis and transplant recipients. In 1996, more than 130,000 people with diabetes underwent dialysis or kidney transplantation. Since the average cost of maintaining a patient with diabetes on dialysis is $55,000 annually, this also creates a major part of the financial burden of the disease. The total cost to the nation of diabetes-related ESRD therapy is $4 billion annually.

Diabetic Nerve Disease

Sixty to 70 percent of people with diabetes will develop some form of nerve disease (neuropathy) during the course of their disease. As with many other complications, the prevalence may be even higher in minority populations. Damage to the nervous system causes a variety of disorders, including impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach,

Carter DeLarosa

I have always been a physically and mentally active person. I was a lifeguard, a runner, a professional football player, a jet engine specialist in the Air Force, a district manager for a telephone company, and a voluntary public speaker for several organizations. I never expected to have to alter my busy and physically active lifestyle until I was diagnosed with diabetes in 1964 during a routine physical at my job with the telephone company.

My blood sugar was 358, which confirmed their diabetes diagnosis. I was surprised because I didn't feel any different. But changes with my health began shortly after my diagnosis. The first problem I had was my vision. I wore glasses that gave me 20/20 vision, but eventually I went completely blind in my right eye. I had to have ongoing laser surgeries for a 13-to-14-year period. That corrected my vision to about 30/20 and also helped clear my cataracts.

I also faced kidney problems, high blood pressure, and nerve inflammation as a result of medication for my high blood pressure. My major problem has been with neuropathy. Eventually I had problems with all my extremities and developed carpal tunnel syndrome in my wrists. At a routine exam in 1990 my doctor told me I had an ulcer on my right foot. The infection in my right leg led to gangrene, and my doctor said it had to be amputated. I was shocked.

This was an extremely difficult time for me. I was used to being athletic and had to learn a whole new way to operate my body. But through this whole ordeal I tried to keep a positive attitude and always did the best I could with what I had. Also, I was curious about my condition and was constantly educating myself with any resources available. My wife was a nurse so I was familiar with much of the medical terminology, and I was an active partner in my own health care.

When my leg healed and I was fitted for a prosthesis, I learned to walk within three days. I believe I learned quickly because of my past disciplined athletic training. I feel there is nothing you can't do if you try. In life you have to fail to win—a good example of this are baseball players who have a 330 batting average. They have struck out 670 times.

Shortly after my leg healed and I was mobile, my kidneys started to fail, and I was put on peritoneal dialysis. Eighteen months went by while I waited for a new kidney that came in 1991. I had the transplant, and I feel so fortunate for new technologies in medicine.

Now I'm 67 years old. After being through these experiences, as a father, neighbor and fellow human being, I tell people to learn all they can about their health concerns. I talk to other diabetics about my own situation about 15 to 20 times a year and share all that I know. Whenever people ask about diabetes I try to help. I continue to learn and explore all that I can about my illness to take the best possible care of myself and set a good example for my children and grandchildren.

I would like to see researchers stress early treatment and intervention. I think back to my situation. If I had seen a podiatrist early on, my amputation may have been prevented. Also, I would like to see the medical profession work more as a team and stress being able to get to a diabetes specialist as soon as possible. Many of the complications from diabetes overlap and everything needs to be working together.

The primary care physician can be viewed as the quarterback, passing off the proper care at the most opportune time. For diabetic care a specialized treatment center would be ideal: a place that can treat all possible complications of the illness, such as dermatology, nephrology, cardiology, podiatry, and nutrition under one roof.

impaired regulation of heart functions that increases the risk of sudden cardiac death and other problems. An estimated 50 percent of men with diabetes experience impotence as a result of neuropathy. Nerve damage to the central nervous system can also affect the body's ability to recognize and respond to low blood sugar, or hypoglycemia. This inability creates an enormous challenge in the management of the diabetic patient, because hypoglycemia is one of the major side-effects of attempts to tightly control blood glucose.

Limb Amputation

Diabetic nerve disease, coupled with the vascular disease of diabetes, is associated with more than 200,000 cases of foot ulcers and 80,000 amputations each year. Diabetic neuropathy is the most common cause of lower extremity amputations in the United States. Indeed, more than half of lower limb amputations occur among people with diabetes. Amputation is not only physically and emotionally debilitating, it is also among the most costly non-life-ending complications of diabetes. The cost of medical care for a patient undergoing an amputation exceeds the cost of coronary bypass surgery. The number of patients requiring amputation continues to climb, despite advances in therapy and greater access to health care.

Heart Disease

Heart disease is the leading cause of diabetes-related deaths. Adults with diabetes have heart disease death rates about 2 to 4 times higher than those of adults without diabetes. Premenopausal women, who are usually protected against atherosclerosis, lose this protection if they develop diabetes, and thus have an even greater increase in risk. The incidence of stroke is 2 to 4 times higher in people with diabetes, and an estimated 60 to 65 percent of people with diabetes have high blood pressure.

Problems for Women

Diabetic women not only face additional challenges in the management of their diabetes, but are also particularly vulnerable to problems during pregnancy. The rate of major congenital malformations in babies born to women with pre-existing diabetes may be as high as ten percent among women who do not receive preconception care but similar to the general population (two percent) in those who do. Between 3 and 5 percent of pregnancies among women with diabetes result in the death of the fetus or newborn, compared to 1.5 percent for women who do not have diabetes.

Other Health Problems

Diabetes can cause many other health problems, including acute life-threatening complications, such as ketoacidosis and hyperosmolar coma, which result from the biochemical imbalance in uncontrolled diabetes. Diabetes also increases susceptibility to other illnesses, particularly infections. Periodontal disease, a type of gum disease that can lead to tooth loss, occurs with greater frequency and severity among people with diabetes. Diabetes may also lead to oral mucosal infections, salivary gland dysfunction and the burning mouth syndrome.

As Congress has recognized, reduction of the enormously high cost of diabetes and of the unacceptable burden placed on individuals with the disease and their families depends upon addressing and solving the factors responsible for these grave statistics through biomedical research. Biomedical science must find effective methods of preventing and curing diabetes and its complications. Otherwise, these human and economic costs will rise rapidly, because diabetes is one of the fastest growing diseases in the country. Fortunately, unprecedented opportunities exist for biomedical research to begin to make progress on these problems. Advances in diabetes research and in the fields of genetics, immunology, molecular and cell biology, epidemiology, and therapeutics have set the stage for an expanded and invigorated program of diabetes research to generate crucial new knowledge and effective new prevention and treatment strategies for all populations with diabetes.

Such progress requires bold new steps and a significantly expanded national investment in biomedical research on diabetes. The recommendations by the Diabetes Research Working Group contained in this report are the first step in this process toward conquering diabetes.

Impact of Diabetes on Special Populations

Diabetes is a very common disorder in all segments of the U.S. population, but it especially impacts children, women, the elderly, and several minority groups. The latter two are among the fastest growing segments of the U.S. population, leading to the prediction that the impact of diabetes will be even greater in the future if nothing is done to reduce the impact of this disease.

Consequences of Diabetes in the United States

- **Diabetes is the leading cause of new blindness in people aged 20–74 years.**
- **Diabetes is the leading cause of kidney disease requiring dialysis.**
- **As a result of the effects of diabetes on nerve and peripheral vascular tissue, diabetes is the most common cause of amputation in the United States.**
- **Diabetes patients suffer heart disease 2 to 4 times more frequently than non-diabetics.**
- **Diabetes patients suffer strokes 2 to 4 times more frequently than non-diabetics.**
- **The rate of congenital malformation in offspring of diabetic mothers may be as high as 10 percent, and fetal mortality occurs in 3 to 5 percent of pregnancies.**

Children

Children with Type 1 diabetes present one of the greatest challenges and in some ways suffer most from the disease. Children are most prone to the acute complications of diabetes, such as coma, and also the prospect of early long-term complications and premature death. Type 1 diabetes affects over 800,000 people. Its overall prevalence in the pediatric population is between 1 in 300 and 1 in 500. Epidemiological studies indicate that this number has risen steadily over the past 50 years.

Children not only have the disease from an early age, but also must endure lifelong treatment and related physical and psychological complications. Children with Type 1 diabetes face the need for life-sustaining, daily, multiple injections of insulin. An individual child will take over 50,000 insulin injections and measure blood glucose as many as 70,000 times in a lifetime. In addition, the child must adhere to strict dietary and physical activity regimens. When the insulin dose does not precisely match food intake and level of physical activity, there is the possibility of incapacitating episodes of low blood sugar. Despite adherence to these rigorous regimens, the disease may progress to serious diseases of the eye, kidney, heart, cardiovascular, and nervous systems, and shortens average lifespan by up to 15 years.

A serious emerging problem is the recent, explosive increase in obesity and Type 2 diabetes among children, adolescents, and young adults. This problem especially impacts minority populations. In some cases, this early-onset Type 2 diabetes is due to unusual genetic defects involving insulin secretion or insulin action. In most cases, however, Type 2 diabetes appears as a complex polygenic disease similar to that seen in adults. There is also increasing evidence that insulin resistance and other risk factors for cardiovascular disease have their antecedents in childhood, and are even influenced by the intrauterine environment. For example, several studies have shown that children of low birth weight have a three- to four-fold risk of developing Type 2 diabetes as adults. Thus, even young children may present the full spectrum of diabetes or be put at risk for development of diabetes by events early in life.

A major recommendation of the Diabetes Control and Complications Trial is to improve glucose control for everyone with diabetes, including children. Even in this highly controlled trial, however, the level of control achieved in adolescents did not equal that obtained in adults. Furthermore, while intensive glycemic control of diabetes has been shown to reduce the risk of serious complications, current treatment approaches for achieving glycemic control are not optimal. Intensive treatment regimens also have side effects, such as weight gain and a three-fold increase in the risk of severe low blood sugar. Both of these limit treatment compliance, and the latter also carries its own potentially significant risks. Hence, many children with diabetes go on to develop the long-term complications of the disease.

Women and the Offspring of Diabetic Pregnancies

Women comprise more than half of the population with Type 2 diabetes and have all of the complications suffered by men, as well as their own special complications. Puberty and pregnancy are periods of particular risk. Many girls first develop diabetes around the time of puberty. Diabetic women often experience a worsening of their disease during menstruation and pregnancy due to hormonal changes. If blood sugar is not kept strictly controlled during pregnancy, the chance for miscarriage is increased, and the fetus placed at risk for serious disorders, including birth defects. Some women who do not have diabetes prior to pregnancy develop gestational diabetes mellitus (GDM) during

Personal Profile

Sandra Silvestri

How does diabetes affect my family? How does it NOT affect my family? When you have a child with a chronic illness that involves food, exercise, and a metabolic function of the body that requires multiple injections every day, then you are talking about impacting every action and decision one makes in the course of a day.

My eight-year-old son has diabetes. He was diagnosed as a two-year-old. Since diagnosis I have been his pancreas. A normal pancreas responds to food, measures metabolic performance, and releases insulin. I do the same thing but a lot less efficiently. So much less efficiently that I am doomed to failure. My son has hypoglycemic reactions when I give too much insulin for too little food or too much exercise. He can get disastrous complications if I do not keep his blood sugar low enough.

This balancing act affects not only my son and me, but our entire family. For my son, it means that his mother must be a part of his life in an on-going, intrusive manner. I am sensitive to the fact that I should give my son room to discover who he is. It is difficult to do this when he refuses to eat, or wants food when there is not enough insulin to cover the need, or exercises without supervision. I plan for his life as silently as I can. I meet with his teachers. I train our hired baby-sitters and our grandparents. I educate myself and work with the Juvenile Diabetes Foundation International to increase support for diabetes research. But this does not change the daily realities of life with diabetes. I inject my child 5 times a day and take his blood 5 times a day. He is older now but in the early days after diagnosis, he hid and screamed with every shot and test. My younger son hid and my daughter covered her ears. There is no good way for any of us to face this. It is an unnatural situation. We endure it because we have no choice. Now that he is older there is less trauma at shot time but diabetes doesn't go away. It just moves along with us through our lives.

Now we worry about school. Can Joey play soccer? Can Joey test and give himself shots at school? Will the other children and parents understand and accept him? Will the school accommodate our needs? Joey is the center of these discussions.

We must be careful not to make him feel different or special. We must take care to make sure our daughter isn't neglected. We must make sure our younger child isn't passed over. We must pause and drop diabetes and be parents and a couple. My husband and I did not take a vacation without our children for 6 years. It is difficult to find a baby-sitter that is willing or able to be a pancreas as well as a baby-sitter. Someone must be aware all day of where Joey is and where he is in his pancreatic life. Does he need to eat? Does he need insulin? It is impossible to be aware but not intrusive. I must be immediately available at any time of the day or night if my son is in the care of anyone else. I wear a pager. I cannot turn it off. When it beeps, I begin to run.

We are a fortunate family. We have many blessings. But this does not change our long-term fear of complications. So, what am I supposed to tell my child about what the future holds? How can I tell him that diabetes is a disease that carries a time bomb waiting to explode at any moment--in your eyes, your kidneys, your heart, or your feet? No matter how we try, we always have that in the back of our minds. The only thing that will change this is a permanent cure. Better meters, better insulin will make our days in waiting a little easier. But only a permanent cure will bring back my son's future and my family's peace of mind.

pregnancy. It is estimated that more than 100,000 women per year in the United States have GDM. Of these, more than 50 percent later develop Type 2 diabetes.

Efforts to improve the outcome of pregnancies complicated by diabetes represent a major medical success of the 20th century. Maternal mortality, which was once greater than 50 percent in pregnant women with diabetes, has been nearly eliminated by insulin replacement and other therapies. Similarly, perinatal infant mortality rates have fallen from more than 50 percent to three to five percent in pregnancies complicated by preexisting diabetes. These rates can be reduced even further when diabetic women participate in preconceptional diabetes care programs. Nonetheless, both preexisting diabetes and gestational diabetes still increase morbidity and mortality among pregnant women and their offspring by over three times.

Groups with Disproportionate Burden of Diabetes

- **Children**
- **Women**
- **Elderly**
- **African Americans**
- **Hispanic Americans**
- **Native Americans**
- **Asian and Pacific Islander Americans**

Research in laboratory animals and humans indicates that fetal exposure to maternal diabetes may also exert a long-term impact on the offspring. Effects may include an increased risk of obesity, glucose intolerance or diabetes, and cardiovascular disease in adolescence and later life. Epidemiological and experimental evidence also suggests that factors that impede nutrition and growth during fetal life and early infancy are associated with an increased risk of cardiovascular disease and diabetes later in life.

Cardiovascular disease (CVD) occurs frequently in men and women with diabetes mellitus. Normally, premenopausal women are protected from CVD. Diabetes eliminates this protective effect. In both sexes, diabetes is a risk factor that is independent of other CVD risk factors, such as smoking, family history, and unhealthy cholesterol levels. Obesity is a risk factor both for diabetes and for CVD. In women, however, obesity's contribution to CVD is magnified, given the strong association between obesity and diabetes in women in most racial groups and the epidemic proportions of obesity in female minority populations.

The Elderly

The aging of America presents a major challenge in terms of efforts to prevent and treat diabetes and care for those who have the disease. Nearly 60 percent of persons with diabetes are 60 years of age or older, and most of these have Type 2 diabetes. The prevalence of diabetes in the elderly is about 3.5 times the rate for the general population. By age 80, 17 percent of the population will have developed diabetes. Because the elderly constitute the most rapidly growing segment of the population, the number of elderly with diabetes is expected to increase dramatically in the first half of the 21st century. By the year 2030, people over the age of 65 will make up 22 percent of the population; and by 2050, the number of people over age 80 worldwide will have increased from 66 million to more than 370 million, of whom over 60 million will have diabetes. Consequently, unless effective methods of prevention and treatment are developed and implemented, the number of older persons with diabetes will expand, as will the unique health care, public health, social, and economic problems presented by diabetes in the elderly.

African Americans

African Americans are at especially high risk for diabetes. African Americans represent about 11 percent of the U.S. population, but account for more than 17 percent of those diagnosed with diabetes. The rate of Type 2 diabetes among African Americans is 50 to 100 percent higher than that seen in Caucasian Americans, and has tripled from 1963 to 1992. The reasons for this are not entirely clear, but obesity appears to be a factor, particularly among women. Genes may also account for the consistently higher rates of Type 2 diabetes in African Americans. In comparison with Caucasians, African Americans with diabetes also have two-fold higher rates of blindness, three- to five-fold higher rates of end stage kidney disease, and two-fold higher rates of lower limb amputation. This results in both higher costs for treatment and higher death rates from diabetes in this population.

Hispanic Americans

Hispanic Americans, including Mexican Americans, Puerto Ricans, and Cuban Americans, comprise the second largest and fastest growing minority group in the United States. Available information suggests that the rate of Type 2 diabetes in Mexican Americans and Puerto Ricans is about 2 times higher than for non-Hispanic white populations. The rate for Cuban Americans is 30 to 50 percent higher than for Caucasian Americans, but considerably lower than the rates for Mexican Americans and Puerto Ricans. As in the African American population, risk factors for Type 2 diabetes in Mexican Americans include age, obesity, and genetic factors. Socioeconomic status may also play a role. Interestingly, the rate for Type 1 diabetes among Hispanic American children is 50 to 70 percent lower than among Caucasian American children. Like African Americans, Hispanics also have higher rates of long-term complications. The reasons for these differences are not yet known.

Native Americans

Native Americans are the population in the United States most disproportionately affected by diabetes, especially Type 2 diabetes, and this problem is increasing. Available

data indicate that the age-adjusted death rate from Type 2 diabetes is 2.7 times higher in Native Americans than in the general population. Among the Pima Indians, who have been studied in detail by NIH since 1965, more than 50 percent of adults have Type 2 diabetes, and the death rates due to diabetes are over 10 times greater than those for Caucasians in the United States. Native Americans also have high rates of complications, including end-stage renal failure and peripheral vascular disease with amputation. Genetic factors and adoption of a "westernized" lifestyle appear to be linked to diabetes in these Native Americans. The prevalence of diabetes is associated with the degree of Native American heritage, with the highest rates of diabetes found among those who are of full Native American heritage. Family history is also a significant factor, suggesting that genes and family lifestyles may increase the susceptibility to diabetes.

Asian and Pacific Islander Americans

Asian and Pacific Islander Americans comprise over 20 population groups. The major Asian groups are the Chinese, Filipino, Japanese, Asian Indian, Korean, and Vietnamese. The major Pacific Islander American groups are Hawaiian, Samoan, and Guamanian. Type 1 diabetes is relatively rare in these populations. These groups, however, are disproportionately affected by Type 2 diabetes. The prevalence of Type 2 diabetes is about two to four times higher in Asians living in the U.S. than in those living in their native country. While data is limited for Pacific Islander American groups, the prevalence of Type 2 diabetes in Native Hawaiians appears to be at least twice that of Caucasians. In Western Samoa, diabetes prevalence is at least twice as high in the urban population than in the rural population. The complications of diabetes affect Asian and Pacific Islander Americans as severely as other groups. Studies in Asian and Pacific Islanders indicate that dietary changes and reduction in physical activity--both of which contribute to weight gain--are lifestyle changes that may be important in the development of Type 2 diabetes in these populations.

Alaska Natives

The rates of Type 2 diabetes in Alaska Natives are similar to rates found in U.S. Caucasians. The complications of diabetes, however, affect Alaska Natives as severely as they affect other groups.

Toward an Answer

In 1997, the United States Congress responded to the threat posed by diabetes by directing the National Institutes of Health (NIH) to establish a panel of leading experts who would recommend a comprehensive approach to future NIH-funded diabetes research.

Language in the House and Senate reports accompanying the Fiscal Year 1998 appropriations for the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) instructed the Director of the NIH to appoint a Diabetes Research Working Group with a chairperson from outside the Government and a membership drawn from leaders in academic and industrial research and organizations representing people with diabetes. The Diabetes Research Working Group (DRWG) first convened in January 1998 to begin developing this comprehensive plan for NIH-funded diabetes research.

Members of the DRWG—with experience gained in academic medical centers, pharmaceutical companies, government agencies, private advocacy and service associations, and organizations representing ethnic groups with especially high rates of diabetes—offer a wide range of expertise in treatment, prevention, and basic research. At meetings held throughout the year, they examined the state of research across the entire field of diabetes. With the assistance of other diabetes experts from around the country, the Group identified specific research opportunities that offer the best prospects for making genuine and significant progress toward understanding, more effectively treating, and ultimately preventing and curing diabetes. These exceptionally promising scientific prospects, along with the projected rise in the number of Americans with the disease, make this a particularly opportune moment for a major national effort against diabetes.

The DRWG believes that the next decade offers unique research opportunities that, if seized now, can greatly improve the lives of Americans who have or are at risk for diabetes. The Group is convinced that taking bold action at the national level now could save many thousands of men, women, and children from the severe consequences of a dangerous, potentially disabling and often fatal disease and also save the Nation many billions of dollars in medical care costs and lost productivity. From both human and scientific perspectives, now is the time for the United States to move decisively against diabetes.

The Strategic Plan for diabetes research developed by the DRWG represents a comprehensive approach which the Group believes will allow the most rapid possible progress toward prevention, improved treatment, and an ultimate cure for diabetes.

Successful implementation of this plan requires a major increase in the NIH diabetes research budget. Federal funding of diabetes research has long been insufficient and disproportionately low relative to the medical and public health consequences of this disease. As a result of chronic underfunding, investment in diabetes research and related infrastructure has been seriously deficient. This deficiency has severely limited progress in understanding the disease, enhancing its treatment, and realizing its ultimate prevention and cure. Although the lead Institute for the diabetes research effort is the National Institute of Diabetes and Digestive and Kidney Diseases, diabetes is truly a multisystem disease, thus this report calls for additional new funds to support diabetes research for many NIH Institutes and Centers.

The FY 1999 NIH budget for diabetes research is estimated at $442.8 million. While this may seem like a lot, this represents only about $30 per person affected per year. Furthermore, the diabetes research effort as a fraction of total NIH spending has decreased by almost 30 percent over the past 20 years. At the current level, diabetes research represents about three cents of each dollar spent on research by the NIH, while the cost of diabetes health care represents between ten and fourteen cents of every dollar spent on health care. Even with the additional funding for research provided by private, nonprofit groups such as the American Diabetes Association, the Juvenile Diabetes Foundation International, other foundations, and the pharmaceutical industry, the total effort is not commensurate with the compelling needs and opportunities in diabetes research.

The DRWG believes that the current effort and scope of diabetes research falls far short of what is needed to capitalize on the research opportunities that exist today and that will ultimately improve life for individuals with diabetes and their families. Immediate and full pursuit of these opportunities can lead to better treatment, prevention, and cure of the disease and reduce the economic cost to the country. The Group believes that, without implementing a comprehensive, coordinated plan to take full advantage of today's rapidly developing research opportunities, the nation cannot achieve maximum progress toward lifting the ever-increasing burden of diabetes from the American people and from people everywhere.

Major Goals

Ultimately, the goal of diabetes research is to develop new approaches for the prevention, cure, and improved treatment of all forms of diabetes and their complications. Finding these answers will require research on many complex, interwoven genetic and environmental factors. If research can isolate the characteristics that cause an individual to be susceptible to diabetes and can determine the many biochemical and cellular mechanisms leading to its complications, it should be possible to design interventions to prevent the disease and its complications.

The Strategic Plan set forth by the DRWG has two overarching goals:

- Understand the causes and define approaches to prevent the development of Type 1 and Type 2 diabetes and related complications.
- Develop methods for optimal management, treatment and ultimate cure of diabetes and its complications.

Additional important objectives of the research plan include the following:

- Reduce the disproportionate burden of diabetes on minority populations, children, women, and the elderly.
- Significantly enhance and broaden support of basic and clinical diabetes research across a wide spectrum of related scientific and medical disciplines related to diabetes.
- Ensure the ability to attract, recruit, and sustain a cadre of talented researchers and physician-scientists to address needs and opportunities in diabetes, including experts from diverse scientific disciplines.
- Expand research resources and other aspects of the research infrastructure in order to establish an environment in which diabetes research will flourish.
- Enhance the flow of knowledge in and out of the diabetes field to promote cross-fertilization of all biomedical research.
- Identify means for the effective translation of important diabetes research advances to medical practice and to the public.

These opportunities warrant immediate pursuit at the highest level of effort. As a result of previous government funding, exciting advances have been achieved in diabetes research. Many challenges remain, however. The scientific stage has been set. Additional resources, now, will enable diabetes research to cross the threshold into a new era of discovery.

The Problem and Where We Stand

Specific Aspects of the Problem

To develop a research plan, we must understand what is known about the pathogenesis of Type 1 and Type 2 diabetes and their complications, as well as the major research advances, current treatment approaches and prevention strategies. We must also take a critical look at the current National Institutes of Health (NIH) research portfolio in diabetes, along with historic funding trends, and other sources of support for diabetes research.

Type 1 Diabetes Mellitus

Like many diseases, Type 1 diabetes is due to an interaction between the genetic makeup of an individual and his or her environment. This interaction somehow causes autoimmune destruction of insulin-producing beta cells in the pancreas, leading to a lack of insulin. Thus, individuals with Type 1 diabetes require daily injections of the hormone to sustain life. Current methods of insulin administration, however, cannot reproduce the normal beta cell's ability to precisely control blood glucose and other metabolic variables. Hence, the Type 1 diabetic remains susceptible to the long-term and devastating complications of diabetes.

Current Treatment and Prevention Strategies

The current treatment of Type 1 diabetes is based on the seminal discovery of insulin, more than 75 years ago. To provide their bodies with sufficient insulin to sustain life, many patients take two, three, and even four insulin injections daily, preceded each time by blood testing to ensure accurate choice of dose. Genetic engineering of the insulin molecule and new methods of delivery have improved insulin therapy, but in essence, the treatment for Type 1 diabetes has changed little since insulin was discovered. Moreover, while treatment with insulin has prevented death from acute metabolic complications of the disease, it has not halted the devastating secondary complications of diabetes, such as blindness, kidney disease, heart disease, stroke, amputations, nerve damage, and premature death.

One of the major accomplishments of NIH-funded research over the past two decades has been the Diabetes Control and Complications Trial (DCCT). This study provided unequivocal proof that tight control of blood glucose levels in patients with Type 1 diabetes can reduce the progression and incidence of microvascular complications. However, achievement of tight control of blood glucose demands a stringent daily regimen with multiple measurements of blood glucose and multiple insulin injections or use of an insulin pump that is difficult to follow by even the most highly motivated of patients. Indeed, it would be fair to say that there is still very limited success in identifying readily applicable methods for truly effective tight blood glucose control. Hence, many individuals continue to develop the long-term complications of the disease and as a result have shortened lifespans. Moreover, patients who strive for tight control of blood glucose are at increased risk for hypoglycemia (low blood sugar), which is not only unpleasant, but can lead to

Major Advances in Type 1 Diabetes

- **Identification of Type 1 diabetes as an autoimmune disease that destroys insulin-producing pancreatic beta cells.**
- **Identification of some of the major genes predisposing to Type 1 diabetes.**
- **Identification of some of the beta cell components attacked by the immune system.**
- **Recognition of the long phase of pre-diabetes where markers of the immune response allow for prediction of disease development.**
- **Demonstration through the DCCT that "tight" glucose control can significantly reduce the microvascular complications of Type 1 diabetes.**
- **Increased understanding of beta cell biology, which set the stage for developing means for replacement of beta cell function, including pancreatic islet transplantation.**

dangerous repercussions, such as seizures, coma, and irrational behavior. Clearly, more effective therapies and prevention strategies must be developed for the 21st century.

Major Advances in Research on Type 1 Diabetes Over the Past Decade

Immunologic Basis of Beta Cell Destruction and Mechanisms of Tolerance

It is now clear that Type 1 diabetes is an autoimmune disease that destroys the insulin-producing capacity of pancreatic beta cells. Research conducted over the past decade in animal models of Type 1 diabetes, as well as in pre-diabetic and recent-onset diabetic patients, has identified some of the elements of the pathway by which certain lymphocytes called T-lymphocytes or T-cells cause a chronic state of inflammation in pancreatic islets (insulitis) that leads to beta cell destruction. Major progress has also been achieved in the past 10 years in identifying the specific components of the islet beta cells that are the targets of these destructive autoimmune T cells. Antibody responses to certain proteins in the beta cells, including insulin, glutamic acid decarboxylase (GAD) and the enzyme IA-2, are found in most patients who develop Type 1 diabetes. Although much remains to be learned about the exact mechanism of beta cell destruction, it appears that the major factor leading to the destruction is the activated T-cells and that the antibody response serves as a marker for this process. This is similar in process to other autoimmune disorders, such as rheumatoid arthritis, lupus erythematosus, thyroiditis, and possibly multiple sclerosis.

Identification of Some of the Genes that Predispose to Type 1 Diabetes

Although multiple genes may contribute to development of Type 1 diabetes, research has shown that the strongest genes predisposing to Type 1 diabetes are alleles of the major histocompatibility complex (MHC). These MHC molecules, also known as Human Leukocyte Antigens (HLA), are intimately involved in the activation of T-cells and regulation of the immune response. The HLA types most associated with Type 1 diabetes are HLA DR3 and DR4. Between 80 and 90 percent of patients with Type 1 diabetes are positive for one or both of these high-risk alleles. However, about 30 to 40 percent of individuals without diabetes also have these HLA alleles. Thus, the HLA type of patients is a necessary, but not sufficient, factor for predisposition to diabetes. Studies in both mouse and man indicate there may be as many as 15 other genes, encoded on other chromosomes, that influence susceptibility to Type 1 diabetes. A major focus in the Type 1 diabetes research community is to identify this group of genes.

Methods for Early Prediction of Type 1 Diabetes

One of the most important observations of the past 20 years has been the recognition that Type 1 diabetes is a slowly progressive autoimmune disease, and that antibody markers can be detected several years prior to development of clinical disease. The ability to detect and predict diabetes is critically important for rational testing of strategies for intervention and prevention of the autoimmune response. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is currently sponsoring one nationwide clinical study to determine whether early intervention in patients at high risk, as detected by these antibodies, can prevent or delay onset of Type 1 diabetes. Since prevention is ultimately the most effective cure of any disease, clearly many more efforts of this type are needed.

Importance of Intensive Glycemic Control—The Diabetes Control and Complications Trial

Although insulin therapy has been used in the treatment of diabetes for more than 75 years, there has been a long debate as to the efficacy of this approach in prevention of complications. The DCCT was a 10-year, federally-funded investigation into the relationship between intensive insulin therapy and the microvascular complications of diabetes. This study involved 27 research groups at top medical centers in the United States and Canada, and was completed in 1993. It is now considered one of the most conclusive and important large-scale clinical trials ever conducted. More than 1,400 patients were divided into two groups. One received traditional, less-intensive insulin therapy, usually involving a single injection of insulin per day and daily blood glucose monitoring. The other group carried out "intensive" therapy, involving multiple blood glucose measurements and insulin delivery via several daily injections or mechanical pumps that infused the hormone continuously over the course of each day.

The trial showed unequivocally that intensive therapy could improve control of blood glucose and that this would very significantly reduce the incidence and progression of the major secondary complications of Type 1 diabetes. Since publication of the findings of the DCCT, it has become clear to patients and physicians alike that application of an intensive insulin therapy regimen to the general population of Type 1 diabetic patients is extremely difficult and not commonly achieved. In addition, the DCCT demonstrated that patients in the intensive therapy group had three times the risk of severe episodes of low blood glucose levels as patients who received more traditional therapy. Taken together, these points emphasize the need for more research on how to apply the best approaches of current therapy. They also underscore the importance of developing strategies for prevention of beta cell destruction or replacement of the lost beta cell function, as better alternatives to current therapy.

Advances in Understanding of Beta Cell Biology

For those who have already developed Type 1 diabetes, optimal control would be best achieved by replacing the lost beta cell function. New strategies for true replacement of beta cell function are focusing on development of safe and effective methods for pancreatic and islet cell transplantation and methods to stimulate growth of human beta cells. They are also pursuing genetic engineering approaches to procure beta cell lines that might serve as replacements for the destroyed human islets. These strategies rely on gaining a basic understanding of how beta cells grow and develop in living animals and the mechanisms by which beta cells secrete insulin in response to appropriate nutritional and hormonal signals. Important breakthroughs have occurred in both of these areas of beta cell biology, including identification of several genes critical for pancreatic development, and the pathways allowing the beta cell to secrete insulin in response to glucose or hormonal signals. However, much more remains to be learned about the fundamentals of beta cell biology if this is to be used as a therapeutic approach.

Challenging Areas of Critical Importance in Type 1 Diabetes

Many critical research challenges must be met if effective and readily applicable glucose control is to be achieved in all individuals with Type 1 diabetes, and if methods are to be developed to prevent the onset of the disease.

The findings of the DCCT emphasize the need to improve strategies for insulin delivery and to develop new approaches to replace lost beta cell function in order to reduce the incidence and progression of the complications of Type 1 diabetes and to prolong life. Diabetes research needs to develop methods for achieving tight glucose control that are effective and generally applicable. These new methods should provide treatment regimens that those with diabetes can follow and that avoid debilitating and sometimes incapacitating episodes of hypoglycemia. Improved methods of insulin delivery are needed that are not dependent upon multiple daily injections, but use new forms of insulin or insulin-like molecules or new

HIGHLIGHTS OF DIABETES RESEARCH

1889	1898	1900's (early)
Drs. Oskar Minkowski and Joseph von Mering discover that removing the pancreas causes diabetes.	Heredity is a factor in causing diabetes.	Urine glucose levels are measured with ferric chloride. The procedure takes about 30 minutes and can only be done in a hospital. Before the discovery of insulin, diabetes can only be treated with diet modification.

Personal Profile

Nicole Johnson
Miss America 1999

I hadn't been feeling well. I was a 19-year old college sophomore and was rationalizing the signs and symptoms as simply part of being a college student. When I didn't get over what I thought was a nagging flu, I sought medical help. I was misdiagnosed a few times before all my symptoms led me to the emergency room. The ultimate diagnosis of diabetes came in the ER when my glucose level was 510. The normal glucose level rarely goes above 150, even after a meal.

As someone with Type 1, or early onset diabetes, I rely on a constant stream of insulin to stay alive. It was very, very difficult for me to adjust at the beginning because I didn't know anything about diabetes. I thought I had been given a death sentence. My family and I experienced the same emotions—depression, anger, resentment. My parents thought it was something they had done or given to me.

I have come full circle since my diagnosis more than five years ago and turned the corner of dealing with diabetes. The most important lesson I've ever learned is that I can control the disease; it doesn't control me. When I figured that out I no longer had a fatalistic attitude and became more proactive in my health care.

Currently, there is no cure for diabetes, and research into its genetic makeup and causes is our only hope. Insulin and other treatments are merely life support. Until a cure can be found, we must minimize the devastating effects of this disease through early detection, testing, and diagnosis. My Miss America platform, "Diabetes in America: Unmasking the Hidden Killer," emphasizes awareness of diabetes, its symptoms, and its consequences. I support programs advocating early detection and testing, but also those that advance effective treatment and a cure. To accomplish this, we must be unified as a collective diabetes community. We must get away from the politics and stay focused on the issue.

I have advocated that Congress increase funding for national diabetes research. In my home state of Virginia, I assisted in the passing of diabetes-related legislation. I have received more than $65,000 in scholarship monies during my quest for the Miss America crown, but nothing is more important than the prevention and treatment of diabetes and its complications.

I wasn't always as open as I am now about my diabetes. There's no benefit in giving in to the fear of disclosure or expending energy guarding the fact. If people don't know, they can't help you, and perhaps you can't help others. Discussing my diagnosis and serving as Miss America afford me many opportunities to help. People come to me and say, "I'm just like you. You really understand me, and I feel comfortable sharing my fears or my hopes with you because of that connection."

I want to give encouragement and inspiration to the people living with the perils of diabetes on a daily basis. Those of us with this disease are often told we cannot realize wonderful things in our lives. I travel 20,000 miles a month, into a different city every other day, on my national speaking tour. I want others with diabetes to know that, if I can become Miss America with Type 1, and function successfully with this kind of schedule, they too can certainly pursue their goals and dreams.

1902	1910	1912	1915
Secretin (a gastric secretion) is discovered and the term “hormone” is introduced.	At this time, the “diabetic diet” consisted of 70% fat, 18% protein, and 12% carbohydrate and was considered to be a diet of “undernutrition.” The artificial sweetener, saccharin, is available although it is recommended that diabetics restrict sweets.	Frederic Allen experiments with restricting the carbohydrate intake of diabetics and develops the “Allen Diet” for treating diabetes.	Glucose monitoring was done using Benedict’s Solution. This was an inexpensive and easy way to measure urine glucose and was called the “Rainbow Test.”

Major Research Challenges In Type 1 Diabetes

- **Development of new, readily applicable methods for achieving "tight" glucose control without hypoglycemia.**
- **Identification of predisposing genes and discovery of the biochemical mechanisms by which these genes create susceptibility to and produce disease.**
- **Identification of causative environmental factors.**
- **Understanding the causes and molecular mechanisms responsible for autoimmune destruction of insulin-producing beta cells.**
- **Identification of specific markers to predict individuals at risk.**
- **Development and testing of methods for replacing beta cell function in patients, including islet transplantation.**
- **Development of a sufficient source of insulin-producing cells for cell-based therapy.**
- **Development and application of more effective therapies for prevention, cure, and better treatment.**

approaches to delivery. Comprehensive investigation of the effectiveness of pancreatic islet transplantation and other approaches to replace damaged pancreatic beta cells must proceed in parallel with development of methods for regeneration of beta cells and stimulation of their growth.

Effective prevention strategies are equally important. These strategies require a concerted research effort to identify the group of genes that interact to cause Type 1 diabetes and to identify the causes and molecular mechanisms responsible for the autoimmune destruction of beta cells. Recent advances in genetic and immunology research, and increased understanding of the biology of the beta cell, provide unprecedented opportunities in this area. Environmental factors precipitating Type 1 diabetes in genetically susceptible individuals must be identified and effective interventions developed to disrupt these gene–environment interactions. This approach presents an enormous challenge to epidemiologic research, because these factors may play their most important role years prior to the clinical onset of disease. Based on recent progress in Type 1 diabetes research, as well as the important understanding of immune mechanisms and basic islet cell biology, the DRWG believes that extraordinary opportunities exist for new and expanded programs that will accelerate our attempts to conquer this disease.

Type 2 Diabetes Mellitus

Type 2 diabetes is a complicated, multifactorial disease in which interactions between multiple genes and multiple environmental factors ultimately result in development of the diabetic state. Type 2 diabetes is characterized by a resistance to insulin action in many different tissues in the body coupled with an inability of the pancreas to deliver insulin in a precisely regulated pattern and quantity to control glucose metabolism. Ultimately these two defects of insulin resistance and relative beta cell failure lead to high blood glucose levels and clinically overt Type 2 diabetes.

Type 2 diabetes is extraordinarily common, affecting about 6 percent of the U.S. population, and is therefore the most significant form of diabetes from a public health perspective. Obesity and reduced physical activity, also major problems in the U.S. today, are important risk factors for Type 2 diabetes, and more than 80 percent of people with Type 2 diabetes are obese. Evidence suggests that controlling these risk factors can help prevent the development of diabetes in many genetically susceptible individuals.

1921	1922	1923		1936
Dr. Frederick Banting and Charles Best discover insulin and save a diabetic dog.	A Canadian man is the first person to be given insulin.	Insulin becomes widely available to patients. At this time, only short acting insulin is available and must be taken before every meal and during the night. Glass syringes are the only type available and must be sterilized. Large steel needles (non-disposable) are used.	The recommended diet consists of 70% fat, 20% carbohydrate, and 10% protein. Diet must be coordinated throughout the day to meet the action of the insulin.	Protamine Zinc Insulin (PZI), the first long-acting insulin, is developed by a Danish physician.

Current Treatment and Prevention Strategies for Type 2 Diabetes

Current treatment for Type 2 diabetes is quite variable and often staged to the progress of the disease. Early on, or in mild cases, diet, weight loss, and exercise are used to improve insulin sensitivity. If this is inadequate, oral hypoglycemic agents are added. These may act to further improve insulin action, stimulate more insulin secretion or alter the absorption of carbohydrates in the diet. If these steps are unsuccessful, the patient is often placed on insulin, just like the patient with Type 1 diabetes. These approaches have limited success in controlling elevated glucose levels in patients with Type 2 diabetes, or in controlling obesity that predisposes to this disease. Thus, current treatment of Type 2 diabetes is far from satisfactory.

The recently completed United Kingdom Prospective Diabetes Study (UKPDS) highlighted this problem. Like the DCCT for Type 1 diabetes, the UKPDS demonstrated that improved glucose control decreased risk of long-term complications in Type 2 diabetes. However, the study showed that, after a marked improvement during the first year of the study, there was a gradual rise in blood glucose (i.e., worsening of control) in the subsequent 15 years of follow-up in both the intensive and less-intensive treatment groups. Indeed, in many individuals this occurred despite increasing the intensity of the therapeutic regimen.

Likewise, there is currently no readily applicable and effective approach to prevention of Type 2 diabetes. Although evidence suggests that controlling obesity and physical inactivity can prevent, or at least delay, the development of disease in many genetically susceptible individuals, success in controlling these risk factors has been limited. As a consequence, the incidence of Type 2 diabetes is steadily rising, and patients with Type 2 diabetes continue to develop the complications of eye disease, kidney failure, heart disease and stroke, nerve damage, and limb amputations. The NIDDK is currently sponsoring a nationwide, multicenter clinical trial to assess the effectiveness of dietary and drug interventions in preventing or slowing the progression to full-blown, clinical Type 2 diabetes in high-risk individuals.

Major Research Advances in Type 2 Diabetes

Genetics of Type 2 Diabetes

Research has demonstrated that Type 2 diabetes is strongly genetically determined, but it appears likely the disease is genetically polygenic and heterogeneous, that is, more than one genetic alteration is probably necessary for development of the disease, and different genetic factors may play a role in different populations or families. Some progress has been made in identifying specific genes involved in some

Major Research Advances In Type 2 Diabetes

- **Identification of genes involved in some subtypes of Type 2 diabetes.**
- **Clear demonstration that obesity, physical inactivity, and other lifestyle factors are important environmental risk factors in genetically susceptible individuals.**
- **Discovery of genes involved in development of obesity in laboratory animals.**
- **Discovery of neurohormones and other proteins involved in control of appetite and energy balance.**
- **Identification of many steps involved in insulin action pathway in cells.**
- **Elucidation of some steps involved in insulin secretion from pancreatic beta cells.**
- **Use of noninvasive technology such as nuclear magnetic resonance (NMR) and positron emission tomography (PET), as well as other new technologies, to study metabolic derangements in affected patients and animals.**

1943	1945	1947	1948
The kidney dialysis machine is invented.	Investigators begin to focus on the liver and its regulation of blood sugar.	Based on an U.S. Public Health Service survey, it is believed that one in 70 people has diabetes.	Hagedorn, a Danish physician, develops another delayed action insulin; referred to as NPH for "Neutral Protamine Hagedorn," and could be mixed with fast-acting "regular" insulin. This enabled many patients to be able to manage their diabetes with a single daily injection. The ADA begins the first nationwide study to determine the prevalence of diabetes in the population.

relatively rare subtypes of Type 2 diabetes, and there are leads in the search for other genes. Studies have demonstrated that mutations in genes controlling the first step of the insulin-signaling cascade, the insulin receptor, can cause a rare form of Type 2 diabetes with severe insulin resistance. Research on a second subtype of Type 2 diabetes, Maturity Onset Diabetes of the Young (MODY), has also provided new insights. Studies have shown that MODY can be the result of alterations in one of several genes for nuclear transcription factors (genes that regulate the expression of other genes), as well as of the control of key enzymes of the beta cell. These findings have helped define these subtypes of Type 2 diabetes, and opened up important new avenues of research into other potential diabetes genes, such as those controlling signaling molecules, transcription factors, and their downstream targets. These studies illustrate the general paradigms for identification of susceptibility genes for diabetes. Recent technological advances in genotyping, sequencing, and methods of gene mapping for complex disorders suggest that continued investment in genetic studies of Type 2 diabetes and related disorders will pay great dividends.

Interaction of Genetic and Environmental Factors

Epidemiological studies in Type 2 diabetes have highlighted the importance of gene–environment interaction in this disease. Thus, based on genetics, some racial and ethnic groups are at very high risk for development of Type 2 diabetes, but only if environmental factors allow or promote its expression. For example, the Pima Indians of Arizona currently have the highest prevalence of diabetes in the world, with about 50% of those over age 35 affected. This high prevalence, however, is strongly dependent on environment and lifestyle factors, such as activity and diet. At the turn of the century, diabetes was unrecognized in the Pimas, and even now, the Pima Indians of Mexico have almost none of this disease. Similar effects of environment and lifestyle have been observed by comparing ethnic Japanese living in Washington State with those living in Japan. Even in a single geographic area, individuals of similar genetic background have differing risks of Type 2 diabetes depending on level of activity, diet, and body weight. These situations serve as models for the study of gene–environment interaction in diabetes and other complex genetic disorders.

Insulin Secretion, Insulin Action, and Insulin Resistance

The earliest detectable defect in most individuals with Type 2 diabetes is a decrease in insulin action on peripheral tissues such as liver, muscle, and fat. This condition is termed insulin resistance. Over the past two decades, substantial progress has been made in defining the molecular steps of insulin action, glucose transport, and the sites of tissue insulin resistance fundamental to the development of Type 2 diabetes. These pathways, however, are extremely complex and involve many different molecules and compartments within the cell and the body. In addition, insulin resistance is an important determinant of other common metabolic diseases including obesity and atherosclerosis. Thus, determining all of the steps and defining which is the "primary" defect in Type 2 diabetes are very important.

The normal response of the body to insulin resistance is to increase insulin secretion. While this response occurs early in Type 2 diabetes, the beta cell begins to fail as the disease progresses. This failure is not due to destruction of beta cells, but rather to a functional impairment, and especially due to a loss in the ability of the beta cell to respond normally to the glucose signal with appropriately increased insulin secretion. Many of the steps in this glucose response pathway are now beginning to be elucidated at a molecular level. These steps involve proteins that enable glucose to enter cells (glucose transporters) and enzymes essential to metabolism of glucose inside the cell.

Defining the steps in insulin action on glucose, lipid, and protein metabolism and the mechanism for regulated insulin secretion provides important new targets for development of antidiabetic drugs. This type of "discovery" research is traditionally the greatest strength of NIH-funded endeavors, but will need considerable enhancement for the development of new therapies of this disease.

1950	1952	1953	1955
Diets are still restricted, with fat now comprising a smaller percentage of the total caloric intake (40% fat, 40% carbohydrate, and 20% protein). Recognition that insulin promotes glucose transport.	Lente, another insulin with intermediate action, is developed.	First human kidney transplant from a live donor is performed. The first meeting of the International Diabetes Federation is held with diabetes organizations around the world attending.	Vascular bypass surgery in the lower leg is developed. Sanger and his colleagues determine the amino acid sequence of insulin.

Obesity

Obesity is a major risk factor for Type 2 diabetes, as well as a significant, independent health problem. Like Type 2 diabetes, obesity has strong genetic and environmental components. During the past few years, genes have been cloned that encode some of the hormones involved in control of appetite and adipose tissue mass, as well as some of their receptors. A major stimulus to this area of research was the discovery of the hormone leptin. This hormone is secreted by fat cells and acts on a receptor on cells in the brain and tissues to help regulate food intake and energy balance. The leptin gene and the gene for the leptin receptor were subsequently cloned. Defects in these and other genes resulting in obesity in rodents, and their roles in human obesity, are under intense investigation. The explosion of exciting new information on the genetics of obesity in laboratory animals lays the groundwork for key clinical advances in this area.

There has been unprecedented progress in other areas of this field. Obesity is the result of an imbalance between energy intake and energy expenditure. Insights into obesity have derived both from studies of metabolism, as well as from neuroendocrinology, that is, how hormones work in the brain to control the body's functions. For example, in addition to leptin, several other hormones that control eating behavior have been discovered. Some of these stimulate appetite, while others inhibit the hunger signal or create satiety. Genetic knockouts of some of these hormones and their receptors have confirmed roles for their ligands in regulation of energy balance. "Uncoupling proteins" (UCPs) are proteins that play an important role in determining how energy is used. Over the past two years, two new UCPs, UCP-2 and UCP-3, have been discovered. These molecules apparently increase the rate of energy expenditure, thus affecting energy balance and body weight. Clearly, however, the key pathways for successful therapy of obesity have yet to be identified, and much more research is needed.

At a clinical research level, several refined measures of energy expenditure and metabolism, including hood and chamber calorimetry and differential excretion of heavy isotopes of water, have been used to identify subtle defects in these pathways in children and adults who have been or are likely to become obese. In addition, investigators have identified some of the molecular switches (nuclear transcriptional factors) that play a central role in determining how fat cells (adipocytes) develop. Interestingly, one of these, a molecule called PPAR (Peroxisome Proliferator Activating Receptor), also serves as the receptor for a new class of insulin-sensitizing drugs, the thiazolidinediones.

Finally, it is important to consider behavior. Substantial research has been done in this area, which indicates that individuals who are obese develop hunger in response to different cues than thin individuals and have different patterns of activity, even when at rest. We still do not understand what determines such behaviors, how to accurately measure them or, most importantly, how to influence them, especially over a long period of time. Research on how to produce behavioral changes that can be maintained long-term at both the individual and population level will have great potential value in preventing obesity and Type 2 diabetes.

Use of New Technologies to Gain Insight into the Metabolic Derangements of Type 2 Diabetes

Understanding the molecular basis of insulin action and insulin secretion in Type 2 diabetes is crucial to unraveling the specific steps that are defective in this disease, and translating basic research findings to clinical practice is essential. The use of high-technology techniques in clinical research to measure these parameters has begun to move this translational goal forward. Through the use of NMR spectroscopy and PET, it is now possible to measure many metabolic pathways in various tissues of living human beings. When coupled with the use of stable, non-radioactive isotopes and mass spectrometry, the tools required for metabolic staging of diabetes are beginning to be assembled in a manner never before possible. The ability to continue to expand the use of these technologies and develop new technologies will provide important tools for future research.

1956	1959	1960	1964
Oral hypoglycemic agents become available to help patients with Type 2 diabetes manage their condition.	Krebs and Fischer discover protein phosphorylation.	Immunoassay is developed which allows researchers to measure insulin in blood. This assay showed that people with Type 1 diabetes produced no insulin, but that individuals with Type 2 diabetes have more insulin than normal. Self-monitoring of glucose begins with "Wet" method using glucose oxidase strips.	Kidney transplants begin in diabetic patients. Diagnostic criteria for gestational diabetes are established.

Major Research Challenges In Type 2 Diabetes

- **Identification of the genes conferring disease susceptibility in common forms of Type 2 diabetes and obesity.**
- **Elucidation of the molecular mechanisms responsible for insulin resistance and defective insulin secretion.**
- **Definition of the pathways of appetite regulation, energy expenditure, and control of body weight and their interaction with insulin action and secretion.**
- **Identification of other environmental factors converting predisposition to Type 2 diabetes into overt clinical disease and the mechanisms by which they do so.**
- **Determination of the mechanisms linking Type 2 diabetes, insulin resistance, atherosclerosis, and hypertension—the "metabolic syndrome."**
- **Development of animal models representative of human Type 2 diabetes.**
- **Development of methods by which behavior modification can be effectively applied to prevent Type 2 diabetes.**
- **Application of noninvasive and other cutting-edge technologies to unravel the metabolic derangements.**
- **Development of more effective therapies for treatment, prevention, and cure.**

Challenging Areas of Critical Importance in Type 2 Diabetes

Although recent research advances afford unprecedented opportunities to understand Type 2 diabetes, major challenges confront researchers in solving the many puzzling aspects of this disease to enable better treatment and ultimately prevention.

Both prevention and better treatment of Type 2 diabetes require a concerted research effort to unravel the complex genetics of this disease and to utilize this information to identify new targets for pharmacologic intervention. Prevention and better treatment of Type 2 diabetes require new knowledge regarding the mechanisms responsible for defects in insulin action and insulin secretion, the two hallmarks of the disease. Research is needed on the genetics and mechanisms of insulin resistance, on genetic and other factors regulating beta cell growth and function, and on the mechanisms responsible for beta cell desensitization or exhaustion.

The lack of good animal models of Type 2 diabetes and obesity seriously hampers research in this area. New programs to develop animal models representative of these disorders in humans are a high priority. Capitalizing upon advances in genetic and epidemiologic research will lead to increased understanding of the environmental factors that precipitate Type 2 diabetes in genetically susceptible individuals and how they interact with genes to do this.

To combat obesity, a major risk factor for the development of Type 2 diabetes and many other health problems, researchers must fully define the highly interacting pathways of appetite regulation, energy expenditure, and insulin resistance. The identification of mechanisms and genes responsible for human obesity and how it leads to insulin resistance is key to developing new therapeutic agents to prevent and treat obesity, and minimize its impact on Type 2 diabetes. There is also a need to simultaneously increase our understanding of how best to change lifestyle risk factors, such as diet and activity, which impact on genetic and other environmental factors to create obesity in these individuals.

1965	1966	1967	1971
Clinical laboratories switch to a Somogyi-Nelson method to measure blood glucose. This method is more accurate and faster.	The first successful pancreas transplant in humans is performed.	Panretinal laser photocoagulation is developed to seal off blood vessels in the retina that have been compromised by diabetic retinopathy. The structure of insulin is determined by X-ray crystallography. The first human heart transplant is performed.	The insulin receptor is identified.

Personal Profile

Pam Fernandes

My first ride on the tandem came about when I worked in community relations at the Massachusetts Association for the Blind. A fellow phoned in wanting to volunteer to take a blind person out on his tandem bike. The call was connected to me simply because I worked out in the gym. I'm blind and people thought I might know where to refer him. When I suggested various programs, he said he'd already been in contact with them but that they weren't doing anything currently, and he wanted to ride now. I told him I'd be glad to oblige. We got together, did a 20-mile ride and I loved it.

I'm going into my seventh season of tandem bicycle racing. In my very first race I came in last but I have progressed. Since then I've won four national championships and two international medals. One of the international medals is the Bronze from the 1996 Paralympic Games in Atlanta and the other is the Silver from the 1994 World Championships for Disabled Cyclists in Belgium.

On a local and regional level I primarily race mainstream. Without exception in 1997, I was the only blind person who raced in New England on tandem. I am racing against sighted people who have a lot more opportunity to train than I do yet we're all equal on the tandem playing field.

At the national, international and world levels I race against other people who are blind and who ride in the mixed category, which is a man and a woman on the tandem. In these races competitors are always mixed teams with a blind stoker. In tandem cycling terms I, the stoker, ride in the rear seat. My partner, the sighted pilot, rides in front.

There are a lot of reasons why I race. For me, it has turned into a platform to demonstrate ability and teach other people through my example. When I'm tandem cycling the true disability is not my blindness; the true disability is the diabetes. If you are blind, once you get used to it, all you have to do is get a tandem bike and find partners who ride. This isn't easy but it's "doable" and consistent—you can ride with the same guy every Wednesday on the same bike. With diabetes, every day is a new day. Too many different things can affect your blood sugar that are difficult to balance and that make it really tough.

Tandem cycling also keeps me very fit. Since I started bike racing I have not been hospitalized overnight. I've made two visits to the emergency room for minor things. The exercise helps my diabetes management by actually increasing my sensitivity to insulin and keeping my weight down, but it's also nice to win—I don't mind!

I was the first one in my family to have Type 1 diabetes. I knew I had diabetes when I was four years old. My Mom told me I was going into the hospital for some tests. She was a nurse and I remember being excited about going to the place where she worked.

The only real memories I have of my hospitalization are of going into the playroom where other kids had physical things wrong with them. I could see a cast or an IV tube. When they asked what was wrong with me, I said I didn't know, but that I had something that begins with 'D.' I remember going home and having to take shots every day.

I was one of seven siblings—five brothers, a sister and myself—and about seven years after I developed Type 1 one of my brothers was also diagnosed. He eventually died from the disease. Other members of my extended family have also been diagnosed. Because of diabetes I lost my sight when I was 21, spent five years on dialysis and underwent more than 30 operations. In 1987 I had a kidney transplant that changed my life. After that I began to exercise fully and became much more athletic.

The best part of having diabetes is being forced to understand nutrition and how our bodies utilize energy. I have a disease where I have to pay attention to those

1972	1973-1975	1974
The Diabetic Retinopathy Study begins to test the effectiveness of laser treatment of the eyes to prevent blindness in patients with diabetic retinopathy. The first successful islet cell transplant in rodents with diabetes is performed. Dextrostix reagent strips and the Ames Reflectance meter are used to measure blood glucose.	Investigators in Europe and the United States describe the association of insulin-dependent diabetes with the HLA genes that control the immune system. No association was found between these genes and non-insulin-dependent diabetes, which indicates a difference in the cause of these diseases.	Report of antibodies to insulin-producing cells in newly diagnosed patients with insulin-dependent diabetes, adding to the evidence that Type 1 diabetes is an autoimmune disease. Federal law provides access to kidney dialysis or transplant to everyone with end stage renal disease.

things so I'm a much healthier person. The worst part about having diabetes is losing people to it—unnecessarily in some cases—and experiencing the complications of the disease.

I have been an advocate for awhile. It's one of the ways I can make some good out of a bad situation. I have diabetes, and it has obviously wreaked a bit of havoc in my life. If there's something I can do to help other diabetics then I feel better having been a spokesperson.

Regarding my tandem cycling, I am at the highest level that I can go but I have yet to win an international Gold. I'm now training for the 2000 Paralympic Games in Sydney, Australia. The Paralympics, for disabled athletes, make up the second-largest sporting event in the world, after the Olympics. I'll continue to race as long as my health will allow me to, but a Gold in Sydney would be the culmination of a great cycling career.

The main thing I've learned through competition is, when you're competing and trying to win, you never settle for anything less than first. If you do, you lose your motivation to win. Even if you take second place, it's not good enough. And the diabetes community should feel likewise. We don't win until we cure the disease. Everything up to that point is positive and important, but it's not the victory—the Gold is a cure.

Research is needed to determine the factors linking Type 2 diabetes, insulin resistance, and atherosclerosis and to develop methods to prevent and ameliorate the resulting metabolic syndrome of obesity, accelerated atherosclerotic heart disease, stroke, dyslipidemia, and hypertension. Increased applications of technologies for noninvasive measurements of metabolism, such as NMR and PET scanning, must be available for and applied to research on Type 2 diabetes and obesity. Appropriate new technologies need to be developed to assess important variables, such as diet and energy expenditure, in individuals during normal life.

The Complications of Diabetes

Type 1 and Type 2 diabetes not only create day-to-day challenges of glucose control, but in fact, are debilitating diseases that cause the gradual breakdown of vital bodily functions and lead to disabling and even life-threatening complications. Abnormally high levels of blood glucose, as well as other metabolites, damage both the small and large blood vessels, producing what are known, respectively, as microvascular and macrovascular complications in both Type 1 and Type 2 diabetes. These affect almost every organ of the body, and thus diabetes is a true multi-system disease.

Microvascular Complications

Microvascular complications is a term applied collectively to the effect of diabetes on the small blood vessels throughout the body that leads to severe damage to the eye, kidney, and nervous system. However, each of these complications presents distinct features of pathophysiology and may require distinct therapeutic approaches.

The Impact of Diabetes on the Eye

The most common form of diabetic eye disease is retinopathy, that is, damage to the retina, the layer of cells at the back of the eye that contains the photoreceptors that produce the electrical and chemical signals that allow us to see. Retinopathy develops when damage occurs to the small blood vessels that supply the retina with oxygen and other nutrients. This damage changes the flow of blood, weakens blood vessel walls, and stimulates the growth of harmful blood vessel components. The damage may be mild (background retinopathy) or it may become severe (proliferative retinopathy). In proliferative retinopathy, new blood vessels form and may rupture and bleed into the retina, threatening sight. Another condition, macular edema, can develop when the fluid leaking from the blood vessels pools in the center of the retina and impairs the area of most precise, central vision. After 15 years of diabetes,

1975	1976
"Insulin drip" is presented as a new approach for treating diabetic acidosis.	Investigators reveal that hemoglobin becomes glycosylated (attached to glucose molecules) easily. This allows glycohemoglobin (HbA1) determinations to become widespread clinically to assess blood sugar control in the preceding two to three months. Evidence for altered insulin receptor function in obesity and diabetes is reported.

most patients show some evidence of diabetic retinopathy. Virtually all people with Type 1 diabetes have retinal damage, and 30 percent have the most severe form. Among patients with Type 2 diabetes who use insulin, 80 percent have retinopathy after 15 years and 10 to 15 percent have proliferative retinopathy. Twenty percent of people with Type 2 diabetes already have retinopathy when they are first diagnosed with diabetes, probably as a result of years of unrecognized and untreated hyperglycemia. These numbers increase with duration of disease. As a result, diabetes is the most common cause of blindness in working age adults.

Kidney Disease of Diabetes

Diabetic kidney disease, or nephropathy, is the result of damage to the kidneys that impairs their ability to function. The damage is usually a silent, gradual process that progresses over many years and becomes symptomatic only when less than 25 percent of kidney function remains. After 15 years with Type 1 diabetes, 25 percent of persons have persistent proteinuria (protein in the urine), a clear manifestation of significant renal damage. Ten percent of those with Type 2 diabetes have clinically detectable proteinuria within five years of diagnosis of diabetes, and 25 percent have signs of kidney damage after 20 years. Diabetic kidney disease is the most frequent kidney disease leading to the need for dialysis. End-stage renal disease (ESRD) is four times more common among African Americans and Mexican Americans with Type 2 diabetes than among Caucasians with the disease, and certain subgroups, such as the Pima Indians, have very high rates of the disease.

Nerve Disease of Diabetes

Diabetes also affects many parts of the nervous system. This damage is due, in part, to the effects of diabetes on the small blood vessels and probably also in part due to direct effects on the nerve tissue itself. This process results in damage to both the peripheral nerves, which are involved in sensation and movement, and the autonomic nerves, which control many internal functions, such as heart rate, gastric motility, bladder function, and ability to have a normal sexual response. Peripheral neuropathy causes pain and loss of sensation, contributing to the increased risk for limb infection, ulceration, and amputation. Autonomic neuropathy may lead to heart arrythmias, poor control of blood pressure, and digestive and sexual dysfunction.

Oral Diseases

Oral complications of diabetes represent another form of microvascular disease and are extremely common. These include mucosal infections, periodontitis, which is increased as much as five-fold in children with diabetes, salivary gland dysfunction leading to difficulty swallowing and speaking, and neuropathies such as burning tongue or mouth. These not only reduce quality of life and are difficult to treat in poorly controlled patients, but may also complicate further diabetes management.

Current Treatment and Prevention Strategies for Microvascular Complications

Until it becomes possible to cure or prevent diabetes, an important goal of research must be to develop successful methods to prevent or successfully treat the debilitating and often deadly microvascular complications of the disease. Current treatments mainly focus in two areas. For prevention of complications, the primary focus is on blood glucose control and treatment of factors that increase the risk of complications, such as hypertension. Once the disease is established, treatment is designed to minimize the level of damage (by laser photocoagulation for retinopathy) or to deal with the end-stage results of disease (by dialysis or transplantation for kidney disease). No definitely effective drugs exist to prevent glucose or metabolic toxicity to peripheral tissues in the eyes, kidneys, and nerves. The search for such drugs to block glucose toxicity is proceeding at an urgent pace, but it must be significantly enhanced. This need is particularly critical for diabetic neuropathy, where research has been extremely limited.

1977	1979
Improved blood sugar control through better monitoring is advocated as a means of preventing congenital malformations in the infants of women with diabetes. Battery-operated insulin pumps become available to deliver a continuous subcutaneous dose. They require frequent monitoring and judgments regarding appropriate doses. The cDNA for rat insulin is cloned.	The National Diabetes Data Group publishes new classification criteria for diabetes. This distinguishes insulin-dependent (Type 1) from non-insulin-dependent (Type 2) diabetes. The World Health Organization publishes similar but simpler criteria in 1980. The Early Treatment of Diabetic Retinopathy Study (ETDRS) begins to refine standards determining when to use laser surgery to prevent vision loss from diabetic eye disease. The cDNA for human insulin is cloned.

Diabetic Retinopathy

Current guidelines for the management of diabetes call for an annual, dilated eye examination to detect early signs of eye damage. However, studies show that about one-half of diabetes patients have this examination. Available therapies include laser photocoagulation and vitrectomy, both of which can help preserve vision, but cannot restore vision once lost. Tight control of blood glucose and treatment of hypertension are also important. No drugs are available other than insulin to modify the effect of diabetes on the development of this complication.

Diabetic Nephropathy

Tight control of blood glucose and vigorous treatment of other risk factors, particularly hypertension and urinary tract infection, are critical in slowing the progression of diabetic kidney disease. Certain classes of antihypertensive drugs, the angiotensin-converting enzyme inhibitors (ACE inhibitors), also slow progression of renal disease. Measurements of small amounts of protein in the urine (microalbuminuria) are used as an early marker of kidney damage, enabling these interventions to be used as a means of slowing disease progression. However, once the kidneys have failed, dialysis and transplantation are the only treatments. Unfortunately, the five-year survival rate for diabetic patients with ESRD is only 21 percent, worse overall than that for all forms of cancer combined. Prevention strategies focus on tight control of blood glucose and treatment of hypertension and urinary tract infections.

Diabetic Neuropathy

There is no definitive, effective treatment for diabetic nerve disease. Treatment and prevention of the neurologic complications of diabetes consist of good control of blood glucose (which may be of limited value once the complications have developed) and symptomatic control of pain, cardiac and blood pressure changes, digestive problems, and sexual dysfunction. Vigorous efforts are made to prevent and rapidly treat injury due to loss of sensation in the feet and legs in order to avoid skin ulceration and infection, which can lead to amputation. At present, a large component of this treatment is simply increasing patient and health care workers' awareness of how best to look for and manage these problems. Pharmaceutical companies are currently testing several new drugs, but their efficacy and safety are unknown. Since the basic mechanisms involved in diabetic neuropathy remain unclear, more fundamental research is clearly required if there are to be major new therapeutic approaches to these problems.

Major Research Advances in Microvascular Complications

Genetic Susceptibility Factors

Genetic factors are known to make people susceptible to diabetes, and now there is evidence that genes are also involved in susceptibility to some of the microvascular complications. Several studies of families in which more than one member has diabetes have found that some families have a very high risk of developing diabetic kidney disease, while others have a very low incidence of such complications. Based on such studies, it now appears that susceptibility to diabetic kidney disease is, in large part, genetically determined and that abnormalities associated with risk for this complication can be seen in skin and blood cells, as well as in kidney cells. One study also found evidence for a genetic predisposition to diabetic retinopathy, and it is possible that the same is true for diabetic nerve disease, although much more work in this area is needed.

Identification of Basic Molecular Mechanisms of Tissue Damage

Although it is likely that microvascular complications are the result of damage from high blood glucose and other metabolites, the exact mechanisms remain uncertain. Researchers have made notable gains in recent years in understanding several of the basic mechanisms that may

1980's	1980's
Syringes and needles are sterile and disposable.	Genetically engineered human insulin is clinically available, alleviating problems of supply and allergic reactions to animal insulins.
Aspartame is introduced as an artificial sweetener.	Home glucose monitoring allows for individualized dosing of insulin.
Fat substitutes are developed.	Diets become much lower in fat (30% of total calories) to help prevent heart disease.
Home glucose monitoring improves meal flexibility.	Discovery of the translocation mechanism whereby insulin increases glucose transport.

contribute to these disorders. These advances include understanding special features of the pathways of glucose metabolism in the tissues involved in complications, such as the sorbitol pathway, and identifying new pathways, which may hold the clue to the mechanisms of hyperglycemic damage. Two promising new research areas are the potential roles of protein kinase C (PKC) and advanced glycosylation end-products (AGEs). PKC is an enzyme found in several forms in all cells of the body. Recent work has shown that hyperglycemia can activate certain isoforms of this enzyme, which can then go on to produce changes in vascular permeability, blood flow, and many other factors. Glucose also links onto the proteins of the cell to form AGEs. Not only do these chemically modified proteins have modified function themselves, but also through receptors on the cell surface, they may activate a number of abnormal pathways. Experimental studies in animals suggest that inhibitors of the enzyme PKC and inhibitors that block formation of AGEs may provide new therapies to reduce diabetes complications. Additional mechanisms and pathways altered by high blood glucose include reduction of blood flow to the retina, increased blood flow to the kidney, and increased cellular oxidation.

Rapid advances in the study of growth factors—small protein molecules that stimulate the growth of specific types of cells—are also contributing to our understanding of microvascular complications. One such molecule, vascular endothelial growth factor (VEGF), appears to be a major cause of new blood vessel growth that occurs in patients with proliferative diabetic eye disease and is a major cause of blindness. VEGF also appears to increase the "leakiness" of blood vessels in the retina. In this condition fluid seeps into the surrounding tissue and causes swelling that can result in substantial loss of vision. Research is now under way to prevent the secretion of or block the action of VEGF in the eye. Growth hormone and other growth factors also appear to contribute to diabetic kidney and nerve disease. Specific drugs given to adult patients who no longer need growth hormone may be able to block this action and prevent blood vessel growth in the retina and the resulting loss of vision.

Many of these mechanisms are genetically controlled and have been shown, in animal and human studies, to be produced by the hyperglycemia of diabetes. Some of these, such as VEGF and AGEs, are now beginning to be tested clinically in humans at sites of action of new therapeutic agents. Because it is possible that the development of each complication is due to an interaction of several different pathways, the actual importance of each needs to be determined. This complexity may also suggest a need for multiple, simultaneous therapeutic approaches to maximize or optimize the prevention of diabetic complications. A complete and effective prevention of all complications, even in the absence of normalized blood sugar, would constitute "functional cure" of the disease.

Markers and Predictors of Microvascular Complications

One of the major problems in dealing with the long-term complications of diabetes is finding suitable yardsticks for measurement of disease activity before the complications become too advanced. Some progress has been made in identifying possible early markers of complications. For example, microalbuminuria presages the onset of severe kidney disease in diabetes, and its early detection enables early intervention. VEGF may also serve as a marker for diabetic retinopathy, but current studies have shown this to be the case only if measured in fluids from the eye. No markers for neuropathy exist, and even precise measurements of nerve function usually correlate poorly with the symptoms of disease. Thus, for most long-term complications, increased research is needed to find the optimal surrogate markers of disease for both clinical purposes and clinical research.

Clinical Trials on Microvascular Complications

Significant advances have been made as the result of various clinical trials in diabetes. Among these are the following:

Benefits of Glycemic Control (The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study)

1981	1983
Studies by the British Diabetes Association demonstrate that environmental as well as genetic factors are involved in causing Type 1 diabetes.	Cyclosporine is approved as an immunosuppressant, which benefits transplanting the whole pancreas in kidney recipients.
Discovery that the insulin receptor is an enzyme—a receptor tyrosine kinase.	The Diabetes Control and Complications Trial (DCCT) begins. This is a 10-year randomized trial to determine the effectiveness of intensive diabetes management in the prevention or delay of complications.
	Researchers identify mutations in the insulin gene that cause rare forms of diabetes.
	Researchers find that islet cell antibodies can identify individuals who are in the process of developing Type 1 diabetes up to 8 years before clinical symptoms appear.

Major Research Advances in Microvascular Complications

- **Discovery that genetic factors, as well as glucose control, predispose individuals to the microvascular complications of diabetes.**
- **Increased understanding of some of the biochemical mechanisms responsible for damage to small blood vessels and nerves.**
- **Discovery that vascular endothelial growth factor (VEGF) is a contributor to new blood vessel formation in patients with proliferative diabetic eye disease.**
- **Identification of microalbuminuria as an indicator of early-stage diabetic kidney disease.**
- **Demonstration that intensive therapy to maintain "tight" control of blood glucose slows the onset or progression of diabetic eye, kidney, and nerve disease in individuals with Type 1 and Type 2 diabetes.**
- **Discovery that laser photocoagulation and vitrectomy surgery can help preserve sight in patients with diabetic eye disease.**
- **Demonstration that control of blood pressure can slow onset or delay progression of diabetic kidney disease.**
- **Demonstration that the ACE inhibitor class of antihypertensive drugs has positive effects in patients with established diabetic kidney disease.**

The DCCT demonstrated that maintaining blood glucose levels as close to normal as possible by intensive therapy slows the onset or progression of retinopathy, nephropathy, and neuropathy in people with Type 1 diabetes. The recently completed UKPDS and a study in Japan found similar results in Type 2 diabetes. There are also encouraging results suggesting that pancreas transplantation in Type 1 diabetes and the return of normal blood glucose levels may even reverse the damage caused by diabetic kidney disease in some patients. These studies indicate the promise, limitations, and challenge of treatment of diabetes. Control of blood glucose is the first step toward reducing the risk of microvascular complications. On the other hand, intensive therapy in the DCCT carried a 73 percent increased risk of overweight and a three-fold risk of severe hypoglycemia. Achieving tight control may require a considerable effort on the part of both the patient and the health care team, and is not possible in a large fraction of patients using current approaches. Thus, an effective means to prevent long-term complications independent of controlling blood glucose will be an extremely important addition to conquering diabetes and its complications.

Benefits of Laser Photocoagulation and Vitrectomy

The Diabetic Retinopathy Study, the Early Treatment Diabetic Retinopathy Study, and the Diabetic Retinopathy Vitrectomy Study showed that laser photocoagulation and vitrectomy surgery can help preserve sight in patients with relatively advanced forms of diabetic retinopathy. In each of these studies, the effects are very significant, and when coupled with improved glycemic control, will markedly reduce the risk of blindness due to diabetes. However, these treatments are being applied relatively late, that is, when there is already visible evidence of damage. Another problem is limited access to ophthalmologic experts. Some newly initiated telemedicine efforts by the Department of Defense and the Joslin Diabetes Center indicate potential avenues by which one could significantly expand the benefits of laser photocoagulation to underserved areas.

Impact of Blood Pressure Control and Angiotensin-Converting Enzyme Inhibitors

A major advance has been the demonstration that controlling blood pressure has a salutary effect on kidney complications. Studies have also shown that both ACE inhibitors and beta-blockers, two classes of drugs used to

1985	1988	1990	1991
Recognition of incipient nephropathy—microalbuminuria—leads to early recognition, treatment, and possible prevention of diabetic kidney disease. Cloning of the insulin receptor gene. Cloning of the first glucose transporter.	Scientists discover that mutations in the insulin receptor gene may cause rare forms of diabetes.	The first transplant of human islet cells that reverses insulin dependency in humans is performed.	One of the genes for Maturity Onset Diabetes of the Young (MODY) is discovered. Investigators begin to uncover the genetic factors that underlie susceptibility to diabetic nephropathy. Microalbuminuria assay becomes available as a routine laboratory test for early detection and treatment of kidney disease.

Major Research Challenges in Microvascular Disease

- **Identification of genes conferring susceptibility to microvascular complications and the biochemical mechanisms by which they act.**
- **Identification of the underlying biochemical mechanisms responsible for diabetic microvascular disease.**
- **Development of animal models of diabetic neuropathy, nephropathy, and retinopathy representative of the human conditions.**
- **Development of new, effective, readily applicable methods for achieving "tight" control of blood glucose without hypoglycemia to prevent microvascular complications in Type 1 and Type 2 diabetes.**
- **Application of noninvasive and other new technologies to the study and understanding of diabetic microvascular disease.**
- **Development of new, effective therapies to prevent, cure, and better manage diabetic eye, kidney, and nerve disease.**

treat high blood pressure, slow the progression of diabetic kidney disease. ACE inhibitors appear to have positive effects, even in patients with normal blood pressure or already advanced diabetic nephropathy. Another small study suggests that ACE inhibitors may also slow the progression of diabetic eye disease. These findings, however, need to be confirmed in a larger study.

Challenges of Critical Importance in Microvascular Complications

Control of Blood Glucose

Although there is no doubt that "tight" metabolic control of diabetes significantly reduces the incidence of complications, it is difficult to achieve in the population of diabetic individuals with any current means. This difficulty relates to a broad range of issues, including challenges of insulin therapy in Type 1 diabetes, limited range and effectiveness of therapeutics for Type 2 diabetes, risks of hypoglycemia, and the limits of knowledge and behavior of health care professionals and patients. Effective, safe, readily applicable, and cost-effective methods for achieving tight blood glucose control must become available for individuals with diabetes to prevent or slow progression of microvascular disease.

Mechanism-Based Therapies for Microvascular Disease

Research must define the specific molecular and biochemical mechanisms by which high blood glucose and other metabolic derangements of diabetes damage small vessels and nerves. It is likely that these vary in different tissues, and may even be different among individual patients. Furthermore, many of these pathways may also serve other important functions. Thus, detailed insight into the mechanisms of damage to microvascular and nerve tissues is needed. Furthermore, this knowledge must be translated into new therapies to prevent or ameliorate the damage with drugs that act directly on the responsible factors.

Genetic Susceptibility to Microvascular Disease

Not all diabetic patients are at equal risk of complications. The specific genetic factors that predispose to the development of microvascular disease must be identified and used to detect patients at highest risk for developing these complications. This would also allow the limited health care resources to be focused on those individuals at greatest risk for development of the most debilitating complications. This information could also be used to identify new therapies to prevent and slow progression of the microvascular complications, and could provide markers for specific therapeutic approaches "customized" to best fit the genetic makeup of the individual patient.

1993	1995	1997
The results of the randomized Collaborative Study of Diabetic Nephropathy show that anti-hypertensive agents (ACE inhibitors) significantly reduce the need for kidney dialysis and transplantation, and result in fewer deaths related to heart disease. The Diabetes Control and Complications Trial (DCCT), a 10-year comparative study of over 1,400 patients, proves conclusively that tight diabetes control reduces or delays the risk of diabetic eye disease, kidney disease and nerve damage.	Cloning of the sulfonylurea receptor and subunit of beta cell potassium channel.	Several new drugs with different methods of therapeutic action from sulfonylureas become available to treat Type 2 diabetes in the United States.

Animal Models to Study Microvascular Complications

Although there are some animal models for Type 1 and, to a lesser extent, Type 2 diabetes, reliable animal models of diabetic microvascular disease are lacking. Thus, at present, most preclinical research focuses on cells in culture, removed from the full influences of the body, and then progresses directly to expensive and difficult human clinical trials without the benefit of good animal models for study. Availability of appropriate animal models for all microvascular complications would greatly enhance progress in this area.

Technology Development

Technologies, such as noninvasive imaging by NMR and PET, have been applied to some areas of metabolism and to the study of some of the tissues involved in diabetic complications. However, at present, clinical studies of complications, particularly nephropathy and neuropathy, often rely more on invasive measurements, such as tissue biopsy, or on surrogate measures of tissue damage, such as the amount of protein in the urine or the rate of nerve conduction. Direct measurement of the impact of diabetes on tissues involved in complications would be of great value for research on diabetic microvascular disease.

Macrovascular Complications

Diabetes is a major cause of cardiac, cardiovascular, and peripheral vascular damage. Indeed, macrovascular disease (damage to large blood vessels) is the most common cause of death in both Type 1 and Type 2 diabetes patients. Interestingly, in some ways, these problems are similar in diabetics and non-diabetics, while in other ways they are very different. Some well-known and long-recognized risk factors for cardiovascular disease (CVD)—such as hypertension, high triglycerides, and low high-density lipoprotein (HDL) cholesterol—are now recognized as common in people with diabetes, especially Type 2. However, recent findings suggest unique features in the diabetic milieu that contribute to large blood vessel damage that demand further research. For example, some lipid and tissue abnormalities involved in the development of atherosclerosis exhibit different patterns in people with Type 1 as compared to Type 2 diabetes. Premenopausal women with diabetes lose their protection against heart disease and have incidence rates of CVD similar to those of diabetic men. Patients with diabetes also have fewer warning signs of heart attack, increased mortality during the first year after a heart attack, poorer response to angioplasty, and higher rates of congestive heart failure.

While deaths from CVD have declined 35 to 50 percent in the past 30 years in the general population, the decline in this type of mortality among people with diabetes has been less than half that of the general population. The reasons for the smaller decline are unclear, but are most likely multiple. Less than half the excess risk of CVD in people with diabetes can be explained by well-known risk factors common in diabetes, such as hypertension, low HDL cholesterol, and high triglycerides. In recent years, other factors have been identified that appear to contribute to increased risk, including blood flow and platelet abnormalities, and altered levels of vascular growth factors, such as VEGF.

Peripheral vascular disease is, in general, less well studied and understood than CVD. In diabetes, the supply of nutrients and oxygen to tissues is impaired by the combination of peripheral vascular disease of the large blood vessels (atherosclerosis) and by the microvascular damage to the small blood vessels and capillaries, which nourish the same area. In addition, diabetic neuropathy increases the risk of unrecognized injury to extremities. This combination sets the stage for the development of gangrene and infection, which leads to the need for amputation in the diabetic patient.

Individuals with diabetes also have some damage to the heart muscle (cardiomyopathy) and to the nerves that supply the heart (cardiac autonomic neuropathy) as a result of the abnormal metabolism present in this disease. These conditions are often difficult to recognize, because complex problems occur simultaneously. These conditions also put the patient at increased risk of arrhythmias, sudden death, and heart failure.

Current Treatment and Prevention Strategies

Current treatment of macrovascular complications consists of glucose control and ways to reduce other cardiovascular risk factors, in particular through lowering of lipid levels with diet and drugs and treating high blood pressure. Thus, the diabetic with existing or incipient macrovascular disease requires multiple modifications of lifestyle and diet, as well as a poly-pharmaceutical approach to address the needs for glucose control, optimization of lipid levels and blood pressure, and other disease risk factors. Prevention strategies are not well defined, except for lifestyle changes in diet and exercise and reduction of lipid levels through drugs. Surgical procedures, such as coronary bypass surgery and angioplasty, are possible, but patients with diabetes have significantly higher morbidity and mortality during and after these procedures compared with non-diabetics. No specific drugs are available to reduce the special risk associated with diabetes, especially in women, which remains poorly understood.

Major Research Advances in Macrovascular Disease

Although only a relatively small number of diabetic patients were included, two recent clinical trials indicated that diabetic individuals may have significant decreases in risk of coronary artery disease events and in low-density lipoprotein (LDL) cholesterol when treated with cholesterol and blood-pressure-lowering therapies. This finding indicates that lowering LDL cholesterol and blood pressure is beneficial in diabetic patients with coronary artery disease. However, even when adjusted to the same level of blood pressure control and serum cholesterol, individuals with diabetes still have more than twice the risk of heart attack than do people without diabetes.

Hyperglycemia has been shown to affect mechanisms known to increase atherosclerosis such as oxidation, thrombosis, inflammation, production of matrix proteins which surround the blood vessel, and the formation of advanced glycosylated end products (proteins linked together by sugars) that potentially can damage the vascular system. Paradoxically, intensive treatment for hyperglycemia may also have potentially adverse effects. These include promoting weight gain and increased abdominal fat, increasing levels of triglycerides, LDL, total cholesterol and apolipoprotein B (components of "bad" fat), and reducing levels of HDL cholesterol and apolipoprotein A1 (components of "good" fat). Such effects may explain the difficulties in proving that simply normalizing glucose levels will eliminate the excess risk for macrovascular disease in people with diabetes.

Even in the absence of diabetes, people with the metabolic syndrome (the constellation of central obesity, insulin resistance, and high blood triglycerides) are at significantly increased risk for coronary artery disease. It is now recognized that insulin resistance is often associated with low levels of HDL (good cholesterol) and elevated levels of triglycerides. These are in turn associated with a preponderance of small, dense LDL, which is the major source of "bad" cholesterol. People with insulin resistance also have increased levels of factors that promote blood clots and abnormalities of cells lining blood vessel walls, further increasing their risk of coronary artery disease.

It has been demonstrated that patients with diabetes can benefit from surgical approaches to cardiovascular disease including angioplasty and coronary artery bypass. However, studies show that these individuals have significantly poorer results from angioplasty compared with bypass surgery due to accelerated restenosis of treated coronary vessels. This factor remains a serious challenge to the use of these therapies in patients with diabetes.

Major Research Advances in Macrovascular Disease

- **Improved understanding of the association between hyperglycemia and the cardiovascular complications of diabetes.**
- **Demonstration that lowering cholesterol and blood pressure in patients with Type 2 diabetes improves CVD event rates and mortality.**
- **Advancement in knowledge of how diabetes can affect lipid metabolism and mechanisms of vessel wall injury leading to atherosclerosis.**
- **Recognition that the insulin resistance of Type 2 diabetes, along with the associated hyperinsulinemia, may be risk factors for coronary artery disease.**
- **Demonstration that diabetic patients can benefit from surgical approaches to cardiovascular disease including angioplasty and coronary artery bypass.**

Challenging Areas of Critical Importance: Macrovascular Complications

Understanding the Mechanisms by Which Diabetes Causes Accelerated Atherosclerosis

Intensified research is needed to identify the factors responsible for accelerated atherosclerosis in diabetes. Advances in atherosclerosis research have significantly enhanced understanding of the causes and course of atherosclerosis in non-diabetic populations. New therapies have been developed to reduce and slow progression and to decrease death due to this disease in the general population. As a result, the age-adjusted death rate from CVD has decreased in the United States by 30 percent since 1980.

However, much less progress has been made in the diabetic population in whom the atherosclerosis process is accelerated, and death rates are much higher than in non-diabetics. Furthermore, the protection against the disease normally afforded to premenopausal women is lost. Existing therapies for atherosclerosis in the general population have not been as effective in the population with diabetes and have not prevented it from being the

major killer of people with diabetes. Moreover, while numerous clinical trials have provided evidence for the importance of blood pressure and cholesterol control, aspirin therapy, and estrogen replacement in the general population, there are limited data on how to prevent and optimally manage CVD in patients with diabetes.

Fundamental research to uncover the specific mechanisms responsible for the marked acceleration of atherosclerosis by diabetes is among the highest priorities if the excessively high incidence of heart attacks, strokes, and peripheral vascular disease in people with diabetes is to be reduced. Research is needed to identify the specific factors that worsen the risk factors involved in the development of atherosclerosis and that cause unique disorders such as diabetic cardiomyopathy, coronary artery restenosis, and the high mortality associated with myocardial infarction in people with diabetes. Investigation, including examination of genetic factors, needs to begin to identify and manipulate the factors that make people with diabetes, especially women, susceptible to CVD. It is also critical to understand how the factors special to diabetes interact with all of the other factors to which the normal population is exposed in order to accelerate this process. For example, special attention is needed for diabetics with end-stage renal disease on dialysis and who are at very high risk for cardiovascular complications.

Improved Outcomes in Persons with Cardiovascular Disease and Diabetes

Methods to prevent cardiovascular complications and improve outcomes of diabetes patients who suffer a clinical CVD event are desperately needed and must be pursued in both basic and clinical studies. Although recent advances in CVD research in people with diabetes have begun to lay the foundation for understanding some of these differences, much remains to be done to attain optimum success and improve quality of life. Efforts must include:

- Clinical trials with meaningful end points for treating and preventing macrovascular complications in both Type 1 and Type 2 diabetes.

- Application of noninvasive imaging technologies, such as NMR and PET scanning, to define alterations in heart and blood vessels in people with diabetes.

Animal Models To Study Cardiovascular Disease in Diabetes

Atherosclerosis is a major problem in humans and some larger mammals, but is very rare in rodents, such as mice and rats. Therefore, for macrovascular disease, there has been a need to use different types of animal models, including rabbit, pig, and even subhuman primates. These animals provide some useful models in which to explore the use of genetic manipulation or pharmacologic intervention to rescue the animal from vascular disease. Such models, however, are not widely available, are extremely costly to study, and still may not accurately reflect humans with diabetes and atherosclerosis.

Major Research Challenges in Macrovascular Complications of Diabetes

- **Understanding the mechanisms by which diabetes causes accelerated atherosclerosis.**

- **Identification of the mechanisms responsible for the loss of protection against atherosclerosis and CVD in premenopausal diabetic women.**

- **Development of methods to prevent cardiovascular complications and improve outcomes of patients who suffer a clinical CVD event.**

- **Application of noninvasive imaging technologies, such as NMR and PET scanning, to define alterations in heart and blood vessels in patients.**

- **Development of small (rodent) and large animal models of atherosclerosis and diabetes representative of the human condition.**

- **Development of effective new therapies to prevent, cure, and better treat the macrovascular complications of diabetes.**

Other Complications of Diabetes and the Impact of Diabetes on Special Populations

Diabetes is associated with many other complications that cannot be specifically ascribed to either microvascular or macrovascular disease (although these probably contribute). Thus, the individual with diabetes is at high risk for periodontal disease and a wide variety of infections. The exact mechanisms that contribute to these problems may relate to the effects of high glucose and other metabolic disturbances on tissues of the gum

and white blood cells. There may also be specific disorders that develop faster in the internal environment created in patients with diabetes. For example, bacteria may grow faster in diabetic urine, which contains glucose, leading to increases in urinary tract infections. The morbidity that these disorders produce should not be underestimated.

Women and their children are at risk for specific complications, including gestational diabetes, effects of diabetes on fetal development, and perinatal mortality. While there has been significant improvement in these areas over the years, the risks remain very high. Thus, these problems too must be addressed to truly conquer the problem of diabetes and all of its manifestations.

Finally, one must consider the special impact diabetes and its complications have on specific populations. The impact of diabetes in both the young and the old creates special needs for management and unique types of problems. Minority populations, including Mexican, African, Asian and Native Americans, have not only the highest rates of prevalence of diabetes — they also have the highest rates of many of the complications of the disease. Specific research must be done to address the mechanisms by which these differences occur, the role of genetics and environment, and how best these challenges can be addressed at a clinical level.

Major Research Challenges in Other Diabetes Complications

- **Elucidation of the mechanisms responsible for increased risk of and poor response to infection among diabetics.**
- **Identification of the factors responsible for the increased risk for periodontal disease and other oral complications of diabetes.**
- **Identification of the factors that influence the course and outcome of pregnancies in diabetic women.**
- **Identification of the mechanisms by which the intrauterine environment affects the immediate and long-term health outcomes for offspring of diabetic pregnancies, including fetal mortality and anomalies.**
- **Identification of the mechanisms which predispose minority populations and other groups to high rates of diabetic complications.**

Diabetes Research Programs

Funded by the NIH

The National Institutes of Health

The NIH supports a wide range of research relating to diabetes mellitus. The portfolio includes basic research projects, clinical studies, intramural investigations, epidemiological and behavioral studies, research training and career development, and outreach and education activities.

Funding Trends for National Institutes of Health Diabetes Research

NIH funding of diabetes research has risen from $134 million in FY1980 to an estimated $442.8 million for FY 1999. When adjusted for inflation, however, the actual amount of growth has been only 32.8 percent over 20 years, or less than 2 percent per year.

The DRWG recognizes the fact that it is important for NIH to maintain a broad portfolio of research efforts and that research support should not be simply related to the financial burden created by a disease. However, from FY1980 to FY1999, the diabetes research budget, expressed as a percentage of the total NIH budget, has never exceeded 4.1 percent, although diabetes-related illness during the same time period represented about ten percent of the health care expenses in the United States.

Indeed, throughout most of the past twenty years, the percentage of the NIH budget directed toward diabetes-related research actually declined, dropping as low as 2.5 percent in 1997. The diabetes proportion of the NIH budget has begun to increase again in the past two years, in part due to the special five-year appropriation for Type 1 diabetes research contained in the FY1997 Balanced Budget Act, and currently rests at 3.1 percent of the total NIH budget.

NIH Funding Mechanisms

The NIH diabetes research program funds both extramural and intramural research. Extramural research includes grants and contracts awarded to medical schools, academic institutions, and other research organizations in more than 200 academic and medical research institutions in congressional districts throughout 44 states in the U.S. Intramural research is conducted by scientists in NIH laboratories and branches in Bethesda, MD and elsewhere.

Most NIH-funded research is through investigator-initiated grants, which have been judged to be of extremely high scientific merit and technical feasibility by the NIH two-tiered peer review system. This peer review system includes initial review groups of scientific experts, as well as each Institute's National Advisory Council.

National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is the lead agency at NIH for diabetes research and accounts for slightly more than 60 percent of the NIH diabetes research budget. This amounts to $267.5 million, or about 27 percent of the Institute's total budget. This fraction has been stable for the last twenty years. More than 85 percent of the NIDDK's budget is used for extramural programs and the remainder for the intramural program. The NIDDK's diabetes research portfolio encompasses genetic, biological, and environmental factors in Type 1 and Type 2 diabetes and their complications. It also targets development of new approaches and technologies to normalize blood glucose, including islet cell and pancreas transplantation; prevention and treatment of diabetes and its complications; diabetes in minority populations; the epidemiology of diabetes; and patient and public education.

Individual investigator-initiated research in the form of RO1 grants constitutes approximately 50 percent of the NIDDK's total budget and approximately 60 percent of its extramural budget. The NIDDK also funds program projects (PO1 grants), which bring several investigators together around a single focus. However, this program has never been robust, and currently represents only 6 percent of the NIDDK portfolio. In general, this grant mechanism has been viewed as being of limited usefulness by extramural investigators, because PO1s have a low budget cap (maximum of $750,000 per year in direct costs) that severely limits their ability to effectively fund complex interdisciplinary interactive research programs.

The NIDDK also has a Diabetes Research Centers Program. The Program currently consists of six Diabetes and Endocrinology Research Centers (DERCs) and six Diabetes Research and Training Centers (DRTCs). Both types of Center focus on "core" laboratory support, which provides centralized research facilities for multiple investigators, and include a small amount of funding for "Pilot and Feasibility" studies and an "Enrichment Program." The DRTCs also include funding for studies on the translation of research to health care personnel and the public through their "Dissemination and Education Programs." The current annual direct-cost caps on these centers are also very low—$750,000 for the DERCs and $1.25 million for the DRTCs.

The NIDDK also funds major clinical trials in diabetes. The most well known of these, the DCCT, was completed in 1993. It demonstrated conclusively in more than 1,400 patients in 27 research centers throughout the country that intensive therapy to lower blood glucose levels significantly reduces or prevents the progression of microvascular complications in people with Type 1 diabetes and minimal vascular damage. How to effect this type of therapy most successfully in the population at large remains the primary question. Two other important NIDDK-sponsored clinical trials have shed light on the treatment of diabetic nephropathy: one focused on modification of diet in renal disease; the other was a trial of ACE inhibitors that demonstrated how these drugs can reduce the risk of ESRD by 50 percent.

Currently, the NIDDK, in collaboration with other NIH Institutes and the private sector, is funding two major primary-prevention clinical trials. The Diabetes Prevention Trial-Type 1 (DPT-1) is a multicenter clinical trial designed to determine if it is possible to prevent or delay the onset of Type 1 diabetes in individuals who have the immunologic markers of the disease. The second trial is the Diabetes Prevention Program (DPP), a nationwide study designed to determine whether it is possible to prevent Type 2 diabetes in high-risk individuals through drug and lifestyle modifications focusing on diet and exercise. Approximately half of DPP volunteers represent minority populations.

The NIDDK's intramural diabetes research takes place in two main locations. At the main campus of NIH in Bethesda, Maryland, research focuses primarily on basic mechanisms of hormone action fundamental to the understanding of both Type 1 and Type 2 diabetes and basic research on islet function, growth factors, and obesity. At the satellite facility at the Gila River Indian Community in Phoenix, Arizona, research focuses on studies of the Pima Indians, who have the highest incidence of Type 2 diabetes in the world.

The NIDDK provides many important elements of infrastructure for diabetes research. These include crucial support for training at various stages of a research career, from initiation to mid-career development, and encouragement of minority representation in scientific careers. In FY1999, NIDDK's research training and career development budgets are estimated at $36 million and $27 million, respectively. The NIDDK also participates in major public health surveys, which document the extent of the impact of diabetes in the United States, and supports the National Diabetes Data Group for the collection, analysis, and dissemination of data on diabetes. The NIDDK has outreach and education programs—the National Diabetes Education Program and the National Diabetes Information Clearinghouse—in cooperation with the Centers for Disease Control and Prevention and the diabetes voluntary community. The NIDDK collaborates with the World Health Organization to address disparities in populations affected by diabetes worldwide.

Trans-NIH Diabetes Research Efforts

In addition to the NIDDK, many other NIH Institutes and Centers support research relevant to diabetes and its complications and provide infrastructure through shared resources.

The National Heart Lung and Blood Institute (NHLBI) and National Eye Institute (NEI) estimate that they will fund about $30 million and $29 million in diabetes-related research in FY1999, respectively. The NHLBI has sponsored several studies on why patients with diabetes have an increased risk of cardiovascular disease (CVD), including both basic and population-based studies. NHLBI is also planning a new clinical trial assessing ways to reduce diabetes-associated CVD to start in FY1999. The NEI has sponsored several major clinical trials for treatment of diabetic retinopathy, as well as studies into the basic mechanisms of disease. The National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy and Infectious Diseases (NIAID) estimate that they will each fund between $15 million and $19 million of diabetes research in FY1999. This research will focus on children with diabetes, effects of pregnancy, and efforts to elucidate the biological mechanisms involved in autoimmunity, a major factor in Type 1 diabetes. In addition to the extramural research on the genetics of diabetes funded by NIDDK, two major genetics efforts for Type 2 diabetes are being conducted as collaborative studies by the intramural program of the National Human Genome Research Institute (NHGRI): one is a collaborative study of a Finnish population, and the other, a population of Type 2 diabetics of African descent. Both studies also involve academic laboratories in the United States. Another area of significant support for diabetes-related research comes from the National Center for Research Resources (NCRR), through its support of General Clinical Research Centers, Biomedical Technology Resources, and other facilities at many academic institutions. There is, however, no specific, formal mechanism for addressing the infrastructural needs of diabetes research, such as animal facilities, very high-cost instrumentation, or device development. Infrastructural support in the area of complex instrumentation and device development, however, could be provided by several of the resource centers supported by NCRR with appropriate adaptation. Several other Institutes, including the National Institute on Aging (NIA), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Mental Health (NIMH), and National Institute of Environmental Health Sciences (NIEHS) also provide small amounts of diabetes research funding.

Strategic Planning, Coordination and Oversight

Strategic planning, coordination, and oversight of NIH diabetes research efforts are pursued through a variety of approaches, but with few overarching, formal, and systematic mechanisms. Scientific program planning for extramural research varies in degree and approach from Institute to Institute. In the NEI, for example, formal strategic planning for research has been conducted, including for the area of diabetic retinopathy; this is outlined in Vision Research: A National Plan: 1999-2003. Frequently, planning concepts originate with scientific program officers of the Institutes, often with the help of an associated workshop, conference, or *ad hoc* planning meeting, in a topic-by-topic approach. Within the NIDDK, there is a program planning process that encompasses diabetes, as well as other diseases. While this process encourages the participation of other NIH components in joint research endeavors, at present there is no uniformity in these activities and no discrete, formal focus for systematic, strategic diabetes research planning across the NIH. Intramural research planning is performed by each Institute's Scientific Director, in consultation with the Institute Director and with a group of external scientific experts, the Board of Scientific Counselors. This Board reviews each intramural laboratory or branch at periodic intervals and makes suggestions about the allocation of resources and future research directions. There is no mechanism for inter-Institute coordination of intramural diabetes research, or approach to determine how to have the intramural and extramural programs serve complementary functions.

The only existing, permanent mechanisms for overall program planning are the National Advisory Councils of the NIDDK and the other NIH components and the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). Each Council is composed of 18 members representing both the scientific and lay constituencies of each Institute and hence is not focused on diabetes *per se*. The DMICC is chaired by the Director of NIDDK. It includes representatives of the NIH components that fund diabetes-related research, as well as representatives from the Centers for Disease Control and Prevention, the Department of Veterans Affairs, the Agency for Health Care Policy and Research, the Indian Health Service, and the Health Care Financing Administration. In accord with its statutory authority, this committee functions primarily as a mechanism for exchange of information and coordination among these various agencies, rather than as a mechanism for strategic planning. The charter of the National Diabetes Advisory Board, which was created in 1976 to help advise the NIH on diabetes-related issues, became defunct in 1994.

Review of the NIH portfolio of diabetes research by the Diabetes Research Working Group reveals a number of issues that must be addressed in any future diabetes research plan. Several of these issues have developed because of the limited amount of diabetes research funding available in the past and the tendency to rely on existing mechanisms of operation rather than to explore new ones. As NIH research funding increases, it is imperative that there be a concomitant increase in the intensity of NIH-wide efforts to conquer diabetes. It is also essential to eliminate factors that could become rate-limiting steps to this progress. These factors include the following:

- The overall size of the diabetes research effort is small by comparison to the health care impact of the disease.

- Diabetes research funding, in general, has not kept pace with the rest of NIH.

- Because it affects all age groups and involves almost every system of the body, specific aspects of diabetes research should be a significant focus in most NIH Institutes and Centers. However, some Institutes have very small commitments to diabetes-related research, even though there are major research challenges that could be best addressed by these Institutes. Examples of this disparity include the major health problem created by diabetic neuropathy and the importance of environment in diabetes, which seem mismatched to the low level of funding of diabetes research by NINDS and NIEHS, respectively.

- Coordination of diabetes research among and within NIH Institutes and Centers is almost non-existent and needs to be significantly enhanced by formal, systematic short- and long-range planning.

- Mechanisms to enhance multidisciplinary research, such as program projects or center grants, and attract new research talent to diabetes are small and have limited funding and need to be enhanced.

- There is inadequate support to develop the infrastructure needs of modern diabetes-related research, especially with regard to use of genetically-modified and other animal models, and expensive, high-technology instrumentation for metabolic studies.

- There is no stable infrastructure for major clinical trials related to diabetes.

- Mechanisms to create new technologies to answer critical questions in diabetes research, such as estimation of beta cell mass or metabolic function of nerve, are limited to traditional research solicitations, and are not adequate to meet the needs and opportunities in diabetes research.

- The limits imposed by funding "caps" on program projects and consideration of average grant size often constrain the scope of diabetes research.

Further information about NIH and NIDDK programs can be found at the following sites on the Internet:
http://www.nih.gov
http://www.niddk.nih.gov

Other Governmental Organizations

In addition to the NIH, several other governmental agencies are involved in addressing the problems of diabetes. Within the Department of Health and Human Services, some of these organizations are:

Centers for Disease Control and Prevention (CDC): Diabetes-related activities are conducted within three Centers at the CDC: the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), the National Center for Environmental Health (NCEH) and the National Center for Health Statistics (NCHS). The NCCDPHP research interests include: evaluation of diabetes health care, surveillance of diabetes in racial/ethnic minority populations, estimates of diabetes prevalence, surveillance of diabetes in the Medicaid population, and other ongoing research. The CDC's Diabetes Translation Program helps translate research findings into public-health oriented programs. The NCEH is involved in the development of testing methodologies, reference measurements and quality storage of samples from clinical trials. The NCHS is responsible for compiling and maintaining statistics on causes of death, death rates from diabetes and its complications, and occupational health. Its national surveys help to provide important epidemiologic information about diabetes.

Indian Health Service (IHS): The primary responsibility of the IHS is to provide health care services to Native Americans and Alaska Natives—both of whom are disproportionately affected by diabetes. The IHS also participates, usually in partnership with outside organizations (NIH and CDC), in health services research, epidemiology, and quality of life improvement projects.

Food and Drug Administration (FDA): The FDA has implemented improved food labeling regulations that allow diabetics to make more informed food choices. The FDA is also responsible for approving all diagnostic devices, home glucose monitoring devices, and all medications utilized in the management of diabetes and its complications.

Health Care Financing Administration (HCFA): The Medicare Program of HCFA includes an End-Stage Renal Disease program, which reimburses for dialysis and transplantation in patients with renal failure. Because renal disease is a major complication of diabetes, patients with diabetes represent a large and growing percentage of those treated for renal failure under this Medicare Program.

Health Resources and Services Administration (HRSA): This component is heading the Healthy People effort that includes five diabetes-specific objectives: increasing the percentage of people with diabetes receiving annual dilated eye exams, helping people with diabetes to learn more about their condition and how to manage it, eliminating racial disparities in health care, reducing the incidence and prevalence of diabetes by improved screening and early diagnosis and enhancing the quality of diabetes management. HRSA-supported community health care centers are becoming the health care provider of choice for low-income people with diabetes.

Agency for Health Care Policy and Research (AHCPR): This part of the Department of Health and Human Services (DHHS) was created to improve the quality of health care, reduce its cost, and broaden access to essential services. The AHCPR carries out its mission by supporting and conducting health services research that can help guide improvements in both clinical care and the organization and financing of health care. It also promotes the incorporation of science into practice through the development of tools for public and private decision-makers, and is involved in the development of the data and information infrastructure to study and track the performance of the health care system. Over the past few years, AHCPR has used its resources to support a number of diabetes initiatives.

In addition to the diabetes-related activities of the components of the DHHS, diabetes efforts are also funded by other government organizations such as the Department of Veterans Affairs and the Department of Defense.

Department of Veterans Affairs (DVA): Research funded by the DVA includes studies of the pathogenesis of diabetes, vascular complications, etiology of insulin resistance, wound healing in diabetes, exercise and nutrition in the management of diabetes, and advanced computer assisted techniques for the design and manufacture of orthotic footwear. While much of the DVA effort is on Type 2 diabetes, in 1996, the DVA and the Juvenile Diabetes Foundation International entered into an agreement to launch a major effort to establish jointly funded Diabetes Research Centers at DVA medical centers across the country to focus on Type 1 diabetes and the complications of diabetes common to both Type 1 and Type 2 diabetes.

Department of Defense (DoD): The DoD does not budget for diabetes research specifically. However, the DoD has supported research to answer mission-relevant questions concerning diabetes, conducted diabetes research requested by the Congress, and performed other medical research potentially applicable to diabetes. Most recently the DoD has been involved in a telemedicine research initiative with the Joslin Diabetes Center focused on diabetic retinopathy. The DoD can also support basic research that may be of mutual interest to military medicine and to the diabetes community, including receptor technology, neuroscience, nerve regeneration, vision technology, and oxygen tension/pressure physiology research.

Non-Governmental Organizations and Diabetes Research

The American Diabetes Association

The American Diabetes Association (ADA) is a voluntary health organization that provides support for diabetes research, information and advocacy. The ADA has offices in all 50 states and the District of Columbia and conducts activities in more than 800 communities. The mission of the organization is to support efforts to prevent and cure diabetes, and to improve the lives of all people affected by diabetes. The Association funds research in all areas of diabetes, and has specifically targeted several areas of special research interest, e.g., cardiovascular risk factors, perfected insulin replacement, and outcomes research. The cornerstone of the Association's Research Program is peer-reviewed, investigator-initiated projects–currently over 250 scientists are being supported at over 100 institutions nationwide. In addition, the Association supports special projects that fulfill a unique, unmet need. For example, in 1993 the Association launched the GENNID project, which has created the world's largest resource of DNA and data from individuals with Type 2 diabetes. The Association also co-sponsored, with federal agencies, two large intervention trials, the DPT-1 and DPP. (For further information about the ADA: http://www.diabetes.org)

The Juvenile Diabetes Foundation International

The mission of the Juvenile Diabetes Foundation International (JDF) is to find a cure for Type 1 diabetes and its complications through the support of research. Founded in 1970 by the parents of children with diabetes who were determined to help find a cure for the disease in their children's lifetime, JDF is now a leading nonprofit, non-governmental funder of diabetes research. Volunteers help define research priorities, select grant recipients, lead advocacy efforts, and provide guidance to overall operations. Funds raised by over 100 chapters and affiliates worldwide have provided close to $300 million for JDF-funded diabetes research since 1970, and in 1998-1999 more than $50 million for diabetes research worldwide. JDF's more than 200 research grants and over 110 fellowship and career development awards are focused in three areas. These are: (1) restoration of normal glucose metabolism through investigation of transplantation, beta cell physiology, and gene therapy; (2) avoidance and improved treatment of complications; and (3) prevention of diabetes and its recurrence through an understanding of the pathogenesis, immune tolerance and genetics of Type 1 diabetes. JDF views its mission to find a cure as a collaborative effort, working with diabetes researchers and academic institutions, such government agencies as NIH, NASA, and the Department of Veterans Affairs; and the Medical Research Councils of Australia, Canada, and Sweden. (For further information about the JDF: http://www.jdfcure.org)

Other Foundations and Organizations

There are also several smaller foundations and non-profit organizations that provide additional funding for the diabetes research effort. For example, the Iacocca Foundation has provided millions of dollars of support for diabetes research since its founding. This support is in the form of grants and endowments to major academic medical centers throughout the U.S.

The Joslin Diabetes Center was founded over 100 years ago and is the largest single organization in the U.S. devoted to direct clinical care and research in diabetes. It has a broad program of research in Type 1 and Type 2 diabetes, as well as all diabetes complications. The Barbara Davis Center for Childhood Diabetes was founded in 1980 and has a mission to provide care for children and adults with Type 1 diabetes, and to support research toward prevention, understanding and cure. Both of these Centers receive support from the NIH, ADA, JDF and other organizations, and have active programs of fund-raising to provide additional research support.

In addition, many academic medical centers have vigorous programs of diabetes research, often supplemented by fund-raising efforts; twelve are designated as Diabetes and Endocrinology Research Centers (DERCs) or Diabetes Research and Training Centers (DRTCs) by virtue of special grants from NIH. Another non-profit organization which has provided important support for diabetes research is the National Disease Research Interchange (NDRI). Founded in 1980, the NDRI is dedicated to the

Science Snapshot

Can Diabetes Be Prevented?

Current treatments for diabetes such as glucose control, laser surgery for sight-threatening eye complications, and ACE inhibitors (a class of drugs to treat hypertension) for kidney disease can significantly reduce the complications of diabetes. They do not however, eliminate complications in all patients. Patients must still live with the day-to-day burden and expense of coping with diabetes. Thus, the National Institutes of Health (NIH) has initiated a program to determine whether diabetes can be prevented.

In the early 1990s NIH began two large, multi-center clinical trials to test interventions to prevent diabetes: the Diabetes Prevention Trial for Type 1 diabetes (DPT-1), and the Diabetes Prevention Program (DPP) for Type 2 diabetes. Both trials require screening the population at-large for individuals at high risk for the development of diabetes. When recruitment is complete, it is estimated that more than 150,000 individuals will have been screened for the trials.

To prevent Type 1 diabetes, relatives of patients with diabetes are screened using a blood test for antibodies involved in the immune destruction of the insulin-producing cells in the pancreas (beta cells). There are over 350 screening locations for DPT-1 in the United States, Puerto Rico, and Canada. Family members who have antibodies and also have evidence of damage to the beta cells are randomly assigned

(randomized) to treatment with insulin by infusion and injection, or close follow-up for development of diabetes. Those who have antibodies but normal beta cell function are randomized to oral insulin. The study tests whether insulin can alter the immune process that is destroying the beta cells, thereby delaying or preventing diabetes.

In the DPP, volunteers have their blood sugar tested to see if a higher risk of diabetes is present. Individuals who are older, overweight, have a family member with Type 2 diabetes, are from high risk ethnic minority populations and women who have had diabetes during pregnancy are at particularly high risk for diabetes, and are targeted in the screening process. These selected volunteers then undergo a glucose tolerance test to see if they have abnormal glucose tolerance, but do not yet have diabetes. Those at greater risk of Type 2 diabetes are randomized into three groups: one with lifestyle recommendations plus placebo, a second with more intensive lifestyle intervention to increase exercise and lose weight, and a third receiving therapy with an oral anti-diabetic drug. All of these interventions have the potential to delay or prevent diabetes.

Preventing diabetes would have enormous benefits, and even modest reductions in the risk of developing diabetes would be of great value. For example, if the risk of those individuals with a 10 percent risk of developing Type 2 diabetes each year could be reduced to 8 percent (per year) it could save 7,000 to 9,000 person-years* from blindness, renal failure, and amputation due to diabetes. If the risk of diabetes can be reduced by 80 percent the savings would be about three times greater (22,000 to 37,000 person years saved). In addition to these health benefits, delay or prevention of diabetes would reduce the cost of treating diabetes and its complications, and is likely to be highly cost-effective if the interventions being tested in the prevention trials are effective. Finally, there is the personal benefit to the individuals involved whose quality of life is obviously immensely improved by not having the burden of diabetes.

*(A person-year is how many people will be affected times the number of years they will be disease free.)

procurement and distribution of human cells, including pancreas for islet isolation, to many investigators.

The role of the pharmaceutical and biotechnology industry in diabetes research should not be underestimated. These industries have active programs in the genetics of diabetes and obesity, basic mechanisms of insulin secretion and action, drug discovery, and pharmaceutical and product development. In some cases, there have also been successful collaborations between industry, academia and NIH, in both clinical and pre-clinical investigation.

Finally, a very important force in recent years for diabetes research has been the Congressional Diabetes Caucus. This Caucus was founded in 1995 and represents a bipartisan group of members of Congress committed to improving the life of Americans with diabetes. The Caucus has been an important driver of a number of legislative initiatives, including support for research funding related to diabetes and diabetes-related complications.

The DRWG, and indeed the entire diabetes community, recognize and deeply appreciate the dedication, counsel and support of each of these groups. Their energy and commitment in the fight against diabetes have been of prime importance and have enabled critical advances in the field.

Overview of the Research Plan

Enormous challenges confront patients, families, and society in dealing with the chronic, multisystem disease complex of diabetes and its complications. In many areas, critical, fundamental information is lacking and must be rapidly acquired for the development of new diagnostics and therapeutics. Other research avenues have provided important fundamental insights about the disease, but progress has been slow in finding practical therapeutic approaches through clinical research. Thus, it should not be surprising that developing a research plan for conquering diabetes is a formidable challenge and an ongoing process.

The first step in the planning process was the symposium on "Diabetes Mellitus: Challenges and Opportunities" held at the NIH in September 1997. This symposium brought together over 100 experts in the field, as well as individuals representing various agencies and organizations with an interest in diabetes. As a result of this initiative, and additional efforts by several groups, including the Congressional Diabetes Caucus, additional funding was made available for Type 1 diabetes research. At the same time, the Congress also directed the formation of the Diabetes Research Working Group (DRWG) to continue the process of review and to develop a Research Plan for all NIH-funded diabetes research. During the year-long planning process of the DRWG, the NIH recognized both the opportunity and the urgency for an increased diabetes research effort, and, despite existing budget limitations, has put forward a number of new initiatives through requests for proposals for new research grants. The DRWG believes, however, that the NIH and the Nation are far from achieving a maximal effort with this difficult problem and that a significant further investment in research today will greatly speed progress in understanding and conquering this disease. In developing this document, the DRWG has divided the Research Plan into the following three major components, and provided specific recommendations concerning the types of efforts, budgetary requirements, and research mechanisms that should be pursued to realize these compelling goals.

- Extraordinary Opportunities
- Special Needs for Special Problems
- Resource and Infrastructural Needs

Five areas of diabetes research have been designated as "Extraordinary Opportunities:" the genetics of diabetes, autoimmunity and the beta cell, cell signaling and cell regulation, obesity research, and clinical research and clinical trials of critical importance. Characteristic of these areas is rapidly expanding knowledge and/or development of new technologies such that intensified research substantially above current NIH-supported levels can be expected to lead to significant research advances in

diabetes and its complications in the near future. In some areas, a need exists not only for increased research but also for a better-coordinated effort or a change in infrastructure to move the field ahead at a maximal pace. In others, the proposed research is directly applicable to more effective treatments to improve the lives of individuals with the disease. Most of these extraordinary opportunities cut across all forms of diabetes and its complications. Ultimately, research advances emanating from each of these will provide the basis for preventing and curing Types 1 and 2 diabetes.

Equally important, but more focused in intent, are areas in the Research Plan designated as "Special Needs for Special Problems." This section of the Plan makes recommendations concerning a wide range of research related to micro- and macro-vascular complications; new methods to optimize glucose control; special issues for women, children, the elderly, and minorities; behavioral medicine; genetic engineering; and the role of the environment in diabetes. Each area presents tremendous challenges, as well as a growing body of information suggesting that increased research will yield important new knowledge fundamental to understanding diabetes and its complications, and major progress towards better treatment, prevention and cure of diabetes. Thus, these "Special Needs" require intensified research substantially above that currently being supported by NIH.

Finally, successful pursuit of any of the initiatives in this plan will require research manpower, technology, and other infrastructure elements. These needs are put forth in the section on "Resource and Infrastructural Needs." In this area, the DRWG has attempted to specifically address limitations in current NIH programs and mechanisms and proposed new approaches and significant changes in existing programs that would greatly facilitate research progress.

Historically, many significant advances have been made as the result of traditional NIH-supported, investigator-initiated research. Indeed, in many areas, investigator-initiated research is still the key to developing new insights and the most effective way to advance diabetes research. This research is typically performed through individual research grants (RO1s) and program project grants (PO1s). However, the number and level of funding of RO1 and PO1 research grants currently fall far below that required for optimal progress. Hence, in many areas, the DRWG recommends a substantial increase in investigator-initiated research as the principal mechanism to achieve its goals.

It is also clear that, in many cases, programmatic mechanisms other than investigator-initiated grants may be better suited to accomplish research goals. The DRWG has, therefore, recommended the creation of several new mechanisms. These include creation of Specialized Centers for Research in addition to those already in existence, Consortia to address specific diabetes-related problems that are difficult to address through current mechanisms, a Diabetes TrialNet of regional centers for cooperative clinical studies, new mechanisms to promote interaction with industry, and several types of training awards.

The DRWG concludes that a major increase in the NIH diabetes research budget is absolutely essential to successful pursuit and realization of the recommendations and goals set forth in this Plan. Chronic underfunding of diabetes research and infrastructure has hindered progress toward understanding and satisfactorily treating the disease and finding means of prevention and cure. While new funds to permit research expansion are especially needed in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the lead NIH Institute for diabetes research, the DRWG believes that diabetes research should be a priority and specific focus in every NIH institute. Hence, the DRWG has recommended a four-fold increase in the diabetes research budget across the NIH over the next five years.

Extraordinary Research Opportunities

Genetics

Almost every aspect of human biology from birth to death is highly influenced by genetic constitution. Genes not only influence the color of hair and eyes but also influence body weight, susceptibility to diseases or their complications, and even response to different therapies for disease. For complex diseases such as diabetes, genetics help define different subtypes of the disease, which have different causes and require different therapeutic approaches. Thus, genetics research is of critical importance to diabetes. Indeed, the DRWG believes that genetic studies offer the single best opportunity for identification of the unknown causes of complex diseases such as diabetes.

Both Type 1 and Type 2 diabetes mellitus have strong genetic determinants. These "diabetogenic" genes, or more precisely "diabetogenic" alleles, make some individuals more susceptible to developing diabetes than others. Furthermore, evidence has accumulated that genetic factors may cause some individuals with diabetes to be more prone to develop complications of the disease or diabetes-associated phenotypes such as obesity and hyperlipidemia. As knowledge of genetics continues to explode, it is imperative that diabetes research capitalize on this momentum and apply genetic advances and tools to diabetes-specific research questions.

Knowledge of the genetic defects underlying diabetes will likely be critical not only for identifying individuals at risk for diabetes and its complications but also for identifying targets for effective treatment and prevention. Furthermore, if genetically susceptible individuals can be identified through these markers, it may be possible to introduce therapeutic measures early to prevent diabetes and its complications. The rapid progress of the Human Genome Project and other efforts in genetics has created a backdrop of general genetic information. A number of other NIH-wide initiatives are also under way, or about to be started, that would directly benefit the effort to identify the genetic contributions to diabetes. Among these are: the Mouse Genome Initiative; an initiative to develop a complete set of full length cDNAs from human and mouse; the Center for Inherited Disease Research (CIDR), which has recently been established to provide high throughput genotyping; an initiative to identify single nucleotide polymorphisms (SNPs) for use in genome-wide association studies; and initiatives for genomic resources for non-mammalian organisms, such as yeast, the fruitfly, and zebrafish. The DRWG believes that knowledge and technology coming from all of these areas are now "ripe" for immediate application to the needs, challenges, and opportunities in diabetes research.

Therefore, a major goal for the coming decade must be to identify the genes predisposing to Type 1 and Type 2 diabetes and their complications, as well as associated

conditions such as obesity, accelerated atherosclerosis, and hypertension. This knowledge is necessary for the successful quest to prevent diabetes and to develop more effective and more specific modes of therapy.

Role of Genetics in Type 1 Diabetes

Type 1 diabetes is an autoimmune disease and is strongly influenced by the genes that control the immune system. A complete genetic picture has yet to be drawn, but researchers have discovered that particular forms, or alleles, of the genes that control the immune response strongly predispose people to Type 1 diabetes. In humans, the major immune-response genes occur on chromosome 6 in the major histocompatibility complex (MHC). Several of the molecules produced by this gene complex serve as receptors on the surface of lymphocytes and other white blood cells and play an important role in allowing these cells to identify foreign substances, become activated, and initiate a process that results in destruction of the foreign material. They do this by binding foreign molecules or small fragments of foreign protein and presenting them to specialized T-lymphocytes, which then initiate the destruction of the foreign material or cells. These MHC molecules are also known as human leukocyte antigens (HLA) or transplantation antigens, because they are also involved in transplantation rejection. Each of the MHC molecules has a number of sequence variations (alleles) that serve as a kind of cellular signature, whose exact pattern for each person is determined by genes.

In most people, the HLA system assures that the immune system recognizes and destroys only foreign substances rather than the individual's own tissues. In people susceptible to Type 1 diabetes, the immune response genes controlling the HLA molecules somehow cause this recognition system to go awry. The immune system then sees its own insulin-producing beta cells as foreign and attacks and destroys them. Particular HLA types have been strongly implicated in the autoimmune process leading to Type 1 diabetes. About 85 to 90 percent of people with Type 1 diabetes are positive for MHC molecules of the HLA types DR3 or DR4. In addition, people who have those HLA types, but do not yet have Type 1 diabetes, are much more likely to develop it than are persons with other HLA types. Thus, their genetic endowment sets up a situation in which the immune system can identify protein molecules of the insulin-producing beta cells as foreign.

Although genes for particular HLA types clearly play a role in Type 1 diabetes, studies in both humans and mice indicate that many other genes have some influence on susceptibility. Type 1 diabetes, then, is believed to be a multi- or polygenic disease. Identification of these diabetes genes will provide an essential marker of individuals at risk for disease who are candidates for preventative therapy.

Extraordinary Research Opportunities

- **Genetic studies to identify the genes predisposing to diabetes and its complications.**
- **Autoimmunity and beta cell research to enable eventual prevention and cell replacement therapy of Type 1 diabetes.**
- **Cell signaling and cell regulation studies to define the fundamental basis of Type 2 diabetes and its complications.**
- **Obesity research – causes, treatment, and relationship to diabetes.**
- **Clinical research and clinical trials of critical importance.**

Genes Contributing to the Development of Type 2 Diabetes

Genetic factors play a critical role in the development of Type 2 diabetes and may be even more important than in Type 1 disease. Indeed, even though Type 2 diabetes is a heterogeneous disease, virtually all forms appear to have strong genetic influences, with the involvement of multiple genes. Important observations have been made about the genes implicated in some of the rare forms of Type 2 diabetes, such as Maturity Onset Diabetes of the Young (MODY) and several syndromes of severe insulin resistance, but the genes involved in the common varieties remain unknown. Some natural sequence variations (polymorphisms) have been observed in the genes that control the synthesis of the proteins involved in insulin action or insulin secretion, but none of these yet explains the familial nature or development of this disease.

A number of population studies have been conducted, but—given the complexity of the interactions and the relatively limited size and variation in the populations sampled—an informative and complete analysis of the genetics has not been possible. In many studies, minority populations who are at highest risk and have especially high prevalence of Type 2 diabetes are under-represented. Furthermore, limited or no metabolic data are available in most of these genetic studies to allow the different subgroups

of diabetes with different metabolic phenotypes to be identified.

Because the basic defect in Type 2 diabetes remains uncertain, defining these genetic influences will not only increase understanding of this disease, but also help in developing new, more effective therapeutic modalities and appropriate prevention programs. Moreover, Type 2 diabetes is strongly associated with many other important genetically influenced traits, including obesity, hyperlipidemia, accelerated atherosclerosis, hypertension (which together form the Metabolic Syndrome), and even polycystic ovarian disease.

Identifying Genetic Factors in Complications

Although many people with Type 1 or Type 2 diabetes will ultimately develop one or more of the devastating long-term microvascular complications of the disease, some patients are completely spared. The risk of developing complications, especially diabetic kidney disease and perhaps other vascular disorders, appears to be genetically determined. Exciting advances in genetics offer extraordinary opportunities for identification of the individuals at greatest risk for development of complications, for finding the tissue-specific factors or molecules involved in causing the complications, and for developing novel therapies, such as nerve or kidney regeneration, as alternative approaches to therapy of the disease.

Science Snapshot

Genetics and the New Technologies

Recent advances in molecular biology and genetic research have revolutionized medical research. Two new technologies that will further impact on our ability to diagnose and treat disease are the rapid accumulation of genetic sequence information and the application of silicon chip technology to measure changes in genetic sequence.

Both Type 1 and Type 2 diabetes result from complex interactions of multiple genetic and environmental factors. With identification of the genetic factors associated with diabetes, individuals likely to develop diabetes can be identified and interventions can be initiated to prevent or delay the development of the disease. The identification of diabetes-causing genes will provide clues to the cause of the disease and serve as guides in the choice of the most useful therapy.

Over the next few years, the Human Genome Project will provide the sequence of all human genes, and the Consortium on the Genetics of Diabetes proposed in this report would accelerate the pace of the identification of disease-causing genes. Both academia and industry are also identifying genetic variations between individuals, called polymorphisms. These genetic differences are used to identify disease-causing genes. Single Nucleotide Polymorphisms, also known as SNPs (pronounced snips), are one of the most useful of these genetic markers because they occur frequently and can be measured by automated techniques. These properties enable thousands of SNPs to be studied in large numbers of individuals in order to help identify the location of a disease-causing gene.

The automated analysis of SNPs uses a new technology to immobilize thousands of DNA samples on a single microchip the size of a dime. These microchips can then be studied for the presence of a discrete set of SNPs in multiple samples and the results read directly into a computer for analysis. Important new technologies in computer bioinformatics will be needed to store and analyze the vast amounts of data that will be generated by this new technology.

In addition to knowing the location and sequence of a gene, the gene's functions must also be identified. The technique of analyzing DNA on microchips is used to identify all of the genes that are active in particular tissues or are activated in particular disease states. This information will provide clues to the function of those genes. Ultimately, in order to understand diabetes, the ability must exist to identify all the genes that are involved in the development of the disease and its complications. The explosion of new genetic technologies provides us with an extraordinary opportunity to uncover the causes of diabetes.

Given the strong possibility that specific genes may be important in the prevention, causation, and progression of microvascular complications, research needs to be greatly intensified in this important area.

What Is Needed To Accelerate Genetic Analysis of Diabetes and Its Complications?

Many basic tools of genetic research are in place and significant progress in defining a few of the genes involved in diabetes has begun. Nevertheless, current approaches to this problem are clearly inadequate to answer the important genetics questions in a reasonable timeframe. At least three major factors contribute to this limitation. First, inadequate resources are being applied to a complex problem. Second, much larger groups of researchers need to work together in a collaborative and coordinated way. Third, a very large collection of DNAs is required from well-characterized patients and well-characterized families to achieve meaningful answers. Furthermore, in most studies, the organization of genetic databases has made it difficult to attain adequate representation of special, high-risk minority groups, and increased efforts, guided by sensitivity to cultural differences, must be undertaken to remedy this deficit. Because genetic information is a rich source of leads for new drug targets, a significant role may exist for the pharmaceutical and biotechnology industry in this effort. Often some of the newest genetic technologies are best represented in large scale in the biotechnology industry.

Recommendations:

- **Establish a National Consortium for the Study of the Genetics of Diabetes to create a strong, coordinated effort for analysis of the role of genetics in diabetes and its complications.**

- **Enhance research in laboratory animals and humans to discover the biochemical mechanisms by which diabetes genes function to create susceptibility to diabetes and its complications.**

The National Consortium for the Study of the Genetics of Diabetes would serve as a highly coordinated and integrated research center without walls. The Consortium would be charged with solving the genetics of diabetes and its complications in the fastest and most efficient possible manner. This task would include enlarging the patient sample size for identifying all major genes for both Type 1 and Type 2 diabetes and their complications, maximizing the rapid exchange of information, facilitating comparative studies, developing centralized database management systems, and standardizing nomenclature of diabetes genes. Inclusive in participation, the Consortium would be directed by a Steering Committee composed of the principal investigators of the participating research groups, together with NIH staff and other advisors. It is envisioned that extramural academic, intramural NIH and industry-based scientists would participate, as well as appropriate non-scientific members, such as ethicists. A Scientific Advisory Committee, composed of experts who are not themselves Consortium participants, could provide additional direction and peer review. The specific structure of the Consortium should be one to allow maximal effectiveness and flexibility. The nidus for this Consortium might be the recently formed "grassroots" consortium that has developed to focus on some early leads for genes involved in Type 2 diabetes.

It is envisioned that the National Consortium for the Study of the Genetics of Diabetes would report to the Scientific Advisory Board for the Genetics of Diabetes and its Complications, appointed by the Director of NIH. This Board would be composed of experts from each appropriate sector, including one or more representatives of the diabetes community. Implementation of the Consortium would involve a close collaboration between the NIDDK and the NHGRI, as well as other Institutes of the NIH. It is also envisioned that the NIH and these Institutes would develop the appropriate mechanisms to assure quality and accountability, including peer review of cooperative agreements and external data monitoring by the Consortium. It is estimated that the majority of this initiative could be completed in 7 to 10 years if adequately supported.

National Consortium for the Study of the Genetics of Diabetes

The proposed Consortium would be responsible for achieving, through collaborative efforts, a sufficiently robust mechanism to search the human genome for all major genes involved in development of Type 1 and Type 2 diabetes and their complications.

Research Agenda

- **Create a repository of human DNA samples large enough to perform the appropriate genetic analyses for diabetes and its complications, as well as for closely associated disorders such as obesity. This repository should include collections of families, sib-pairs and other genetically informative groupings, and an adequate representation of minority groups disproportionately affected by diabetes or its complications. This initiative should take advantage of existing genetics efforts by the NIH and other groups both nationally and internationally, but may require additional approaches, including a national registry approach, given that thousands of samples will likely be needed for this complex analysis.**

- **Provide resources for adequate metabolic phenotyping of a significant subset of the DNA donors in the repository to allow a full analysis of intermediate phenotypes of diabetes and its associated disorders.**

- **Coordinate efforts to use all modern technologies, including single nucleotide polymorphisms (SNPs), to scan these samples to identify the genes involved in diabetes and its complications. The goal of this analysis is to identify potential diabetes-related genes and also to determine the range of sequence variations in these genes, or the proteins they encode, which might affect the risk of diabetes or its complications. Standardized or centralized genotyping, possibly in part by the Center for Inherited Disease Research, with common sets of markers may offer substantial advantages.**

- **Create a catalog of all of the genes expressed in various tissues, which play a role in diabetes or its complications, including islet cells, insulin-responsive peripheral tissues, and tissues affected by complications. In addition, potential diabetes-related genes should be identified by comparing expression patterns of genes in these different tissues from normal and diabetic individuals.**

- **Develop a database of polymorphisms with a likelihood of relevance to diabetes by direct sequence analysis of a sufficiently large sample population.**

- **Apply genomic research, differential expression studies, and sequence polymorphism studies to high throughput detection of diabetes-related variants and gene expression from accessible tissues, using powerful new technologies, such as DNA chips. Indeed, one ultimate goal may be development of a "diabetes DNA chip" or chips that could be applied to determine the risk of diabetes and its complications in large population studies or used in basic cell biology studies. The NIH through the proposed National Consortium for the Study of the Genetics of Diabetes could provide to diabetes investigators centralized access to expensive, high technology such as DNA chips, as well as to methods to analyze them in a standardized fashion.**

- **Successful identification of gene variants that predispose to diabetes will introduce a host of challenging ethical, legal, and social (ELSI) issues surrounding the proper introduction of such tests into clinical medicine. Risks of stigmatization, psychosocial injury, destabilization of family dynamics, invasion of privacy, and genetic discrimination will have to be balanced against the very real and exciting possibility of efforts for disease prevention in genetically susceptible individuals. Vigorous research into these issues will be essential, prior to introduction of genetic testing into the practice of medicine.**

Funding

- **Provide adequate appropriations to enable a commitment of resources needed to launch this major new initiative and meet these bold goals. The Steering Committee of the Consortium, with oversight by the Scientific Advisory Board, would have the authority to define the specifics of the research agenda. The Scientific Advisory Board would recommend to the Institutes research solicitations, such as Requests for Applications, cooperative research agreements, and other methods to deploy the resources among participating research groups; make recommendations of awards of grants and contracts to appropriate**

academic and industrial investigators; and participate in the peer review mechanism.

Planning

- **Advise the NIH about opportunities that exist for functional genomic studies, to be pursued through investigator-initiated research. These will elucidate the mechanisms by which genes induce susceptibility to diabetes or its complications.**

- **Advise NIH on the need for family collections (including multiplex families), databases, and repositories of biomaterials for genetic studies of Type 1 and Type 2 diabetes, their complications, and obesity.**

Coordination

- **Maintain close-working relationships with the existing Human and Mouse Genome initiatives and other existing NIH efforts to maximize efficiency and minimize redundancy of effort. The Consortium would also have a close working relationship with the proposed new Centers for Animal Models of Diabetes, one of whose specific missions would be to use this new genetic information to create animal models carrying these human diabetes genes to enable their complete analysis** *in vivo* **and** *in vitro*.

- **Maintain a close-working relationship with international collaborators in the same area to promote maximum efficiency in completion of this task.**

Autoimmunity and the Beta Cell

Type 1 diabetes is an autoimmune disease in which unknown environmental factors combine with genetic susceptibility to destroy the insulin-producing pancreatic beta cells. Genetics, especially the genes coding for the human leukocyte antigens (HLA), play a major risk role in the disease; however, the final process is much more complex. Lymphocytes are activated in the immune process and produce a response against the individual's own proteins (autoantigens) in a process that involves both B- and T-lymphocytes and antibody production. The identification and molecular cloning of some of these autoantigens in Type 1 diabetes have provided a set of standardized autoantibody assays that allow some measurement of the disease process, even prior to onset of clinical manifestations. Current therapy, however, is still limited to replacement of insulin by daily injections rather than blockade of the immune response to prevent destruction of beta cell function and preserve normal insulin secretion. As a result, the patient with Type 1 diabetes remains at high risk for the development of long-term complications of the disease.

Vital groundwork has been laid by the important discoveries and emerging concepts from the past decade of research in basic immunology, cell biology, and autoimmune diseases, including Type 1 diabetes. Based on this strong research foundation, the DRWG believes that aggressive pursuit in three areas over the next decade could lead to dramatic improvements in diabetes therapy and prevention. These are:

- Understanding the immunological basis of Type 1 diabetes, and development and application of methods for preventing the disease and its recurrence, including appropriate clinical trials.

- Development and clinical testing of methods for replacing beta cell function in patients with diabetes through islet transplantation.

- Intensification of basic investigation of beta cell biology to gain the critical knowledge essential for developing a replenishable supply of insulin-secreting beta cells for transplantation or for expansion of pre-existing cells to provide enhanced insulin secretion.

Understanding the Immunological Basis of Type 1 Diabetes and Developing Methods for Preventing the Disease or Its Recurrence

Perhaps the most important long-term goal of research on Type 1 diabetes is to gain an understanding of the immunological basis of the disease. Such insights would allow development of appropriate methods for prevention

of the disease or its recurrence in genetically susceptible individuals. Early attempts at immunologic modulation have suggested the value of this approach. However, a number of problems must be overcome for this approach to be useful. These impediments include the need for more specific and long-lasting immunomodulation, the need to optimize approaches to detect the immunological process in prediabetic individuals, and possibly, the need for more than one approach to deal with the heterogeneity of the disease.

To accomplish the long-term goal of prevention, a multi-stage process must begin. The first stage will focus on expanding the base of knowledge about the fundamental immunologic underpinnings of Type 1 diabetes and identifying the antigens and nature of the T-cell response involved. Another stage in the process will be initiating clinical trials to test the two major approaches for immunological intervention (antigen-based immuno-modulation *versus* antibody- or cytokine-based immuno-modulation). These trials will determine which of these methods produce an effective and safe approach to prevention of Type 1 diabetes, as well as its recurrence in individuals undergoing pancreatic or islet transplantation. The DRWG believes it should be possible to determine, in the next 10 years, whether these techniques can be successfully applied to prevention of Type 1 diabetes in humans. The multistage process that could lead to such clinical trials is described in the following sections.

Expanding the Base of Fundamental Information

The fundamental cause of autoimmune diseases such as Type 1 diabetes remains unknown, although some understanding of pathogenetic mechanisms has emerged. These advances have come through many areas of basic immunology and through the study of animal models, such as the nonobese diabetic (NOD) mouse, the BB rat, and genetically modified mice, as well as through studies of humans predisposed to the disease. Progress in research will further enrich the picture of the pathogenesis of Type 1 diabetes over the coming years and permit a detailed analysis of autoimmune mechanisms involved in human susceptibility. Contributing to continued progress will be analysis of the cytokines (hormones) produced by white blood cells, analysis of the functional characteristics of the genes predisposing to diabetes in these situations, and use of predictive markers and "humanized mouse models" (transgenic mice that express the human diabetes susceptible MHC molecules). Thus, if the ultimate goal is development of effective methods to block the immune response in Type 1 diabetes by antigen-, cytokine-, or antibody-based therapy, fundamental research is required in several areas to further elucidate the immunologic mechanisms underlying the disease.

Identifying Islet Antigens and Determining the T-Cell Response

Through human studies and the use of diabetic mouse models such as the NOD mouse, researchers have been able to identify important target antigens for T-cells that attack the islets of Langerhans in Type 1 diabetes. These include the best defined of the known islet antigens: insulin, glutamic acid decarboxylase (GAD), and IA-2. Studies have also shown that "prediabetic" patients and "prediabetic" mice of the same MHC type, that is, with the same immune-response genes, have T-lymphocytes that recognize peptide fragments of these antigens. These findings suggest the potential for antigen-based therapy. The NIH is currently supporting a clinical trial for prevention of Type 1 diabetes (the Diabetes Prevention Trial – Type 1 or DPT-1) at 10 Clinical Centers with multiple satellites throughout the United States. The trial involves administration of insulin or fragments of insulin to patients considered genetically susceptible for developing the disease, by virtue of having antibodies to at least two of the three islet cell peptides. The objective is to develop immune "tolerance" in these patients and thereby prevent or slow the progression of Type 1 diabetes. Additional research on the autoantigens that are targets in the autoimmune destruction of beta cells may hold the key to specifically modifying the immune response in Type 1 diabetes.

Cytokines and Monoclonal Antibodies That Modify the Immune Response

The second approach for immune prevention of Type 1 diabetes involves suppression or modulation of lymphocyte function using cytokines or monoclonal antibodies. Recent studies have shown that certain antibodies can dramatically modify the inflammatory process that occurs in and around beta cells in animal models of diabetes. It may also be possible to engineer T-cells to express protective cytokines (for example, IL-4 or IL-10), which suppress the inflammatory effects of the other types of cytokines. These reagents may not only be useful for prevention of diabetes in prediabetic patients, but are also likely to be applicable to blocking rejection/destruction of transplanted islet tissue.

Over the next 3 to 4 years, studies should be performed in suitable animal models, such as the NOD mouse or BB rat, to identify the optimal cytokine-based or monoclonal antibody-based immunotherapy. This research might include studies of protective cytokines, such as IL-10, and antibodies against destructive cytokines, such as interferon-gamma or IL-12. Also included should be monoclonal antibodies to cell surface molecules such as CD3, CD4, CD40, accessory molecules, integrins, or selectins, as well as studies with synthetic immunomodulatory gene products, such as CTLA4-Ig.

Recommendations:

- **Intensify research to understand the immunological basis of Type 1 diabetes.**

- **Complete mapping of T-cell specificity of autoimmune responses to major pancreatic islet cell proteins and identify optimal strategies for immunotherapy.**

Expand Studies for Screening and Prediction of Type 1 Diabetes in the Population At Large

Only 15 percent of those who develop Type 1 diabetes have any family history of the disease. This is because a large number of different genes, as well as environmental processes, must act in concert to create the clinical disease. To conduct the needed clinical studies, researchers must identify individuals at risk for, but not yet stricken with, Type 1 diabetes. Such identification involves not only the collection of large number of individuals over a 5-year period, but genotyping of all subjects upon enrollment, yearly autoantibody measurements, and calculation of the relationship between incidence of diabetes and autoantibodies at the end of a 5-year clinical study.

To find susceptible individuals, therefore, a means of large-scale population screening will be needed. Fortunately, advances in genetic technology have produced inexpensive and efficient means of determining which MHC molecules people have. These methods could identify the percentage of the population who have the HLA types related to Type 1 diabetes. When coupled with means for identifying the immune response, this approach will allow studies for prevention of Type 1 diabetes in the population as a whole, rather than just the small percentage of individuals with a family history.

In patients with a family history of Type 1 diabetes, presence of two of the three major autoantibodies has been shown to predict onset of the disease with 90 percent accuracy. However, it is not yet known if the same is true in individuals with the high-risk genotypes for Type 1 diabetes found by population screening. Given that the goal is to prevent development of Type 1 diabetes in the population as a whole and intervene as early as possible in the immune destructive process, two major research efforts are necessary. First, it is essential to test segments of the population at large and determine the applicability of the currently available tests for detecting prediabetes in the general population. Second, it is necessary to apply testing at an earlier age in families with genetic predisposition to diabetes, with the objective of developing strategies for prevention of autoantibody formation.

Recommendation:

- **Expand the scope of efforts to identify immune response markers that reliably detect individuals predisposed to Type 1 diabetes in the population at large.**

  To fulfill this recommendation, the DRWG believes the NIDDK should consider at least two potential mechanisms. The first would be to expand the mandate of the existing DPT-1 Centers to include screening studies of prediabetes in general population groups. Alternatively, it may be desirable to establish additional regional research centers to conduct large-scale population studies to identify individuals at risk for developing Type 1 diabetes based on the detection of immune response factors.

Further understanding of the fundamental mechanisms involved in autoimmune destruction of beta cells is being sought via expansion of traditional funding mechanisms. While that research is under way, the DRWG concludes that the time is ripe to begin studies in humans, which seek to test approaches that have already emerged as possible methods for prevention of Type 1 diabetes.

Recommendation:

- **Conduct additional clinical trials of immunoprevention of Type 1 diabetes using antigen-specific, cytokine- or antibody-based immunotherapy.**

One of the major long-range goals of the research plan for Autoimmunity and the Beta Cell is to develop a program to prevent diabetes in genetically susceptible individuals who have evidence of an early immune response. Although this Strategic Plan focuses primarily on the next five years, to fully explore immunoprevention for Type 1 diabetes will require a well-developed program of clinical trials over a period of 10 or more years. The DRWG believes that the preliminary efforts towards such trials should begin immediately. At least two basic intervention strategies should be tested for their ability to modify the immune response toward beta cells that leads to Type 1 diabetes. The first is antigen therapy, that is, the administration of peptides or proteins thought to be recognized by the immune system. The second is antibody or cytokine therapy, that is, administration of antibodies or cytokines that may block or suppress the immune response.

The fundamental research efforts described above should help identify the optimal antigen, cytokine, and monoclonal antibody for immunotherapy to be tested, and provide appropriate markers to detect the early autoimmune response of Type 1 diabetes in the general population. Based on these studies, an expert panel should be convened by the year 2002 to recommend to the NIH additional basic studies and new clinical trials for immunotherapy of Type 1 diabetes. Such clinical trials of immunomodulation in Type 1 diabetes will likely require additional preclinical studies of any reagents for antigen-, antibody-, or cytokine-based immunotherapy in animals models, such as the NOD mouse and the BB rat, as well as the ultimate implementation of human clinical trials. These studies might include research on whole protein versus peptides as antigens, dominant epitopes for each susceptible DR and DQ allele, route of administration, and dosing considerations. In addition, development of methods will be needed to produce clinically useful amounts of these immunomodulators and to perform animal toxicity studies.

The clinical trial itself will consist of three phases: Phase 1, safety, toxicity, and early efficacy; Phase 2, human studies to determine optimal dose, route, frequency and duration of effect; and Phase 3, double-blind, multicenter trial in genetically at-risk, autoantibody-positive, prediabetic individuals with moderate insulin reserve. If a concerted effort is made now, it is envisioned that at least two or three major clinical trials of this type might be completed in 10 to 12 years.

Developing Methods for Replacing Beta Cell Function in Patients with Type 1 Diabetes Through Islet Transplantation

The recently concluded Diabetes Control and Complications Trial (DCCT) has clearly demonstrated the importance of tight glycemic control for limiting onset and progression of the crippling secondary complications of Type 1 diabetes. Unfortunately, improvement in glycemic control via self-injection of insulin multiple times each day and self-monitoring of blood glucose is extraordinarily demanding, requires a high level of compliance and discipline, and places the patient at significantly enhanced risk for dangerous hypoglycemic episodes. These findings emphasize the need to design and develop better methods for insulin replacement in Type 1 diabetes, which not only replace the function of the normal pancreatic islet beta cell but also reproduce the normal beta cell's exquisitely regulated delivery of the hormone in response to appropriate physiological cues.

Whole Pancreas Transplantation

One approach to solving this problem is whole pancreas transplantation. While the success rate for pancreas transplantation has improved dramatically, it still remains a major surgical procedure with significant risks. Broad-based application of this type of surgery to the millions of individuals with insulin-requiring diabetes is also not possible due to the limited number of suitable donor organs—estimated to be in the range of several thousand pancreases per year. Furthermore, whole pancreas transplantation requires life-long immunosuppression with its attendant risks in order for the graft to be protected from the immune system. The requirement for immunosuppression and the complexity and the risk associated with the surgical procedure make whole pancreas transplantation an unlikely first option for children with newly diagnosed Type 1 diabetes.

Pancreatic Islet Transplantation

Transplantation of isolated islets of Langerhans has been investigated as an alternative to whole organ transplantation for more than three decades, yet only a small number of patients have been successfully treated using this approach. Major issues remain to be overcome in order for cell-based insulin replacement in Type 1 diabetes to become widely applicable.

These issues include: (1) availability of a replenishable cell supply, (2) consistency of performance of the population of cells to be used for transplantation, and (3) immunoprotection of transplanted cells. Although the optimal cell-based approach has not yet been determined, strategies under active investigation include use of human islet allografts, animal islet xenografts, or genetically engineered insulin-secreting cell lines. In addition, a better understanding of islet cell development may make it be possible to devise methods for stimulation of islet cell growth or protection of islet cells from death both in cell culture and in individuals who need additional insulin secretion. Finally, delivery of insulin by insulin pumps, coupled with a glucose sensor, could enable insulin delivery in response to changes in circulating glucose levels. In this section on "Extraordinary Opportunities," the DRWG evaluates the current status of research on pancreatic islet transplantation and proposes a plan for pursuing this extraordinary opportunity. In the section on "Special Needs for Special Problems," the DRWG evaluates the mechanical and other approaches for replacing beta cell function.

The NIH has funded research on pancreatic islet transplantation since the late 1960s. Since that time, encouraging reports have appeared of long-term efficacy in a variety of rodent models, but translation of these findings into large animal models or humans has proven difficult. Although there are several human patients with functional human islet transplants, the general conclusion is that this technology has not yet been successfully translated to the clinical setting. However, very recent trials with immunomodulatory agents, such as anti-CD40 antibodies or CTLA4-Ig, are showing very promising results. In addition, research has made progress toward development of automated methods for isolating functional pancreatic islets from animals and humans. Advances have likewise occurred in the development of micro- and macro-encapsulation methods for partial immunoprotection of the transplanted islet tissue. Furthermore, evaluation of clinical end-points in patients with pancreas and islet transplantation have provided evidence that individuals with successful transplants have improved glucose control and stabilization or reduction in markers of complications.

If islet transplantation is to be a clinically useful alternative to therapy, a multidisciplinary approach is needed to address several diverse problems. A major problem is the need to understand the factors that contribute to the current low success rate of islet transplantation, including the mechanisms of immunological destruction and nutritional or oxygen deprivation. Another impediment is lack of knowledge about the relative efficacy and safety of human islet allografts versus animal islet xenografts. Similarly, it is necessary to develop potential approaches to local protection by micro- and macro-encapsulation, as well as methods to modulate the immune response to transplanted tissue. During the process of preparing this report, the NIDDK recognized the importance of this area and began to address the goal of islet transplantation through a request for applications for RO1 and Interactive Research Project Grants on human islet transplantation. While this is an important start, the DRWG believes that the proposed program is too small and that a more vigorous approach is required, of significantly greater scope and level of funding. In addition, more investigator-initiated work will be required to test reagents that may be used to block islet rejection, as well as to perform studies of cross-species xenotransplantation in rodents and large animal models.

Recommendations:

- **Establish Centers for Islet Transplantation with appropriate funding to undertake immediate clinical trials of islet transplantation in patients with Type 1 diabetes and to evaluate various methods of immuno-intervention.**

- **Support an expanded system for national collection of human pancreas for isolation and distribution of islets for clinical studies, clinical trials and basic research, and establish a Task Force to make recommendations on approaches to increase this process.**

These trials should be significantly broader in scope and of larger commitment of effort and funding than those studies currently proposed by the NIH. It is important to recognize that, given the present state of the art, these are not necessarily clinical trials to cure diabetes. Rather, these trials are intended to provide the information necessary to determine optimal approaches for providing highly functional islets, and thus, set the stage for larger scale "curative" transplant studies.

Beta Cell Biology and Development of a Replenishable Supply of Insulin-Secreting Cells for Therapy of Type I Diabetes

A major limitation of islet transplantation as a therapy for Type I diabetes is tissue supply. Only a few thousand human pancreases are currently available for islet isolation in the United States each year. This number is clearly inadequate to provide the therapeutic needs of the hundreds of thousands of patients with Type 1 diabetes and the millions of patients with Type 2 diabetes who require insulin. Thus, a major focus must be placed on development of new methods to stimulate human beta cell growth. New initiatives are needed to expand research on the mechanisms controlling islet cell growth and development, and the mechanisms involved in stimulation of insulin secretion from beta cells by glucose and its potentiators. This research is essential for solving the cell supply problem for cell-based therapy of Type 1 diabetes and is central to understanding the beta cell failure that occurs in Type 2 diabetes.

During normal growth and development of the pancreas, insulin-producing beta cells develop from a pool of poorly defined precursor, or stem cells. By understanding this process, it may become possible to recapitulate normal development of beta cells in tissue culture using stem cells obtained from the patient or from other human donors, or to cause stimulation of beta cell growth *in vivo*. Such approaches would overcome the risks of immune reaction to foreign tissues and many of the other potential problems associated with transfer of tissue from donor to patient.

Enthusiasm for this line of research is spurred by important recent advances in the field of developmental biology in general, and by the recent discovery of several genes that are important for islet cell development. However, much remains to be learned about this complex process to permit the development of beta cells as an adjunct to therapy of Type 1 diabetes.

Recommendations:

- **Increase basic research on the control and regulation of islet cell differentiation, growth and development, and devise methods for stimulating growth or regeneration of islet cells.**
- **Create Interdisciplinary Centers for Beta Cell Biology to expand current efforts and bring new investigators into the field. These Centers should be applicable to research efforts for both Type 1 and Type 2 diabetes.**

Recent Advances in Developmental Biology and Genetics that Set the Stage for Islet Cell Development

- **Increased understanding of the developmental mechanisms in the early embryo that allow individual cell types to differentiate.**
- **Greater understanding of some of the morphological events involved in the development and regeneration of the pancreas, the islets, and the beta cells; identification of some of the signaling molecules involved.**
- **Understanding the genes required for normal function of the beta cell.**
- **Identification of transcription factor genes involved in the formation and the maturation of the pancreas and islets.**
- **Identification of some of the growth factors that can stimulate, at least to a limited degree, growth and regeneration of the islet cells.**

Thus, expanded research is critical to:

- **Develop improved methods for the growth and differentiation of islet cells *in vitro*, including the identification of islet precursor cells.**
- **Outline the hierarchy of transcription factor genes involved in beta cell development, and identify the signals that control their activation.**
- **Develop a better understanding of the extracellular signals that control the formation of the pancreas and the growth and differentiation of the islet cells, during normal development and during regeneration.**
- **Develop a method for expanding beta cells in culture, while maintaining the differentiated characteristics of the cell, including the capacity to make insulin and to sense glucose, that is, to maintain the features required of transplanted cells.**

Cell Signaling and Cell Regulation

A fundamental component of the regulation of all cellular functions is the ability of cells to communicate with one another and the ability of signals to be carried within the cell itself. These are the processes of inter- and intra-cellular communication. Cell signaling is critical to virtually all functions of the body – the ability of the beta cell to grow and secrete insulin, the ability of insulin to stimulate glucose metabolism, and the ability of the brain to recognize satiety versus hunger versus hypoglycemia. In Type 2 diabetes, defects in signaling lead to a decrease in the ability of the liver, muscle, and fat to respond to insulin—a phenomenon called insulin resistance. Insulin-producing beta cells fail to respond normally to the high glucose created by the insulin resistance and do not appropriately increase insulin secretion. Signaling defects also play a fundamental role in development of obesity and other diabetes-associated problems, including the many vascular complications of Type 2 diabetes.

Over the past decade, research has paved the way to the beginnings of major new insights into these signaling pathways through the development of powerful technologies now available in modern biochemistry, physiology, cell and molecular biology, and structural biology. Studies using these technologies have also demonstrated an enormous commonality of signaling systems.

Research has shown that many of the same molecules are involved in insulin signaling in peripheral tissues, beta cell function, regulation of hormonal control of body weight, and even in the immunological signaling that controls the autoimmune response in Type 1 diabetes. This new knowledge has created an extraordinary opportunity to determine, through basic research, the exact mechanisms of signal communication and their alterations in diabetes. Furthermore, this type of "discovery" research, traditionally the greatest strength of NIH-funded, investigator-initiated research, provides the impetus for critically needed targets for new drug development and new treatments for diabetes. These approaches also provide an excellent complement to the information obtained from genetic studies, and together, they offer the greatest prospect for new approaches to diabetes and its complications.

Completing the Dissection of Hormone Signaling Pathways, Particularly the Pathways of Insulin Action, and Defining Their Alterations in Diabetes

Insulin action at a cellular level is the result of a complex network of intracellular signaling molecules. Alterations in insulin action are among the earliest defects detectable in individuals genetically prone to development of Type 2 diabetes. Similar defects are also observed in a number of other common metabolic disorders, including obesity, gestational diabetes, and individuals with accelerated atherosclerosis. Defining the alterations in insulin action in Type 2 diabetes will create unprecedented opportunities to combat the insulin resistance in this disease. It will also open the possibility of discovering new drugs that mimic insulin action and thus would be applicable for the treatment of all types of diabetes. To begin this process, however, it is also necessary to define the normal signaling pathways.

Recommendations:

- **Significantly increase research in the fundamental science of cellular signaling as it relates to diabetes and its complications.**
- **Remove the limits currently present on research project (RO1) and program project (PO1) grants, such as budget caps, limitations for growth of programs, and considerations of average grant size, to maximize the opportunity for effective research teams to be formed.**
- **Establish Research Centers to focus on development of methods to study cellular signaling at the molecular and genetic level in humans with diabetes to allow correlation between the physiological defects and the molecular alterations.**

Understanding and Countering Insulin Resistance in Type 2 Diabetes

Insulin resistance refers to a decrease in the ability of insulin to stimulate its actions on all tissues of the body, especially those involved in glucose homeostasis. Insulin resistance in muscle and fat is perhaps the earliest detectable defect in the pathogenesis of Type 2 diabetes, often detectable 15 to 20 years prior to the onset of disease, and appears to be an inherited feature of the disease.

Many individuals prone to develop Type 2 diabetes are also obese. It is well known that obesity itself induces insulin resistance, compounding that already present in the genetically susceptible individual. The physiological responses to this insulin resistance include increased insulin secretion, causing hyperinsulinemia, and elevated free fatty acids. This results in further increases in the insulin resistance. Together these genetic and acquired defects are major contributors to the pathophysiology of Type 2 diabetes. Thus, to unravel the specific defects in Type 2 diabetes and other insulin-resistant states it is crucial to understand insulin action at the molecular level. This includes the many steps in regulation of glucose and lipid metabolism, as well as the ability of insulin to regulate the expression of genes involved in control of metabolic processes.

Major accomplishments over the past decade have helped unravel some of the early steps in insulin action. Many cellular proteins and structures have been identified in the insulin-signaling pathway and in trafficking of the insulin responsive glucose transporter. Studies of tissues from diabetic humans and rodents have revealed defects in many of these steps, including defects in insulin action on glucose uptake/phosphorylation and decreased glycogen synthesis.

Some of the mechanisms involved in induction of secondary components of insulin resistance have been revealed, such as the effects of adipocyte-derived factors in the insulin resistance of obesity, the accumulation of hexosamine pathway products, and hyperglycemia-mediated activation of protein kinase C (PKC). Insulin has been shown to elicit striking effects on the transcription and translation of genes, potentially making an important connection to the genomics of diabetes. Creation of new genetic models of diabetes has established the concept that

Promising Areas of Cell Signaling Research

Some areas of signaling research that are moving rapidly, are of critical importance to diabetes, and which urgently need expanded efforts are:

- **Defining the normal signaling pathways involved in insulin action and their alterations in Type 2 diabetes.**
- **Determining the three-dimensional structures of the key signaling molecules, with an effort to develop agonists and antagonists. This research may require development of new methods of structural biology, because many of the molecules are complex glycosylated membrane proteins for which good structural techniques do not yet exist. Furthermore, many of these molecules exist as multiple isoforms, because of RNA splicing and post-translational modifications. These isoforms may function differently and thus need to be characterized individually.**
- **Elucidating the molecular basis for the insulin resistance of Type 2 diabetes, particularly the primary defects.**
- **Developing surrogate measures of insulin resistance.**
- **Developing new methods for assessment of cellular signaling in intact tissues, intact animals, and humans to facilitate clinical research and allow metabolic staging of Type 2 diabetes.**
- **Enhancing and applying the above principles to other hormones involved in regulation of glucose homeostasis and diabetes pathogenesis.**
- **Developing a systematic approach to the study of signaling molecules as candidate genes for Type 2 diabetes in collaboration with the proposed National Consortium for the Study of the Genetics of Diabetes.**
- **Promoting the development of transgenic and knockout animal studies to define the role of various signaling molecules in physiology.**
- **Expanding molecular research on all of the components of the hormonal response systems involved in control of blood glucose, body weight, and lipids. This research is critical to the development of appropriate therapeutics for the metabolic syndromes associated with diabetes and obesity.**

specific defects in the insulin-signaling GLUT-4 trafficking pathways, and insulin-signaling regulation of gene expression, can cause diabetes in animal models. A better understanding of insulin resistance is a critical step in developing new therapies for Type 2 diabetes.

Recommendation:

➤ **Expand research to identify the underlying genetic and biochemical basis of insulin resistance, and to develop interventions to prevent, reverse, and ameliorate it in Type 2 diabetes and obesity.**

Expanded research is needed to:

- Determine the primary or earliest defect in insulin action present in the development of Type 2 diabetes.
- Identify the exact molecules and pathways involved in the insulin-signaling pathways in muscle, fat and liver.
- Determine the 3-dimensional structure of the proteins involved in insulin action to allow rationale drug development.
- Find the gene products that contribute to insulin resistance and discover their mechanisms.
- Determine the energy-sensing mechanisms used at the cellular level and how they translate to the pathophysiology of insulin action.
- Ascertain the defects in glucose transport, glucose phosphorylation, and gluconeogenesis in Type 2 diabetes.
- Reveal how the brain senses and regulates metabolic pathways in insulin-sensitive tissues.

Defining Mechanisms Regulating Beta Cell Function and Their Alterations in Type 2 Diabetes

Despite intensive investigation over several decades, a detailed understanding of the pathways that mediate insulin secretion in response to glucose and other secretagogues is not yet available. Attaining full understanding of these pathways is likely to be essential for achieving a readily replenishable supply of normally functioning, insulin-producing cells for transplantation therapy of Type 1 diabetes, and for improving the defect in beta cell function in Type 2 diabetes.

Prospects for gaining full understanding of the regulation of beta cell growth and insulin secretion have been enhanced by several recent seminal discoveries. These include the cloning of the genes for several key regulators of insulin secretion, such as the sulfonylurea receptor, the ATP-sensitive potassium channel, and the receptor for the hormone glucagon-like peptide-1 (GLP-1). Another major advance was the demonstration that some forms of diabetes are caused by genetic defects in the glucokinase gene or nuclear transcription factors that control beta cell function and glucose-stimulated insulin secretion.

To gain a complete understanding of regulation of beta cell growth and insulin secretion by glucose and its potentiators, we must determine the:

- Detailed mechanism by which glucose stimulates insulin secretion.
- Mechanisms by which other secretagogues and fuels, such as fatty acids, modify beta cell function.
- Coupling between ion channel activities (such as the ATP-sensitive potassium channel and voltage-gated calcium channels) and the exocytotic apparatus.
- Biology of secretory granules, and factors that cause their movement and exocytosis.
- Growth factors and transcription mechanisms that regulate beta cell growth.

Recommendations:

➤ **Increase research on signaling pathways involved in the regulation of normal beta cell function and their derangements in diabetes.**

➤ **Use the proposed Interdisciplinary Centers for Beta Cell Biology to study the alterations in signaling in Type 2 diabetes.**

These Interdisciplinary Centers for Beta Cell Biology are described in the section on "Autoimmunity and the Beta Cell." They could include collaborations or consortium agreements among different institutions. The goal is to recruit high-quality, interdisciplinary research teams to study fundamental aspects of islet development, growth, and function. Investigators from outside the field might enhance such teams.

Metabolic Staging of Type 2 Diabetes

Assessment of patients with Type 2 diabetes or pre-Type 2 diabetes provides specific challenges. The close link between Type 2 diabetes and hyperlipidemia, hypertension, central obesity, and atherosclerosis means that the assessment of the Type 2 diabetic patient must evaluate many metabolic risk factors other than just control of blood glucose. In addition, the slow and progressive pathogenesis of the disease indicates that there is a progressively evolving set of metabolic abnormalities in peripheral tissues and liver and beta cells, which eventually reach a level allowing expression of clinical disease. Thus, defining other signaling pathways is critical to the development of new therapeutic approaches to diabetes.

A tremendous need exists to develop simple and accurate markers of the insulin-resistant state that researchers can use in their studies and that will help physicians monitor the clinical status of patients. These markers should offer both qualitative and quantitative information about the level of insulin resistance in the whole body and in individual tissues, such as muscle, fat, and liver. Insulin resistance in different tissues may play different pathogenetic roles in complications. Therefore, metabolic staging and surrogate measures of insulin resistance must also be developed to measure this important parameter in different tissues and on different metabolic and growth pathways.

The goals of this research program are multiple, and must include research to:

- Develop accurate methods to assess insulin's action in all tissues, as well as surrogate measures of insulin resistance.

- Develop methods to assess the capacity of the beta cell to meet the challenge of insulin resistance and the potential for beta cell failure.

- Devise methods of defining identifiable stages of Type 2 diabetes. This might be determined on the basis of altered expression of sets of genes in different target tissues, or other biochemical or pathophysiologic criteria.

- Uncover methods, such as genetic markers, which indicate which subset of patients will respond best to a given therapeutic regimen.

- Discover and apply methods to assess the impact of the metabolic and genetic risk factors on the likelihood of development of long-term complications.

- Develop appropriate techniques and measures to allow metabolic staging of the diabetic patient and to identify those individuals at highest risk for development of complications. Because the micro- and macro-vascular complications of Type 2 diabetes represent the single largest dollar cost to society of this disease, and they account for some of the most severe impacts of the disease on quality of life, this area of research is particularly important.

Recommendation:

➤ **Develop a program of research to allow metabolic staging of Type 2 diabetes and to detect individuals at high risk for this form of the disease and its complications.**

Defining Alterations in Signaling Pathways That Lead To Development of Diabetes Complications

Both Type 1 and Type 2 diabetes can lead to widespread damage to small blood vessels throughout the body, leading to serious, debilitating, and at times incapacitating disability due to disease of the nervous system, kidney, and eye. These microvascular complications, when coupled with the macrovascular complications, are responsible for most of the morbidity and mortality in both Type 1 and Type 2 diabetes. Their prevention and reversal will greatly reduce the burden of this disease on both individuals and on the Nation as a whole. Understanding and combating the microvascular complications of diabetes will require significantly expanded research in genetics, cellular mechanisms, and biochemical pathways that are most likely involved in the development and progression of microvascular complications.
These mechanisms include:

- Protein Kinase C

  Protein kinase C (PKC) is a family of enzymes that can catalyze the phosphorylation (transfer of phosphate groups) to a variety of proteins within the cell, resulting in an increase or decrease in their biological activities. There are multiple forms of PKC present in different tissues and involved in specific pathways of cellular regulation. High glucose levels stimulate the activity of certain forms of PKC, and this appears to lead to some of the adverse alterations observed in tissues of diabetic patients. Specific drugs or natural substances, such as vitamin E, can inhibit some isoforms of PKC. Understanding the role of PKC in

diabetic complications, as well as development and testing of its inhibitors, may provide new approaches to treating diabetic retinopathy, nephropathy, and cardiac disease.

- Glycation Proteins and Glucose Transporters

  Hyperglycemia also promotes the attachment of glucose to protein molecules, a process termed non-enzymatic glycosylation or glycation. These glycated proteins may link together, forming large macromolecules, callbd AGE (advanced glycosylation end product) proteins. AGEs alter cell function and also may act on specific receptors to stimulate inflammatory pathways in tissues involved in complications of diabetes. At least one drug to block their formation is currently being studied clinically to prevent progression of diabetic nephropathy. Understanding the role of these pathways, as well as development and testing of drugs to block formation of AGE proteins or their receptors, should be continued and expanded. Cell membrane glucose transporters, which allow glucose to enter and exit cells, may also contribute to this process, but have received little study.

- Oxidative Damage and Antioxidants

  Reaction of tissues with oxygen and the formation of free radicals may also promote tissue damage in diabetes. Oxidative damage is thought to be involved in a number of other diseases, including atherosclerosis and cancer. Research in diabetic animals indicates that antioxidants may prevent some of the changes associated with diabetic complications. Laboratory and clinical research on a variety of drugs and natural substances, such as vitamins C and E, which may protect tissues from oxidative damage should be pursued.

- Blood Flow

  Damage to the kidney or retina may be a direct result of the stressful impact of blood flow and pressure, or of alterations in blood flow early in diabetes, which affect the delivery of oxygen and other nutrients or the removal of toxic waste products. Recent demonstration of the beneficial effect of the anti-hypertensive angiotensin converting enzyme (ACE) inhibitors in preventing the progression of Kidney disease, and possibly eye disease, may be related to the influence of these drugs on blood flow. Factors regulating blood flow, as well as the role of blood flow in diabetic complications, clearly need further study.

- Aldose Reductase and the Sorbitol Pathway

  Aldose reductase is an enzyme that converts glucose to sorbitol, a sugar alcohol that may contribute to tissue damage in the eyes, kidneys, and nerves. Increased activity in this pathway was one of the first recognized for a potential role in diabetic complications. Although initial clinical trials of two drugs that block the action of aldose reductase have been disappointing, recent evidence suggests that the existing drugs may not have been sufficiently strong inhibitors of the enzyme or that treatment was too late. More powerful drugs are now available and should be tested.

- Genetic Factors

  Genetic factors have been implicated in increasing the risk of developing microvascular complications in some individuals. As discussed in the section on "Extraordinary Opportunities," identification of the genes that confer such susceptibility and the mechanisms by which they act will provide unprecedented opportunities for specific and effective new therapies.

Recommendation:

➤ **Expand support of interdisciplinary research to identify the mechanisms of the complications of diabetes, including interactive mechanisms and program project grants, which bring together investigators with different areas of expertise.**

Obesity—Critical in Diabetes and a Major Problem of Its Own

Obesity is a major risk factor for the development of Type 2 diabetes and insulin resistance. It is also a major cause of morbidity and mortality in the United States in its own right. Overweight now affects more than one out of every three Americans, and its prevalence has increased 30 percent over the past decade alone. Obesity disproportionately affects minorities, with over 60 percent of African American, Mexican American, and Native American women meeting the criteria for obesity. Overweight is defined as a body mass index of 25-29 kilograms per square meter and obesity is defined as 30 kilograms per square meter or more. Moreover, the prevalence of obesity in children and adolescents is increasing at alarming rates, leading to development of Type 2 diabetes in these younger groups.

In understanding these relationships, the broad spectrum of problems associated with obesity must be realized. It is apparent that the effects of obesity on morbidity and mortality differ across ethnic groups. Moreover, the effects of obesity on morbidity and mortality depend not only on total fat mass, but also on fat distribution. Thus, central abdominal obesity is associated with a much greater health risk than peripheral obesity. These differences in fat deposition are well recognized and have been referred to as "apple" versus "pear" shaped body types. However, at molecular, genetic and cellular levels, these important differences remain unexplained. Physical activity and fitness are related to the risk of obesity, and may also influence Type 2 diabetes independently of obesity. Finally, obesity is related not only to the risk of Type 2 diabetes but also to insulin resistance, hyperlipidemia, hypertension, accelerated atherosclerosis, and coronary heart disease. Clearly, these associations create much of the heath hazard of obesity, even in the absence of full-blown diabetes.

What Causes Obesity?

Obesity results from an imbalance between energy intake and energy expenditure. In normal-weight individuals, energy intake and expenditure are precisely regulated. Indeed, even a very small imbalance between these variables over an extended period would have a marked cumulative effect on body weight. For example, if a person eats just one percent more in calories than he or she uses each day (this could be as little as one pat of butter or two teaspoons of sugar), over a period of 10 years, this individual would gain 25 pounds. The delicate coordination of energy intake and expenditure occurs through a variety of endocrine and neural signals that emanate from adipose tissue, various regions of the brain, the endocrine system, and gastrointestinal tract. Over the past few years, tremendous progress has begun to define these complex pathways. Research has demonstrated that obesity is not simply due to overeating, but is the result of misregulated pathways that normally control the balance between appetite and energy expenditure.

One important new insight is that fat is not simply a passive recipient of the overeating process, but actively secretes leptin, a hormone that may play a major role in regulation of appetite, energy storage, and energy expenditure. Thus, leptin, from fat—together with other hormones including melanocyte stimulating hormone (MSH) and cholecystokinin (CCK) from the brain, gut, and other tissues—acts on a region of the brain termed the hypothalamus to suppress appetite. Other hormones, such as neuropeptide Y (NPY), melanin concentrating hormone (MCH), and the oxerins, act in other regions of the hypothalamus to stimulate appetite. The intricate signaling pathways created by these hormones and their receptors have vital importance in determining whether one feels hungry or full, and how much that individual is likely to eat in response to this feeling.

This balance between energy storage and energy expenditure is ultimately played out in other tissues of the body, particularly fat cells (adipocytes). Interestingly, there are two types of fat cells – white adipocytes and brown adipocytes – which are specialized to fulfill two very different roles. White fat is the major site of energy storage. In obese individuals, the mass of white fat is greatly expanded due to either an increase in the number of fat cells or the size of the fat cells or both. Brown adipocytes, on the other hand, represent one of the major sites of energy expenditure. This occurs through the presence of another protein, called uncoupling protein-1 (UCP-1), present in these cells. Over the past few years, tremendous progress has also been made toward defining the transcription factors that act as the molecular switches that control development and

differentiation of white and brown fat cells. At least four of the transcription factors needed for fat cell development have been identified, as well as some of the other proteins in the nucleus of the cell with which they interact to produce their effects. In addition, two new members of the family of uncoupling proteins have been discovered. These uncoupling proteins are present in tissues other than brown fat, suggesting that several tissues may be involved in regulation of energy expenditure.

The recent unparalleled, almost explosive, increase in understanding the molecular mechanisms involved in obesity has suggested that eventually new therapeutics could be developed to correct these abnormalities. For example, drugs that regulate the expression levels and activity of uncoupling proteins could stimulate energy expenditure, while drugs that mimic the action of appetite-suppressing hormones could reduce energy intake. Interestingly, one of the transcription factors involved in regulation of fat cell development, PPAR, is also the target of a new class of anti-diabetic drugs used in Type 2 diabetes, suggesting a close link between adipocyte metabolism and insulin action. Now is the time to define these pathways more fully and to use the resultant knowledge to develop new therapeutic approaches to obesity-associated diabetes and other complications.

Obesity – Genes and Environment

Like diabetes, obesity is the result of an interplay between genes and the environment. The strong genetic components of obesity have been demonstrated in both animals and humans. Researchers have identified several specific genetic defects that can lead to obesity. This has been achieved by applying genetic techniques and the knowledge rapidly evolving from cellular and molecular studies to rodent models and human studies in families and populations with obesity. Genetic defects have been found that alter secretion of different appetite regulating hormones, alter the function of their receptors, or change the activity of the fat cell differentiation regulator PPAR. Thus far, however, these genes can only explain a small percentage of obesity in humans. Indeed, as in diabetes, body weight is determined by the interaction of multiple genes, many of which remain unknown. The proposed National Consortium for the Study of the Genetics of Diabetes should help address this problem.

The environment also plays a major role in development of obesity. The importance of environment is seen most clearly in the Pima Indians. Pimas living in a rural area of Mexico differ greatly in their prevalence of obesity and Type 2 diabetes from Pimas living in Arizona, who have a more "westernized" lifestyle. Similarly the increased prevalence of obesity in the past decade and the strong relationships between obesity and socioeconomic status suggest the importance of the environment in influencing obesity. Various aspects of the environment, including an increasingly sedentary lifestyle and increased access to calorie-dense foods, are potentially related to this increased prevalence of obesity.

Finally, in obesity, the interaction between genes and environment is made more complex by a variety of behavioral and lifestyle factors. Dietary composition, such as the content of fat, carbohydrates, and simple sugars, is a major focus of much popular diet therapy and may be important in development of obesity, but there is little definitive research on this subject. Indeed, it is extremely difficult using current approaches to measure dietary content and eating behavior under normal living conditions. Also, there has been increased recognition of how different ethnic groups may gain excessive weight when exposed to "westernized" diets, and of high-risk periods for weight gain, including puberty, pregnancy, menopause, and following smoking cessation. However, there is limited research into how to effect changes in lifestyle and eating behavior in these populations with the highest risk of obesity.

Long-term research goals are to develop effective ways to prevent the development of obesity and treat this disease in those who are already affected. These goals will require truly multidisciplinary efforts, involving genetics, neuroscience, endocrinology, behavioral medicine, and many other disciplines.

Recommendations:

➤ **Increase the size, scope, number and funding level of NIH-sponsored Obesity Research Centers to meet appropriately the severity of this problem in the U.S.**

The NIH has already recognized the need for expertise from many disciplines to address the research challenges presented by obesity. However, the current Obesity Centers program, funded by NIDDK, is limited in that there are too few Centers and the Centers are too small to adequately address the complex of problems presented in obesity research. The DRWG believes that a significantly enhanced Obesity Centers program would create an improved effort to bring together the high-quality, interdisciplinary research teams necessary to study the fundamental and clinical aspects of this problem. These new Centers could also include collaborations or consortium agreements among different academic

institutions, and possibly support by several Institutes of NIH. An active interface also needs to be created between obesity research and the proposed National Consortium for the Study of the Genetics of Diabetes to define the genes involved in predisposition to obesity.

➤ **Significantly increase research in the basic sciences underlying obesity to capitalize on recent advances in hormonal control of appetite, energy regulation, metabolism, and adipocyte development.**

The signaling pathways involved in metabolic regulation and obesity represent a variety of targets, in both the central nervous system and periphery, and need to be precisely defined. Although some of this research will take place in the Obesity Centers, considerably more research is needed beyond these Centers.

➤ **Develop stronger industry-NIH relationships to support obesity-related research.**

In many areas of obesity-related research, a strong interface could potentially advance knowledge. For example, it may be possible to develop collaborations with the food industry to ascertain what affects food preferences and ways to change them that might reduce the risk of obesity. A desperate need exists for accurate, reliable, and affordable measures that can be used to quantify energy intake and energy expenditure in populations under normal living conditions. These new techniques are needed to facilitate research on energy balance and increase understanding of the specific environmental factors that affect the development of obesity. Such research should include investigator-initiated research, as well as funding through Small Business Innovation Research initiatives. Development of more effective pharmacologic treatment approaches for obesity is an excellent area for increased interaction among the pharmaceutical industry, the NIH, and academia.

➤ **Enhance behavioral research in obesity.**

This initiative should include randomized studies evaluating strategies for the prevention and treatment of obesity, research into causes of weight gain and ways to prevent weight gain and obesity in high-risk individuals, and development of more effective long-term treatments for obesity in adults and children. It should also include basic behavioral research on the development of preferences for different foods and lifestyles, community-level and school interventions to prevent obesity, and specific strategies for minority populations.

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My interest in the genetics of obesity wasn't preplanned but grew out of an initial interest in the molecular mechanisms that regulate behavior. Several factors drew my interest to this area. In the late 1970s, endorphins had been first identified. The available evidence suggested that these natural peptides could change the emotional state of an individual. I found this to be profound. In 1981 I went to work in the lab of Mary Jeanne Kreek at Rockefeller to study in this area. She was interested in addictive diseases and the possible relationship of endorphins to addiction. This notion that natural substances could change behavior in a meaningful way was attractive to me.

Another factor contributing to my growing interest in behavior regulation was my participation in a collaborative project on the development of a blood test for the measurement of endorphin levels. Bruce Schneider, the lead expert and researcher in this collaborative effort, was working on another hormone called cholecystokinin, or CCK. Cholecystokinin is made in, and secreted by, the intestine. When you eat, it is released into the blood and stimulates the gallbladder and the pancreas as part of a system that helps digestion. Prior to our collaboration, other laboratories had reported that CCK also suppresses appetite. It was suggested that after you eat, CCK acts

on the brain, telling it that you've just eaten and thus turns off the appetite. I was as interested in this problem as in endorphins because, in both cases, a small protein changes behavior.

In 1980 I also became aware that other investigators had proposed that CCK was defective in a peculiar mouse that is massively obese, the ob mouse. Ob mice have a defect or mutation in a single gene and, as a consequence, weigh three times more than normal mice. These animals also manifest a behavioral abnormality in that they eat excessively. At that time human syndromes equivalent to that of ob mice had not yet been identified, necessitating the use of this animal model. Based on our work in mice, some cases of human obesity have been shown to be a result of mutations in the ob gene. In the late 1970s, it had been suggested that the problem with these obese mice is that they don't make enough CCK. In 1984 Bruce Schneider, Don Powell and I succeeded in becoming the first researchers to identify the CCK gene in brain tissue. This work provided a way to test formally the possibility that CCK was responsible for the obesity evident in ob mice.

In 1984 the methodology to map genes to individual chromosomes was just evolving. The defective form of the ob gene, which causes obesity in the ob mouse, is carried on chromosome six. Working with another scientist, Peter D'Eustachio, we were able to show that CCK mapped to chromosome nine. This meant that CCK could not be the ob gene, and that the ob gene provided the blueprint for some other protein. This finding planted the seed for future study. We had a mouse that was massively obese because of a defect in one gene, and thus this gene was likely to play a fundamental role in regulating body weight. I also realized that the methodology for finding that gene was being developed.

With an interest in this peculiar obesity mutation and the knowledge that there was an approach to find the causal gene, I embarked on an eight-year effort to understand the molecular basis for the obesity evident in ob mice. My excitement about this project was heightened after becoming exposed to some earlier research work published by a scientist at Jackson Laboratories named Doug Coleman. His experiments were the first to suggest that ob mice are missing a weight-regulating hormone and that a related strain of mice, the db or diabetes mice, are missing the receptor for this hormone. Given my prior interest in how genes or proteins might change behavior, this possibility was especially exciting.

When I began my own laboratory in 1986, I had the opportunity to apply the evolving methodology, known as positional cloning, to find the ob gene. My hope was that the gene that was defective in ob mice would, in fact, turn out to be a hormone that regulated weight. This turned out to be the case.

The most difficult aspect back then was that available technology to clone such a gene was relatively primitive. The initial phase of studies to identify defective genes is to find particular traits, or markers, that are co-inherited with obesity. The basic genetic principle is that if one trait is co-inherited with another trait at a higher-than-expected frequency, those traits are near one another on a chromosome. The traits that are evaluated for this purpose are bits of DNA, which can be used to reveal a difference between individuals or, in this instance, between different mouse strains. With the DNA available in two forms, derived from two different strains of mice, the question to ask is: Is one form of the DNA always associated with obesity among the progeny (offspring) of a cross between obese and lean strains of mice? If it is, then we can conclude that the trait, or piece of DNA, is near the ob gene and can be used to clone it. The problem was that, during this phase of our research, information about these markers was not available.

Today such markers are available in huge numbers as part of the Human Genome Project, but in the 1980s and early 1990s they were not. This points to how powerful the progress of the Genome Project has been, because it now provides the technical resources that allow scientists to move much more quickly.

Cloning the ob gene holds great potential for diabetes. The vast majority of individuals with adult onset diabetes are obese. In almost all cases, successful treatment of the obesity will also improve the diabetes. The problem is that it's very difficult for most people to maintain weight loss over a long period of time. Moreover, for many obese patients, insulin therapy is a problem, because insulin doesn't work well enough in them. Treatment of obesity improves this abnormality. The ability to treat obesity among people with diabetes would be an enormous help.

The cloning of the ob gene may ultimately yield new therapies for obesity and could have major implications for diabetes. There is some reason to believe that the protein product made by the ob gene, the hormone leptin, may also be able to lower blood

glucose independent of its effects on weight. The ob gene is actually an obesity and diabetes gene in that when it is defective, both obesity and diabetes result. In either case, when leptin is given to ob mice, their diabetes is improved even at a dose that doesn't change their weight. In addition, leptin increases the utilization of glucose, an attribute that is desirable in anti-diabetic treatment. Thus, leptin has some impact on blood glucose that may be helpful even independent of beneficial effects of weight loss.

Leptin also works on the brain to modulate blood glucose metabolism. It has long been known that the brain has an important role to play in regulating glucose. In time, leptin may also reveal new pathways and mechanisms by which glucose is controlled.

Research of this sort couldn't have been done without substantial resources. I'm a Howard Hughes Medical Institute investigator and am privately funded, but the specific project to clone the ob gene was funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

As to what is next for our laboratory, it's back to my original interest. The available evidence says that leptin acts on the brain and somehow activates (or inhibits) nerve cells, and in so doing, ultimately changes an animal's behavior. We're now trying to understand how this happens and how the nervous system is wired such that leptin can alter an animal's behavior. We're also in search of the obesity and diabetes genes in humans.

Clinical Research and Clinical Trials of Critical Importance

Translation of basic research into human therapies depends on an active and vigorous clinical research program. Studies in test tubes, cells, and animals can answer questions of fundamental importance to understanding diabetes and its complications and provide the basis for development and initial testing of potential interventions. However, it is clinical studies in patients with diabetes that are essential for validating these fundamental observations. Clinical studies yield many of the key insights into the genetic, immune, hormonal, metabolic, and environmental factors involved in the disease, and allow true testing of therapeutic strategies. Several major clinical trials in areas of relevance to diabetes and its complications over the past two decades have yielded important information about treatment of the disease, resulting in improved care and outcomes for diabetic patients. These include the Diabetes Control and Complications Trial (DCCT), which proved that tight control of blood glucose reduces long-term complications of disease; the Early Treatment of Diabetic Retinopathy Study (ETDRS), which demonstrated the value of early laser photocoagulation in prevention of blindness due to diabetes; and the angiotensin converting enzyme (ACE) trial to delay or slow progression of renal disease.

A number of prevailing forces, however, have significantly hampered clinical research and clinical trials in diabetes and its complications. In general, investigator-initiated clinical research is decreasing, as is the number of clinical investigators. Another negative factor is limitation in funding of clinical research, which by its very nature tends to have higher costs than basic research. The complexity of the clinical challenges presented by the disease is also an impediment. For diabetes, the very long-term nature of the complications adds complexity to any clinical trials. In most clinical studies, adequate representation of special high-risk minority groups is difficult to achieve. Robust and effective clinical research in diabetes demands more well trained clinical investigators, increased funding of meritorious clinical studies, and efficient systems for clinical research. Such systems need to provide the numbers of patients required for meaningful conclusions, stability of operations for long-term studies, and opportunities to include sufficient numbers of appropriate minority groups.

Clinical Trials

A comprehensive program for tackling a major public health problem such as diabetes requires a major investment in clinical trials. Large-scale clinical trials are needed to document the safety and efficacy of

various therapeutic strategies. They are also essential for generating the knowledge base that will lead to better treatment of diseases—the foundation on which physicians are able to practice evidence-based medicine. In other common diseases that impact dramatically on public health—such as hypertension and cardiovascular disease—scores of clinical trials over the past few decades have led to a significant reduction in disease mortality. In contrast, relatively few trials have been carried out on the serious public health problem of diabetes, where the age-adjusted disease mortality has actually risen. Thus, it is imperative to increase the number of clinical trials and expand the body of knowledge based on such definitive trials that will lead to the optimal practice of medicine for people with diabetes. Some clinical trials can be predicated on interventions currently available or already in use, but the need and opportunity for others will only become apparent as research identifies new targets of therapy over the next several years.

Specific recommendations with respect to clinical trials to prevent Type 1 diabetes have already been discussed in the section on "Autoimmunity and the Beta Cell." Other categories of clinical trials that are urgently needed must define optimal methods for treatment of Type 2 diabetes, determine the most effective treatments to reduce the risk of micro- and macrovascular complications, and develop strategies for delivering optimal health care to these patients. For example, in Type 2 diabetes, several different categories of oral anti-diabetic agents are already available and others are being added to the pharmacopoeia. Some of these agents act by sensitizing various tissues to the action of insulin (insulin sensitizers), some by modifying insulin secretion or glucose absorption, and still others by mechanisms that remain undefined.

The United Kingdom Prospective Diabetes Study (UKPDS) has demonstrated that more intensive control of Type 2 diabetes will reduce the risk of some complications of diabetes using two of these oral agents, but several remain to be explored. Likewise, all of the therapeutic regimens used in the UKPDS tended to lose efficacy over several years of treatment. Thus, the question still remains as to how to effectively lower blood glucose most effectively in Type 2 diabetes over long periods of time, and especially what approach to therapy is most likely to reduce the risk of atherosclerosis, the major killer of patients with Type 2 diabetes.

In addition to glycemic control, other modalities for preventing diabetic complications need to be more systematically evaluated, including the effects of lipid lowering treatments, antioxidants, anti-inflammatory agents, and possibly agents, such as aminoguanidine, which directly interfere with the formation of advanced glycation end products. Finally, clinical trials are needed in health services research, that is, studies of the best way of implementing already proven therapies in actual clinical practice. For example, the Diabetes Control and Complications Trial (DCCT) firmly established that intensive management with insulin and home glucose monitoring can markedly reduce the risk of microvascular complications, yet most survey data indicate that this form of therapy is still not widely implemented in routine clinical practice.

Two major needs cut across all these areas. The first is the need to create the infrastructure to facilitate clinical trials, thus improving efficiency and lowering cost. This need is especially pressing in diabetes research in which clinical trials to "hard end points" may take many years and even decades, and where currently, all clinical trials are established *de novo*, requiring a tremendous input of energy and resources. The second need is for a commitment on the part of the NIH to clinical trials as a mechanism to develop the proper base of knowledge for "evidence-based medicine" in order to ensure a steady and more rapid improvement in the care of people with diabetes.

Recommendations:

➤ **Establish a national diabetes trial network (Diabetes TrialNet) of cooperative clinical research groups to create the stable, high-quality infrastructure necessary for the conduct of effective and efficient clinical trials in diabetes and its complications.**

As noted above, a major limitation of clinical trials in diabetes is the *ad hoc* nature of their organization. Each new trial requires identification of appropriate test sites, cadres of patients for study, and a well-trained and efficient investigational team. A diabetes trial network could provide a stable infrastructure for the long-term and complex clinical trials required for the study of diabetes. It is expected that the Diabetes TrialNet would consist of five or six regional coordinating centers, each linked to multiple (5-10) sites throughout the United States for the conduct of diabetes-related clinical trials.

The TrialNet sites would develop and maintain an informational registry of patients for study and perform clinical trials in diabetes and its complications. These sites could provide systems for coordination and monitoring of data and other functions. Some recommendations for specific clinical studies and trials are presented in this

Science Snapshot

Surrogate Markers

A surrogate marker is a reliable, easily measured biological event that can be used by physicians and researchers to gauge the health of the patient, without having to wait for the full-blown disease, such as diabetes, to develop. An appropriate surrogate marker can also be used as an indication of whether a patient is responding well to treatment, or is at risk of developing diabetic complications. Good surrogate endpoints could save time and money in clinical trials of new drugs for treating diabetes, allowing more potential therapies to be tested.

One very successful surrogate marker used for following the treatment of diabetes is hemoglobin A1c (HbA1c). Blood sugar undergoes a spontaneous chemical reaction with hemoglobin in red blood cells, forming the compound HbA1c. The HbA1c level is easily measured in a clinical setting, and correlates with a patient's average blood glucose from the previous six-to-eight weeks. The physician then has an objective way to evaluate how well the patient with diabetes is responding to therapy for high blood sugar. Microalbuminuria, or small amounts of protein in the urine, is another important surrogate marker used to diagnose the early stages of kidney disease in diabetes. Early markers of retinopathy include changes in blood and leakage of the injected dyes administered during angiography from the blood vessels in the eye.

Because disease is most successfully treated in its early stages, it is important that surrogate markers be developed which can help doctors identify patients before they become very ill. Surrogate markers may soon be found that will indicate whether people will develop diabetes.

Type 1 diabetes occurs following autoimmune destruction of the beta cell, the pancreatic islet cell which manufactures insulin. One such future marker might be whether an individual's lymphocytes, which normally kill foreign cells, are reactive toward specific components of his own beta cells. Islet transplantation holds great promise as therapy, and future surrogate markers may enable identification of transplant rejection at the very earliest stages so that it can be successfully treated. Good surrogate markers could identify diabetic patients highly prone to blindness, kidney failure, or heart disease, and this would have special benefit for prevention therapies.

Research Plan. These include, but are not limited to, clinical studies or trials of methods for treatment of diabetes and its complications; new approaches for prevention and treatment of microvascular and neurologic complications of diabetes; prevention and treatment of macrovascular disease in diabetes, including the excess cardiovascular risk in diabetic women; prevention and treatment of obesity; and the insulin resistance of Type 2 diabetes. In addition, the Diabetes TrialNet could serve as an important infrastructural component in epidemiologic research, behavioral research, and in providing the infrastructure for the trials for prevention of Type 1 diabetes described in the section on “Autoimmunity and the Beta Cell.” The investment in the Diabetes TrialNet not only meets an important need, but also exploits the opportunities presented by advances in information technology and telemedicine to improve the efficiency and quality of clinical trials in diabetes.

- **Increase funding of meritorious clinical trials of emerging new therapies for diabetes.**
- **Support critical trials on how to most effectively apply the current methods of therapy and identify new, more generally applicable methods for achieving tight blood glucose control without hypoglycemia.**
- **Support clinical trials on the prevention of microvascular and macrovascular disease, the major causes of morbidity and death in people with diabetes.**
- **Develop effective partnerships among the NIH, academia, and industry for collaboration and cofunding of clinical trials in diabetes and to provide training in the science of clinical trials.**

Clinical Research

In addition to clinical trials, tremendous needs and opportunities exist to enhance clinical research on metabolic and physiologic topics relevant to diabetes, as well as to conduct single-center clinical trials to test innovative interventions. These smaller scale trials would be able to use more sophisticated physiological endpoints rather than clinical outcomes and surrogate endpoints used in most clinical trials; however, the development of surrogate endpoints would be a potential consequence of this type of research. In addition, clinical research can continue to provide the critical analysis of the pathophysiology of diabetes and its complications that can provide cross-fertilization with the basic studies. Clinical research is also essential to define the metabolic stages of disease and the critical characteristics of disease progression. These studies would include a wide range of investigator-initiated projects, including projects related to development of novel therapeutic agents and approaches.

It is anticipated that the increased clinical research efforts will utilize both the Diabetes TrialNet and the network of General Clinical Research Centers (GCRCs) located at academic institutions throughout the country and supported by the NCRR. The GCRCs provide much of the required infrastructure (inpatient and outpatient facilities and staffing, biostatisticians, nutritionists, core laboratories and informatics) to conduct clinical research and innovative pilot studies, and will need appropriate additional support. The GCRCs also participate in clinical research training through the Clinical Associate Physician (CAP) Program.

Recommendations:

- **Increase funding of meritorious clinical research for physiological studies and development of new technologies for metabolic assessment.**
- **Initiate clinical studies of promising new therapies for diabetes, such as gene therapy, or tissue-specific approaches to microvascular complications.**
- **Initiate studies to determine why women and some minority populations with diabetes have higher risks for diabetic complications.**
- **Increase opportunities for and support of clinical research training in diabetes.**
- **Perform clinical studies to establish and validate surrogate endpoints for the complications of diabetes to be used in clinical research and clinical trials.**

Complications of Diabetes

Special Needs for Special Problems

The complexity of diabetes creates special needs and challenges for biomedical research. To address these needs, a concerted effort is required from scientists spanning the full spectrum of research expertise, including genetics, basic cell biology and biochemistry, immunology, clinical physiology, pharmacology, engineering, epidemiology, behavioral medicine, and outcomes research. Some of these disciplines are fundamental to understanding the cellular and molecular aspects of disease and are the source of the knowledge and technologies required for new therapeutic and diagnostic approaches. Others focus on patient-oriented research and address questions, such as, who is at risk for diabetes, how diabetes affects body functions, how patients and their families cope with the challenges presented by management of a chronic and potentially disabling disease, and what the final costs and benefits are to the patient and to society.

In most of these areas, NIH-funded research programs exist and significant advances have been made. However, the level of past and current research falls far short of what is needed and what can be done to improve understanding, to apply advances in basic science for the benefit of patients, and to ultimately conquer this devastating disease. As a result, limited progress has been made in several critical areas in diabetes.

The DRWG believes optimal progress in the search for prevention, cures, and better treatments requires a redoubling of the ongoing research effort coupled with initiation of new programs in areas of special need, as described in this section of the Research Plan. This expansion of effort will require not only increased research by the existing community of scientists working in diabetes, but also new input from scientists currently outside the field. Because the spectrum of issues facing diabetes research cuts across virtually every area of medicine, active support and participation will be required from most Institutes and Centers of the NIH. The resultant knowledge gained from attacking the special needs of diabetes will also have an important impact on many other areas of biomedical research and human disease.

Areas of Special Need

- **Microvascular complications: nerve, kidney, and eye disease**
- **Macrovascular complications: cardiovascular disease**
- **New methods to optimize blood glucose control without hypoglycemia**
- **Women, children, and the elderly**
- **Minority groups**
- **Diabetes and the environment**
- **Genetic engineering**
- **Behavioral and health services research**
- **Oral complications of Diabetes**

Vascular Complications – Living With Diabetes for a Lifetime

Microvascular and macrovascular complications represent the ultimate burden of diabetes on both the patient and society. Although considerable evidence exists that the risk for microvascular complications can be reduced by a substantial improvement in glycemic control, this is often difficult to achieve. In addition, clinical studies have not yet proven that control of blood glucose will markedly reduce the rate of macrovascular complications, such as myocardial infarction and stroke. Therefore, significantly increased funding is urgently needed for basic and clinical research on diabetes complications. The DRWG considers this to be not only a special need, but also a high priority.

Microvascular Complications

Both Type 1 and Type 2 diabetes can lead to widespread damage to small blood vessels throughout the body. This damage can cause serious, debilitating, and incapacitating disability due to diseases of the nervous system, the kidney, and the eye. These microvascular complications of diabetes, when coupled with the macrovascular complications, are responsible for most of the morbidity and mortality in both Type 1 and Type 2 diabetes. Understanding and combating the microvascular complications of diabetes will require significantly expanded research in genetics, cellular mechanisms, and biochemical pathways involved in their development and progression.

Although specific recommendations for increased basic research into the genetics and signaling mechanisms involved in complications have been presented in the section on Extraordinary Opportunities, it is important to point out the multisystem nature of microvascular complications. The microvascular complications of diabetes not only affect many organ systems but they also appear to be the result of alterations in multiple pathways of cellular metabolism created by the diabetic milieu, as well as by the genetics of the individual. Some of these alterations involve enzymes of the protein kinase C family, which are activated by high glucose levels and the process of non-enzymatic glycosylation. Other alterations involve formation of advanced glycosylation end products (AGE) proteins that may act on specific receptors to stimulate inflammatory pathways in tissues involved in complications of diabetes. Oxidative damage and the formation of free radicals may also promote tissue damage in diabetes. Also implicated in complications are alterations in hemodynamics, as well as the conversion of glucose to sorbitol by aldose reductase, causing osmotic damage to cells, and genetic factors.

Both similarities and important differences are found in the microvascular complications of diabetes. Because of similarities, some approaches for addressing the needs for research on microvascular disease can be shared and general recommendations can be made to propel progress on all the microvascular complications of diabetes.

Recommendations:

- **Expand support of research to identify the mechanisms of the microvascular complications of diabetes.**
- **Enhance clinical research and clinical trials.**
- **Develop valid surrogate markers for disease staging.**
- **Establish centers dedicated to the study of microvascular complications.**
- **Recruit scientists from outside the field to enrich research on diabetic complications.**

At the same time, important differences among the microvascular complications require that highly targeted approaches be pursued as well. Indeed, not only does each complication involve a different organ system and potentially different mechanisms but also the primary research responsibility for each falls within a different Institute of the NIH. Therefore, the DRWG has focused on specific approaches to each of the microvascular complications.

Urgent High Priority Need

Dedicated, focused, multidisciplinary basic and clinical research to understand and develop effective new therapies for the micro- and macrovascular complications of diabetes and reduce the ultimate burden of diabetes on the patient and society.

Diabetic Kidney Disease – Nephropathy

Diabetic kidney disease accounts for over 42 percent of all new cases of end-stage renal disease and is the leading cause of the need for kidney dialysis. People with diabetes represent the fastest increasing group of patients requiring renal dialysis and transplantation and account for more than $4 billion annually in costs in the United States, most of which is paid by Medicare.

Diabetic kidney disease develops due to damage to the small blood vessels that supply oxygen and other nutrients to the kidney and filter toxic waste products from the blood. Current thinking is that diabetic nephropathy results from changes in blood flow, an increase in certain cells of the kidney (mesangial cells), and an excess accumulation of extracellular matrix, the fibrous-like tissue that surrounds cells. Inability to remove extracellular matrix leads to an imbalance that causes the kidneys to malfunction. A number of mechanisms may contribute to this abnormality, including increased glycation of extracellular matrix protein molecules and impaired secretion or functioning of growth factors, enzymes, or cell-signaling molecules (cytokines). The tendency to develop diabetic nephropathy also appears to be linked to a family history of hypertension and to be genetically determined, but the exact genes have not yet been defined.

Current therapy for prevention or delay of onset of diabetic nephropathy is based on improvement in glycemic control and the use of drugs that alter renal blood flow, such as angiotensin converting enzyme (ACE) inhibitors. This combination of approaches does significantly reduce the rate of renal damage caused by diabetes. Nonetheless, the disease progresses in many patients, and ultimately they develop end-stage renal failure requiring dialysis or transplantation. In some diabetic patients who have received a pancreas, but not a kidney, transplant that has functioned for many years, the pre-existing diabetic nephropathy and the associated morphological changes can be partially reversed. Understanding the mechanism by which this switch from matrix accumulation to healing takes place can lead to novel approaches to prevent and treat kidney disease. Defining other tissue-specific targets, molecules and the genes involved in this complication may also lead to new forms of drug therapy.

Recommendations:

- **Increase the study of the basic mechanisms involved in diabetic nephropathy, including studies of extracellular matrix, growth factors, cytokines, and genetic factors, and develop strategies to prevent and reverse this process.**
- **Initiate clinical studies to establish and validate additional surrogate markers for staging of disease and for use in clinical trials on diabetic nephropathy, including functional imaging and other minimally invasive approaches.**
- **Establish multidisciplinary centers for the study of diabetic nephropathy in order to expand basic and clinical research studies and identify leads for prevention and treatment.**

Diabetic Eye Disease – Retinopathy

In the United States, diabetic eye disease is the leading cause of new blindness in people 20-74 years of age, resulting in 12,000 to 24,000 new cases of blindness each year. Diabetic eye disease is caused by damage to the small retinal blood vessels and nerve cells in the eye that produce visual impulses.

Multiple biological mechanisms have been identified that may contribute to retinopathy. These include increased protein glycosylation, activation of the protein kinase C pathway, increased activity of the sorbitol pathway, and increased secretion of angiogenic growth factors, such as vascular endothelial growth factor (VEGF). Evidence for a role of reduced blood flow to the retina has also been found. Because of ease of accessibility of the eye for both direct evaluation and treatment, tissue-specific treatments, including gene therapy, may be particularly attractive as approaches to reverse these metabolic or functional alterations.

Substantial progress has been made in understanding the neurophysiology of the retina and the visual pathways in the brain. These advances could lead to the development of prosthetics and transplantation technology for diabetic retinopathy. Thus, investment in research on nerve regeneration and rescue would be of value not only to patients with diabetic neuropathy, but would potentially benefit patients affected by the late stages of eye disease. Advances in the development of miniaturized electronic devices to aid vision impaired by diabetic retinopathy can make the goal of designing a functional visual prosthesis plausible. In order to pursue fully and to achieve the goal of regeneration of retinal function and the development of prostheses, expanded research is needed. This research should evaluate the use of growth factors, cell-signaling molecules, and other methods to enhance nerve regeneration in the retina and to facilitate and accelerate repair of peripheral nerve tissue.

Recommendations:

- **Increase basic and clinical research on the role of hormones, growth factors and other molecules in the development and progression of diabetic retinopathy.**

- **Increase research into the potential for tissue-specific gene therapy and drug delivery, including approaches for regeneration and rescue of retinal function.**

- **Increase basic and clinical research to develop and improve prosthetics and transplantation technology for diabetic retinopathy.**

Diabetic Neuropathy: A Special Challenge

Diabetic neuropathy presents a special problem. Although this complication causes significant morbidity in up to 60 percent of patients with diabetes at some time during their lives, it represents one of the least well-studied and least understood areas of diabetes-related complications. In 1997, the NIH expended less than 1 percent of its diabetes research budget, or under $3 million, on research related to nerve damage in diabetes.

Diabetic neuropathy occurs in many forms—from peripheral neuropathy with either pain or loss of sensation, to autonomic neuropathy involving the heart, vascular tone, and bodily functions such as digestion, bowel movements and the ability to perform normal sexual function. The exact mechanisms involved in the neuropathic process are presumed to be similar to those involved in other microvascular complications. One of the problems is, however, that very little direct experimental evidence for this hypothesis exists, because the nervous system is difficult to study directly and very few investigators have been attracted to this field. Thus, a major increase is needed in studies to determine the nature of the nerve damage that occurs in diabetes. Research should be expanded to determine the mechanisms and nature of these neuropathic changes, and to develop methods for enhancing regeneration and approaches to rescue damaged peripheral and autonomic nerves.

Likewise, clinical research in diabetic neuropathy has been very limited. Major impediments exist to clinical trials of new drugs. The peripheral nervous system is difficult to evaluate quantitatively and the measures used correlate poorly with symptoms of the disease. Long periods of time and many patients may be required to determine clinical outcomes, since the disease is extremely variable. Surrogate clinical end points have the potential to make such clinical trials feasible, but no useful markers have been identified.

The peripheral nervous system is capable of at least some degree of regeneration following disease or injury, but until now, research has been limited as to how to stimulate this process to improve outcomes in the diabetic patient. In the past several years, a number of factors that promote nerve health have been identified. These "neurotrophic factors" include Nerve Growth Factor (NGF) and the neurotropins. Basic fibroblast growth factor (BFGF) and ciliary neurotrophic factor (CNTF) have been shown to promote survival in animal models of retinal disease and may have similar effects on peripheral nerve tissue. In addition, improvements in cell culture technology now enable the preservation of cells from the central nervous system for at least short periods of time. Although further work needs to be done, these developments make nerve regeneration a realizable goal. Investment in research on nerve regeneration would be of immediate benefit not only to patients affected by diabetic neuropathy, but also possibly to those with the late stages of eye disease.

Area of Special Challenge

Basic and clinical research on diabetic nerve disease, a largely neglected area and cause of major disability and amputation.

Recommendations:

- **Significantly increase the investment in fundamental research to determine the mechanisms of the nerve damage in diabetes, to expand research on nerve regeneration and rescue, and to evaluate methods to enhance peripheral and autonomic function.**

- **Initiate clinical studies to establish and validate surrogate markers for use in clinical trials on diabetic neuropathy, including new technologies to aid in the measurement and evaluation of nerve function in people with diabetes.**

- **Establish new multidisciplinary centers for the study of metabolic nerve diseases, with an emphasis on diabetic neuropathy, and to develop prevention and treatment.**

Personal Profile

Jerrold Weinberg

I was diagnosed with diabetes in 1963, when I was four and a half years old and immediately put on insulin and an “exchange-type” diet to keep my blood sugar stable. That was a long time ago and the beginning of a history of many health complications—besides having diabetes.

Everyone has something to deal with in his or her lifetime. Ever since I was diagnosed as a child I have always had to be careful about knowing my blood sugar level. Doctors considered me a “brittle” diabetic—because fluctuations in my blood sugar could be more severe as a result of exercise, diet or other lifestyle factors.

I have been fortunate and have never had drastic complications such as a diabetic coma, but I have the problem of not noticing when my blood sugar has dropped excessively low. My fingers get sore from having to prick them so many times throughout the day. I am still waiting for an easier way to monitor my glucose.

One of the complications of diabetes I suffered was a change with my eyesight. I had success with laser treatments in 1974 and now have pretty good vision. Another complication resulted after I had a bout with the flu and needed an IV. I felt some discomfort in my chest when I had the IV and the medical staff discovered 80-95 percent blockage in my arteries. This all happened while my wife was eight months pregnant—we wanted to postpone any surgery until after the baby was born. Unfortunately, the surgery couldn't be held off and our baby was born a few hours after my bypass surgery.

Another serious complication for me was kidney failure. After a series of tests, it was discovered that I needed peritoneal dialysis and eventually I had to have a kidney transplant. Several days after healing from my transplant I suffered a heart attack. I had angioplasty, which was successful for some of the blockage, but the doctor was unable to reach the small vessels during the procedure. I still have blockage in these vessels known as small vessel disease. Because of this it is difficult for me to walk. It can be very frustrating and painful.

After having my kidney transplant I had to have my blood taken every month to monitor the success of the procedure. I had two rejections to the transplant and was put on an experimental new drug at the University of Pittsburgh instead of an older existing medication. I noticed at this point that in addition to my coronary small vessel disease, which restricted my ability to do what I used to do, that I also had nerve damage to my hands and feet. They felt numb all the time.

I think the dialysis saved my life, but unfortunately it did some damage. I had to have my parathyroid glands removed. Also, after my kidney transplant, I was put on steroids. They had many side effects and have led to a problem with my hip, which eventually may need to be replaced.

The latest complication I have is gastroparesis. This is also a stomach complication of diabetes, and has made me sick for the last couple of years. My digestive system gets so out of whack that I can't keep food down and I can get dehydrated, may not be able to absorb my medication or nutrients and may need an IV.

I have good days and bad days. On the good days I take advantage of being able to get out and enjoy life. On the bad days it's difficult for me to even walk because of the blockage to my small blood vessels. I have to cut way back and rest until I have enough energy to go out or to resume my normal activities.

Macrovascular Complications – The Major Killer of People With Diabetes

Macrovascular disease is the major killer of people with diabetes, responsible for shortening the average lifespan by up to 15 years. It leads to heart attacks, strokes, and peripheral vascular disease, including limb amputation. Atherosclerosis is accelerated and particularly severe in patients with Type 1 and Type 2 diabetes, but the causes are not known. Moreover, the normal protection afforded to premenopausal women against atherosclerosis is lost if they have diabetes. Knowledge generated over the past decade provides attractive opportunities to unravel the puzzle and to develop effective new interventions against the major killer of persons with diabetes. The DRWG has identified a number of areas of focus in this complex disease problem.

Understanding How Diabetes Enhances the Atherosclerotic Process

Even if other risk factors are not present, diabetes is a strong independent risk factor for cardiovascular disease (CVD). However, the underlying causative mechanisms remain poorly understood. Little is known about the direct toxicity of sustained hyperglycemia or of glycosylated end products formed in this environment. Interactions between the metabolic abnormalities of diabetes and lipids, blood pressure, and coagulation factors that may promote atherogenesis are also incompletely understood. Investigations to improve understanding of the diabetes-CVD association must include both basic and clinical research.

Factors that may contribute to atherosclerosis in diabetes include insulin resistance and hyperinsulinemia, oxidative stress, inflammation, and alterations in coagulation. Questions over the possible toxicity to the macrovascular system of insulin and of sulfonylurea drugs commonly used to treat Type 2 diabetes have led to concern about the vascular effects of treating hyperglycemia. Because aggressive glucose control has been demonstrated to be beneficial in reducing microvascular complications of diabetes, it is very important to determine if different approaches to lowering glucose levels have different effects on the risk of cardiovascular complications. Although most studies of this issue have been conducted in animal models and in patients with Type 2 diabetes, a clear answer would also have implications for approaches to controlling blood glucose levels in people with Type 1 diabetes.

A major impediment to understanding how diabetes increases CVD risk has been the lack of appropriate animal models with both diabetes and atherosclerosis or other cardiovascular abnormalities. The current exciting era of research provides an opportunity for genetic manipulation to enable the development of small animal models with both diabetes and cardiovascular lesions that closely mimic human disease.

Understanding Angiogenesis: Growth Factors in Macrovascular Disease

The mechanisms of angiogenesis (increased growth of new blood vessels) and their alterations in diabetes must be understood. Ultimately, research must determine whether the use of angiogenic factors to improve blood flow within large vessels will stabilize plaque and prevent acute myocardial infarction in diabetes or restore blood supply to ischemic tissue. In the last decade, the feasibility of using recombinant formulations of angiogenic growth factors to improve blood flow in animal models of myocardial and limb ischemia has been extensively investigated. More recently, the clinical application of these angiogenic factors in the treatment of ischemic heart and peripheral vascular diseases has provided encouraging early results. However, caution must be taken in stimulating the growth of new blood vessels in patients with diabetes and coronary artery disease. Systemic effects of such treatment could adversely affect retinopathy, and local effects in the artery wall could be harmful by promoting plaque rupture, leading to an acute coronary event. Important new therapies could emerge from understanding how to control angiogenesis locally, and enhance or retard new blood vessel growth elsewhere in the body.

Predicting which Diabetic Patients will Develop Macrovascular Disease

It is imperative to identify the presence, predict the progression, and assess the response to therapy of macrovascular complications in patients with diabetes. Advances in understanding the pathogenesis of macrovascular disease provide opportunities to improve markedly the ability to predict which patients with diabetes will develop this complication. A number of biological mechanisms newly identified as CVD risk factors can further improve risk prediction. These mechanisms include measures of coagulation system activity, platelet function, and monocyte adhesion; markers of vascular damage or inflammation; adhesion molecules; altered lipid particle size or oxidation; glycosylation of tissue; and altered endothelial function. Chronic periodontal infection has been associated with increased risk of cardiovascular disease in patients with diabetes. Moreover, genetic epidemiologists and molecular biologists are just beginning to explore genetic factors contributing to susceptibility for end-organ damage.

Decreasing Mortality Related to Myocardial Infarction

Research is needed to identify the mechanisms that lead to the high mortality in diabetics in the peri- and postinfarction period and to develop interventional approaches. In patients with known coronary artery disease, the subgroup with diabetes suffers a two-fold excess in morbidity and mortality following a heart attack. This subgroup also has a greater rate of post-myocardial infarction remodeling and congestive heart failure, twice the rates of coronary reocclusion following percutaneous transluminal coronary angioplasty (PTCA) and poorer near- and long-term outcomes following bypass surgery. Expanded research is necessary to characterize myocardial function and the cardiac micrometabolic environment in the ischemic heart in Type 1 and Type 2 diabetes. Research emphasis also needs to be placed on improved understanding of factors that contribute to excessive mortality related to myocardial infarction in people with diabetes and on establishment of the best medical and interventional procedures for the treatment of the ischemic myocardium.

Peripheral Vascular Disease

Peripheral vascular disease in diabetics can produce many serious problems, and can ultimately lead to amputation of the lower extremity. The factors leading to peripheral vascular disease are often assumed to be identical to those leading to cardiovascular disease and stroke, but there are many patients who suffer severely from peripheral vascular disease without significant cardiovascular complications, and conversely. Thus, major initiatives are needed to understand the specific factors leading to peripheral vascular disease, which results in the high personal and societal cost of these complications. These initiatives should include innovative new approaches to improved vascularization through localized gene therapy as well as more conventional systemic approaches.

Insulin Resistance and Regulation of Lipid Metabolism

Insulin resistance is believed to be a factor contributing to the development of atherosclerosis and cardiovascular disease in Type 2 diabetes and obesity, although the mechanism by which this occurs is not known. Alterations in lipid and lipoprotein metabolism, fatty acid metabolism, and other factors have been implicated in animal models and humans. Hyperinsulinemia, in response to the insulin resistance, may stimulate lipid metabolism and also have direct effects on the vascular response to the hyperlipidemic environment. Unraveling these mechanisms is critical to development of interventions for prevention and treatment of the accelerated atherosclerosis and CVD in diabetes. Studies are needed to test new methods for regulating lipid metabolism, prevention of obesity, and reduction of insulin resistance and hyperinsulinemia in Type 2 diabetes.

Recommendations:

- **Increase research on the mechanisms by which diabetes and insulin resistance enhance the atherosclerotic process and on the mechanisms of angiogenesis and its use in the treatment and prevention of macrovascular disease.**
- **Increase research to determine the mechanisms responsible for the loss of the vascular-protective effect in premenopausal women.**

- **Increase basic and clinical research to study myocardial function and the cardiac micrometabolic environment in diabetic heart disease in order to identify the mechanisms that lead to the high mortality in the peri-infarction period and in patients undergoing surgery, and to develop effective preventive interventions.**

- **Support research to develop appropriate animal models of diabetes and atherosclerosis.**

- **Support further analysis of existing studies and new clinical research to identify the presence, predict the progression, and assess the response to therapy of macrovascular complications in patients with diabetes.**

- **Create Multidisciplinary Centers for Diabetes and Vascular Disease**

Optimizing Glucose Control

A major advance in diabetes research has been the demonstration that intensive treatment regimens to achieve tight control of blood glucose can significantly reduce the incidence and progression of diabetic complications in both Type 1 and Type 2 diabetes. This finding emerged from both the Diabetes Control and Complications Trial (DCCT) and the recently concluded United Kingdom Prospective Diabetes Study (UKPDS).

The major recommendation of both studies is to improve glucose control for all persons with diabetes to levels as close to normal as possible–so called "tight" glucose control. However, current treatment modalities for control of blood glucose have limited success in producing truly effective results. Even the most highly motivated patients find it extremely difficult to comply with the regimens required to achieve desirable glucose control. Hence, patients with diabetes continue to develop debilitating and life-threatening microvascular and macrovascular complications at an alarming rate. Furthermore, intensive treatment regimens are associated with a three-fold increase in the risk of severe hypoglycemia or low blood sugar. This aspect of tight glucose control not only limits treatment compliance but carries its own serious risks.

Research is clearly and urgently needed to develop better treatment methods for control of blood glucose without producing hypoglycemia. As with the research directly attacking the complications of diabetes, the DRWG considers research to develop new methods and treatments to optimize blood glucose control an area of extremely high priority.

Hypoglycemia and Hypoglycemia Unawareness

The risk of severe hypoglycemia, primarily in persons with Type 1 diabetes, represents the single greatest barrier to full implementation of the recommendations of the DCCT. The risk is magnified as a result both of impaired recognition of an impending episode (hypoglycemic unawareness) and compromised counter-regulation to restore euglycemia (normal blood sugar). Severe hypoglycemia is commonly followed by intense fear of recurrence that may impair the individual's capacity to achieve or maintain "tight" glycemic control. Efforts to detect and prevent hypoglycemia would be enhanced by the development of new techniques for self-monitoring the circulating concentration of glucose. Such new methods need to be continuous, reliable, minimally invasive, and affordable. Basic behavioral science research on hypoglycemia is also needed to understand fully how humans monitor and cognitively encode changes in physiological and symptomatic aspects of perturbations in blood sugar. Studies are needed of glucose transport across the blood-brain barrier and of potential insulin effects in the central nervous system. Likewise, research is vitally important on the biology involved in the brain loci that sense the development of hypoglycemia and the feedback pathways between the central nervous system and peripheral organs that mediate counter-regulatory responses. Technology that could provide methods to sense early stages of hypoglycemia reliably, before the onset of neuroglucopenia, would represent an important tool for clinical investigation and for prevention of this serious complication of contemporary treatment. Previous research on "Blood Glucose Awareness Training" promises

significant achievement in this area.

The ultimate goal is to devise the means to prevent or limit hypoglycemia, which not only limits implementation of current methods for optimal glucose control but also has the potential for devastating effects on individual patients. Interventions also need to be developed to facilitate recovery from hypoglycemia unawareness without the need for exposure to periods of less than optimal glycemic control.

Mechanical Approaches to Insulin Replacement

The mechanical approach to insulin delivery does not depend on live tissues, but instead makes use of sophisticated biomedical engineering and clinical research. The first phase of this work is to perfect a surgically implanted insulin delivery system that is controlled by the patient, but does not respond automatically to blood glucose level (an "open loop" system). Some of the major accomplishments in this field over the past 5 to10 years include:

- Design and successful use of several remote-controlled insulin-delivery devices that can be implanted under the skin and used to manage Type 1 diabetes;
- Development of an insulin formulation that is fully stable for up to 3 months inside the implanted pump;
- Clinical use of implanted insulin pumps in over 600 people with Type 1 diabetes for periods as long as 11 years; and
- Demonstration of significant advantages to the use of implanted insulin pumps over multiple daily insulin injections in a randomized, controlled clinical trial sponsored by the Department of Veterans Affairs.

The NIH initially supported this work, and several companies have taken on commercial development.

The second phase of mechanical device development is to engineer a glucose sensor that can be linked to the delivery system. The resulting device would automatically deliver insulin in a close-to-normal pattern, without patient involvement ("closed loop"). This linking of a pump to a glucose sensor will require considerably more developmental and clinical research, particularly on glucose sensors. The NIH has supported research in this area for a number of years and some progress has been made, but a clinically useful glucose sensor that can be integrated into a closed loop system of insulin delivery practical for daily home use has not been attained. The DRWG believes that further attention and support in this area is important if it leads to improved glucose control.

Development of New and Novel Methods of Control of Hyperglycemia

Alternative methods for control of hyperglycemia in patients with diabetes are clearly needed. Such alternatives must not be based on multiple daily injections of insulin. They must also provide better and more sustained control of hyperglycemia than currently achievable with available oral hypoglycemic agents. Enhanced research on islet transplantation, discussed in Extraordinary Opportunities, and on mechanical devices discussed previously are two avenues the DRWG recommends for pursuit of this goal. A compelling need also exists for novel methods to control hyperglycemia.

New insights now provide opportunities to develop molecules that mimic the action of insulin on its target tissues: muscle, adipose tissue and liver. A current obstacle is the difficulty in developing molecules small enough to be administered by routes other than injection. Thus, research is needed to develop effective small, insulin-mimicking molecules that are orally bioavailable and to develop new technologies for insulin delivery.

Similarly, increased research is needed to discover and design molecules that overcome defective insulin action caused by insulin resistance in Type 2 diabetes. Increased understanding of the biology of the beta cell provides new opportunities to design drugs that stimulate insulin secretion in a physiologic manner in Type 2 patients with abnormal beta cell function. Some progress has recently been made in discovering new therapies based on this knowledge, but the effort is insufficient and the treatment of hyperglycemia in diabetes remains inadequate.

Recommendations:

- **Increase basic and clinical research to discover novel approaches for controlling hyperglycemia in diabetes, including development of small, orally bioavailable molecules mimicking insulin action; a means of overcoming insulin resistance or stimulating insulin secretion in a physiologic manner; and technologies that enable insulin administration by routes other than injection. This research could involve enhanced collaboration with the pharmaceutical and biotechnology industry.**

- **Develop a focused, multi-disciplinary research program on hypoglycemia and hypoglycemic unawareness. This research should include the neuroendocrine and neuroscience mechanisms that underlie these problems, and increased clinical research to find simple, reliable**

techniques to identify patients at greatest risk for severe hypoglycemia.

➤ **Initiate immediate review of the research program to develop mechanical approaches to insulin replacement by the Diabetes Technology Task Force. (See "Resource and Infrastructural Needs")**

This review should include a detailed assessment of the current status and recommendations for research on mechanical insulin delivery systems and reliable methods for glucose sensing that would allow a fully automatic, mechanical insulin delivery system. Consideration should be given to the establishment of multidisciplinary consortia or of research centers as a means of bringing together and focusing the efforts of scientists with the needed expertise.

Diabetes and the Environment

Environmental Agents that Trigger the Autoimmune Process in Type 1 Diabetes

While irrefutable evidence documents a genetic basis of Type 1 diabetes, environmental factors also contribute importantly to development of the disease. The best illustration of the importance of environment comes from studies on identical twins. In fewer than 40 percent of cases do both twins develop Type 1 diabetes. These cases of "discordance" in which one twin gets the disease and the other does not, suggest that an environmental factor or trigger has interacted with genetic susceptibility to cause the disease in one twin, but not the other. However, it has been very difficult to pinpoint the specific environmental factors that contribute to development of Type 1 diabetes. To do so may require the development of completely new and different epidemiological methods, since these environmental triggers are likely to play their most important role years before the onset of clinical disease. Likewise, no clear evidence exists as to whether these triggers are infectious agents, dietary factors, or another environmental substance.

Recommendations:

➤ **Hold a series of conferences and workshops to explore new methods to search for the environmental triggers of autoimmune diseases such as diabetes. These conferences should bring together classical epidemiologists, immunologists, virologists, and other experts in environmental science to explore the problem in novel ways.**

➤ **Perform epidemiologic analysis of suspected triggering factors, such as latent or endogenous viruses (including retroviruses) or other substances, whose activation may initiate the autoimmune process.**

➤ **Explore with the Centers for Disease Control and Prevention the possibility of a national registry for Type 1 diabetes as a mechanism to enhance epidemiologic research.**

Environmental Risk Factors and the Development of Type 2 Diabetes

Environmental factors play a major role in the development of Type 2 diabetes. In contrast to those linked to Type 1 diabetes, the factors that are diabetogenic in persons predisposed to Type 2 disease are common to the lifestyles of most Americans and people throughout the world. In populations with a strong genetic predisposition to Type 2 diabetes, clinical diabetes and its complications remain infrequent unless the environment is also "diabetogenic." This accounts for the dramatic increase in the incidence of Type 2 diabetes in populations undergoing rapid westernization. "Westernization" is typically accompanied by a decrease in physical activity (i.e., an increase in sedentary activity), changes in dietary intake with increased total caloric consumption, increased fat consumption and decreased consumption of complex carbohydrates, and increases in obesity. These factors may contribute significantly to the high risk for Type 2 diabetes in minority populations in the United States. Evidence has also been presented for a role of intrauterine and neonatal nutritional deprivation on the subsequent development of Type 2 diabetes as adults. While all of these factors have been associated with increased risk of Type 2 diabetes, it remains unclear whether any of them are more specifically associated with susceptibility to the disease. Furthermore, it is possible that other, yet undefined factors play major roles. Accurate assessment of physical activity and dietary intake is very difficult due to the unreliability of self-

reports, and little is known about these other factors or how to measure them.

Recommendations:

- **Support research to develop and apply new technologies to provide accurate, affordable, quantitative measures in normal, living humans of individual-specific energy expenditure, energy intake and macronutrient composition which contribute to obesity and Type 2 diabetes.**

- **Initiate new epidemiological studies taking into account genetic susceptibility to help identify additional environmental risk factors for Type 2 diabetes, such as stress levels, and bacterial/viral infectious agents.**

- **Study environmental factors responsible for the increase in Type 2 diabetes in children and ways to modify them.**

Special Needs for Diabetes in Women, Children and the Elderly

Women and children have special problems related to diabetes. During pregnancy, women are at increased risk for developing the disease. For women who already have diabetes, pregnancy poses increased health risks for them, as well as the risk of fetal mortality, morbidity, or malformation. Elimination of the excess morbidity and mortality that occur in mothers and their children when diabetes complicates pregnancy is an important goal. Behavioral research is critically needed to address the widespread failure of women with diabetes to participate in programs of family planning and preconception diabetes care. Basic developmental research is needed to understand mechanisms by which diabetes disrupts embryogenesis. Emphasis should be placed on identification of specific developmental and cellular processes that are related to specific types of malformations. Genetic determinants of susceptibility to diabetic malformations must be identified in rodents so that analogous chromosomal regions can be tested for association with malformations in human diabetic pregnancies.

Annually, more than 100,000 women in the United States are estimated to have gestational diabetes mellitus (GDM), a form of diabetes that occurs during pregnancy. Of these women, more than 50 percent later develop diabetes. Thus, research is needed to exploit the unique opportunity GDM provides to study the pathogenesis and prevention of diabetes, especially Type 2, in young women. A large-scale trial is needed to compare management of GDM based on standard glycemic parameters to an approach based on a combination of glycemic parameters and fetal ultrasound measurements.

Diabetes also affects a woman's reproductive health. Studies should be initiated on the risk of hormonal contraceptives and intrauterine devices in women with diabetes compared with the general population. The long-term risk/benefits of hormonal contraception with combined and progestin-only agents on development of cardiovascular disease and diabetes in women with previous gestational diabetes should be assessed.

Diabetic women are also at risk for developing atherosclerotic cardiovascular disease due to the loss of the normal protective effect of estrogen against this disorder. Epidemiologic and mechanistic studies should be initiated to understand pre- versus post-menopausal influences on cardiovascular disease risk and to clearly delineate specific risks for women with Type 1 and Type 2 diabetes. More fundamental research should be undertaken to understand the relationship of insulin resistance syndrome and the risk of cardiovascular disease risk in women.

Children of diabetic pregnancies appear to suffer health consequences later in life, such as increased risk for diabetes, obesity, and cardiovascular disease. Thus, understanding the impact of the intrauterine environment on subsequent development is an important goal. Exposure to maternal diabetes *in utero* increases the risk of obesity and glucose intolerance in adolescence. Minority groups with diabetes are at particularly high risk for cardiovascular disease and for morbidity and mortality. Epidemiological and experimental evidence also indicates that factors impeding nutrition and growth during fetal life and early infancy are associated with increased risk of cardiovascular disease and diabetes later in life.

Type 1 diabetes is usually diagnosed in infancy, childhood, adolescence, or young adulthood. Children with this disease face a lifelong regimen of daily insulin injections. Management of children to meet the DCCT principles is particularly difficult, and requires a thoughtful team approach. Complications of diabetes can be a special problem for children with Type 1 disease because the severity of the complications tends to correlate with duration of the disease.

For the elderly with diabetes, life poses extremely serious problems. Diabetes patients aged 55 and older experience higher rates of cardiovascular disease, stroke, kidney disease, neuropathy, cataracts, and glaucoma than do their non-diabetic counterparts. Older diabetic men and women also have a higher prevalence of risk factors, such as obesity and

hypertension, associated with diabetes. Diabetes among the elderly often limits the ability to function normally. The majority of those with diabetes over the age of 65 suffer from lowered functioning in such areas as seeing, walking, hearing, and reaching. In some surveys, more than 25 percent of such patients report that they are unable to perform such activities as eating, bathing, dressing, shopping or doing housework without the assistance of others. Persons over the age of 55 with diabetes are twice as likely as non-diabetic individuals of the same age to reside in a nursing facility. Research is needed on the contribution of age-related changes and processes to the development and impact of Type 2 diabetes in the elderly, and on the effects of these changes on responses to prevention and treatment strategies in older persons.

Recommendations:

- **Increase basic and clinical research to identify the mechanisms by which the intrauterine environment, including the diabetic environment, affects the immediate and long-term health outcomes for children and their risks of diabetes and obesity.**

- **Support research to determine the impact of Type 1 and Type 2 diabetes on women, including their reproductive health; cardiovascular disease; the relationship of insulin resistance syndrome and polycystic ovarian disease; and the risk of diabetes following gestational diabetes mellitus.**

- **Increase studies about specific psychosocial issues that face women, children and the elderly with diabetes, including eating disorders, impact of school settings on diabetes, and management of diabetes in assisted-living situations.**

- **Increase studies of how to implement effectively the principles of the Diabetes Control and Complications Trial (DCCT) in children with Type 1 diabetes in an effort to improve glucose control and reduce the complications of disease.**

- **Increase studies on age-related changes in the development of Type 2 diabetes and their effects on responses to treatment and prevention strategies in older persons.**

Special Research Needs for Diabetes in Minority Populations

Certain ethnic and racial populations are more frequently affected by diabetes and comprise 25 percent of all patients with diabetes in the United States. Diabetes disproportionately affects two of the Nation's fastest growing demographic groups: Americans of African and Latin American descent. Other minority groups, including Native Americans, Native Hawaiians, and Asian and Pacific Islanders, also suffer particularly high rates of diabetes and the complications it causes. The majority of diabetes in minority populations is Type 2 diabetes. Furthermore, although Type 2 diabetes has been considered a disease of older adults, minority populations are experiencing an alarming increase in the numbers of children and adolescents diagnosed with this disease. The increasing prevalence of diabetes in minority populations underscores the need to study more extensively the lifestyle and other factors that may impact on the development of diabetes and effective management once it is diagnosed.

Complications of diabetes are also more common in minority populations. Minority groups with diabetes are at particularly high risk for cardiovascular disease and for morbidity and mortality. The prevalence of retinopathy is 50 percent higher in African Americans, 80 percent higher in Mexican Americans, and up to 100 percent higher in some Native Americans with diabetes, compared with non-Hispanic whites. For the Medicare population, the incidence of end-stage renal disease in African Americans with Type 2 diabetes is 4.3 times that of whites. Furthermore, while 42 percent of all new cases of end-stage renal disease (ESRD) in the United States are attributed to diabetes, this proportion is much higher in Native American tribes. For example, among Ute, Sioux, and Pima Indians, the proportion of all ESRD due to diabetes is greater than 80 percent.

The incidence of lower extremity amputations in African Americans and some Native Americans with diabetes is two-fold or more the incidence in whites. Angina, myocardial infarction, and other forms of coronary heart disease are in general less common in African Americans, Native Americans, and Mexican Americans than in non-Hispanic whites; however, even these complications are increased in minority patients with diabetes.

Because it appears that the majority of cases of diabetes are due to gene-environment interactions, much more research is needed to identify and better understand the genetic and environmental determinants of diabetes in these minority populations. Research is likewise needed to develop innovative, community-based strategies to deal with important environmental determinants including diet, physical activity, enhanced quality of life and other factors in minority populations.

Recommendations:

- **Increase efforts in genetic studies in minority populations as part of the Consortium for the Study of Genetics in Diabetes.**
- **Support research to identify other physiologic and environmental determinants for development of Type 2 diabetes and its complications in minority populations, including children and adolescents.**
- **Support research to identify risk factors, comorbidities, and primary and secondary prevention strategies for micro- and macrovascular complications of diabetes in minority populations.**
- **Initiate research to develop culturally sensitive preventive and therapeutic approaches utilizing appropriate innovative communication and education techniques applicable in relevant, "real-world" settings, such as rural clinics, county clinics, and urban health centers.**
- **Design and conduct studies in partnership with minority communities to better understand the cultural, familial, and other factors that influence adoption of health promotion and to change high-risk behaviors in those with or at risk for Type 2 diabetes.**

Working with Communities

Pima Indians and the NIH

The Pima Indians of the Gila River Indian Community near Phoenix, Arizona, have collaborated with the Intramural Program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and with the Indian Health Service for 30 years in a unique research program. Pima Indians have the highest rates of diabetes in the world, and the Pimas and NIH research scientists want to know why.

Working together, researchers at NIDDK, Pima volunteers, and the Indian Health Service conducted a health survey in the mid-1960s. It revealed that half of Pima Indians ages 35 and older have Type 2 diabetes. The Pimas provide valuable insights into Type 2 diabetes.

Many families have lived in the Gila River Indian Community for generations. Because of this, scientists can search for root causes of disease through several generations of different families using epidemiologic research.

These studies have provided knowledge about the disease and its complications that would have been impossible to obtain without the long-term contributions of thousands of Pima Indians. The collaboration between the NIH and this group of Native Americans has helped researchers:

- Develop a definition of diabetes and diagnostic criteria used worldwide.
- Identify characteristics of insulin action and secretion conferring increased risk for subsequent development of Type 2 diabetes.
- Document the relationship between diabetes and obesity.
- Increase understanding of the roles of high insulin levels and insulin resistance in diabetes.
- Gain insights into the influence of genetics in the development of diabetes, obesity, and even susceptibility to diabetic kidney disease.
- Demonstrate how *in utero* exposure of a fetus to a mother's high blood sugar may increase the risk for diabetes and unhealthy weight later in life.
- Provide evidence of the beneficial effects of exercise and weight loss in lowering blood sugar and reducing weight.

These insights have provided a foundation for combating Type 2 diabetes in the Pimas and around the world. In their attempts to discover what makes Native Americans so highly prone to developing diabetes, the NIDDK researchers and Pima Indians have changed the way diabetes and obesity are understood and treated, well beyond Arizona's Gila River.

Use of Genetic Engineering in Diabetes Research

Use of Genetic Engineering in Development of Alternative Therapies for Type 1 Diabetes

In addition to emerging strategies for intervention and therapy of diabetes by stimulation of beta cell growth and islet transplantation presented in the "Extraordinary Opportunities" section, the Diabetes Research Working Group finds it imperative to continue long-term development of strategies that could eventually replace current and near-term therapeutic methods. Development in the following three areas is strongly recommended.

Bioengineered Insulin-Secreting Cell Lines

The isolation of large numbers of functionally consistent human or animal islets is difficult and costly. Thus, several laboratories have been developing methods for procurement of cell lines that simulate the function of the normal islet beta cell. The potential advantage of this approach is that cell lines could be grown in very large scale at relatively low cost, possibly solving the issue of cell supply for transplantation therapy of diabetes. The challenge to investigators is to produce cell lines that simulate the performance of normal islet beta cells. The cell lines need to have high insulin content, preferably human insulin; efficient processing of proinsulin to insulin; physiologically relevant glucose-stimulated insulin secretion, including appropriate response dynamics, glucose concentration threshold, and magnitude of response; and normal potentiation of insulin secretion by other secretagogues and hormones. In addition, engineered cell lines must have a stable genotype and phenotype in vitro and in vivo and be amenable to scale-up in large-scale bioreactors if they are to replace normal islets for transplantation therapy.

Important accomplishments have been made in this emerging area over the past decade. First, researchers have developed rodent cell lines by transgenic expression of T-antigen in pancreatic islet beta cells. Some of the cell lines developed in this fashion have been reported to maintain phenotypic characteristics of normal islet beta cells. Second, it has been possible to genetically engineer cell lines for enhanced function, involving overexpression of human insulin and expression of "glucose sensing" proteins such as GLUT-2 and glucokinase. Third, scientists have developed methods for immunoprotection of transplanted cells, including strategies for blocking expression of class I MHC molecules, protective cytokines, anti-apoptotic genes, and enzymes involved in oxygen radical metabolism.

These advances now set the stage for aggressive pursuit of research in the use of genetic engineering for two goals: development of fuel-responsive insulin-secreting cell lines and immunoprotection of transplanted cell lines in patients with Type 1 diabetes.

Development of Fuel-Responsive Insulin-Secreting Human Cell Lines

There are currently no human beta cell lines available. Historical experience has been that human insulinoma tumors, unlike rodent insulinoma tumors, are not easily cultivated as cell lines. Furthermore, direct transformation of human islets with viral constructs has also proven to be inefficient. In those cases in which cell lines have been reported, they appear to rapidly lose their differentiated genotype. Development of new strategies for overcoming these problems should be strongly encouraged, based on findings that emerge from studies funded under "Extraordinary Opportunities."

Development of Methods of Immunoprotection of Transplanted Cell Lines

Immunoprotection can be derived from the following approaches or combinations thereof: (1) development of encapsulation devices or membranes suitable for cell lines; (2) modulation of the immune response via anti-lymphocyte antibodies or related approaches; and (3) genetic engineering of cell lines for protection against immune attack. The first two of these are considered under "Extraordinary Opportunities;" the third is considered here.

The immune response against transplanted cells is complex. It is dependent on factors such as the nature of the engrafted cells, the existence of an autoimmune disease, and the nature of encapsulation of the transplant. Approaches requiring investigation include expression of "protective"

cytokines (IL-4 or IL-10), protection of cells from inflammatory mediators and other types of damage, and induction of resistance to immunological destruction.

Gene Therapy Approaches for Treatment of Diabetes

Studies with transgenic animals or with recombinant viral vectors have provided support for the idea that expression (or suppression) of specific genes in animal models of diabetes have the potential for correcting metabolic abnormalities and, possibly, complications associated with the disease. There are several examples of success in this area.

First, researchers have found that overexpression of glucose transporters in muscle, or the glucokinase enzyme in liver, allows partial normalization of blood glucose in transgenic animals with experimental diabetes. Second, adenovirus vectors have been developed for studies of the metabolic impact of specific genes in isolated primary cells or in the liver of whole animals. Third, the immunoprotective effects of certain genes expressed in islets or in cells of the immune system have been demonstrated in animal models of diabetes.

The foregoing progress has led to the idea that gene therapy of Type 2 diabetes may be more feasible than for other complex disorders. In addition, with improvements in current vector technology, many of the peripheral tissues involved with the insulin resistance of Type 2 diabetes could be accessible for therapy. Animal experimentation with transgenic mice supports the feasibility of such approaches.

Gene Therapy Approaches for Diabetes Complications

Gene therapy may also be an alternative for the complications of diabetes. Specific therapies may be used to counteract effects of altered genes in individuals identified by genetic screening as being at risk for micro- and macrovascular complications (drug or gene therapy). Methods to block specific biological mechanisms involved in vascular complications of diabetes should be developed. However, such therapies may have side effects elsewhere in the body where these same mechanisms serve a useful purpose. For example, the development of new blood vessels is always harmful in the retina, but is essential for wound healing in other organs or tissues.

A drug to inhibit neovascularization may prevent proliferative retinopathy, but increase the likelihood of a severe heart attack or gangrene in the foot or leg. Thus, therapies need to be developed that are specific for the tissues in which these complications occur–nerve, eye, and kidney. It is also important to develop methods to apply broadly active therapeutic agents to the specific tissues without harming other tissues.

The DRWG recommends continued research in genetic engineering. Further investigation is required of genes with desirable metabolic impact in cells and in animals with diabetes. In addition, vectors must be developed that enable efficient transfer of genes to tissues involved in control of fuel homeostasis, while providing long duration of expression and less immunogenicity.

Recommendations:

➤ **Increase investigator-initiated research to explore the possible use of genetic engineering as a strategy for beta cell replacement and immunomodulation of transplanted cell lines.**

The NIDDK will convene a special panel to meet in 2001-2002 to consider the status of the field and make recommendations for RFAs for further development or translation of findings or funding of clinical trials of the most promising technologies.

➤ **Support investigator-initiated research to explore the potential for gene therapy for Type 2 diabetes.**

Gene therapy of Type 2 diabetes may be more feasible than for many other complex disorders because there are many genes already identified that would be good candidates for gene therapy even in individuals without defects in those genes (e.g. insulin, transcription factors). In addition, many of the peripheral tissues involved with the insulin resistance of Type 2 diabetes are accessible for therapy. Animal experiments have demonstrated some feasibility of this approach, but few, if any research groups are working toward human application.

➤ **Support research to explore unique applications of gene therapy for tissue-specific approaches to micro- and macrovascular complications.**

Behavioral and Health Services Research

Behavioral factors play a major role in the current management of diabetes and its complications. For example, based on recent clinical trials, it is now recognized that lowering blood glucose levels will reduce the risk of diabetic complications. In order to optimize glycemic control with the treatments currently available, patients with Type 1 or Type 2 diabetes must follow a complex regimen of frequent glucose monitoring, insulin injection or other drugs, and diet regulation. The translation to both physicians and patients of the importance of glycemic control, as demonstrated in clinical trials, thus requires an understanding of the behavioral and psychosocial factors that facilitate or impede adherence to a complex therapeutic regimen. In many cases, success depends on changing the behaviors of patients, physicians, and persons at risk for development of diabetes. A critical need exists for research into how to most effectively implement knowledge of the pathophysiology of diabetes and the findings of these clinical trials. Such translation will help to both minimize the complications of the disease and to maximize the effectiveness of current therapies.

The dramatic increase in the prevalence of Type 2 diabetes derives from changes in lifestyle behaviors, particularly those associated with obesity. Achieving and maintaining ideal body weight is a key goal in the prevention and treatment of Type 2 diabetes because it improves not only insulin sensitivity and reduces blood glucose levels but also impacts favorably on other risk factors for heart disease. Although some existing behavioral programs have been shown to be effective in controlling or preventing obesity, successful long-term weight loss is difficult to achieve. Furthermore, epidemiological evidence indicates that obesity in childhood is also rapidly increasing, setting the stage for a further major increase in the prevalence of Type 2 diabetes. Thus far, safe pharmacological approaches to long-term therapy of obesity are also limited.

Development of behavioral interventions that can produce sustained changes in lifestyle behaviors and maintenance of weight loss may be a cost-effective way of preventing obesity and Type 2 diabetes on a larger scale. In many cases, this approach depends on changing the behaviors of patients, physicians, and persons at risk for development of obesity and Type 2 diabetes. These programs could also serve as a paradigm for management of other disorders in which lifestyle modification and strategies to change behavior play major roles.

Important opportunities exist for behavioral research related to the complications of diabetes. Coronary heart disease is the major cause of mortality in individuals with diabetes. Diabetes patients who smoke are at particularly high risk of coronary heart disease. Other behavioral factors such as high fat diet, low exercise, and stress have all been shown to increase the risk of coronary heart disease. Psychological problems such as depression and eating disorders also increase the risk of diabetic complications. The development of complications creates psychosocial difficulties that must be addressed.

Thus, there are two primary aims for behavioral research related to diabetes:

- To elucidate the nature, origins, and effects of health-related behaviors that contribute to diabetes.
- To apply behavioral principles to modify an individual's health-impairing behaviors and lifestyles.

Health services research is also an important component of a broad and balanced portfolio of research on diabetes. It is a complement to the biomedical research agenda, and can help to assure that the quality of care of diabetes is improved, that its outcomes are enhanced, and that access to that care is available.

Health services research related to diabetes is supported by the NIH and the Agency for Health Care Policy and Research (AHCPR). This research focuses on the effectiveness and the quality of health care and the outcomes which they produce. Health services research can:

- Assess the comparative effectiveness of different clinical practices, interventions and technologies.
- Help identify population subgroups for which these interventions and technologies are most effective.
- Develop tools that enable clinicians and patients to effectively apply this new knowledge in daily practice.
- Develop and validate new measures to assess the quality and outcomes of the management and treatment of diabetes.
- Identify deficiencies in access to care for diabetic patients, and study the impact of interventions that are designed to improve access.
- Study factors that influence the cost of diabetes care to identify ways to control costs while improving quality.

This research should help identify the best strategies for ensuring that clinicians and diabetic patients take full advantage of our existing knowledge about what works best.

Recommendations:

- **Support clinical behavioral research to develop interventions to improve patients' adherence to diabetes treatment and their quality of life and to promote sustained improvements in lifestyle behaviors, particularly diet and exercise, which will effectively prevent and reduce the risk for diabetes.**

- **Support research on and development of valid methodologies to measure psychosocial and behavioral factors in diabetes.**

- **Integrate behavioral and pharmacological approaches to reduction of risk factors for diabetes and its complications.**

- **Develop interdisciplinary research teams and training programs to bring together individuals who have training in behavioral sciences with those who have training in diabetes, nutrition, and exercise physiology.**

- **Study the effectiveness of different clinical practices, interventions and technologies; and identify deficiencies in access to care for diabetic patients.**

- **Support research to address lifestyle risk factors and behavioral modification/counseling programs, including obesity, unhealthful dietary preferences, and smoking cessation.**

In carrying out these recommendations, the Diabetes Research Working Group encourages controlled clinical studies on the efficacy of various approaches to improving adherence to diabetes treatment regimens. It also urges studies to evaluate different methods to improve the counseling skills of primary care physicians, nurses, and other professional team members to aid patient adherence to therapeutic regimens. This effort should also include controlled clinical studies to evaluate the effectiveness of different strategies for long-term maintenance of weight loss and establishment of the relationship between the magnitude of risk factor change and relevant health outcomes for different populations, as well as in individuals. Also to be evaluated are the effects of debilitating symptoms on social and emotional development; overall family functioning; the cognitive and emotional sequelae of diabetes and patients' perceived quality of life; and the interaction between psychological disorders and diabetes. Promising interventions such as social support, problem solving, coping skills improvement, and provider-client partnerships need to be studied using clinical trials with all ethnic populations.

Oral Complications of Diabetes

Oral complications of diabetes can be grouped into four categories: periodontal diseases, mucosal infections, salivary gland dysfunction, and neurological disorders. These complications are common, as well as problematic, in that they are difficult to treat and greatly interfere with essential daily tasks such as eating and speaking.

Periodontitis is now recognized as one of the six major complications of diabetes. Periodontal diseases tend to be more prevalent, more severe, and progress more rapidly in persons with diabetes than in non-diabetic subjects. Certain groups of patients are at particularly high risk, including individuals with other complications of diabetes, teenagers, pregnant women, and individuals with a history of poor glucose control. Diabetes mellitus also increases the rate of infections of the oral cavity. These occur more frequently in poorly controlled patients and may further destabilize the metabolic balance of diabetes. These oral complications may be the first indication of diabetes. Indeed, the dentist or dental hygienist often refers previously undiagnosed patients for medical treatment.

The molecular and cellular basis for the increased oral diseases in diabetes mellitus remains to be investigated. Research to prevent and treat these complications is critically needed in order to address the overall health and well being of patients with diabetes.

Recommendation:

- **Establish multidisciplinary Centers for Oral Complications of Diabetes and identify means for prevention and treatment.**

- **Increase studies of the oral complications of diabetes, particularly with respect to the chronic destruction of gingival tissues, the immune response to oral bacteria, salivary dysfunction, healing of oral wounds, and oral neuropathies.**

Resource and Infrastructural Needs

An effective program of diabetes research can exist only if there is a supportive infrastructure. This section of the Research Plan attempts to address issues of human resources, research training and recruitment, clinical research, special needs for animal research, and high-cost technology, and recommends mechanisms for ongoing review, evaluation, and continued research planning.

Strengthening of Research Training and Human Resources Development

Successful implementation and achievement of the goals of the Research Plan of the DRWG will require a cadre of exceptionally talented and dedicated researchers who bring the power of their intellects and expertise to bear on solving the puzzle of diabetes. In order to ensure that a national pool of high-quality biomedical researchers will be available in sufficient numbers to meet the needs of diabetes research, the DRWG considers it essential to:

- Enhance development of established diabetes investigators, especially in high-risk and high-technology areas.
- Recruit and train scientists with recently completed postgraduate degrees (Ph.D./M.D.) in research areas related to diabetes, as well as in important related disciplines, and help them make a transition to mature investigators.
- Recruit and train individuals with interests in clinical research.
- Increase the flow of potential trainees with interest in diabetes, beginning with pre-college and college/university programs, from all areas of science.

Current Trends and Estimated Needs in Human Resources for the Next Decade: A Framework for Future Initiatives

Although it is difficult to obtain a precise figure for the total number of scientists engaged in NIH-funded diabetes research, approximately 740 M.D. and 845 Ph.D. principal investigators (PIs) are currently receiving NIH support for research in diabetes and related disciplines. Each of these PIs leads a laboratory team composed of additional doctoral and non-doctoral investigators or trainees, research technicians, nurses, and other support personnel. Many of the M.D. and Ph.D. postdoctoral trainees come from foreign countries, are not supported directly by the NIH, and return home for permanent positions. The DRWG considers the total pool to be insufficient, given the clear need to increase diabetes research in the United States and to implement its Research Plan.

The DRWG estimates a need for 500-750 new M.D. and 1,000-1,500 new Ph.D. investigators to enter the field over the next decade. A concerted national effort led by the NIH will be required to attract this number of qualified M.D.s and Ph.D.s into diabetes research. There is already a shortage of M.D. investigators in biomedical research, and, in the case of diabetes, this will almost certainly increase in the future, since the major "pipeline" of physicians for research comes from people receiving clinical training in endocrinology and metabolism, and this number has decreased by more than 30 percent in the past 10 years. Thus, special attention must be directed toward recruiting and training M.D.s with clinical research interests. While adequate numbers of Ph.D. investigators are being trained in biomedical research, too few are being attracted into the field of diabetes to meet research needs. Special efforts will be required to attract Ph.D. researchers into diabetes.

A Plan for Attracting and Training Researchers for Diabetes Research

The congressionally initiated national effort to enhance diabetes research must include a component designed to address increased human resources needs. The objective of such a program is to increase the number of well-trained, highly motivated, and innovative investigators in diabetes research, but there is a pressing need for appropriate mechanisms to attract them to the field. Mechanisms are needed for retention of already productive scientists, the development of new generations of scientists devoted to diabetes research, and the recruitment of individuals from other scientific disciplines, whose expertise could bring creative, new approaches to this field.

Several factors must be addressed if we are to attract investigators to the many exciting research opportunities in diabetes. These factors include stable funding, competitive remuneration, opportunities for career development, the ability to increase risk-taking in pursuit of research objectives, and a national awareness of the importance of diabetes. It is also necessary to increase options for career development by allowing for growth in traditional academic career paths, as well as in careers in the pharmaceutical and biotechnology industries, research administration, and public affairs—all of which are relevant to the overall national effort against diabetes.

The level of support and the exact funding mechanisms to be used must be tailored to meet the specific needs. Investigators trained in clinical trials research are needed in academia and in industry for the translation of research advances to patient care. Steps must be taken to solve one of the major problems limiting the recruitment of clinically trained individuals into diabetes research—the level and extent of debt they have from their medical training. Thus, new mechanisms, including some level of debt-forgiveness, need to be considered as part of a commitment to a career in diabetes research. Opportunities need to be exploited to establish partnerships with voluntary health organizations, such as the American Diabetes Association (ADA) and the Juvenile Diabetes Foundation International (JDF), as well as with the pharmaceutical and biotechnology industry.

A wide array of established NIH mechanisms already exists to support research training and research career development for Ph.D.'s and M.D.'s at various stages in their careers—from new researchers, to those in transition to independence, and mid-career researchers who wish to acquire new research techniques. However, awareness and availability of these awards need to be promoted by the NIH, especially to those individuals at the critical period of transition to independent investigators and to those interested in careers in clinical research. In addition, new types of training awards with greater flexibility will be of crucial importance in attracting talented and dedicated scientists and physicians into diabetes research.

To retain investigators in research, it is also critical to provide career paths that are seen as viable and secure. Long-term stability allows for the novel thinking and risk-taking that can spearhead the development of new research advances. Exploiting and adapting the mechanisms at hand and developing new ones should make it possible to provide appropriate means to build the essential pool of diverse, qualified, motivated, and innovative investigators committed to advancing the knowledge base in diabetes. This goal will require defining clear career paths for M.D. or Ph.D.

investigators so that they may strategically plan for a career in diabetes research.

Recommendation:

➤ **Create new mechanisms and significantly modify existing programs to maximize recruitment, training, and career development of diabetes investigators, including special initiatives to promote clinical research and to attract investigators from other disciplines.**

The new programs should:

- Establish effective Career Development Awards (CDAs) and Career Investigator Awards (CIAs) in the area of diabetes. These awards need to be of adequate size and duration to provide a realistic incentive for investigators to enter this field. Such CDA and CIA awards could also be made to institutions engaged in diabetes-related research and committed to fostering long-term career planning and faculty development for the trainees.
- Develop mechanisms to enlarge the critically needed pool of clinical investigators in diabetes. These mechanisms should include a loan forgiveness program similar to the existing congressionally authorized NIH loan repayment program designed for recruitment of investigators to AIDS research and other disciplines. They should also include enhancement of award programs for clinically trained individuals who wish to pursue clinical, patient-oriented research, including the science of clinical trials.
- Develop special programs to promote dual training. It is important to establish programs that provide incentives for combined research training in diabetes and other disciplines that might enhance or expand research perspectives, such as cardiovascular disease (CVD), neuroscience, molecular virology, immunology, genetics, epidemiology, biophysics, and mathematics.
- Create mechanisms to provide institutional support for recruitment and training of new investigators into the field, especially minority investigators. This support could occur through the new, expanded Comprehensive Diabetes Research Centers (CDRCs; see below) and other specialized centers of diabetes research that will be created as a result of this Research Plan. Similarly, additional clinical research training could be promoted through combined use of the existing Mentored Patient-oriented Research Career Development Award (K23) and the Clinical Research Curriculum Award (K30), as well as with existing Clinical Associate Physician (CAP) award and at General Clinical Research Centers (GCRCs).
- Explore and initiate new mechanisms to increase the cadre of nurse investigators. Nurse investigators could play an expanded and critical role in many areas of clinical research related to diabetes and could help fill the physician gap in some instances.
- Increase the availability and effectiveness of existing programs by modifying and expanding them to eliminate any barriers to their use, such as citizenship status; to increase salary caps and research expenses; and to allow investigators to develop expertise in new technologies and acquire preliminary data for novel ideas. Also enhance minority participation, and foster awards to move newly trained and clinically trained scientists to the status of independent investigators.
- Attract qualified individuals from other disciplines into the field of diabetes by expanding the use of existing awards and develop new awards. These disciplines might include genetics, mathematics, physics, engineering, basic immunology, molecular virology, cell biology, neuroscience, epidemiology, and biostatistics. In addition, an aggressive program should be initiated to identify scientists in eye, kidney, nerve, and atherosclerosis research who could be retrained to focus their research on the complications of diabetes.
- Encourage use of ADA/JDF/industry partnerships for training and development of new faculty support.
- Increase the attractiveness of diabetes research as a career choice by developing better information systems about available grant mechanisms for trainees and investigators, and by seeking expert guidance in human resource development and recruitment. This enhancement could begin with precollege and university programs, but needs to extend throughout professional life.

Enhancement of the Diabetes Research Centers Program

A major mechanism for infrastructure support of diabetes research is the Diabetes Research Centers program funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This program currently consists of six Diabetes Endocrinology Research Centers (DERCs) and six Diabetes Research and Training Centers (DRTCs). Both types of center provide infrastructure support for some of the services required for basic and clinical research, a small amount of funding for "Pilot and Feasibility" studies, and funds for an "Enrichment Program," usually in the form of seminar speakers and conferences. The DRTCs also include funding for translation of research to health care personnel and the public through their "Dissemination and Education" Programs. The DERCs and DRTCs have "caps" on their direct costs of $750,000 and $1.25 million, respectively. The DRWG believes that centers are an important component of an effective research program, but that the limitations on the funding, scope, and structure of the current diabetes centers significantly impede their effectiveness in support of research.

Recommendation:

➤ **Create new Comprehensive Diabetes Research Centers (CDRCs) to provide enhanced infrastructure support and enhance the effectiveness of existing Diabetes Centers (DERCs and DRTCs) by significantly increasing their funding levels and expanding their mission.**

The DRWG recommends an immediate doubling of the direct-cost cap on funding of the DERCs and DRTCs to $1.5 million and $2.5 million, respectively. This increase would allow significant enhancement of the research services provided to the pool of diabetes investigators at these institutions and would foster the addition of new activities such as the pre- and postdoctoral training programs described above.

In addition, the DRWG recommends the creation of a new type of diabetes centers program within NIDDK, the CDRC program, in order to have diabetes research centers of excellence with the broadest possible scope and impact. The new CDRCs would provide increased support of center infrastructure, broaden the scope of programs and disciplines brought to bear on diabetes, and enhance interdisciplinary approaches to basic, clinical, and behavioral research. They would also enhance and make more meaningful pilot and feasibility studies; permit "proof of concept" studies; provide funding for pre- and postdoctoral fellowship training, as well as faculty development awards; and strengthen programs for translation of research to health care personnel and the public. These centers would be based at institutions that have a large base of both clinical and basic diabetes research, with programs important to multiple areas of diabetes research, and a large base of NIH-supported diabetes research. The CDRCs would have a funding base at a level equal to 25 percent of the existing NIH diabetes-related grant base of the parent academic institution. This funding base would be used for core laboratories, pilot and feasibility studies, enrichment, and translational research, as well as for additional funding for the support of pre- and postdoctoral fellows, development of new faculty, and recruitment of new investigators from other disciplines into the field of diabetes. It is expected that some existing DRTCs may want to undertake a transition to the CDRC program.

Science Snapshot

Imaging in Diabetes

The past ten years have seen a revolution in our understanding of the molecular basis of life. However, much less is known about the way in which genes and proteins function within the living human; gathering such information has been hampered by the lack of noninvasive techniques to study biochemical processes in human subjects.

Since the discovery of X-rays more than 100 years ago, physicians and researchers have developed many new and powerful imaging technologies important for the study and management of diabetes. Fluorescein angiography is used for detecting blood capillary dilatation, occlusion, "leakiness," and new vessel formation in diabetic retinopathy. MRI (Magnetic Resonance Imaging) can be used to diagnose emergencies such as brain swelling during severe diabetic ketoacidosis. MRI can also discriminate between fat and water, and has been used to measure the level of obesity in patients with Type 2 diabetes. Imaging techniques also help researchers visualize the metabolic abnormalities underlying diabetes at the molecular level.

Positron Emission Tomography (PET) and Nuclear Magnetic Resonance (NMR) spectroscopy are what can be termed "functional imaging". They allow researchers to directly measure sugar and fat metabolism in the patient's body. PET images show that the heart and skeletal muscle of diabetic individuals take up much less sugar from the bloodstream than those of healthy individuals. These images also show any heart muscle damage after a heart attack since those regions will absorb almost no sugar. NMR studies indicate that when diabetic patients are treated with insulin, their skeletal muscle uses sugar to make energy at a normal rate, but makes glycogen, a stored form of sugar, at only half the normal rate. Studies like these will allow researchers to design drugs that specifically target the impaired step.

Recently chemists have developed agents that can be detected with PET or MRI that bind only to certain cells, such as cancer cells. This will soon allow scientists to make images showing the location and number of these cells. In the near future, they may be able to measure the number of pancreatic beta cells, which make insulin, in order to learn more about the process that destroys the cells and causes Type 1 diabetes. Thus, imaging technologies hold great promise for the study and treatment of diabetes.

Recent developments in both *in vivo* NMR spectroscopy and functional MRI now allow one to image biochemical pathways and physiology within the living body. By tracking the dependence of the NMR frequency on chemical environment, *in vivo* NMR spectroscopy can measure the concentrations and synthesis rates of individual chemical compounds within precisely defined areas of organs such as brain, liver, and muscle. Thus it has the unique capability of revealing how critical metabolic pathways actually work in healthy individuals and how they are altered in disease. By measuring alterations in the physical properties of water, functional magnetic resonance imaging provides high spatial resolution maps of tissue perfusion and oxygen consumption. This approach is now being used by neuroscientists to provide maps of brain neuronal activity at unprecedented spatial resolution.

The continued development of *in vivo* NMR spectroscopy and functional magnetic resonance imaging of humans depends critically on expensive equipment/technology. Ideally studies are performed on a magnet of 4 Tesla or higher magnetic field strength. A high field magnetic resonance system for these applications typically costs between $3 and $7 million. Presently only a small number of centers are available for researchers due to the limited funding sources available. The importance of making these technologies available to the wider research community is that they form a critical bridge between progress in molecular and cellular biology and the understanding of metabolic and physiological function in the living human.

Developing and Harnessing New Technologies

Currently there are few, if any, effective mechanisms for development of new technologies to support diabetes research. Technology needs fall into two broad categories. The first need is to identify, improve, and modify existing technologies to be appropriate or optimal for diabetes research. One example is miniaturization of metabolic measurement techniques to permit their use in the rapidly expanding number of genetically modified mice that form important models of diabetes and its complications. The second technology need is to develop totally new technologies for diabetes research, such as identifying a method to measure beta cell mass in humans with diabetes or prediabetes. At present, no concerted effort is being made by either academic or industrial researchers to do this type of research. Because NIH depends heavily on investigator-initiated research mechanisms, requests for grant applications go unanswered if there are no investigators in the field with pre-existing interest in solving a technological problem. Therefore, mechanisms must be found to encourage and support development of new technologies critical to the diabetes research effort.

Recommendation:

➤ **Create a National Diabetes Technology Task Force.**

The Diabetes Technology Task Force would be a standing panel of basic and clinical scientists from academia, industry, and the NIH. These working scientists would represent different areas of diabetes-related research and have expertise in various technological disciplines (for example, imaging, sensing, and device development). The Task Force should be appointed by and report to the Director of NIDDK. The goals of this Task Force would be to identify those new or needed technologies most important for development of both diabetes-related research and clinical care and then to identify mechanisms for their accomplishment. The Task Force would also analyze and evaluate emerging or existing technologies in other fields and determine which of these would accelerate the pace of diabetes research or clinical care.

It is envisioned that this panel would meet regularly and be empowered to bring together experts from diverse disciplines to present and evaluate technologies of value to the diabetes research effort. The panel would work with appropriate Institutes of NIH, the Food and Drug Administration (FDA), and industry to ensure efficient development and implementation of the technology. Funds should be provided to the National Center for Research Resources (NCRR) and set aside in the budget to provide support for peer-reviewed academic and industrial work on given diabetes-related technologies. The National Diabetes Technology Task Force could provide the nucleus of a peer review group to review research applications in this area. This initiative is an important opportunity for collaboration between the NIH and industry.

Recommendation:

➤ **Create new regional centers with advanced technologies required for metabolic and functional imaging studies, such as nuclear magnetic resonance (NMR), positron emission tomography (PET), and related technologies, required for contemporary diabetes research and provide ongoing support for their operation.**

Noninvasive techniques are already available for metabolic studies in intact human beings that allow characterization of differences between the normal and diabetic state. These technologies include functional NMR and PET scanning, use of doubly labeled isotopes and mass spectrometry, and others, but their availability is limited to only a very few sites. The cost of establishing new centers or expanding existing centers is measured in millions of dollars, is beyond the scope of investment of most universities or hospitals, and exceeds the current mechanisms of funding through large NIH instrumentation grants.

The NIH, through the NCRR, can provide some funding for such resources, but with its limited budget, has not been able to commit to development of more such centers. The DRWG recommends that additional funds be appropriated to enable NCRR to expand existing centers, and establish and fund additional centers, for this type of research over the next five years. These Centers should be distributed geographically throughout the United States and focus on technologies appropriate for both human and animal studies.

Potentially Important New Technologies for Diabetes Research

New Methods to Assess Physiology and Diabetes Pathogenesis:

- **Methods for estimation of beta cell mass or level of "insulitis" in Type 1 diabetes.**
- **Nuclear magnetic resonance (NMR) and positron emission tomography (PET) scanning for metabolic studies in humans and rodents.**
- **Glucose sensing for both long-term physiological studies and development of an automated, mechanical insulin delivery system.**
- **Miniaturization of techniques for metabolic studies in animal models and ultimately new, less invasive systems for patients.**

New Technologies for Study of Diabetic Complications:

- **Methods to evaluate oxygenation and blood flow in the retina, kidney, and peripheral nerves.**
- **New techniques for evaluating nerve structure and function in diabetic neuropathy.**
- **Noninvasive or minimally invasive technologies to make tissue sampling a more widely available and useful clinical and research tool, and to detect and study diabetic complications at their earliest stages.**
- **New methods for assessment of metabolism in vascular, nerve and cardiac tissue in vivo, and to assess risk in diabetic patients with clinical cardiovascular disease and to evaluate response to therapeutic interventions.**

Telemedicine in Diabetes Research and Markers of Disease:

- **Ability to transmit retinal photographs and other clinical and research data on diabetic subjects to centers where expert evaluation is available for clinical research, clinical trials, and ultimately patient care.**
- **Ability to detect molecular, biochemical, physiologic, and genetic markers that predict increased or reduced risk of diabetes or its complications and allow metabolic staging of disease.**

Animal Models for Study of Diabetes

A major impediment in diabetes research has been the lack of appropriate animal models of the human disease. Animal models provide an essential research tool for understanding diabetes and its complications in humans and for testing potential interventions. Animals can be used to conduct studies at the molecular, cellular, and tissue level not possible in humans and can help answer important questions raised by human studies. At present, there are a number of well-characterized models of Type 1 diabetes and of insulin resistance. Some models of Type 2 diabetes also exist, although they do not accurately mimic the human condition. Opportunities exist for combining these models with genetically altered mice with advanced atherosclerosis, thereby enabling detailed studies not possible in humans of the accelerated atherosclerosis that occurs in diabetes. Additional areas for exploration include the role of hyperglycemia, insulin resistance, and hyperinsulinemia in the atherosclerotic process; the impact of diabetes on oxidation of circulating lipids and vessel wall proteins; and the effect of antioxidants on specific mechanisms of atherosclerosis. Other avenues of research include the role of vascular inflammation and clot formation on vessel injury, and the loss of the physiologic protection against atherosclerosis among women with diabetes. Ultimately, the roles of these new genes/factors/pathways can then be investigated in clinical studies in humans, and some of these specific pathways will emerge as novel therapeutic targets.

A critical need exists to develop and characterize new animal models of Type 2 diabetes that mimic the disease in humans. Understanding the molecular basis of the microvascular complications of Type 1 and Type 2 diabetes will be significantly advanced by the development of representative, well-characterized animal models of human diabetic eye, kidney, and nerve disease.

Animal models are expensive to develop and maintain, and currently, they are not adequately distributed to qualified investigators in the field. Furthermore, most NIH grants provide inadequate funds to individual investigators for this purpose, and most institutions have increasingly overcrowded and limited animal facilities. At present, one commercial, nonprofit firm is the major source for most mice for diabetes studies, and the orders are often "backlogged," or pharmaceutical customers with large, standing orders take precedence over the smaller academic users.

Recommendation:

➤ **Establish regional Centers for Animal Models of Diabetes and Related Disorders.**

These Centers could be established at academic institutions or at commercial sites and would be charged with maintaining large colonies of animals (primarily rodents) of both pre-existing strains and newly created strains for diabetes research. In many cases, these colonies would be new animal models in which particular diabetes-relevant genes have been over-expressed or inactivated by genetic knockout. These Centers should also be involved in the creation of additional new models as requested by the National Consortium for the Study of Genetics of Diabetes or other groups and would be equipped to do physiologic studies in these mice. It is envisioned that most of these Centers will be distinct from those being created for random mutagenesis studies, although in some cases, it is quite possible that the same academic or commercial suppliers could perform both functions. These Centers should also relate to the Mutant Mouse Regional Resource Centers supported by NCRR. The Mid-Career Investigator Award supported by NCRR to train scientist to conduct pathobiology research, should also encourage a focus on the pathobiology of mouse models of diabetes.

Recommendation:

➤ **Support mechanisms to develop and characterize larger animal models of Types 1 and 2 diabetes and their complications and distribute these models for enhanced approaches to genetic and metabolic studies and the full range of diabetes complications.**

This initiative could be realized through expansion of existing programs that support regional animal centers, such as the Primate Centers supported by NCRR, but may require new centers for other types of large animal models more appropriate for certain diabetes studies. These large animal models will allow studies not possible in either humans or smaller animals. They will have multiple applications, from studies of the genetic and molecular mechanisms of diabetes and its complications, to identification of specific new molecular and cellular targets for therapy, to testing of new therapeutic interventions for disease prevention, cure, and treatment.

Enhanced Mechanisms for Obtaining Human Materials for Diabetes Research

Expanded and long-term support needs to be provided for national human tissue resources for research studies. Human tissues and organs are needed for research studies where there are few, if any, animal models, such as studies of the eye, kidney, and nerve complications of diabetes. Human tissues and organs are needed from "brain dead cadavers," "autopsy," and "surgical procedures."

Recommendation:

➤ **Expand support of programs for procurement of human tissues and organs in order to serve cutting-edge diabetes research; to provide adequate numbers of pancreases for islet cell clinical trials and research; to obtain appropriate tissues for study of diabetes complications and genetic research; and to ensure availability of a range of human tissues required to establish DNA and RNA libraries.**

NIH, Pharmaceutical and Biotechnology Interactions

Recent years have witnessed significant new collaborations among industry, academia, and the NIH. However, the situation is far from optimal, and greater cooperation is both necessary and possible. An extraordinary opportunity exists to influence the fight against diabetes by bringing closer together, in a cooperative effort, the research and development activities of these diverse components of the biomedical research community. The challenge is to establish workable funding mechanisms to support cooperative research and development by academic, industry, and NIH scientists and to identify research opportunities in diabetes best suited for such ventures. Several areas of diabetes research described in this Research Plan appear to the DRWG as potential opportunities for NIH–Industry cooperation (see box).

Recommendation:

➤ **Establish an NIH–Industry–Academia Task Force to foster interactive research initiatives.**

It is envisioned that this Task Force would be composed of a broad representation from the pharmaceutical and biotechnology industry, the academic community, NIH representatives, and the lay public. The mandate of the Task Force would be to bring the relevant parties together to identify, plan, and help implement opportunities for industry–academia–NIH cooperation in diabetes research and to recommend to Congress programmatic mechanisms to broaden and enhance such cooperation.

Opportunities for NIH–Industry Cooperation

- **Clinical trials of promising new therapies for Type 1 and Type 2 diabetes.**
- **Research on the genetics of Type 1 and Type 2 diabetes and their complications.**
- **Research resources, such as animal models of Type 1 and Type 2 diabetes and human materials for diabetes research.**
- **Research programs in diabetes mellitus for high-quality basic and clinical research scientists, including training in clinical trials science.**

Optimizing Diabetes Research Activities Through Strategic Planning

Strategic planning is an ongoing process that requires regular re-evaluation and assessment of research programs, opportunities, needs, and initiatives. The DRWG believes this function is essential in diabetes research, where emerging developments are likely to change the course of the field rapidly. Diabetes research requires individuals with a broad range of expertise working in an interdisciplinary and properly structured environment to make optimal progress. This progress can only be achieved by ongoing review and strategic planning, with efforts to maximize advances in the many areas of research that ultimately impact on the health and well-being of Americans. Therefore, it is critical to have both a continuation of the process of review and planning of extramural NIH diabetes research efforts, as well as to take a similar approach for the intramural programs.

Intramural Programs of the National Institutes of Health

Important work relevant to diabetes is currently taking place in NIH intramural programs and in other Federal agencies. The intramural program of the NIH, in particular, provides a unique and valuable resource for the conduct of diabetes research. Much of what is known about insulin resistance and the importance of the insulin receptor in Type 2 diabetes has emanated from the NIH intramural program. Traditionally, the intramural program has had the stability and resources to undertake long-term, high-risk projects or to work in uncharted areas that challenge the field. Such research endeavors are often not amenable to the research grant mechanism or to industrial research and development.

At present, however, some parts of the intramural diabetes program parallel those in many academic centers, rather than provide a complementary function. In addition, there is a limited amount of coordination or collaboration of diabetes research among intramural laboratories of various NIH Institutes, or between NIH intramural laboratories and those in other Federal agencies engaged in diabetes research. This limitation lessens both the efficiency and potential impact of the diabetes research coming from these agencies. The DRWG believes that NIH intramural research programs in diabetes research, when functioning optimally, are important. Thus, this resource should be strengthened and used to the fullest of its productive capacity.

Recommendation:

➤ **The Director of NIH should create an advisory panel to review and make recommendations concerning the intramural NIH diabetes research effort in all Institutes and Centers.**

This advisory panel should be composed of both intramural and extramural research scientists, chaired by an extramural research scientist. It should conduct a complete review of all intramural programs, basic and clinical, of relevance to the diabetes research effort. The panel should make recommendations as to how to modify the existing program to be both unique and complementary to the extramural diabetes efforts. The findings and recommendations of this panel should be presented as a report to the Director of NIH and the Task Force for Strategic Planning in Diabetes, described below, for their review and approval.

Extramural Diabetes Research and Ongoing Strategic Planning

Coordination and interaction among extramural programs of the several NIH Institutes and between NIH and other Federal agencies involved in diabetes-related activities will enhance and make more efficient the overall effort against diabetes. The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) currently serves as the mechanism for achieving this coordination. The Diabetes Research Working Group encourages the Committee to enhance its efforts to recommend trans-NIH and interagency cooperation that will more rapidly advance diabetes research and ensure that research advances are effectively translated to medical practice. However, to both follow the progress of these recommendations and to make optimal progress in new areas of diabetes research, the DRWG believes that a more robust and ongoing planning effort must be present.

Recommendation:

➤ **Create a Task Force on Strategic Planning in Diabetes Research that would report to Congress and the Directors of NIH and NIDDK.**

The Native American Diabetes Project

Diabetes is a major health problem for Native American communities nationwide. In New Mexico these communities are disproportionately affected by diabetes with some tribes having one of three adults with the disease. Dramatically rising diabetes mortality rates for Native Americans exceed other ethnic groups in the state. The Native American Diabetes Project (NADP) was established to improve the health of Native American people with diabetes, and that of their families, in a number of Rio Grande Pueblo communities throughout New Mexico.

The NADP, based at the University of New Mexico, represents a model of how government, industry, and nonprofit organizations can work together to extend and enhance lives. In this instance, each partner needed the other to bring the project to fruition over the last three years. The National Institutes of Health (NIH) identified the need for such a project and provided seed funding to the University of New Mexico for curriculum development. The Bristol-Myers Squibb Foundation provided a grant that takes the program's curriculum from the academic arena into the Pueblo tribes, and the American Diabetes Association would, ultimately, facilitate dissemination of the NADP to other ethnic communities. The various tribal governments serve as the core link and contact in coordination and support of this ongoing model project.

The tone of the intervention is nonjudgmental and is built upon strengths of Native American communities: the health of the community and the importance of children and raising them to be strong in body and spirit. The main goal of the NADP is to encourage and entrust participants with diabetes to make behavioral changes to improve their health and prevent complications associated with diabetes. Family members and friends are included in the project.

Those holding the keys to the true success of the project are the bilingual community members called mentors, who are hired and trained to teach "Strong in Body and Spirit!" Mentors attend training about diabetes, exercise, diet, family/community support and maintenance of behavior changes. They also learn how to implement the curriculum in their community. Thus they become the leaders who will continue to address diabetes issues when the time comes for a transition from the NIH-and UNM-directed efforts to community initiated, directed and operated activities.

A strength of this intervention is its sensitivity to the cultural attitudes and behaviors of the Native American communities. The NADP utilizes a diabetes lifestyle curriculum, "Strong in Body and Spirit!" An innovative feature of the curriculum includes the central employment of stories. Stories and observation of elders are particularly important in Native American traditions and are the methods through which values are passed from generation to generation.

Georgia Perez, who lives in Nambe Pueblo, New Mexico, is the community coordinator, a community educator and mentor for the NADP. She has worked with the project since its inception. "The use of stories is the most special feature of the curriculum and is the part our participants really enjoy. The stories and spiritual focus are aspects which are different from existing materials on diabetes," she said. She authored the curriculum's opening story, "Through the Eyes of the Eagle"—a tale of recognition and acceptance of the problem of diabetes among tribal members.

Through the Eyes of the Eagle (The eagle represents strength, courage, and wisdom.)

This is the land of my Native People. As I soar high above through the clouds, I see the beauty of Mother Earth that she provides for my people, from the high peaks of the mountain tops, where the rivers begin, to the valleys below where the waters run through. I see Brother Sun as he greets each day with his morning light and I see him fade, to make room for Sister Moon.

As each day comes, the bear, the cougar, the deer, and I see the children, so pretty with a tan of golden brown, playing and running in their communities. The men with their legs so strong as to keep up with the antelope as they run. The women so beautiful as they work in their fields, as they grow all the things that make their families so healthy and strong.

I remember when running was a way of life for everyone and so was living off Mother Earth with what she provided. Times were hard, but the Native People all worked together and shared in their labors and good fortunes through many feasts and celebrations. People came from far and near to join them in giving thanks to the Great Spirit for all that they were given and for a long and healthy life.

Brother Sun and Sister Moon have come and gone many times as I continue to fly over the land of my Native People. As each passing day goes by, I have seen many changes, some good and some bad. Mother Earth is still the same, for she continues to provide the nourishment for all living things, large and small. And also for the beauty that she provides for all to see and enjoy.

But, I now feel troubled and sad that I no longer see my Native People enjoying what Mother Earth has for them. With changing times, their labors are still hard but I see them not as strong as they could be. Modern days have brought about many changes where my people no longer run like the antelope. Children seldom play but watch what they call television. My people are getting sick by threes and fours with this thing called "Too Much Sugar in the Blood."

My Native People of golden brown no longer have the strength of their ancestors. As I soar through the clouds, I now see my people no longer active. They suffer from lost vision and strength. Their feet, that once carried them over the lands of their birth, suffer great pain. Some of my people of golden brown now use wheels to get around. And others need machines to keep their bodies clean.

Oh, what a sad vision that my eyes now see. If only there was some way to give my people of golden brown my courage and strength to turn this around.

As I come to rest on my mountain top, I close my tired eyes of what I have seen and begin to see another vision of how it can be to bring back the strength and courage and long life to my people of golden brown.

My Native People are getting out and around. Slowly they come out by ones and twos to work and enjoy the riches and beauty that Mother Earth gives. They are walking and beginning to run and slowly get stronger as their sugars come down. As others see them getting stronger, so they join in until all are doing the same. They once again talk and share their ideas of what they can do to continue to grow healthier too.

They begin slowly by making one change, then two, to eat less sugar and less fat things too. As they get stronger and continue to make these changes, they come to know they are healthier, not only in body but in mind and spirit too, as they now can control this thing called "Too Much Sugar in the Blood."

Their children and grandchildren now know what they can do to grow and become stronger and healthier, too. By learning, and through examples taught by their parents and grandparents, they have obtained the wisdom of knowing what they need to do to keep their sugars down and have a healthier lifestyle.

The Task Force shall be composed largely of scientists and physician/investigators from extramural and intramural programs, as well as interested lay groups, and be chaired by an extramural scientist. It should review progress in implementation of the DRWG's Research Plan annually. It should prepare a biennial report to Congress and the Director of the NIH about the implementation process and make additional recommendations as to how best to further the diabetes research effort. This Task Force should work with the Directors of the NIH and NIDDK, and the Chair of the DMICC, to continue the strategic planning process on an ongoing basis. Based on this process, it should keep the Congress apprised regarding the extent to which initiatives in diabetes at the NIH, as well as other Federal agencies, are being maximized to reach the goals set forth.

The Task Force should serve as a catalyst and vehicle for developing collaborative, leading-edge initiatives for intramural and extramural investigation across the NIH. The Task Force should review the report of the Task Force on Intramural Research to facilitate trans-NIH intramural efforts. The Task Force can advise not only on a more coordinated intramural research effort for diabetes, but also on more effective intramural–extramural interactions and coordination of extramural diabetes-related activities within and between NIH Institutes and other Federal programs concerned with diabetes.

Budget Recommendations

BUDGET RECOMMENDATIONS

The Strategic Plan developed by the DRWG represents a bold and far-reaching proposal. Although there are many important, special interests in any field of biomedical research, the DRWG has worked hard to develop a consensus and present a Plan which is both comprehensive and balanced. The Plan is comprised of recommendations for Extraordinary Opportunities, Special Needs for Special Problems, and areas related to Resource and Infrastructural Needs. In all, there are over 80 major recommendations. While some recommendations build on existing programs, many propose completely new initiatives and mechanisms to speed the research process. To begin to implement this encompassing Plan will require tremendous effort on the part of the National Institutes of Health and the scientific community.

To realize the recommendations in the Plan, a significant increase in the NIH budget for diabetes research is needed. The DRWG believes that diabetes should be among the nation's highest priorities for biomedical research and warrants increased support. At the same time, the DRWG recognizes the necessity of NIH to fulfill a broad mission, and that taking resources from one important area to meet the needs of another can be detrimental. Thus, the DRWG requests that the Congress consider these recommendations and make additional appropriations to the NIH to allow implementation of this Strategic Plan.

The DRWG calls for an increase in the diabetes research budget of $384.5 million for FY2000, rising to an increment of $1.166 billion for FY2004. This gradual ramp-up is designed to allow the program an appropriate rate of growth to meet both scientific and personnel goals, and is calculated as a proposed increment on the FY1999 budget of $442.8 million. Assuming a doubling of the total NIH budget over the next five years, as has been suggested by Congress, implementation of these budgetary recommendations would bring diabetes research funding to about 6 percent of total NIH spending. This is not only more consistent with the impact of diabetes on the U.S. population from both human and economic perspectives, but is what would be required to have a robust and effective diabetes research effort – one which will reduce the rising burden created by this debilitating disease.

A breakdown of the budget is presented by project area and by year in Table II. The greatest increments in budget are needed for the Extraordinary Opportunities, beginning with an incremental increase of $210.5 million in FY2000 and rising to $606 million in FY2004. To achieve the goals proposed for the equally important areas of Special Needs will require additional funding of $143.5 million initially, increasing to $467.5 million over the 5-year period covered by this Plan. Resource and Infrastructural Needs represent the smallest component by budget ($30.5 million rising to $92.5 million), but provide several critical elements for implementation of the Plan.

Since research at NIH is supported by specific Institutes and Centers, the DRWG has also provided suggested allocations of these additional funds to the individual Institutes and Centers of NIH based on their share of the proposed work (Table III). It is recommended that the major fraction of the additional funds (55-60 percent) go to NIDDK, the primary Institute for diabetes-related research. However, due to the multisystem nature of the disease and its complications, many Institutes and Centers are being asked to significantly enhance their diabetes research efforts and should also receive appropriately increased allocations, including NHLBI, NICHD, NEI, NINDS, and NCRR.

In summary, conquering diabetes and its complications represents a formidable task. Biomedical research supported by the NIH and other agencies has moved us forward in this important battle. Based on rapid advances in scientific knowledge and technology and the sense of urgency felt by patients and society, the scientific community is now poised and ready to increase its efforts even further. The Strategic Plan put forward by the DRWG describes a path for this advance and sets an agenda for increasing diabetes research efforts over the next five years. The DRWG hopes that the Congress and citizens of the U.S. will provide the support that is needed to allow this plan to proceed.

Table I
Summary of Budget Recommendations

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
Extraordinary Opportunities					
Genetics of Diabetes	40.5	72.0	85.0	99.0	101.0
Autoimmunity and the Beta Cell	30.0	45.0	58.0	66.0	79.0
Cell Signaling and Cell Regulation	38.0	57.0	73.0	86.0	94.0
Obesity	15.0	25.0	37.0	46.0	52.0
Clinical Research and Clinical Trials	87.0	139.0	191.0	252.0	280.0
Subtotal	**210.5**	**338.0**	**444.0**	**549.0**	**606.0**
Special Needs for Special Problems					
Microvascular Complications	51.0	80.0	106.5	124.0	129.5
Macrovascular Complications	34.0	58.0	79.0	95.0	102.0
Optimization of Glucose Control	9.5	16.0	24.0	29.0	36.0
Diabetes and the Environment	3.0	4.0	6.0	8.0	10.0
Special Needs in Women, Children, and the Elderly	20.0	40.0	60.0	80.0	80.0
Special Needs in Minority Populations	9.0	15.0	22.5	30.0	32.0
Genetic Engineering	8.0	15.0	22.0	28.0	35.0
Behavioral and Health Services Research	8.0	13.5	20.0	27.0	40.0
Oral Complications of Diabetes	1.0	1.5	2.0	2.5	3.0
Subtotal	**143.5**	**243.0**	**342.0**	**423.5**	**467.5**
Resource and Infrastructural Needs					
Research Training and Manpower Development	3.0	5.0	8.0	10.0	10.0
Diabetes Research Centers Program	6.0	15.0	25.0	40.0	40.0
Technology Taskforce	13.0	17.0	21.0	13.0	13.0
Regional Centers for Animal Models	5.0	10.0	16.0	26.0	26.0
Human Materials for Diabetes Research	2.0	2.0	2.0	2.0	2.0
NIH-Pharmaceutical and Biotechnology Interactions	0.5	0.5	0.5	0.5	0.5
Review of Intramural Programs of NIH	0.5	0.5	0.5	0.5	0.5
Taskforce for Strategic Planning	0.5	0.5	0.5	0.5	0.5
Subtotal	**30.5**	**50.5**	**73.5**	**92.5**	**92.5**
Increment over FY99 Base to Implement Recommendations in DRWG Strategic Research Plan	**384.5**	**631.5**	**859.5**	**1065.0**	**1166.0**
FY99 Base for Diabetes Research	442.8	442.8	442.8	442.8	442.8
Grand Total for Diabetes Research	**827.3**	**1074.3**	**1302.3**	**1507.8**	**1608.8**

Table II
Detailed Budget – Extraordinary Opportunities

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
Genetics					
Support of trans-NIH resources for Mouse genome, cDNA libraries, SNPs and CIDR	4.0	5.0	5.0	5.0	5.0
Consortium - Family collections, phenotyping of patients, databases, analysis, and repository	10.0	16.0	16.0	16.0	12.0
NHGRI Intramural efforts (Part of the Consortium)	1.5	2.0	2.0	3.0	4.0
Genomic library analysis, including polymorphisms (Part of Consortium)	9.0	18.0	24.0	30.0	30.0
EST library creation and analysis (Part of Consortium)	2.0	6.0	8.0	10.0	10.0
Creation and application of DNA chip (Part of Consortium)	5.0	10.0	15.0	20.0	25.0
Additional investigator work for functional genomics	9.0	15.0	15.0	15.0	15.0
Subtotal	**40.5**	**72.0**	**85.0**	**99.0**	**101.0**
Autoimmunity and the Beta Cell					
Mapping of T-cell specificity of autoimmune response	5.0	7.0	10.0	7.0	7.0
Identification of optimal cytokine or monoclonal antibody-based immunotherapy for Type 1 diabetes	5.0	5.0	7.0	7.0	10.0
Expand DPT-1 or to create new centers	3.0	5.0	7.0	10.0	12.0
Clinical trials of immunoprevention of Type 1 diabetes	3.0	5.0	6.0	8.0	15.0
Establishment of three Centers for Islet Transplantation	6.0	9.0	12.0	15.0	15.0
Basic and clinical research in new methods of islet cell transplantation for Type 1 diabetes	2.0	3.0	3.0	3.0	4.0
Research in islet growth and development	3.0	5.0	7.0	10.0	10.0
Creation of Interdisciplinary Centers for Beta Cell Biology	3.0	6.0	6.0	6.0	6.0
Subtotal	**30.0**	**45.0**	**58.0**	**66.0**	**79.0**
Cell Signaling and Regulation					
Basic science research in cellular signaling	10.0	15.0	20.0	25.0	30.0
Creation of Centers for Cell Signaling in Humans	6.0	7.5	9.0	9.0	9.0
Genetic and biochemical basis of insulin resistance in Type 2 diabetes and obesity	4.0	8.0	10.0	12.0	15.0
Increase in research of regulation of normal beta cell function versus diabetic beta cell function	3.0	5.5	8.0	10.0	10.0
Inter-institutional grants for beta cell research	5.0	5.0	5.0	5.0	5.0
Metabolic staging of Type 2 diabetes	3.0	5.0	8.0	10.0	10.0
Identification of the mechanisms of the microvascular complications of diabetes	4.0	6.0	8.0	10.0	10.0
Establishment of multidisciplinary centers to study microvascular complications	3.0	5.0	5.0	5.0	5.0
Subtotal	**38.0**	**57.0**	**73.0**	**86.0**	**94.0**
Obesity					
Hormonal control of appetite, energy regulation, metabolism and adipocyte development	3.0	5.0	8.0	10.0	12.0
Enhance the Obesity Research Centers program	5.0	8.0	15.0	15.0	15.0
Genetics and methods to measure energy intake and expenditure	2.0	4.0	4.0	6.0	8.0
Enhance behavioral research in obesity	5.0	8.0	10.0	15.0	17.0
Subtotal	**15.0**	**25.0**	**37.0**	**46.0**	**52.0**
Clinical Trials and Clinical Research					
Creation of Diabetes TrialNet	15.0	20.0	25.0	30.0	30.0
Clinical trials within the TrialNet	30.0	60.0	80.0	100.0	100.0
Epidemiological studies within the TrialNet	6.0	12.0	18.0	25.0	25.0
Increase funding in clinical studies	30.0	35.0	50.0	75.0	100.0
Exploratory studies on novel therapeutic approaches	6.0	12.0	18.0	22.0	25.0
Subtotal	**87.0**	**139.0**	**191.0**	**252.0**	**280.0**
Total Incremental Funding for Extraordinary Opportunities	**210.5**	**338.0**	**444.0**	**549.0**	**606.0**

Table II (continued)
Detailed Budget – Special Needs for Special Problems

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
Microvascular Complications:					
Diabetic Kidney Disease--Nephropathy					
Function of candidate genes					
Transgenic and knockout animal models	2.0	4.0	6.0	8.0	10.0
Differentiation of nephropathy and other microvascular complications of Type 1 and Type 2 diabetes		1.0	1.5	1.5	
Mechanisms of diabetic nephropathy	3.0	5.0	7.0	9.0	10.0
Creation of Centers for Diabetic Nephropathy	6.0	7.5	9.0	9.0	9.0
Surrogate markers of nephropathy	2.0	4.0	6.0	7.5	7.5
ESRD in diabetes	3.0	5.0	7.0	7.0	7.0
Imaging technologies for microvascular complications	2.0	2.5	3.0	3.0	3.0
Tissue specific drug delivery and gene therapy for microvascular complications	2.0	2.0	4.0	4.0	4.0
Mid-career scientist development awards	2.0	2.0	2.0	2.0	2.0
Subtotal	**22.0**	**33.0**	**45.5**	**51.0**	**52.5**
Diabetic Eye Disease--Retinopathy					
Mechanisms of diabetic retinopathy	3.0	5.0	7.0	9.0	10.0
Tissue specific drug delivery and gene therapy for microvascular complications	2.0	4.0	5.0	6.0	7.0
Retinal nerve regeneration	2.0	4.0	5.0	6.0	7.0
Promotion of interdisciplinary research	3.0	5.0	7.0	9.0	10.0
Mid-career scientist development awards	2.0	2.0	3.0	3.0	3.0
Subtotal	**12.0**	**20.0**	**27.0**	**33.0**	**37.0**
Diabetic Neuropathy					
Study of the mechanisms of diabetic neuropathy with increased participation of neurobiologists	3.0	5.0	7.0	10.0	10.0
Surrogate markers of neuropathy	2.0	4.0	6.0	7.5	7.5
New technology to measure and evaluate nerve disease	2.0	4.0	6.0	7.5	7.5
Creation of Centers for Diabetic Neuropathy	6.0	9.0	10.0	10.0	10.0
Tissue specific drug delivery and gene therapy for microvascular complications	2.0	2.0	2.0	2.0	2.0
Mid-career scientist development awards	2.0	3.0	3.0	3.0	3.0
Subtotal	**17.0**	**27.0**	**34.0**	**40.0**	**40.0**
Macrovascular Complications					
Mechanisms of diabetic enhancement of the atherosclerotic process	5.0	10.0	15.0	20.0	25.0
Basic and clinical research to study ischemic heart disease in diabetes	4.0	6.0	8.0	10.0	10.0
Mechanisms of angiogenesis and treatment and prevention of macrovascular disease	4.0	6.0	8.0	10.0	10.0
Animal models of diabetes and atherosclerosis	6.0	12.0	15.0	15.0	17.0
Clinical research to study progression and therapy of macrovascular complications	5.0	10.0	20.0	25.0	25.0
Analysis of existing epidemiological and clinical studies on patients with diabetes	3.0	2.0	1.0		
Macrovascular Disease and Diabetes Centers	7.0	12.0	12.0	15.0	15.0
Subtotal	**34.0**	**58.0**	**79.0**	**95.0**	**102.0**

Table II (continued)
Detailed Budget – Special Needs for Special Problems

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
Optimization of Glucose Control					
Basic initiatives on hypoglycemia & hypoglycemia awareness	2.0	4.0	8.0	10.0	10.0
Clinical initiatives on hypoglycemia & hypoglycemia awareness	3.0	5.0	7.0	8.0	10.0
Basic and clinical research for development of novel therapeutic agents for control of blood glucose	3.0	5.0	7.0	8.0	12.0
Recommendations of the Diabetes Technology Taskforce for development of mechanical devices	1.5	2.0	2.0	3.0	4.0
Subtotal	**9.5**	**16.0**	**24.0**	**29.0**	**36.0**
Diabetes and the Environment					
Environmental risk factors and development of Type 1 diabetes	1.5	2.0	3.0	4.0	5.0
Environmental risk factors and development of Type 2 diabetes	1.5	2.0	3.0	4.0	5.0
Subtotal	**3.0**	**4.0**	**6.0**	**8.0**	**10.0**
Special Needs for Women, Children, and the Elderly					
Effect of intrauterine environment on long-term health outcomes for offspring, Loss of vascular protective effects in premenopausal women, Impact on reproductive health, Psychosocial issues, Implementation of DCCT principles in children	10.0	20.0	30.0	40.0	40.0
Special Needs for Diabetes in the Elderly	10.0	20.0	30.0	40.0	40.0
Subtotal	**20.0**	**40.0**	**60.0**	**80.0**	**80.0**
Special Needs in Minority Populations					
Preventative and therapeutic approaches	3.0	5.0	7.5	10.0	12.0
Studies of familial, cultural, and other factors affecting lifestyles	3.0	5.0	7.5	10.0	10.0
Identification of risk factors, co-morbidities, and prevention strategies in cardiovascular disease	3.0	5.0	7.5	10.0	10.0
Subtotal	**9.0**	**15.0**	**22.5**	**30.0**	**32.0**
Genetic Engineering					
Basic research in development of gene therapy for diabetes	3.0	5.0	7.0	8.0	10.0
Generation of fuel-responsive insulin-secreting cell lines and methods of immunoprotection	2.0	4.0	6.0	8.0	10.0
Gene therapy of complications	3.0	6.0	9.0	12.0	15.0
Subtotal	**8.0**	**15.0**	**22.0**	**28.0**	**35.0**
Behavioral and Health Services Research					
Interventions to improve adherence to treatment and quality of life, improved measurement of psychosocial and behavioral factors, behavioral and pharmacological approaches to reduction of risk factors, effectiveness of combined treatments	6.0	10.0	15.0	20.0	30.0
Health services research	2.0	3.5	5.0	7.0	10.0
Subtotal	**8.0**	**13.5**	**20.0**	**27.0**	**40.0**
Oral Complications of Diabetes	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**
Total Incremental Funding for Special Needs for Special Problems	**143.5**	**243.0**	**342.0**	**423.5**	**467.5**

Table II (continued)
Detailed Budget – Resource and Infrastructural Needs

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
Strengthening of Research Training and Manpower Development					
Methods to maximize recruitment, training, and career development and promotion of clinical research	3.0	5.0	8.0	10.0	10.0
Enhancement of the Diabetes Research Centers Program					
Enhance effectiveness of existing DERCs and DRTCs	6.0	10.0	15.0	20.0	15.0
Create Comprehensive Diabetes Centers		5.0	10.0	20.0	25.0
Subtotal	**6.0**	**15.0**	**25.0**	**40.0**	**40.0**
Developing and Harnessing New Technologies					
Creation of a National Diabetes Technology Taskforce	3.0	5.0	8.0	10.0	10.0
Creation of three to four new regional centers with advanced technologies for imaging studies	10.0	10.0	10.0		
Ongoing support of the new regional centers		2.0	3.0	3.0	3.0
Subtotal	**13.0**	**17.0**	**21.0**	**13.0**	**13.0**
Animal Models for the Study of Diabetes					
Establishment of four regional centers for animal research in diabetes and related disorders	3.0	6.0	10.0	20.0	20.0
Development and characterization of larger animal models of Types 1 and 2 diabetes	2.0	4.0	6.0	6.0	6.0
Subtotal	**5.0**	**10.0**	**16.0**	**26.0**	**26.0**
Mechanisms for Obtaining Human Material for Diabetes Research					
Support of program for national procurement of human tissues and organs, Establishment of DNA and RNA libraries	2.0	2.0	2.0	2.0	2.0
NIH-Pharmaceutical and Biotechnology Interactions					
Establishment of an NIH-Industry-Academia Taskforce	0.5	0.5	0.5	0.5	0.5
Intramural Programs of NIH					
Advisory panel to review intramural diabetes research effort	0.5	0.5	0.5	0.5	0.5
Mechanisms to Review Progress and to Continue Strategic Planning					
Create a Strategic Planning Group that would report to Congress and the Directors of NIH and NIDDK	0.5	0.5	0.5	0.5	0.5
Total Incremental Funding for Resource and Infrastructural Needs	**30.5**	**50.5**	**73.5**	**92.5**	**92.5**
Increment over FY99 Base to Implement Recommendations in DRWG Strategic Reseach Plan	**384.5**	**631.5**	**859.5**	**1065.0**	**1166.0**
FY99 Base for Diabetes Research	**442.8**	**442.8**	**442.8**	**442.8**	**442.8**
Grand Total for Diabetes Research	**827.3**	**1074.3**	**1302.3**	**1507.8**	**1608.8**

Table III
Budget Recommendations by NIH Component

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
	(in millions of dollars)				
NIDDK					
Incremental Recommendations in DRWG Strategic Plan	233.6	387.3	523.9	659.2	722.2
FY99 Base for Diabetes Research	267.5	267.5	267.5	267.5	267.5
Total for Diabetes Research	**501.1**	**654.8**	**791.4**	**926.7**	**989.7**
NHLBI					
Incremental Recommendations in DRWG Strategic Plan	37.5	62.7	89.7	110.9	121.1
FY99 Base for Diabetes Research	30.1	30.1	30.1	30.1	30.1
Total for Diabetes Research	**67.6**	**92.8**	**119.8**	**141.0**	**151.2**
NIDCR					
Incremental Recommendations in DRWG Strategic Plan	1.0	1.5	2.0	2.5	3.0
FY99 Base for Diabetes Research	3.3	3.3	3.3	3.3	3.3
Total for Diabetes Research	**4.3**	**4.8**	**5.3**	**5.8**	**6.3**
NINDS					
Incremental Recommendations in DRWG Strategic Plan	19.1	30.5	39.1	46.1	46.1
FY99 Base for Diabetes Research	4.4	4.4	4.4	4.4	4.4
Total for Diabetes Research	**23.5**	**34.9**	**43.5**	**50.5**	**50.5**
NIAID					
Incremental Recommendations in DRWG Strategic Plan	6.6	8.6	11.9	11.4	15.9
FY99 Base for Diabetes Research	15.5	15.5	15.5	15.5	15.5
Total for Diabetes Research	**22.1**	**24.1**	**27.4**	**26.9**	**31.4**
NIGMS					
Incremental Recommendations in DRWG Strategic Plan	2.2	3.1	4.1	4.8	5.4
FY99 Base for Diabetes Research	2.1	2.1	2.1	2.1	2.1
Total for Diabetes Research	**4.3**	**5.5**	**6.2**	**6.9**	**7.5**
NICHD					
Incremental Recommendations in DRWG Strategic Plan	17.1	29.1	41.8	53.5	61.7
FY99 Base for Diabetes Research	18.5	18.5	18.5	18.5	18.5
Total for Diabetes Research	**35.6**	**47.6**	**60.3**	**72.0**	**80.2**

Table III (continued)
Budget Recommendations by NIH Component

	Year 1 2000	Year 2 2001	Year 3 2002	Year 4 2003	Year 5 2004
			(in millions of dollars)		
NEI					
Incremental Recommendations in DRWG Strategic Plan	15.6	25.3	33.7	40.8	45.4
FY99 Base for Diabetes Research	28.8	28.8	28.8	28.8	28.8
Total for Diabetes Research	**44.4**	**54.1**	**62.5**	**69.6**	**74.2**
NIEHS					
Incremental Recommendations in DRWG Strategic Plan	3.9	6.5	9.8	13.3	14.5
FY99 Base for Diabetes Research	1.5	1.5	1.5	1.5	1.5
Total for Diabetes Research	**5.4**	**8.0**	**11.3**	**14.8**	**16.0**
NIA					
Incremental Recommendations in DRWG Strategic Plan	6.5	12.4	18.8	24.6	25.0
FY99 Base for Diabetes Research	8.4	8.4	8.4	8.4	8.4
Total for Diabetes Research	**14.9**	**20.8**	**27.2**	**33.0**	**33.4**
NIMH					
Incremental Recommendations in DRWG Strategic Plan	1.2	2.0	3.0	4.1	6.0
FY99 Base for Diabetes Research	2.1	2.1	2.1	2.1	2.1
Total for Diabetes Research	**3.3**	**4.1**	**5.1**	**6.2**	**8.1**
NINR					
Incremental Recommendations in DRWG Strategic Plan	3.7	6.5	9.8	13.1	14.9
FY99 Base for Diabetes Research	0.8	0.8	0.8	0.8	0.8
Total for Diabetes Research	**4.5**	**7.3**	**10.6**	**13.9**	**15.7**
NHGRI					
Incremental Recommendations in DRWG Strategic Plan	7.5	13.0	16.3	20.5	22.8
FY99 Base for Diabetes Research	4.6	4.6	4.6	4.6	4.6
Total for Diabetes Research	**12.1**	**17.6**	**20.9**	**25.1**	**27.4**
NCRR					
Incremental Recommendations in DRWG Strategic Plan	29.1	42.9	55.9	60.3	62.0
FY99 Base for Diabetes Research	25.8	25.8	25.8	25.8	25.8
Total for Diabetes Research	**54.9**	**68.7**	**81.7**	**86.1**	**87.8**

Note: In accord with the congressional language directing the Diabetes Research Working Group to develop a comprehensive plan for all NIH-funded diabetes research, including cost estimates, this budget table only addresses NIH and its components. However, the Working Group recongizes that many other government agencies fund diabetes-related programs and that their resources need to be expanded as well in order to maximize the entire national effort to conquer diabetes and its complications.

Members of the Diabetes Research Working Group

"Conquering Diabetes: A Strategic Plan for the 21st Century," is the culmination of year-long efforts by numerous individuals and organizations. All members of the congressionally-established Diabetes Research Working Group have made major contributions to the Research Plan. Their efforts, insights, contributions, and commitment have helped to ensure that this document represents a comprehensive Strategic Research Plan for all NIH-funded diabetes research, as directed by the Congress. This Research Plan is intended to help increase the effectiveness of diabetes research and find solutions to the serious problems posed by diabetes. The Working Group is composed of scientific experts in the field of diabetes, external to the NIH, as well as lay leaders in the diabetes community.

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During its deliberations, the Diabetes Research Working Group formed several subgroups to focus efforts on specific aspects of diabetes research. The following is a list of those subgroups and the individuals who served as chairs and/or co-chairs.

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A Special Note of Appreciation

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Individuals who Provided Oral Presentations or Written Statements

As part of its planning process the Diabetes Research Working Group heard public commentary on future directions for diabetes and diabetes-related research funded by the NIH. Comments came from private citizens and from individuals representing voluntary health, research, and professional organizations, and other organizations concerned about diabetes. The Working Group acknowledges and thanks these individuals for their oral presentations and written statements.

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Congressional Language for the Diabetes Research Working Group

Senate Report 105-58
Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill, 1998

National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes—Diabetes affects 16 million Americans and is a leading cause of blindness, kidney disease, heart disease, and amputations. Given the enormous human and economic costs of diabetes, the Committee urges the Director of the Institute to work closely with the Director of the NIH in establishing a diabetes research working group to develop a comprehensive plan for all NIH-funded diabetes research efforts. The Director of the Institute and the Diabetes Mellitus Interagency Coordinating Committee is encouraged to work closely with the working group in the development and implementation of the diabetes research plan. (p. 76)

Office of the Director
Diabetes—In light of the enormous human and economic costs of diabetes and the cross-Institute nature of diabetes research at the NIH, the Committee urges the Director, in collaboration with the Director of the NIDDK, to consider the establishment of a diabetes research working group to develop a comprehensive plan for NIH-supported diabetes research. Members of the working group could include: high-level representatives from those Institutes that have diabetes research portfolios; leading diabetes researchers; representatives from industry; and leaders of organizations that represent people with diabetes. The Director of the NIDDK and the Diabetes Mellitus Interagency Coordinating Committee should work closely with the working group in the development and implementation of the diabetes research plan. (p. 110)

House Report 105-205
Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriation Bill, 1998

National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes—Diabetes affects 16 million Americans and is a leading cause of blindness, kidney disease, heart disease, and amputations. According to recent estimates, diabetes costs society over $130 billion per year. Given the enormous human and economic costs of diabetes, the Committee urges the Director of the Institute to work closely with the Director of NIH in establishing a Diabetes Research Working Group to develop a comprehensive plan for all NIH-funded diabetes research efforts. This plan should recommend future diabetes research initiatives and directions. The Working Group should submit its plan to Congress within twelve months of the enactment of this appropriations bill. The Director of NIH is urged to appoint a non-NIH member of the Working Group as its chairman. Members of the Working Group should include high-level representatives from the NIH Institutes that have substantial diabetes research portfolios. Other members should include leading diabetes researchers, representatives from industry, and leaders of organizations that represent people with diabetes. The Director of NIDDK and the Diabetes Mellitus Interagency Coordinating Committee should work closely with the Working Group in the development and implementation of the diabetes research plan (p. 69).

Office of the Director
Diabetes—In light of the enormous human and economic costs of diabetes, and the fact that diabetes research is funded in many of the Institutes, the Committee urges the Director of NIH in collaboration with the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), to establish a Diabetes Research Working Group to develop a comprehensive plan for NIH-funded diabetes research. The NIDDK section of this report describes in more detail the composition of the Working Group and its mission. (p. 98)

House Report 105-635
Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill, 1999

National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes—As recommended by the Committee, a scientific Diabetes Research Working Group has been established to develop for the Congress a comprehensive research plan for all NIH-funded diabetes research. The Committee is pleased that the Working Group has already reviewed the NIH diabetes research portfolio; heard public commentary and presentations from the diabetes voluntary community; and drafted preliminary subgroup reports. While the Committee awaits the full Working Group's final research plan, it notes that the Group has identified a number of "extraordinary research opportunities." Therefore the Committee urges all NIH institutes and centers to consider implementing the recommendations in a timely fashion so that no time is lost in bringing potential research benefits to diabetic patients and their families. The Committee also encourages the Working Group to include overall cost estimates to accomplish its recommendations in the final research plan. (p. 69)

Glossary of Scientific and Medical Terms

Acarbose – A drug that reduces hyperglycemia by altering intestinal absorption of carbohydrates.

ACE Inhibitors – *See:* Angiotensin Converting Enzyme Inhibitors.

ADA – American Diabetes Association.

Adipocyte – Fat cell.

AGE Proteins – Advanced Glycation End-products proteins. High concentrations of glucose in the blood and tissues may cause glucose to attach to protein molecules which link together forming large macromolecules called AGE proteins. These are thought to contribute to the complications of diabetes.

Adult-Onset Diabetes – Former term for Type 2 diabetes mellitus.

Agonist – A drug or other substance that mimics the action of a hormone.

Albuminuria – Abnormally high levels of the protein albumin in the urine; may be a sign of kidney disease in people with diabetes.

Aldose Reductase – An enzyme that converts glucose to sorbitol, a sugar alcohol normally present in only small amounts in the eye and other parts of the body. Excess sorbitol may contribute to tissue damage in the eyes, kidneys, and nerves.

Allele – Any of two or more alternative forms of a gene that occupy a specific site on a chromosome. For example, the alleles DR3 and DR4 predispose to Type 1 diabetes.

Allograft – A graft of tissue between people who are not genetically identical. The only genetically identical people are identical twins.

Alpha Cell – A type of cell found in the pancreatic islets that makes and releases glucagon, a hormone that raises the level of glucose in the blood and counteracts insulin.

Angiography – An X-ray study of the heart and blood vessels conducted after the injection of dyes.

Angiopathy – A disease of the blood vessels. In macroangiopathy, fat, fibrous tissue, and blood clots build up and adhere to the large blood vessel walls, blocking the flow of blood. In microangiopathy, the small blood vessel walls become so thick and weak that they leak blood and protein, and slow the flow of blood.

Angiogenic – Related to the growth of blood vessels. Several natural factors in the body stimulate the growth of blood vessels. They may play a role in diabetic retinopathy. Research on recombinant formulations of angiogenic growth factors is being conducted in the treatment of ischemic heart and peripheral vascular diseases.

Angiogenesis – The growth of blood vessels. The control of angiogenesis in specific regions of the body could lead to new treatments for retinopathy and other diabetes-related vascular diseases by retarding or enhancing new blood vessel growth.

Angioplasty – Any of various techniques for repairing damaged blood vessels using surgery, lasers, or tiny inflatable balloons that are inserted into blood vessels via catheters and used to open a blocked vessel.

Angiotensin Converting Enzyme (ACE) Inhibitors – A class of drugs used to treat high blood pressure. These drugs can slow the progression of kidney disease in patients with diabetes.

Antagonists – An agent that opposes the action of another. For example, insulin—which lowers the level of glucose in the blood—is an antagonist of glucagon, which raises it.

Antibodies – Proteins that the body's immune system produces to protect itself from foreign substances.

Antigens – Substances that the immune system identifies as foreign or harmful, causing it to produce antibodies.

Antioxidants – A drug or natural substance, such as vitamins C and E, that prevents or reduces the process of oxidation, thereby protecting the cells or tissues from the damage of toxic oxidative end-products.

Atherosclerosis – A disease in which fat and other material builds up in the large and medium sized arteries, leading to decreased or blocked blood flow.

Autoantibodies – Antibodies that react against a patient's own body. As an example, the antibodies against a persons own beta cells may react against and destroy these insulin producing cells to cause Type 1 diabetes.

Autoimmune disease – Disorder in which the body's immune system attacks and destroys body tissue it mistakenly identifies as foreign. In Type I diabetes, the immune system identifies certain proteins on the body's insulin-producing beta cells as foreign materials, attacking and ultimately destroying them.

Autonomic Neuropathy – A disease of the nerves that function automatically to control such internal organs as the bladder, digestive tract, genitals, and cardiovascular system, disrupting the functions of these organs. As an example, impairment of the nervous system's ability to regulate heart functions can cause sudden cardiac death.

Beta Cell – A type of cell in the pancreatic islets that makes and releases insulin.

Blood Glucose – The sugar that is the major source of energy for living cells and is carried to each cell through the bloodstream. The hormone, insulin helps cells to use glucose. *See also:* Oral Glucose Tolerance test.

Biguanides – Drugs such as metformin that improve the body's use of glucose and are being used as a treatment for Type 2 diabetes.

Biphasic Insulin – Glucose stimulated insulin release from pancreatic beta cells occurs in two phases, a rapid first phase and a slower more long lasting second phase.

CAD – Coronary Artery Disease.

Calcium Channel Blocker or calcium antagonist – A drug that prevents calcium from entering smooth muscle cells, reducing muscle spasms. Used to treat heart diseases such as angina that are marked by coronary artery spasms.

Calorimetry – A method of measuring energy content or consumption, especially as body heat (calories) used in activity.

Central Obesity – An excess amount of fat stored in the abdominal area and assessed by measurement of waist to hip ratio.

CHD – Coronary Heart Disease

Closed Loop System – Mechanical device that combines a glucose sensor and delivery system to automatically deliver insulin in a nearly normal pattern without patient involvement.

CNS – Central Nervous System

CSII – Continuous Subcutaneous Insulin Infusion
See: Insulin pump.

CVD – Cardiovascular Disease

Cytokines – Proteins secreted by different cell types of the immune system that serve as chemical messengers, promoting cell growth, immune interactions between antibodies and T cells, and immune reactivity.

DCCR – *See:* Diabetes Cooperative Clinical Research groups.

DCCT – *See:* Diabetes Control and Complications Trial.

DERC – Diabetes and Endocrinology Research Center.

Diabetes Control and Complications Trial (DCCT) – A 10-year study funded by the National Institute of Diabetes and Digestive and Kidney Diseases to assess the effects of intensive therapy on the long-term complications of diabetes. The study demonstrated that intensive management of insulin-dependent diabetes prevents or slows the development of the complications of the disease.

Diabetes Prevention Program (DPP) – A large-scale clinical trial on Type 2 diabetes sponsored by NIDDK.

Diabetes TrialNet – Proposed regional cooperative clinical groups linked together to form a network, which would create and maintain an informational registry of patients, coordinate and perform large-scale, long-term clinical trials in diabetes and have facilities for both physiologic and clinical trials research.

Diabetic Amyotrophy – A disease of the nerves leading to muscle degeneration, pain, and weakness occuring most often in older men with mild diabetes.

Diabetic Eye Disease – *See:* Diabetic retinopathy.

Diabetic Ketoacidosis (DKA) – A major acute complication of diabetes characterized by severe elevation of blood glucose levels usually occurring in persons with Type 1 diabetes who have very low blood insulin levels. DKA occurs when the body begins using stored fat for energy, producing ketones and acids that build up to excessive levels in the blood. Without emergency treatment, the metabolic disturbances that result from ketoacidosis may lead to coma and death.

Diabetic Nephropathy – Kidney disease that results from damage to the small blood vessels and cells of the kidneys, impairing their ability to function, possibly leading to kidney failure (end stage renal disease).

Diabetic Neuropathy – Disease of the nerves that can affect any part of the nervous system: a single nerve (mononeuropathy); multiple nerves (polyneuropathy); the autonomic nervous system; or the central nervous system. *See also:* Autonomic neuropathy; peripheral neuropathy

Diabetic Retinopathy – Damage to the small blood vessels of the retina at the back of the eye, which supply oxygen and nutrients to the retina. This leads to changes in the flow of blood, weakening blood vessel walls, and stimulation of growth of harmful blood vessels. Retinopathy may be mild (background retinopathy) or it may become severe (proliferative retinopathy). In proliferative retinopathy, new blood vessels form which may rupture and bleed into the retina, threatening sight.

Diabetogenic – Causing diabetes.

DPP – *See:* Diabetes Prevention Program.

DR3, DR4, DQ Alleles – Alleles of the Major Histocompatibility Complex (MHC) molecules also called human leukocyte antigen (HLA) which are strongly associated with susceptibility to Type 1 diabetes. About 85-90 percent of patients with Type 1 diabetes are positive for the HLA DR3 or DR4 molecules. *See also;* Human Leukocyte Antigen System; Major Histocompatibility Complex.

DRTC – Diabetes Research and Training Center.

Dyslipidemia – Abnormal concentration of serum lipoproteins—proteins in which fats (lipids) form a part of the molecule. For example, levels of high-density and low-density lipoprotein cholesterol are implicated in a person's risk for heart disease.

EMG – Electromyography. Tests used to diagnose neuropathy and to check for nerve damage.

End Stage Renal Disease (ESRD) – The point in any disease when the kidneys are so badly damaged or scarred that they fail, with the consequence that either renal dialysis or kidney transplantation is required.

Endothelium – The layer of cells that lines the heart, blood vessels, lymph vessels and fluid-filled cavities of the body.

ESRD – *See:* End stage renal disease.

Enterovirus – One of several types of viruses that flourish in the intestinal tract.

Euglycemia – Normal level of glucose in the blood. *See also:* Oral Glucose Tolerance test.

Extracellular Matrix – Fibrous-like tissue that surrounds cells; an excess accumulation of this matrix may contribute to diabetic nephropathy.

Fatty Acids – A form of fat that circulates in blood. When insulin levels are too low or the body does not have enough glucose to use for energy, it may burn fatty acids for energy.

Fluorescein Angiography – A method of examining the blood flow in the vessels of the eye by tracing the progress of an injected dye.

GDM – *See:* Gestational Diabetes Mellitus

Genome – Complete genetic complement of an organism.

Genotypic – Having to do with genetically inherited characteristics; related to the complete set of genes of an individual.

Gestational Diabetes Mellitus (GDM) – Abnormally high levels of blood glucose developed during pregnancy. The level may return to normal after delivery or can be a precursor to the development of diabetes later in life.

Glucokinase – An enzyme that catalyzes the formation of glucose-6-phosphate from glucose. It contributes to the glucose-sensing activity of beta cells. Mutation of the gene producing this enzyme may contribute to Maturity Onset Diabetes of the Young.

Gluconeogenesis – The formation of glucose from non-carbohydrate sources, such as fat or protein metabolism.

Glucosamine – The amino sugar derivative of glucose thought to be involved in altered metabolism.

Glucose – A simple sugar found in the blood that is the body's main source of energy. *See:* Blood Glucose.

Glucose Intolerance – Abnormally high levels of blood glucose after an oral glucose tolerance test (OGTT)
See: Impaired glucose tolerance

Glutamic Acid Decarboxylase – An enzyme produced by the beta cells in the pancreas that, along with insulin and the enzyme IA-2, is targeted by autoimmune T cells that destroy the beta cell's ability to produce insulin. Antibody response to this protein is found in most patients who develop Type 1 diabetes, often appearing months to years before the progression to overt Type 1 diabetes.

Glycemic Response – The differential effects of foods on blood glucose levels over a period of time.

Glycogen – The stored forms of glucose in the body. Glycogen is stored primarily in the liver and muscles and is changed back to glucose and released into the bloodstream when needed by the body for energy, e.g., during fasting or exercise.

Glycogenesis – The process by which glycogen is formed from glucose.

Glycogenolysis – The breakdown of glycogen into glucose.

Glycosuria – Abnormal presence of glucose in the urine; an indicator of the presence of diabetes mellitus.

Growth Factors – Small molecules that stimulate the growth of specific types of cells. *See also:* Vascular Endothelial Growth Factor (VEGF).

HDL cholesterol – High Density Lipoprotein cholesterol, often thought of as the "good" cholesterol.

Hemoglobin A1c – The substance of red blood cells that carries oxygen to the cells and binds with glucose. Because the glucose stays attached for the life of the cell, a test to measure hemoglobin A1c shows the patient's average blood glucose level for that period of time.

Heparin – A substance that occurs naturally in the body and is used as a drug in therapy to prevent clotting in the veins.

Hepatic – Related to the liver.

Hexosamine – A class of amino sugars derived from six-carbon sugars or hexose; involved in the metabolism of carbohydrates.

HLA antigens – *See:* Human Leukocyte Antigens

Homeostasis – A relatively constant state within the body that is naturally maintained by various sensing, feedback and control systems, including the brain and hormone-producing glands.

Human Leukocyte Antigens – Genetically derived molecules on the surface of cells that determine the similarity of cells and susceptibility to disease and are involved in the activation of T-lymphocytes. *See also:* DR3, DR4, DQ Alleles.

Human Leukocyte Antigen (HLA) system – This system assures that the immune system recognizes the individual's own tissues as self rather than as foreign. In people susceptible to Type 1 diabetes, this recognition system goes awry and produces an autoimmune response to insulin-producing beta cells.

Hyperglycemia – Abnormally high level of blood glucose, a hallmark of diabetes. Uncontrolled hyperglycemia may damage large and small blood vessels and lead to othercomplications of diabetes.

Hyperinsulinism – A high level of insulin in the blood that occurs because the body is producing large amounts of insulin in an effort to overcome insulin- resistance.

Hyperlipidemia – An abnormally high level of lipids in the blood.

Hypertension – Abnormally high blood pressure.

Hypertriglyceridemia – An abnormally high level of triglycerides in the blood.

Hypoglycemia – An abnormally low level of glucose in the blood.

IA-2 – An enzyme produced by the beta cells in the pancreas that, along with insulin and the enzyme glutamic acid decarboxylase 65, is targeted by the autoimmune T cells that destroy beta cells. Antibody response to this protein is found in many patients who develop Type 1 diabetes, before progression to overt disease.

IDDM – *See:* Insulin-Dependent Diabetes Mellitus

IGT – *See:* Impaired Glucose Tolerance

Immunosuppressive Drugs – Drugs that prevent an immune response to foreign or self proteins. Often administered to prevent rejection of transplanted tissue and to prevent autoimmune disese.

Impaired Glucose Tolerance (IGT) – A disorder in which blood glucose levels are intermediate between normal and diabetic. Studies have shown that IGT increases the risk of developing Type 2 diabetes and its macrovascular complications.

Insulin – A hormone secreted by the pancreas that regulates the metabolism of glucose. Insulin is produced by the beta cells in the area of the pancreas called the islets of Langerhans.

Insulin-Dependent Diabetes Mellitus (IDDM) – *See:* Type 1 Diabetes.

Insulin-like Growth Factor (IGF) – A hormone with insulin-like actions and structure, but which functions mainly as a mediator of cell growth and replication.

Insulin pump – A mechanical device that pumps a continuous, steady supply of insulin into the body through a plastic tube that is connected to a needle inserted into the body. The pump may also be activated by the person to deliver extra boosts of insulin when needed, e.g., at mealtimes.

Insulin reaction – *See:* Hypoglycemia.

Insulin Receptors – Specialized protein molecules on the outer surface of a cell that bind circulating insulin, allowing insulin to produce its effects on the cell, including taking up glucose from the blood and using it for energy.

Insulin Resistance – Impaired ability of muscle and fat cells to respond to the glucose metabolizing action of insulin. Insulin resistance is a major contributor to and precursor of Type 2 diabetes and may appear many years prior to the onset of clinical disease.

Insulin Resistance Syndrome – A constellation of metabolic abnormalities associated with resistance to the action of insulin including obesity, hyperlipidemia, hypertension, accelerated atherosclerosis, and impaired glucose tolerance.

Ischemia – Poor blood supply to an organ, such as the heart, that is often marked by organ dysfunction and pain.

Islet Cell Transplantation – Transplanting pancreatic islets of Langerhans from a donor pancreas into a person whose pancreas has ceased to produce insulin.

Islets of Langerhans – The pancreatic structure containing alpha, beta, and delta cells, which produce and secrete hormones that aid in the metabolism of food.

Juvenile-Onset Diabetes – Former term for Type 1 diabetes.

JDF – Juvenile Diabetes Foundation International.

Ketone Bodies – Chemical compounds produced by the liver from fats that may accumulate in the blood at excessive levels because the body does not have sufficient insulin and must break down fat for its energy instead of carbohydrates.

Ketoacidosis – *See:* diabetic ketoacidosis.

Ketosis – The build up of excessive ketone bodies in body tissue and fluids. In diabetes, ketosis results when there is insufficient insulin in the blood and the body must break down fat for energy. Untreated, ketosis may lead to diabetic ketoacidosis.

LDL Cholesterol – Low density lipoprotein cholesterol, sometimes called the "bad" cholesterol.

Leptin – A hormone that is secreted by fat cells and controls a key pathway in regulation of food intake and energy balance.

Lipids – Fat or fat-like substances in animal (or plant) tissues that are stored in the body as an energy reserve. Lipids include cholesterol and triglycerides. Elevated levels of lipids are associated with diseases such as atherosclerosis.

Lipolysis – The breakdown of fats.

Lymphocytes – Small white blood cells that are critical components of the immune system and of the autoimmune response in Type 1 diabetes. There are several types of lymphocytes. B cells are primarily involved in the production of antibodies. Helper T cells release chemicals that activate and direct the movements of other cells to help fight infection or attack foreign matter, including the production of antibodies by B cells. Suppressor T cells suppress the activity of B cells.

Macrovascular – Related to large blood vessels. Macrovascular complications of diabetes can lead to coronary disease, cerebral artery disease and peripheral vascular disease.

Macular Edema – Eye disease in which leaking fluid from the blood vessels pools in the center of the retina and impairs central vision functions, such as reading.

Major Histocompatibility Complex (MHC) – Genes that control the body's immune response. They produce molecules that are expressed on the white blood cells of the immune system, including the human leukocyte antigen (HLA) molecules that contribute to the autoimmune response in Type 1 diabetes.

Matrix – A mixture of proteins found between tissue cells.

Maturity Onset Diabetes of the Young (MODY) – A subtype of Type 2 diabetes, this is characterized by early onset, autosomal dominant inheritance, and a primary defect in insulin secretion.

Matobolic Syndrome – *See:* Sydrome X.

MHC – *See:* Major Histocompatibility Complex.

Microvascular – Related to small blood vessels. Microvascular complications of diabetes affect the eye, kidney, and nerve and can lead to blindness, kidney failure, and limb amputation.

MODY – *See:* Maturity Onset Diabetes of the Young.

Monoclonal Antibodies – Immunologically homogeneous antibodies, usually mass-produced from a single somatic cell hybrid that is formed by the fusion of normal lymphocytes and tumor cells.

MRI – Magnetic Resonance Imaging, a technique for obtaining images of the internal structure or processes within the body. The nuclei of certain atoms absorb the energy in a strong magnetic field, and the energy forms an image released by the spinning nuclei

Murine – Pertaining to rats and mice.

Neovascularization – The growth of minute new blood vessels in a new location, such as out from the retina in diabetic eye diseases.

Nephropathy – *See:* Diabetic Nephropathy.

Neuropathy – *See:* Diabetic Neuropathy.

Neurotrophic factors – Substances that promote nerve health, such as basic fibroblast growth factor (BFGF), ciliary neurotrophic factor (CNTF), and nerve growth factor (NGF), which may promote regeneration of nerve tissue, including in the retina.

NHLBI – National Heart, Lung, and Blood Institute.

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases.

NIDDM – *See:* Type 2 Diabetes.

Nitrates – Salts of nitrous acid that include amyl, ethyl, potassium, and sodium nitrate. Amyl nitrate is an example of a medicine to dilate blood vessels and to control spasms.

Nitrosamines – Compounds resulting from the reaction of nitrates with substances normally found in the body; may cause cancer.

NMR – Nuclear Magnetic Resonance *See:* Magnetic Resonance Imaging

Non-Insulin-Dependent Diabetes Mellitus (NIDDM) – Former term for Type 2 Diabetes.

Nuclear Transcriptional Control Factors – *See:* Transcription.

Ocular Coherence Tomography – An X-ray technique that makes a detailed cross section of the structure of eye tissue at a predetermined depth.

OGTT – *See:* Oral Glucose Tolerance Test.

Open Loop System – Mechanical insulin delivery system controlled by the patient that does not contain a glucose sensor and does not respond automatically to blood glucose level. See: Insulin Pump.

Oral Glucose Tolerance Test (OGTT) – A test to measure the level of plasma glucose at 1 hour, 2 and 3 hours after ingestion of 75g of glucose (glucose challenge). Diabetes and IGT are diagnosed by changes in these glucose levels.

Oral Hypoglycemic Agents – Class of drugs that are taken by mouth and are used to lower blood glucose levels by stimulating the pancreas to release more insulin, increasing tissue glucose uptake, decreasing glucose production by the liver, or inhibiting glucose absorption.

Oxidation – The process by which the oxygen content of molecules is increased, changing their chemical structure.

Oxidative Stress – Damage due to the accumulation of toxic end-products resulting from oxidation in cells and tissues. This process has been implicated in diabetic complications as well as in atherosclerosis and cancer.

Pathogenesis – The processes which occur in the development of a disease.

PCR – *See:* Polymerase Chain Reaction

Periodontitis – Inflammation of the tissue that surrounds the teeth, gums, and/or the jaw bone.

Peripheral Neuropathy – Nerve disease that causes pain and sensory loss, usually affecting the feet and lower extremities; can lead to foot ulcers and even to amputation, especially when accompanied by impaired circulation.

Peripheral Vascular Disease (PVD) – Disease in the large blood vessels of the limbs that is caused by blocked vessels and impaired circulation. PVD is characterized by aching pain in the arms, legs and feet and by foot sores that heal slowly. PVD can contribute to foot and other amputations, especially when co-occurring with peripheral nerve damage (neuropathy).

PET Scan – *See:* Positron Emission Tomography

Phagocyte – A white blood cell that ingests and destroys other cells or foreign matter. In Type 1 diabetes, phagocytes and T cells attack and inflame the islets of Langerhans, as part of an autoimmune process that ultimately destroys the insulin-producing beta cells.

Phenotypic – Having to do with the characteristics of an individual (or group) that can be seen and that result from the interaction of genetic and environmental factors.

Phosphorylation – The metabolic process of introducing a phosphate group into an organic molecule; important in diabetes because it is involved in the breakdown of glucose, action of insulin, cell signalling and other processes.

Pima Indians – A Native American tribe in Arizona with an extremely high rate of diabetes mellitus (i.e., 50 percent). The natural history of diabetes in this tribe is being documented in longitudinal epidemiological studies.

PKC – *See:* Protein Kinase C

Plasmin – An enzyme that dissolves the protein (fibrin), especially small fibrous clots in the blood.

Platelets – The smallest cells in the blood, necessary for blood clotting.

Polymerase Chain Reaction (PCR) – A method that allows for the amplification of very small quantitites of DNA. May be used to detect bacterial or viral nucleic acid in tissue and other substances.

Positron Emission Tomography (PET) – A radiographic technique that through the use of special tracers can show the metabolism of glucose in the body, especially the brain.

PPAR gamma – A nuclear hormone receptor involved in the differentiation and function of fat cells. Certain classes of oral hypoglycemia agents act through this receptor. *See:* Thiazolidinedione

Prosthesis – A device designed to replace a part of the body that is missing (e.g. an artificial limb) or to improve the functioning of a part of the body (e.g., a hearing aid).

Protein Kinase C (PKC) – An enzyme that transfers phosphate groups to specific proteins, changing their biological activity. Several hormones and growth factors activate PKC, including VEGF, which may contribute to diabetic proliferative retinopathy. The development of inhibitors for the different types of PKC may improve treatment for diabetic retinopathy, nephropathy, and cardiac disease.

Proteinuria – Proteins in the urine; measurements of small amounts of protein (microalbuminuria) can detect kidney disease at an early stage. Large amounts of protein reflect late stages of kidney disease.

PTCA – Percutaneous Transluminal Coronary Angioplasty. A technique to treat cardiovascular disease that uses a tiny inflatable balloon attached to the end of a catheter that is inserted through the skin. The balloon is inflated and deflated many times flattening plaque (fatty deposits) against the walls of blood vessels, opening up blockages, and improving blood flow.

RAS – Renin Angiotensin System. Renin — an enzyme made and stored by the kidneys—helps produce angiotensin—a substance in the blood that causes vessels to constrict and thus raises blood pressure.

Receptors – Any one of a group of protein substances found on the surface of or within a cell that bind with specific molecules, antibodies, viruses, or hormones.

Restenosis – Renarrowing of coronary blood vessels that have already been treated (e.g., by angioplasty).

Retinopathy – *See:* Diabetic Retinopathy

Retrovirus – A virus that converts its ribonucleic acid (RNA) into deoxyribonucleic acid (DNA), causing a cell to produce more of the virus. The human immunodeficiency virus (HIV) is a retrovirus.

SES – Socioeconomic status.

Sorbitol – A sugar alcohol which may be produced by aldose reductase, an enzyme that converts glucose to sorbitol, and may contribute to tissue damage in the eyes, kidneys, and nerves.

Sulfonylureas – A class of orally active hypoglycemic drugs commonly used to treat Type 2 diabetes by promoting increased insulin secretion by the pancreas.

Syndrome X – Accelerated atherosclerosis resulting from a combination of several disorders and diseases, including insulin resistance, hyperinsulinemia, hypertension, hyperglycemia, dyslipidemia and impaired glucose tolerance or Type 2 diabetes. Also called the Metabolic Syndrome.

Telemedicine – The provision of consultant services by off-site physicians to health care professionals on the scene; for example, by closed-circuit television.

Thiazolidinedione drugs – A class of insulin sensitizers that improve the body's use of insulin by acting on PPAR gamma.

Tomography – A technique of X-ray photography by which a single plane is pictured without the outlines of the structure of other planes.

Transcription factors – Proteins localized to the nucleus of cells that regulate the expression of genes and control cell growth and function.

Transgenic – Pertaining to the experimental insertion of a segment of DNA from one genome onto the DNA of a different genome. This technique is used to make genetically-modified mice.

Triglyceride – A type of lipid that circulates in the blood. High levels of triglycerides may be associated with atherosclerosis in diabetes. Because insulin is needed to remove triglycerides from the blood, people with diabetes, have elevated levels of triglycerides in their blood and are at increased risk for vascular disease.

Type 1 Diabetes – A condition in which the pancreas makes little or no insulin because the beta cells have been destroyed by an autoimmune response. Because the body is thus unable to use glucose for energy, insulin must be replaced through injection or another mechanism such as an insulin pump. Previously referred to as Insulin-Dependent Diabetes Mellitus (IDDM) and juvenile-onset diabetes.

Type 2 Diabetes – The most common form of diabetes, which results from insulin resistance and abnormal insulin action. About 90-95 percent of the people with diabetes have Type 2 diabetes, which is associated with obesity and controlled with diet, exercise, and/or medication including oral hypoglycemic agents and insulin. Previously referred to as Non-insulin-Dependent Diabetes Mellitus (NIDDM) and adult onset diabetes.

Uncoupling Proteins – Molecules that influence energy expenditure and body weight in humans.

Vascular Endothelial Growth Factor (VEGF) – A molecule that stimulates new blood vessel growth. It may play a role in proliferative diabetic retinopathy and macular edema. VEGF may play a beneficial role in stimulating vessel growth in persons with peripheral vascular disease (PVD).

VEGF – *See:* Vascular Endothelial Growth Factor

Vitrectomy – A surgical procedure in which the gel found behind the lens of the eye is removed because it contains blood and scar tissue that blocks sight. The cloudy gel is replaced with a clear fluid.

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