Conquering

DIABETES

Highlights of Program Efforts, Research Advances and Opportunities

A Scientific Progress Report
on the Diabetes Research
Working Group's Strategic Plan

2002

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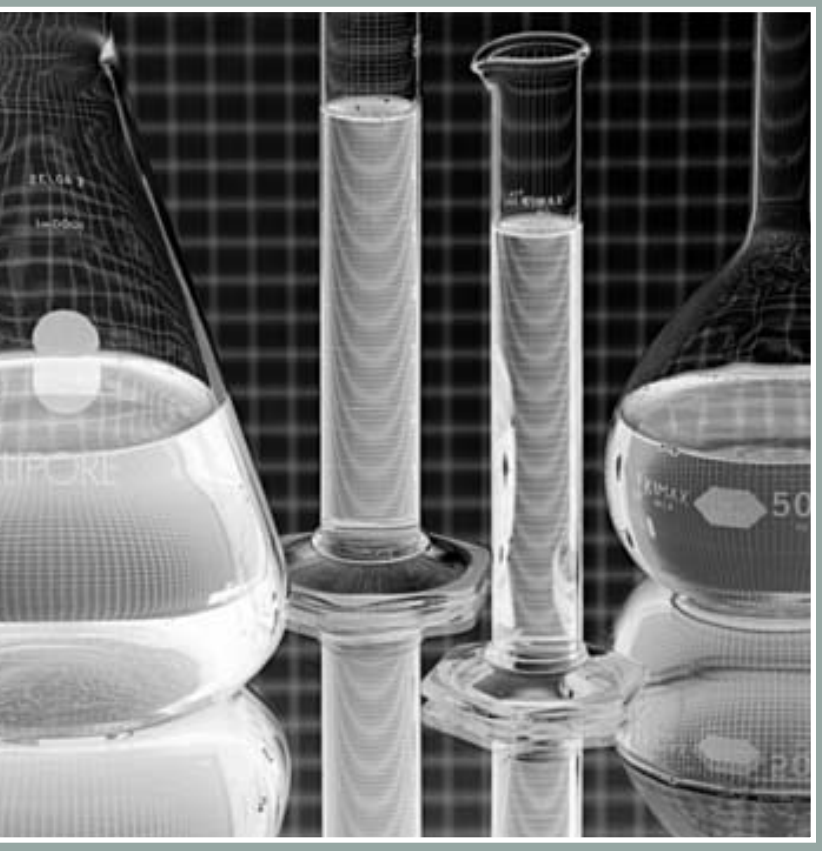

Photo: Richard T. Nowitz, for NIDDK.

The Nature and Impact of Diabetes

Diabetes mellitus afflicts an estimated 17 million people in the U.S. and is the sixth leading cause of death. The disease lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two- to four-fold, and is the main cause of kidney failure, lower limb amputations, and adult-onset blindness[1]. About 5 to 10 percent of people with diagnosed diabetes suffer from type 1 diabetes, an autoimmune disease in which the body's immune system mistakenly destroys its own insulin-producing beta cells, which are found in clusters called islets within the pancreas. Type 2 diabetes accounts for up to 95 percent of diabetes cases and affects about eight percent of the U.S. population aged 18 and older. It is strongly associated with obesity; more than 80 percent of people with type 2 diabetes are overweight or obese. The increase in overweight and obesity is thought to be largely responsible for the 49 percent increase in the number of adults with diabetes in the U.S. between 1990 and 2000[2]. Type 2 diabetes is also associated with aging, affecting 20 percent of Americans over 65 years of age. Other important risk factors include physical inactivity, family history of diabetes, history of diabetes during pregnancy (known as gestational diabetes), and racial or ethnic background other than Caucasian[1].

Rates of diabetes are expected to rise substantially as the U.S. population ages and becomes increasingly overweight, sedentary, and racially and ethnically diverse. In addition to the burden on those affected and their families, the projected increase in diabetes will also have major consequences for health care costs and the economy. In addition to the estimated 17 million Americans who have diabetes, another 16 million have "pre-diabetes," in which blood glucose levels are higher than normal but not yet as high as in diabetes[1]. Pre-diabetes is itself associated with an increased risk of cardiovascular disease and with a high rate of progression to diabetes over a five to ten year interval. Yet, new research has shown that we can turn back the clock, and dramatically reduce the development of type 2 diabetes in those at highest risk through changes in lifestyle or medication.

[1] National Diabetes Statistics. Available at: www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#

[2] Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, and Koplan JP.
The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001; 286: 1195-1200.

Recent Success and Future Promise of Diabetes Research

NIH-supported research has vastly expanded our understanding of how diabetes and its complications develop. This new knowledge has important implications for prevention and therapy. At the same time, clinical trials have demonstrated that dramatic improvements in outcomes are possible for people with diabetes, in particular reductions in the development or progression of complications. While recent years have seen substantial improvements in therapy for diabetes, much remains to be achieved.

- In type 1 diabetes, researchers can now identify those at highest risk before the onset of disease. One family of immune response genes accounts for almost half of the genetic risk for developing type 1 diabetes. The presence of antibodies directed against insulin-producing cells in the pancreas constitutes a second important risk factor signaling that the autoimmune process has begun. Although type 1 diabetes often manifests clinically with life-threatening metabolic abnormalities, we now know from careful observation of individuals at high risk, that insulin production is often lost gradually over time. This loss can be detected prior to the onset of clinical disease. These findings create tremendous opportunities to identify environmental triggers of disease in those at high genetic risk and to test promising new interventions to modulate autoimmunity and prevent onset of type 1 diabetes. New research consortia are pursuing these key opportunities.

- In type 2 diabetes, researchers have identified two key factors that are critical to the development of the disease. First, the body develops resistance to the action of insulin in the muscle, fat, liver and other tissues, which is strongly associated with overweight and inactivity. Next, the beta cells in the pancreas, which initially compensate for this insulin resistance with increased insulin production, become overwhelmed. Ultimately, beta cell failure precipitates the onset of diabetes. These insights have already borne fruit in the successful Diabetes Prevention Program (DPP), which showed that lifestyle change or medication to reduce insulin resistance could dramatically reduce the development of diabetes. Already, new classes of insulin-sensitizing drugs have greatly improved therapy for type 2 diabetes and are under study for its prevention. Further molecular understanding of the multiple steps in insulin action and the mechanisms by which metabolic changes damage the beta cell will identify new molecular targets and give rise to new therapies for prevention and treatment of diabetes.

- The dramatic rise in type 2 diabetes in the U.S. is largely a consequence of the ongoing increase in overweight and obesity, which in turn is due to: (1) unlimited availability of food; (2) an environment that promotes consumption of a high calorie diet; and (3) an increasingly sedentary lifestyle. Yet, even in this current environment, the DPP showed that Americans of diverse racial and ethnic groups, both genders, and many ages could achieve lifestyle change sufficient to prevent or delay type 2 diabetes. This trial was based on a strong foundation of behavioral research, which rigorously examined approaches to achieve and maintain weight loss. The success of the DPP provides an impetus for further research to develop weight loss methods that are more cost effective and can be sustained over longer time intervals.

- Current guidelines for control of glucose levels, blood pressure and LDL cholesterol in patients with diabetes reflect information developed in carefully designed, well-controlled clinical trials. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed the importance of strict blood glucose control in delaying diabetic complications in types 1 and 2 diabetes, respectively. Clinical trials have also demonstrated that rigorous blood pressure and lipid control prevent cardiovascular complications, that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers slow the progression of kidney disease, and that laser therapy of leaky blood vessels in diabetic eye disease preserves vision. However, important questions remain to be answered about the optimal management of diabetes. Among the most pressing issues to be addressed through clinical trials are: the value of weight loss in preventing complications once type 2 diabetes has developed; the risks and benefits of even more rigorous control of glucose and blood pressure in people with diabetes; optimal targets for blood pressure control in type 1 diabetes; the benefits of reducing triglyceride and/or increasing HDL cholesterol levels in type 2 diabetes; and the relative advantages of the multiple classes of medications now available to control blood glucose and blood pressure.

- Improved therapy of diabetes has led to measurable improvements in patient outcomes. For example, death rates 10 to 20 years after diagnosis of type 1 diabetes fell from 8.4 percent in those diagnosed between 1965 and 1969 to 3.5 percent in those diagnosed between 1975 and 1979[3]. Recent evidence has shown that improved glucose control continues to yield dramatic reductions in the risk of eye, kidney, and nerve complications of diabetes. Follow-up of participants in the DCCT shows that major benefits persist at least seven years beyond the period in which improved therapy was provided. Yet, with the tools currently available, even the most highly motivated and trained patients often cannot achieve the levels of glucose control that are proven to reduce the risk of complications. Recent exciting success with islet transplantation underscores the critical importance of research to expand availability of islets for transplantation and to develop improved methods of immune suppression or tolerance. Also urgently needed are new methods for assessing and monitoring glucose control, new forms of insulin and methods for its delivery, and new classes of medicines for treating high blood glucose levels.

[3] Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, and Orchard TJ. Mortality trends in type 1 diabetes. *Diabetes Care.* 2001;24: 823-827.

- Scientists are unraveling the molecular mechanisms by which elevated glucose levels damage blood vessels and the tissues and organs that are affected by diabetes. Already, classes of medications that alter production or action of a key signaling molecule involved in regulation of blood pressure have been shown to block progression of the kidney disease of diabetes. A novel pharmacologic agent under development for diabetic eye and nerve disease targets a signaling molecule shown to play an important role in mediating glucose toxicity. This promising medication has slowed development of eye and nerve disease in animal models of diabetes and is now moving into clinical trials. Further delineation of the cell signals involved in glucose toxicity is a key step toward defining additional molecular targets for drug development, which can lead to new medicines to block diabetes complications.

The Challenge of Diabetes in the 21st Century

Despite all the advances in knowledge and progress in therapy, diabetes poses a greater challenge than ever. Fueled by the upsurge in obesity, diabetes rates continue to rise. After increasing by 49 percent between 1990 and 2000[2], diabetes prevalence is expected to increase by another 165 percent by the year 2050[4].

Especially alarming are the increasing reports of type 2 diabetes in children and adolescents. This disease, once found almost exclusively in adults, is now affecting the next generation of Americans and is disproportionately affecting minority youth. These reports are of particular concern for several reasons. First, the onset and severity of complications correlate with duration of diabetes; thus, those with early disease onset are at greater jeopardy with respect to complications. Second, maternal diabetes during pregnancy — either type 2 diabetes with onset before pregnancy or gestational diabetes developing during pregnancy — confers an increased risk of diabetes in the offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could fuel a vicious cycle of ever-growing rates of diabetes. Third, diabetes often becomes more difficult to control over time. With longer duration of disease, health care providers may find it increasingly difficult to strictly control a patient's blood sugar and thus prevent or delay the onset of complications. Moreover, if current trends continue unabated, we may be seeing just the tip of the iceberg with respect to the future public health burden of diabetes on our society.

With current U.S. direct and indirect health costs of diabetes already conservatively estimated at $98 billion annually[1], the implications of these trends for future health care expenditures are staggering. The challenges posed by diabetes in the 21st century demand a clear but flexible research agenda to maximize our prospects of preventing, more effectively treating, and curing the disease.

[4] Boyle JP, Honeycutt AA, Venkat Narayan KM, et al. Projection of diabetes burden through 2050. *Diabetes Care*. 2001;11: 1936-1940.

Influence of the DRWG Strategic Plan as a Scientific Guidepost for the NIH Diabetes Research Agenda

In framing a cogent and productive research agenda in diabetes, the NIH relies on a broad consultative process that incorporates the scientific advice and recommendations of external experts.

The research agenda is continually being refined through workshops and conferences targeting specific aspects of diabetes, advice from the National Advisory Councils of each Institute and Center, and interactions with voluntary organizations such as the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA). The Diabetes Mellitus Interagency Coordinating Committee (DMICC) plays a key and vital role in facilitating diabetes research and fostering coordination among the Institutes and Centers at NIH, as well as with the Centers for Disease Control and Prevention (CDC) and other agencies.

The current NIH diabetes research agenda has been significantly shaped by the five-year Strategic Plan issued in 1999 by the congressionally established Diabetes Research Working Group (DRWG)[5]. The DRWG was an independent, non-government panel of 12 scientific and 4 lay experts in diabetes, who formulated their plan based on a full year of deliberations and with advice from a wide range of scientific leaders in the diabetes community. The NIH diabetes research agenda reflects the five priority areas of extraordinary research opportunity identified by the DRWG: (1) genetics of diabetes; (2) autoimmunity and the beta cell; (3) cell signaling and cell regulation; (4) obesity: a problem in its own right and a risk factor for diabetes; and (5) clinical research and clinical trials of critical importance. The DRWG also made recommendations regarding special needs for special problems, such as diabetes complications and populations disproportionately affected by diabetes, and for resource and infrastructural needs for more effective support of diabetes research.

The NIH has mobilized all available resources to pursue the major scientific recommendations of the DRWG's Strategic Plan. This trans-NIH effort, led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and coordinated through the DMICC, encompasses studies supported by most NIH Institutes and Centers. It also involves collaboration with the CDC for diabetes surveillance, education, and other public health efforts. Since issuance of the DRWG's Strategic Plan, the NIH has vigorously sought to apply the latest technologies available to researchers to answer critical questions, to exploit emerging scientific opportunities, to foster translation of basic research into clinical application, and to ensure that all Americans benefit from new research discoveries.

This Executive Summary highlights key steps the NIH has taken to implement scientific recommendations of the DRWG Strategic Plan and identifies key research advances and opportunities that have occurred since the DRWG issued its plan.

[5] A Report of the Congressionally-Established Diabetes Research Working Group. *Conquering Diabetes: A Strategic Plan for the 21st Century.* 1999. Available at: www.niddk.nih.gov/federal/dwg/fr.pdf.

Five Areas of Extraordinary Opportunity: Program Efforts and Achievements

GENETICS

In both type 1 and type 2 diabetes, multiple genetic and environmental factors interact, leading to the development of disease. Identifying the relevant genes is a major challenge because of the number of genes involved and differences in their relative contribution to the disease process, especially among subsets of the population. Illustrating this complexity is the identification, subsequent to issuance of the DRWG report, of several genes that appear to be important for development of type 2 diabetes only in selected racial and ethnic groups. This complexity means that large sets of samples need to be collected from many different groups to identify the important genetic determinants of diabetes. Although this is a difficult task, identifying diabetes susceptibility genes is critical to our understanding of the causes and mechanisms of diabetes. It is also a key step in revealing new targets for drug development, and has the potential to greatly improve early identification and prevention efforts in those at increased risk.

Critical to meeting the challenge of identifying common variants of the genes that contribute to diabetes is the formation of resource-sharing consortia that provide access to expertise, information, technologies, and patient populations beyond the reach of individual research groups.

The newly established International Type 1 Diabetes Genetics Consortium will analyze combined results of genome-wide scans from U.S., European, and Australian family collections, and collect and analyze additional patient samples as required. A related initiative will expand current efforts to establish a central repository of genetic data relevant to type 1 diabetes and provide an Internet-based information service for researchers through the International Histocompatibility Working Group. The International Type 2 Diabetes Genetic Linkage Consortium, representing 24 scientific groups from five countries, is combining data from multiple genome scans to locate susceptibility genes. A consortium is being formed to search for genes involved in obesity, a serious risk factor for type 2 diabetes. Several efforts are under way to identify genes that contribute to susceptibility to the complications of diabetes, including the Family Investigation of Nephropathy and Diabetes (FIND) and the collection of genetic samples from participants in the DCCT and their family members. These consortia benefit from their ability to collect many samples from a variety of populations and to analyze the data with the most up-to-date methods.

These efforts to find genes involved in diabetes and its complications are facilitated by more general efforts, including completion of sequencing of the human, mouse, and other model organism genomes. Comparison of genomes of multiple organisms has identified important regulatory sequences whose function will need to be elucidated. The mouse genome sequence is critical not only for understanding the human sequence but also for identifying diabetes and obesity susceptibility alleles in a variety of mouse models, such as the mouse model that spontaneously develops type 1 diabetes, the NOD mouse.

Application of new technologies will enhance the prospects for identifying susceptibility genes for diabetes and its complications. For example, the ability to determine with efficiency which genes are expressed in tissue samples has been greatly aided by one such method: the use of DNA microarrays. Similarly, a new approach called haplotype mapping should improve the efficiency of identifying genetic variations. New methods are needed to analyze large datasets in order to make multiple comparisons. Importantly, NIH-supported studies are helping to clarify the ethical, legal, and social implications of using such genetic information. While costly, efforts to identify the genetic basis of predisposition to diabetes and its complications are essential for two reasons. Identifying the genetic basis of disease is the first step in understanding disease mechanisms and thus generating new approaches for intervention. It also is key to our ability to predict those at risk, and permits the tailoring of prevention and intervention efforts.

AUTOIMMUNITY AND THE BETA CELL

Loss of the insulin-producing beta cells in the islets of the pancreas, or of beta cell function, is the key precipitating factor in both type 1 and type 2 diabetes. Unraveling the mechanisms by which aberrations in the body's immune system lead to the destruction of insulin-producing beta cells in type 1 diabetes will provide the foundation for developing interventions to stop or reverse this process. Similarly, understanding how metabolic changes lead to loss of beta cell function is key to arresting the progressive worsening of blood glucose control, and eventual need for insulin, common in type 2 diabetes. The importance of the beta cell in type 2 diabetes is also underscored by the finding that all five genes identified as causing Maturity Onset Diabetes of the Young—a rare form of type 2 diabetes—are involved in regulating gene expression or insulin secretion in the beta cell. The recently reported success in islet transplantation using the Edmonton protocol has rekindled strong interest in cell therapy to cure type 1 diabetes. The shortage of islets available for transplantation and the need for safe and effective methods to prevent both transplant rejection and autoimmune destruction are the two major challenges that must be overcome before cell therapy for type 1 diabetes can become a reality. Advances in achieving immune tolerance offer hope both for overcoming autoimmunity and enhancing islet and other organ transplantation. Expanded efforts to develop novel sources of islets and beta cells will address the shortage of islets for transplantation. Insights from cell and developmental biology are being applied to the study of the beta cell in an intense effort to find methods to produce sufficient quantities of islets for transplantation or to regenerate islets once the autoimmune process is curtailed. The goal is to learn how to grow adequate numbers of progenitor cells that can be differentiated into islets useful for cell therapy.

The NIH is supporting a coordinated effort to apply the newest technologies to understanding how the beta cell develops and functions. As part of this effort, the NIH will provide researchers with a comprehensive set of tools to investigate the beta cell, including genetic probes called cDNAs, expressed proteins, antibodies to cell-surface proteins, and informatics support. Another component of the initiative aims to develop methods for noninvasive imaging of beta cell mass, function, and inflammation. This would facilitate evaluation of measures to preserve beta cell function and to prevent type 1 diabetes. Identification of the components of the beta cell that elicit autoimmunity has been of critical importance in developing methods to identify those at risk for type 1

diabetes and is the basis for some immune interventions. Discovery of immune targets on the beta cell is of vital importance due to its potential significance for new therapeutic development.

Building on the accumulation of fundamental knowledge of the immune system, researchers are now poised to make further inroads into understanding and interdicting the autoimmune disease process in type 1 diabetes, both as a prelude to preventing the disease itself and to preventing recurrent disease after islet transplantation. Tremendous insights are being gained from the study of animal models for type 1 diabetes, such as the NOD mouse and the BB rat. These models have not only facilitated investigations into the underlying cause(s) of disease, but also have revealed potential approaches to prevent or delay disease development. While existing models have played a pivotal role in elucidating mechanisms of type 1 diabetes and testing potential therapies, improved models that more accurately reflect the human disease are of critical importance.

The search for environmental trigger(s), such as infectious agents or dietary factors, that set the autoimmune process in motion is another key challenge with major implications for prevention efforts. Relatively small-scale epidemiologic studies are ongoing in several states in the U.S. In addition, a broader, coordinated epidemiologic effort is being launched. That initiative will include efforts to identify environmental trigger(s) and to characterize the earliest steps in the initiation of the autoimmune process in genetically susceptible individuals. While uncertain of success, this effort has the potential to yield strategies for a "vaccine" for type 1 diabetes and to generate entirely new approaches to prevention.

Identification of the signals that are essential for activation of the immune system has led to development of potential therapeutic agents that interfere with key steps in the process of immune activation. Particularly desirable are highly selective agents that block specific mediators involved in autoimmunity without compromising aspects of immune function that are important for elimination of infectious agents or damaged cells. Already, one such agent, a modified antibody directed at a molecule on the surface of a specific population of immune cells, has shown promise in preserving beta cell function. A small, early trial of this agent in patients studied shortly after the onset of type 1 diabetes will now be expanded into a larger study. Several other promising agents are also entering clinical trials in patients with new-onset type 1 diabetes.

CELL SIGNALING AND CELL REGULATION

Type 2 diabetes is usually preceded by the body's resistance to the action of insulin. This state of "insulin resistance" is marked by reduced uptake of glucose in fat and muscle cells coupled with impaired suppression of glucose production in the liver despite high levels of circulating insulin. Moreover, insulin resistance is associated not only with glucose intolerance and diabetes, but also with abnormalities in lipid levels and in blood vessel function, which are both implicated in cardiovascular disease.

Identifying the molecular basis for insulin action at its target tissues is critical for the development of new therapies, but this is proving challenging. After insulin binds to its cell surface receptor, the insulin-signaling cascade appears to involve

a complex network and sequence of events, rather than a simple, linear pathway. Almost every component of the insulin-signaling network exists in multiple forms (e.g., four subtypes of insulin-receptor substrates), with varying degrees of expression in tissues. This variability makes it a daunting task to attain a complete understanding of insulin action and a precise definition of the primary basis for insulin resistance. Yet, we are already reaping the benefits of the information that has been developed so far. For example, the discovery that a nuclear receptor, the peroxisome proliferator-activated receptor-gamma, is the target of the insulin-sensitizing thiazolidinedione drugs will permit further refinement of this class of drugs. Already, two medicines that are substantially safer than the first drug in this class have been approved for clinical use and many other agents in this drug class are under development. Other recently identified signaling molecules already show promise as the targets for development of improved or completely novel drugs for treatment of type 2 diabetes. As researchers gain new knowledge about how insulin acts and how insulin resistance occurs, they will be positioned both to develop new therapies for type 2 diabetes and to devise strategies for intervening before individuals with insulin resistance develop full-blown diabetes and its attendant complications.

Beyond the challenge of understanding insulin action, similar opportunities exist for understanding the mechanisms underlying the function of other key signaling systems involved in diabetes and diabetes complications. To address this challenge and to complement the genetic approaches previously described, the NIH is initiating new, large-scale efforts to apply cutting edge genomic and proteomic technologies to diabetes. In these Diabetes Genome Anatomy Projects, researchers will employ tools, such as DNA and protein microarrays, to determine how genes and proteins actually function in animal and human tissues; these two approaches constitute the fields of functional genomics and proteomics, respectively. It is critically important to correlate the presence of a gene (genotype) with its actual activity or "expression" in an organism (phenotype). Establishing these correlations will provide researchers with enormous insights into the disease processes underlying diabetes. It will also aid them in developing therapeutic and preventative interventions that are targeted to specific subsets of patients or to subsets of individuals at risk for developing the disease.

Transgenic and gene knockout mouse models represent another powerful approach to dissecting the steps in the insulin-signaling network. By altering the expression of key genes in specific tissues and by creating mice with defects in several key genes through mating of particular transgenic and knockout mice, researchers are defining much more precisely the key disease-determining steps leading to insulin resistance and type 2 diabetes. Tissue-selective knockouts of the insulin receptor, for example, have provided novel insights into the causes of type 2 diabetes, including the demonstration of an important role for the insulin receptor in the beta cell itself. To enable careful analysis of engineered mouse models with sophisticated technology, the NIH has established Mouse Metabolic Phenotyping Centers. While human studies will ultimately be required to define the molecular defects in human type 2 diabetes and to test therapeutic interventions, mouse models offer a powerful and cost-effective approach to drug development efforts.

OBESITY

The dramatic increase in obesity in the U.S. is a harbinger of numerous adverse health outcomes, with type 2 diabetes the most prominent. Obesity, defined as a body mass index (BMI) of 30 or greater[6], confers a five-fold greater risk of diabetes compared to a desirable BMI of less than 25. Yet, according to the CDC, over 60 percent of American adults are overweight or obese. Thirteen percent of American children are seriously overweight, and the numbers are steadily rising[7]. Genetic factors play an important role in susceptibility to obesity and, in rare cases, single-gene defects have been identified as the cause of extreme obesity in humans. In most cases, though, as with type 2 diabetes, obesity is caused by the interplay of multiple susceptibility genes with environmental factors. Reversing the increasing incidence of obesity is a major challenge and opportunity. It is imperative if the nation is to stem the rising tide of type 2 diabetes.

Research on obesity took a major leap forward with the discovery of the obesity *(ob)* gene and its product, leptin. This peptide hormone is secreted by fat cells and has revolutionized our understanding of fat tissue by demonstrating that fat is not merely a static depot of stored calories, but rather an endocrine organ. Leptin signals through receptors in the brain to regulate appetite and metabolism, as well as to influence insulin action in peripheral tissues. Identification of additional factors secreted by fat—such as resistin and adiponectin—has enabled researchers to determine that these factors are also involved in regulating insulin responsiveness by signaling to liver, muscle, and other organs. These findings have provided a mechanistic link between obesity and insulin resistance. The paradox of insulin resistance and type 2 diabetes in patients lacking fat, known as lipoatrophic diabetes, may now be explained by a deficiency of fat-secreted factors such as leptin and adiponectin. The profound implications of such mechanistic understandings for improved therapy are illustrated by a recent clinical trial of leptin treatment in patients with lipoatrophic diabetes. In this rare and extraordinarily severe form of diabetes, leptin therapy yielded dramatic improvements in diabetes control, lowered extremely high levels of blood lipids, and diminished stores of fat in inappropriate tissues such as muscle and liver. Major progress in understanding regulation of food intake, energy expenditure, and fat storage will also derive from the identification of specific neuroendocrine regulatory pathways within the hypothalamus and other brain regions with key roles in regulating energy balance. Researchers are pursuing a detailed elucidation of the key signaling molecules involved in appetite regulation in this critical region of the brain. In addition to leptin and other hormones produced in fat cells that act on the brain to suppress appetite, the stomach and intestine have recently been shown to produce a hormone, ghrelin, that is secreted before mealtimes and stimulates appetite. It now appears that weight loss after bariatric surgery ("stomach stapling" or intestinal bypass) may in part be due to decreased production of this newly described appetite stimulator. The NIH vigorously supports the identification of the factors and pathways that are responsible for regulating appetite, metabolism, and energy storage, recognizing that they offer rich prospects for drug development. The explosion of information newly emerging from this NIH-supported research is actively being pursued by the pharmaceutical industry for drug development to prevent weight gain in

[6] Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Available at: www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm.

[7] The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity. Available at: www.surgeongeneral.gov/topics/obesity/calltoaction/toc.htm.

susceptible individuals, to facilitate weight loss, and to blunt obesity-induced insulin resistance.

The recent dramatic increase in obesity is clearly due to environmental and behavioral changes rather than genetic ones. Lifestyle change is essential if we are to stem the tide of type 2 diabetes. Although many environmental factors have been cited as contributing to obesity, there have been few controlled studies showing that changes in these factors will prevent weight gain. Factors to be rigorously examined through research on environmental approaches to obesity prevention include: the impact of economic factors, such as food pricing, and neighborhood characteristics, such as venues for safe exercise, on food choices and physical activity; the efficacy of establishing environments supportive of physical activity or healthy food choices; and the implementation of culturally appropriate interventions in collaboration with community-based organizations to enhance physical activity and healthy food choices. The success of the DPP was predicated on behavioral research that established methods to foster and maintain lifestyle change. This multicenter clinical trial in 3,234 overweight people with pre-diabetes provided definitive evidence that modest improvements in diet and physical activity, resulting in a 5 to 7 percent weight loss, can reduce the risk of developing type 2 diabetes by 58 percent in individuals at high risk for the disease. Now that the dramatic benefits of such change have been demonstrated, the challenge is to find cost-effective ways to translate the results of this trial to the millions of Americans with pre-diabetes. We must redouble our efforts to develop cost-effective approaches that require fewer health care resources and can be implemented in community, worksite, and school-based programs.

CLINICAL RESEARCH AND CLINICAL TRIALS OF CRITICAL IMPORTANCE

The overarching goals of the NIH diabetes research program are to develop and validate effective new measures for prevention and treatment of diabetes and to bring evidence-based treatment and prevention into clinical practice as rapidly as possible. To that end, the NIH facilitates therapeutic application of new findings from basic research by fostering collaboration among basic and clinical researchers focused on bringing new therapies from bench to bedside. For example, the Type 1 Diabetes TrialNet, in partnership with the Immune Tolerance Network, is bringing together leading immunologists and clinical investigators to test promising new approaches to prevent type 1 diabetes or to preserve beta cell function in people with recent onset of type 1 diabetes. Different challenges arise at the other end of the clinical research spectrum, when clinical trials such as the DPP, the DCCT, or the UKPDS yield strong proof of clinical benefit. Then, research is needed to address barriers to implementation of effective therapy and methods to ensure that all Americans who can benefit do so.

Despite all that we have learned about improved management of diabetes and prevention of complications through clinical trials, and the guidelines for clinical management that have been developed as a result, every day health care providers and patients must make important health care decisions that are not informed by clinical trial results. For example, now that there are multiple classes of medicines available to treat type 2 diabetes, there is a need for studies that explore optimal initial therapy of type 2 diabetes and how to identify patients for whom specific therapies may be particularly advan-

tageous. Many questions remain about optimal practices for blood pressure and lipid management in diabetes. Moreover, clinical trials addressing optimal management to prevent cardiovascular disease generally involve patients with the more prevalent type 2 diabetes and questions remain about the applicability of their results to type 1 diabetes. Important information about cardiovascular disease in type 1 diabetes is expected to emerge from an ongoing study of former participants in the DCCT. However, many important questions remain to be explored regarding optimal management of both types of diabetes. Careful and painstaking decisions about prioritization of important clinical research questions are required to wisely invest the limited research funds available.

In the area of cardiovascular disease, for which individuals with diabetes are at two- to four-fold increased risk, the NIH has recently initiated several major new trials to answer some of the most pressing questions. The Look AHEAD (Action for Health in Diabetes) Study will answer two major questions. First, do interventions designed to produce sustained weight loss in obese people with type 2 diabetes improve health, particularly with respect to cardiovascular outcomes? Second, how do the benefits and risks of these interventions compare with the benefits and risks of treating obesity-related conditions without weight loss? The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is comparing cardiovascular outcomes of therapy based on: current evidence-based guidelines for treatment of blood glucose, blood pressure and lipids in people with type 2 diabetes, *versus* the effects of even more intensive management. The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics (BARI 2D) is comparing the effects of insulin-providing and insulin-sensitizing strategies and examines the benefits of revascularization in people with type 2 diabetes and coronary artery disease. The critical public health importance of the questions being addressed justifies the substantial resources required to provide definitive answers.

These large multi-center clinical studies may require hundreds or thousands of patients to address endpoints such as mortality, and development of serious chronic complications. Smaller, less costly clinical studies are also important for development of new approaches to therapy or prevention. For example, pilot studies are useful for exploring new approaches to islet transplantation or evaluating new devices for monitoring blood glucose and preventing hypoglycemia. Ideally, small pilot studies can be used to gather preliminary information before investing substantial resources on larger clinical trials. Pilot studies may require validated surrogate markers that accurately predict clinical events important in diabetes. Such markers are urgently needed for studies on the chronic complications of diabetes. With surrogate markers, promising new agents for prevention or delay of complications could be initially evaluated in studies requiring the participation of fewer patients and having shorter durations of follow-up. Lower study costs would allow more potential therapies to be tested. The development and validation of surrogate markers are thus of major importance to development of new therapies.

Special Needs for Special Problems

COMPLICATIONS

It is the vascular complications of diabetes that are responsible for the increased risk of heart disease, stroke, blindness, kidney failure, amputation, and premature death associated with diabetes. The DRWG's Strategic Plan identified obstacles to developing new therapies to prevent or delay complications, including the need for animal models and surrogate markers — both vital for testing new therapies. Moreover, relatively few Americans with diabetes are achieving the recommended targets for control of glucose, blood pressure, and lipids that are proven to prevent complications. In large part this is because, while the tools available for control of diabetes have improved dramatically, control remains remarkably burdensome. Complicated regimens for management of diabetes can require as many as ten medications, frequent monitoring of blood glucose levels, and careful attention to diet and physical activity. Even the most well-informed and motivated patients have difficulty meeting these goals and many patients must also contend with economic hardships and other life stresses. Furthermore, intensive management carries with it the risk of life-threatening hypoglycemia; particularly at risk are young children and some individuals who lose the ability to recognize and respond to symptoms of low blood glucose. The NIH is utilizing all available resources to address these barriers through research and outreach efforts. Nonetheless, prevention of complications is a formidable challenge and will require a sustained and substantial research effort.

SPECIAL POPULATIONS

The prevalence of type 2 diabetes varies widely among racial and ethnic groups in the U.S. Compared to Caucasians, African American adults are twice as likely to develop type 2 diabetes, and Hispanic adults are 1.9 times more likely to develop the disease[1]. Native Americans, such as Arizona's Pima Indians, have the highest prevalence of type 2 diabetes: 50 percent of Pima adults age 35 and older have the disease[8]. Over 25 percent of all adults with diabetes in the U.S. are minorities. Expanded research efforts are needed to develop culturally sensitive and effective programs for prevention and control of type 2 diabetes in underserved and minority populations.

Although there are no national data on diabetes in children, diabetes clinics in several locations report an alarming increase in type 2 diabetes in young people, especially minority adolescents, and it is thought that most children with type 2 diabetes are members of minority groups. The NIH is collaborating with the CDC on a population-based registry that will identify all children with diabetes in six regions of the country and help researchers understand trends in disease development. The NIH is also developing a clinical trial to determine how best to treat type 2 diabetes in children as well as a multi-center primary prevention trial with a focus on cost effective, school-based interventions with the potential for broad application. However, it will not be a simple matter to overcome the environmental changes underlying the new epidemic of childhood type 2 diabetes. In the past decade, type 2 diabetes, formerly called "adult onset diabetes," has changed from a disease of older adults to one that now affects Americans of all ages.

[8] *Diabetes in America, 2nd Edition.* Available at: www.niddk.nih.gov/health/diabetes/dia/contents.htm.

EDUCATION AND OUTREACH

Research advances must be put into practice if health outcomes are to improve, and the NIH is keenly aware of its responsibility to ensure that all Americans benefit from its research efforts. In addition to the National Diabetes Education Program (NDEP)—a joint effort of the NIH, the CDC, and 200 public and private organizations—the NIH supports multiple programs for information dissemination and/or public education programs that are relevant to diabetes. These include the National High Blood Pressure Education Program (NHBPEP), the National Cholesterol Education Program (NCEP), the Obesity Education Initiative, the National Eye Health Education Program (NEHEP), and the newly launched National Kidney Disease Education Program (NKDEP). The NIH also funds a statutory National Diabetes Information Clearinghouse (NDIC), and a Weight Control Information Network (WIN).

These programs seek to educate the public and health care providers about diabetes, with an emphasis on dissemination of findings from clinical trials. For example, while the NDEP was begun to disseminate the results of the landmark DCCT and encourage improved blood glucose control, it has subsequently expanded to promote results of other trials. Its new "Be Smart About Your Heart: Control the ABC's of Diabetes" campaign promotes control of hemoglobin A1c (measure of blood glucose control), blood pressure, and cholesterol. This effort complements those of the NHBPEP and NCEP, which are also promoting evidenced-based targets for blood pressure and cholesterol in people with diabetes. The NDEP is now developing a campaign translating the impressive results of the DPP to the general population, with culturally sensitive public health messages and intervention strategies. It will focus on the message that prevention of type 2 diabetes is possible, and that modest improvements in diet and physical activity yield major benefits. If the important results of this clinical trial can be successfully translated, there is real hope of reversing the alarming rise in the incidence of diabetes over the past decade.

Moving Forward on the Research Continuum

The enduring cornerstone of NIH support of fundamental research is the conviction that clarifying the molecular underpinnings of disease will yield improved diagnosis, prevention, and treatment. That expectation applies even more vividly today as the pace of discovery accelerates, fueled by knowledge of the human genome sequence, insights gained from animal models, and powerful research tools such as bioinformatics and microarray technology. Eighty years after the discovery of insulin, it is a realistic hope that major clinical advances such as new drugs, immunomodulatory agents, and cell replacement therapies will flow from discoveries that were unimagined just a few decades ago.

CAPITALIZING ON RESEARCH OPPORTUNITIES

The goals reflected in the DRWG Strategic Plan's five extraordinary opportunities continue to inform and drive the NIH diabetes research agenda. In the three years since this Strategic Plan was issued, the NIH's strong commitment has yielded significant progress in each of the five areas and these opportunities have become increasingly compelling. As a result of NIH investments guided by the Strategic Plan, scientists are now poised:

- To find additional genes that predispose people to developing type 1 and type 2 diabetes and the devastating complications that occur with both forms of the disease;
- To exploit new knowledge of autoimmunity and the beta cell to develop and test strategies for cell replacement therapy and for immune modulation to halt the immune destruction of insulin-producing beta cells;
- To delineate cell signaling pathways for insulin and for other molecules that regulate metabolism and body weight and thus bring to light new molecular targets for drug development to combat insulin resistance;
- To discover the molecular links between obesity, insulin resistance, and type 2 diabetes as a foundation for effective treatments and prevention strategies; and
- To translate the results of basic and behavioral research into new therapies and prevention strategies through clinical studies and large-scale clinical trials.

To achieve these goals, the NIH is pursuing a wide range of emerging opportunities, many of which have been made possible through the five-year doubling of the NIH budget (over the period 1999–2002 and proposed for 2003), and the special funding for type 1 diabetes research. Remarkable opportunities have emerged as a result of the advent of new technologies, such as the ability to efficiently analyze the expression of genes through the use of microarrays. Other opportunities have been made possible by the formation of research consortia that coalesce research talent and resources and thus enhance the scope and power of research investigations. These consortia are especially important in the field of genetics, where large amounts of data from multiple sources must be carefully sifted in order to pinpoint causative diabetes genes. Thus, the diabetes research community now has access to the tools of modern molecular biology, coupled with the types of large-scale scientific infrastructure that can efficiently deploy them. With these resources, diabetes researchers are poised, as never before, to capitalize on recent scientific advances, to sustain current research momentum, and to move the diabetes research agenda rapidly forward. Leaders in the diabetes community have identified the following major opportunities that have emerged or become more significant since the issuance of the DRWG's 1999 Strategic Plan:

OPPORTUNITIES FOR SPEEDING BIOLOGIC DISCOVERIES THROUGH THE USE OF CONSORTIA AND OTHER COLLABORATIONS

- To broaden the search for diabetes genes and maximize the effective use of collective genetic data and resources made possible through the establishment of the International Type 1 Diabetes Genetics Consortium and the International Type 2 Diabetes Genetic Linkage Analysis Consortium. It is imperative to consolidate and analyze combined data from different studies and to collect additional data, especially from disproportionately affected minority populations.

- To facilitate interdisciplinary approaches that will advance understanding of pancreatic islet development and function. By delineating pathways of islet and beta cell signaling, by investigating beta cell development and regeneration, by exploring new ways of producing islet cell types, and by generating important research tools and making them available to the diabetes research community, the new Beta Cell Biology Consortium and the Comprehensive Programs in Beta Cell Biology offer enormous opportunities to advance research in both type 1 and type 2 diabetes.

- To catalogue genes and map the complex network of cellular interactions in tissues relevant to diabetes and its complications through the use of Diabetes Genome Anatomy Projects.

- To unite immunologists and experts in clinical diabetes research to develop and test new approaches to immunomodulation to prevent type 1 diabetes or preserve beta cell function through the Type 1 Diabetes TrialNet, the Immune Tolerance Network, and other collaborating consortia.

- To forge collaborations between behavioral scientists, clinical diabetes researchers, public health experts, and community groups for the purpose of developing effective behavioral interventions for combating the epidemic of obesity that has been linked to an increase in the prevalence of type 2 diabetes.

- To promote collaborations between surgeons specializing in bariatric surgery and clinical diabetologists, in order to investigate surgical interventions to prevent obesity, to collect outcome data on this procedure, and to study the mechanisms underlying the effects of this procedure.

OPPORTUNITIES TO APPLY REVOLUTIONARY TECHNOLOGIES TO MEET THE CHALLENGES OF DIABETES RESEARCH

- To apply new genetic tools, including a new database of single nucleotide polymorphisms (SNPs) and the novel and efficient approach of haplotype mapping, to facilitate genome-wide searches for genes that influence diabetes and its complications.

- To employ advanced imaging and other technologies to detect diabetes and its complications in the earliest stages, and to develop and validate bioimaging approaches for use as surrogate outcomes in clinical trials.

- To employ gene therapy techniques to develop new approaches to modulation of the immune system, or to delay or prevent diabetes complications.

- To use genomic and proteomic tools to identify signatures of the different subtypes of type 2 diabetes as a means of tailoring intervention and prevention strategies.

- To use state-of-the-art assays for genotyping, pathogen discovery, and identification of the earliest manifestations of autoimmunity to pinpoint the trigger(s) of the immune-mediated destruction of insulin-producing beta cells in newborns at high genetic risk for type 1 diabetes.

- To use new approaches to metabolic and physiologic characterization, along with sophisticated genetic and genomic tools, to help unravel the web of genetic and environmental interactions underlying the current epidemic of obesity and type 2 diabetes.

- To exploit the new sciences of computational biology and bioinformatics, which enable researchers to extend the scope of data analysis beyond individual investigations to the global evaluation of data from many studies. In addition, opportunities exist to apply the systems biology approach in order to facilitate the integration of genetic and genomic data with clinical and other biological data.

- To capitalize on the value of animal models for furthering diabetes research. New technologies allow generation of mice specifically designed to answer research questions. Additional opportunities are presented by the establishment of repositories for mouse models of diabetes and its complications, as well as phenotyping centers for careful analysis of mouse models.

- To generate resources such as repositories, which will enhance the accessibility of researchers to important biologic samples and associated clinical information from well-characterized populations, including DNA samples, cell lines, and other types of biological samples.

OPPORTUNITIES TO MOVE DIABETES RESEARCH FROM THE BENCH TO THE BEDSIDE

- To support intensive research on the burgeoning field of stem cell biology. Resulting insights could lead to new approaches to creating an unlimited supply of cells for islet transplantation or other cell therapies, as well as to discovering ways to regenerate lost beta cell function.

- To develop and perfect ways to modulate the immune response. New methods of immunomodulation offer hope of arresting the autoimmune disease process in type 1 diabetes. Methods of re-educating the immune system to accept transplanted tissue (tolerance induction) could help islet transplant recipients avoid a lifetime regimen of harsh immunosuppressive drugs.

- To bolster research on substances that promote or impede the formation of blood vessels (angiogenesis)—a process critically important in the complications of diabetes.

- To exploit the potential of drug development based on new knowledge about the role of fat cell hormones, neuropeptides, and gastrointestinal tract hormones in signaling pathways that link obesity and diabetes.

- To complement large, multi-center clinical trials having long-term outcomes with other types of clinical studies, including small ancillary studies, studies using surrogate markers of health status, and studies that make use of repositories of tissue samples and data.

- To integrate new technological approaches into the design and conduct of clinical trials, including: the development and use of more effective and less invasive methods for measuring and monitoring blood glucose levels; methods for imaging both the integrity and function of the insulin-producing beta cell and inappropriate immune cell infiltration of the pancreas or the vascular system; approaches to assessing T cell function in studies of immune system modulation; and use of genomic and/or proteomic technology to monitor responses to interventions.

- To identify and exploit targets for drug development for prevention of complications based on molecular understanding of the pathways involved in glucose toxicity.

- To find ways to promote the rapid translation of fundamental discoveries in the laboratory into clinical testing. Opportunities exist to apply to diabetes research models that have been successful in other diseases, such as the National Cancer Institute's program for Rapid Access To Intervention Drugs (RAID).

OPPORTUNITIES FOR CLINICAL AND MEDICAL PROGRESS IN THE FIGHT AGAINST DIABETES

- To initiate studies that shed light on the disproportionate burden diabetes places on minority populations and that identify ways to reduce this health disparity.

- To obtain maximum benefit from large multi-center clinical trials by supporting follow-up cohort studies to address long term effects of interventions. For example, the landmark findings of the DPP, that individuals at risk of developing type 2 diabetes could prevent or delay disease onset through modest improvements in diet and exercise, will generate a follow-up study to assess the durability and effect of DPP interventions on cardiovascular disease.

- To initiate new clinical trials to inform medical decision-making in areas of critical importance for diabetes management.

- To ensure that people benefit from what scientists have discovered about the treatment and prevention of diabetes. As additional, important findings emerge from clinical research, there are increased opportunities to enhance public education programs to convey these messages to health care providers, patients with diabetes, and people at risk. For minority populations who are disproportionately affected by diabetes and obesity, opportunities exist to frame effective, culturally sensitive health messages.

OPPORTUNITIES TO SUSTAIN AND EXPAND THE CADRE OF SCIENTISTS WHO WILL MOVE DIABETES RESEARCH FORWARD

- To find innovative ways to attract and retain exceptionally talented and dedicated researchers, who will focus their intellects on the challenges and opportunities in diabetes research. Efforts should include attracting new investigators to diabetes research and encouraging those with expertise or technologies relevant to diabetes to apply their skills to diabetes research.

- To foster collaboration among scientists from disparate fields to promote multidisciplinary research and to bring together basic and clinical researchers to help translate basic discoveries into pre-clinical research or clinical trials.

- To help fundamental scientists expand their understanding of diabetes and to foster research training and career development of endocrinologists and diabetologists in order to effect the translation of laboratory discoveries to rapid clinical testing.

- To increase the number of pediatric diabetologists trained to conduct basic and clinical diabetes research.

THE PAST, PRESENT, AND FUTURE OF DIABETES RESEARCH

In the three years since the DRWG issued its Strategic Plan, the NIH has made significant progress in understanding and combating diabetes. Scientific advances have opened up promising avenues of investigation, including cell-based therapeutic approaches for type 1 diabetes and effective primary prevention strategies for type 2 diabetes. New knowledge is continuously accumulating about genetic, metabolic, and environmental factors central to the onset and progression of all forms of diabetes and its complications. In response to the scientific recommendations of the DRWG and to opportunities that have subsequently arisen, the NIH has initiated a wide range of new programs since 1999. Many of these new initiatives involve consortia and other large-scale scientific endeavors that pool investigative talent and pair this talent with collective research resources ranging from patient populations to mouse models to genetic data. At the same time, the fruits of the biotechnology revolution have never been greater—with a virtual cornucopia of sophisticated analytic techniques and information now available to biomedical researchers. The convergence of these events has generated ever more compelling opportunities to conquer diabetes. The stage is now set for the diabetes research community to capitalize on these opportunities as it continues to pursue the broad goals outlined by the Diabetes Research Working Group.