Prospects for Research in Diabetes Mellitus

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Diabetes mellitus is the sixth leading cause of death in the United States, and morbidities resulting from diabetes-related complications such as retinopathy, kidney disease, and limb amputation cause a huge burden to the national health care system. Identification of the genetic components of type 1 and type 2 diabetes is the most important area of research because elucidation of the diabetes genes will influence all efforts toward a mechanistic understanding of the disease, its complications, and its treatment, cure, and prevention. Also, the link between obesity and type 2 diabetes mandates a redoubled effort to understand the genetic and behavioral contributions to obesity.

Diabetes mellitus affects between 6% and 7% of the US population equating to about 16 million people. It is projected that there will be 800,000 new cases per year and a total of 23 million affected people within 10 years. Diabetes occurs in all populations and age groups but is increasing in prevalence in the elderly and in blacks, Hispanics, Native Americans, and Asians. Although deaths due to cancer, stroke, and cardiovascular disease are declining, the death rates due to diabetes have increased by about 30% in the past 12 years (Figure 1), and life expectancy for persons with diabetes is approximately 15 years less than in those who do not have diabetes. Diabetes is the sixth leading cause of death in the United States and accounted for more than 193,000 deaths in the US in 1997. However, this is an underestimate because diabetes contributes substantially to many deaths that are ultimately ascribed to other causes, such as cardiovascular disease.

Due to its complications, diabetes causes an enormous national burden of morbidity. For example, diabetic retinopathy is the leading cause of blindness in adults aged 20 through 74 years, and diabetic kidney disease accounts for 40% of all new cases of end-stage renal disease. Diabetes is the leading cause for amputation of limbs in the country. Heart disease and strokes occur 2 to 4 times more frequently in adults with diabetes than in those who are healthy. Diabetes causes special problems during pregnancy, and the rate of congenital malformations can be 5 times higher in the offspring of women with diabetes. In aggregate diabetes mellitus costs $105 billion annually and involves 1 of every 10 US health care dollars and 1 of every 4 Medicare dollars. Clinical and Research Advances

Diabetes mellitus refers to a number of disorders that share the cardinal characteristic feature of elevated blood glucose levels. The 2 most common general categories of this disease are termed type 1 and type 2 diabetes. Research has enormously increased our understanding of type 1 and type 2 diabetes, but much more remains to be done.

Documentation that elevated blood glucose levels are a direct cause of long-term complications of diabetes has been a major accomplishment. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) both showed that control of blood glucose levels as close to normal as possible prevents and retards development of diabetic retinopathy, nephropathy, neuropathy, and macrovascular disease.

The fact that each increment of improved control of blood glucose levels reduces complications has focused clinical and research efforts to elucidate disease mechanisms and to design new therapies. This insight coincided with the development of home glucose monitoring systems that make it possible to measure blood glucose levels throughout the day and coincided with the availability of new insulin preparations; insulin delivery devices, such as insulin pumps; and oral antidiabetic agents.

Likewise, fetal malformations and perinatal morbidity are now known to be due to elevated maternal glucose levels, and blood glucose control before and after conception can reduce these risks to normal. As a consequence, intensive efforts are now being made to diagnose and control glucose levels in
pregnant women with diabetes. Although these advances have certainly helped improve the lives of patients, they do not provide an answer because most patients with diabetes do not obtain adequate blood glucose control.

Type 1 diabetes accounts for 5% to 10% of diabetes, usually occurs in children or young adults, and was formerly termed insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. This disease is caused by autoimmune destruction of the pancreatic β cells that secrete insulin. The process involves a smoldering destructive process that can persist for several years and ultimately leads to failure of insulin secretion. This autoimmune process is due to genetic and environmental factors, and many genes contribute to the pathogenesis. During the preclinical phase, a variety of autoimmune antibodies directed against β-cell antigens serve as markers for the prediabetic state, allowing for early detection and possible prevention strategies. Patients with type 1 diabetes require insulin therapy for survival, but blood glucose is still difficult to control, and most patients ultimately develop devastating complications of this disease. The present need is for improved means of treating type 1 diabetes until it is practical to prevent its development.

New methods to achieve tight glucose control are needed that are practical and can be administered to all persons with type 1 diabetes, including methods of insulin delivery, better forms of insulin, and practical, affordable methods of noninvasive self monitoring that can be coupled to patient-specific insulin treatment regimens. Cure of diabetes will require permanent replacement of lost β-cell function, which could involve islet cell transplantation, regeneration of β cells, or development of immortalized insulin secreting cell line. The ultimate aim in preventing disease onset will require a major multidisciplinary effort to identify the genes that predispose to type 1 diabetes and to identify the interacting environmental factors that trigger the disease. A thorough understanding of the cellular and molecular causes of the autoimmune destructive process will also be necessary.

Type 2 diabetes accounts for 90% to 95% of all patients with diabetes and is increasing in prevalence, especially in minority populations. Type 2 diabetes is a heterogeneous, polygenic disorder, and the responsible genes have been identified in selected subtypes of this disease. Multiple genes exist, and more than 1 gene is likely to be involved in an individual patient. Some of the known environmental factors are obesity, a sedentary lifestyle, and aging. Obesity probably is the major environmental factor contributing to the increasing incidence of type 2 diabetes, and some of the hormonal, genetic, and environmental factors that predispose to obesity have been identified.

Insulin resistance is a characteristic metabolic defect in the great majority of patients with type 2 diabetes, and this defect can be demonstrated in the pre-diabetic state many years prior to the development of hyperglycemia. As a consequence of insulin resistance, the β cell produces increased amounts of insulin, and, if sufficient, the compensatory hyperinsulinemia maintains glucose levels within the normal range (Figure 2). In those individuals destined to develop diabetes, β-cell function eventually declines, and relative insulin insufficiency occurs. Thus, insulin resistance combined with β-cell failure leads to the decompensated hyperglycemic diabetic state.

A number of the molecular steps in the insulin action cascade have been identified, and several components of the β-cell insulin secretion pathway have been elucidated. Researchers are beginning to understand the complex heterogeneous, genetic determinants of type 2 diabetes susceptibility. Efforts to understand genetic variation, gene expression profiling, and the interaction between genetic factors and environmental triggers must be intensified. This information will reveal new targets for pharmacologic intervention. Researchers also must continue work to understand the basic mechanisms that cause insulin resistance and limitation of compensatory insulin secretion. Truly effective...
The new knowledge and technology are available for application to diabetes research, and a rigorous, multidisciplinary, well-funded effort is needed to achieve these goals. Increased funding for individual scientists should be a cornerstone of this approach, but new enhancements to the scientific infrastructure are equally important. A multidisciplinary approach will require coordination of many centers and different disciplines to identify the diabetes genes. This will necessitate the establishment and availability of repositories of DNA samples from phenotypically well-characterized diabetes patients spanning a number of ethnic groups. A coordinating and planning agency should be established to bring together and integrate the efforts of the National Institutes of Health and of nongovernment organizations such as the American Diabetes Association and Juvenile Diabetes Foundation International so that information is broadly disseminated as rapidly as possible. Once the diabetes genes are identified, it will be necessary to deal with the ethical, legal, and social issues involved in the availability of such information.

Since type 1 diabetes is an autoimmune disease, the mechanisms underlying this process must be thoroughly understood. Expanded efforts are needed to identify the environmental triggers and how they interact with the genetic predispositions. The basic cell biology of the immune destructive process must be solved, and the specific β-cell autoantigens must be identified. Hopefully this will lead to development of highly specific immunosuppressive agents that will produce relatively few adverse effects.

Insulin resistance and impaired insulin secretion are the key metabolic defects in type 2 diabetes. Increased efforts are necessary to dissect the molecular components involved in insulin signaling, insulin secretion, and β-cell growth and development. This research coupled with the efforts to identify the diabetes genes, will provide a mechanistic understanding of the specific defects in these pathways in type 2 diabetes, which should...
lead to the development of more specific, and more effective, pharmaceutical agents directed against defined molecular targets.

It is also essential to redouble efforts to understand the genetic and behavioral contributions to obesity. Excess body weight is a widespread and increasing problem in the United States and contributes to the high and increasing incidence of type 2 diabetes. A thorough understanding of basic mechanisms will enhance development of new methods of prevention and treatment. To facilitate the country’s ability to make rapid progress in these areas of scientific opportunity, the Diabetes Research Working Group has recommended changes in the infrastructure. These include the following:

1. Create new mechanisms and modify existing programs to maximize recruitment, training, and career development of diabetes investigators.
2. Substantially strengthen and enhance National Institutes of Health–sponsored diabetes centers by increasing the funding levels and expanding their mission.
3. Create new regional centers for advanced technologies required for metabolic and functional imaging studies, such as nuclear magnetic resonance and positron emission tomography.
4. Enhance efforts to develop and characterize small- and large-animal models of type 1 and type 2 diabetes and establish regional centers for these animal models.
5. Expand procurement of human tissues, DNA samples, and organs for diabetes research.

**Forecast of Major Research Advances**

If aggressive efforts across the broad front of diabetes research are accompanied by increased research funding in the areas of exceptional opportunity, the future does indeed look promising and it is likely that major accomplishments over the next 25 years will change the picture of diabetes prevention, treatment, and cure.

For patients with type 1 diabetes, the procedures of cadaveric islet cell transplants will be largely perfected so that this can be performed either without the need for immunosuppression or with the use of specific highly focused immunosuppressive agents that will produce minimal adverse effects. However, that supply of freshly isolated human islets will be insufficient to provide transplants for all patients with type 1 diabetes. Replenishable sources of β cells for replacement could be derived from xenografts, possibly from genetically modified animals, or by creating a relatively inexhaustible, functional insulin secreting β-cell line. Such cell lines will be developed by learning to expand and grow large amounts of β cells from progenitor cells or by genetically engineering immortalized β cells.

Identification of the genes that predispose to type 1 diabetes will make it possible to identify individuals destined to develop the disease. Coupled with the elucidation of the basic immunologic

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**Research Opportunities and Forecast: Diabetes Mellitus**

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mechanisms that cause autoimmune β-cell destruction and the development of specific targeted treatments to interrupt this process, the prevention of type 1 diabetes will become a reality. On the way to reaching these goals, substantial advances in glucose monitoring and insulin delivery mechanisms, which will lead to patient-specific treatment algorithms, will improve the outlook for patients with type 1 diabetes.

The genes responsible for the predisposition to type 2 diabetes and the mechanisms by which environmental factors bring about this predisposition will be identified. In parallel with this genetic information, identification of the cellular defects responsible for insulin resistance and impaired insulin secretion in type 2 diabetes will lead to development of new drugs that will be specific for defined molecular targets and that will be relatively free of unwanted adverse effects. This should include new ways to prevent or treat obesity. Once the predisposing diabetes genes are identified, it will be a straightforward matter to genotype individuals for diabetes susceptibility. The availability of new pharmaceutical treatments, together with the ability to predict diabetes susceptibility will provide a sound basis for early intervention and will lead to the prevention of type 2 diabetes in susceptible individuals. If an appropriate health care delivery system can disseminate these new therapeutic modalities to all diabetic patients, then control or prevention of diabetes will be a reality. In this event, the burden of diabetes complications will gradually diminish and ultimately disappear. Advances in methods of gene therapy may make genetic interventions a reality for this disorder.

The surest way to treat diabetic complications is to prevent them by glycemic control in patients with established diabetes or preferably by prevention of diabetes. While moving toward these goals over the next 25 years, it is critical to improve treatment and prevention of the microvascular and macrovascular complications of diabetes because these complications account for the excessive morbidity and mortality associated with this disease.

All of these predictions are fully achievable if adequate resources (financial and human) are applied to the field of diabetes. With appropriate effort, future generations could be freed from the scourge of diabetes.

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