



# Advances and Emerging Opportunities in Diabetes Research:

A STRATEGIC PLANNING REPORT OF THE  
DIABETES MELLITUS INTERAGENCY  
COORDINATING COMMITTEE

FEBRUARY 2011



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Having volunteered for the Diabetes Prevention Program (DPP) clinical trial and now participating in the DPP Outcomes Study, **Irish Stovall** says she would advise anyone interested in his or her health to take part in studies like these. Although she was at high risk for type 2 diabetes at the time she enrolled in the DPP, she says “I didn’t have diabetes at that time and, thanks to the study, I still don’t.”



Two of **Toni and Rob Berg’s** three children have type 1 diabetes, which made the family eligible to participate in the Type 1 Diabetes Genetics Consortium study. Toni encourages other families to participate in type 1 diabetes clinical research studies, saying, “The larger the pool of people they have to study, the more they can learn about combating the disease.”



**Dan Lamb** enrolled in the Diabetes Control and Complications Trial (DCCT) clinical trial in 1983, and participates in the Epidemiology of Diabetes Interventions and Complications (EDIC) study to this day. He says, “Had I not been part of the DCCT, I probably would not have paid attention to my diabetes as closely as I have, nor possess the same understanding of the disease and its complications that I have now. The study has been a huge part of my life, and has contributed greatly to my success as a person with diabetes.”



The NIH-supported Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational, or pregnancy-related, diabetes. This research has increased understanding of GDM and risk for subsequent type 2 diabetes. **Modesta Solórzano**

participated in the study, and says, “It’s been very helpful to me and my family.” (“Ha sido muy útil para mí y para mi familia.”)



# **SUMMARY AND FUTURE RESEARCH DIRECTIONS**





## SUMMARY AND FUTURE RESEARCH DIRECTIONS

Diabetes is a common, chronic, and costly disease that is threatening the health of generations of people in the United States and around the world. Support for biomedical research efforts that can lead to prevention, treatment, and possibly even cures for diabetes is an integral part of Federal efforts to improve public health and reduce the cost of health care in the Nation. Developed through a dynamic

planning process involving multiple stakeholders in the diabetes research enterprise, *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee (DMICC)* is meant to serve as a guidepost for these efforts over the next decade.

### BURDEN OF DIABETES IN THE UNITED STATES

Diabetes affects an estimated 25.8 million people of all ages, racial and ethnic groups, and socioeconomic status in the United States. Another 79 million Americans are estimated to be at greatly increased risk of developing diabetes in the next several years. One in three American children born in 2000 are predicted to develop diabetes at some point in their lives. Diabetes lowers life expectancy by up to 15 years and is the seventh leading cause of death. People with diabetes have a higher rate of cardiovascular disease than those without diabetes and are at increased risk for kidney failure, lower limb amputation, and blindness. Total costs of diabetes, including medical care, disability, and premature death, reached an estimated \$174 billion in 2007 in the United States.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a

hormone that helps the body absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels that, over time, damages organ systems and leads to debilitating complications.

Type 1 diabetes affects approximately 5 percent of individuals with diagnosed diabetes. While it most often develops during childhood, the disease can strike at any age. Type 1 diabetes results from an autoimmune process in which a person's immune system launches a misguided attack that destroys the insulin-producing beta cells of the pancreas. People with type 1 diabetes require daily insulin administration to regulate their blood glucose as close to normal levels as possible.

Type 2 diabetes accounts for 90 to 95 percent of diagnosed diabetes cases in the United States. Type 2

diabetes is strongly associated with obesity and aging and occurs at higher rates in certain minority populations. In type 2 diabetes, the body becomes resistant to insulin signaling, which can eventually result in impaired insulin production. Treatment approaches for type 2 diabetes include diet, exercise, orally administered medications, and, in some cases, injected insulin. Type 2 diabetes is increasingly being diagnosed in younger individuals, particularly in minority youth, adding to the enormous public health burden of diabetes. Research led by the National Institutes of Health (NIH) has shown that type 2 diabetes can be prevented or delayed in adults at high risk through modest weight loss with diet and exercise or through use of the diabetes medication metformin. Other forms of diabetes include gestational diabetes, which affects at least 7 percent and possibly as many

as 18 percent of pregnancies in the United States, and diabetes that results from rare genetic conditions, surgery, medications, infections, pancreatic disease, and other illnesses.

Diabetes eventually damages nearly every organ system in the body. People with diabetes are at increased risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurologic problems, limb amputation, chronic wounds and skin ulcers, gum disease, sleep apnea, erectile dysfunction, and bladder, gastrointestinal and pregnancy-related problems. NIH-supported research has shown that intensive control of blood glucose can prevent or delay the development of many of these complications.

## NIH SUPPORT FOR DIABETES RESEARCH

### NIH Funding and Coordination of Diabetes Research

The NIH is the primary source of Federal support for diabetes research. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is the lead NIH component for supporting diabetes research. Because it is a systemic disease, diabetes and its complications are also addressed by many other NIH Institutes and Centers, as well as the Centers for Disease Control and Prevention (CDC), the Veterans Health Administration (VHA), and other Federal agencies.

Diabetes research funded by the NIH is supported by regularly appropriated funds that the U.S. Department of Health and Human Services (HHS) receives through the Labor-HHS-Education Appropriations Committees. It is also supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which is a special appropriation to the Secretary of HHS to pursue research on type 1 diabetes and its complications. Total NIH funding for diabetes research in fiscal year 2009 was \$1.03 billion. Support from the American Reinvestment and Recovery Act also enabled the NIH to spend an additional \$121 million for diabetes research during that fiscal year.

The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) coordinates the Federal investment in diabetes programs to improve the health of Americans. Chaired by the NIDDK, the DMICC provides a forum for communication and collaboration to promote diabetes research across the Federal government. Components of the NIH and other government agencies that support diabetes-related activities are represented on the DMICC. Through the DMICC, government agencies identify ways to work together and build on each other's expertise and resources. This approach reduces duplication of Federal diabetes activities and stimulates collaboration.

NIH-led planning processes for diabetes research also involve voluntary agencies, such as the American Diabetes Association and the Juvenile Diabetes Research Foundation International, in an attempt to avoid duplication and enhance efficiency in providing resources. In addition, the NIH seeks input from the external scientific community, through venues such as scientific meetings and conferences, to inform its planning efforts.

## Current Efforts and Recent Advances in NIH-Supported Diabetes Research

The NIH vigorously pursues and supports diabetes research across a broad range of disciplines and research areas, from basic to clinical to translational research, including genetics, genomics, proteomics, immunology, developmental biology, obesity, behavioral studies, cell biology, imaging, stem cell research, bioengineering, glucose sensing, and insulin delivery. Most fundamental research is accomplished through investigator-initiated regular research grants. The NIH also leads a variety of major efforts to support and extend the investigator-initiated research portfolio and foster innovative approaches. Multiple consortia,

clinical research networks, and clinical trials have been established to pursue specific goals for bench-to-bedside translational research and testing of prevention and intervention strategies. Shared research resources, including diabetes centers and central repositories, support a broad array of diabetes investigations. Many of these efforts were undertaken in response to research priorities identified in the 1999 strategic plan, *Conquering Diabetes: A Strategic Plan for the 21st Century*, the strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research*, and the 2006 report, *Advances and Emerging Opportunities for Type 1 Diabetes Research: A Strategic Plan*.

Over the past decade, NIH support for biomedical research has led to major discoveries benefiting people with or at risk for diabetes. Progress has been made on multiple fronts, including better understanding the causes of diabetes and the molecular pathways that are affected by the disease, as well as developing new approaches to prevent or treat diabetes in individuals and within communities. Examples of diabetes research advances include:

### *Reducing Diabetes Complications*

- ▶ **Diabetes complications can be reduced by over half with intensive glycemic control early in the course of the disease.**
- ▶ **Benefits of intensive control of glucose endure with reduced complications long after the period of good control. Continuous glucose monitors have been developed that improve glycemic control and reduce hypoglycemia in adults with type 1 diabetes.**

- Weight loss in people with type 2 diabetes results in improved control of glucose, blood pressure, and cholesterol with less use of medications.
- Good control of blood glucose, blood pressure, and lipids can reduce by half cardiovascular death in diabetes.
- Some people with diabetes and cardiovascular disease can do as well with medical management as with revascularization procedures.
- Intensive control of blood glucose during pregnancy can reduce birth defects, birth injuries, and the need for Cesarean section.
- Diabetes self-management training and improved health care delivery practices can improve diabetes outcomes.

#### *Preventing or Delaying Type 2 Diabetes*

- Risk of developing type 2 diabetes can be dramatically reduced in people at high risk for developing the disease through diet and exercise to promote modest weight loss or by treatment with the diabetes drug metformin. Benefits persist for at least 10 years.
- Women with gestational diabetes can lower their substantial risk for developing type 2 diabetes postpartum either through diet and exercise to induce weight loss or with diabetes medication.

- Affordable community-based approaches to lifestyle change for type 2 diabetes prevention have been developed.

#### *Restoring Insulin Production and Reversing Diabetes*

- Insulin independence has been achieved in people receiving islet transplants as treatment for severe type 1 diabetes. Residual insulin secretion has been found in many people with type 1 diabetes at diagnosis and beyond, spurring research on ways to preserve or expand this capacity.
- Insulin-producing cells have been generated in the laboratory from non-beta-cell sources, providing proof-of-principle for regenerative approaches to beta cell replacement.

#### *Discovering New Therapeutic Pathways*

- Many new susceptibility genes for type 1 and type 2 diabetes have been identified.
- New genetic tests can identify infants with neonatal diabetes—a rare form of diabetes—who may be treatable with oral drugs (sulfonylureas) rather than insulin injections.
- New treatments for type 2 diabetes are available based on discoveries about how gastrointestinal tract hormones influence insulin secretion.

- **Gastric bypass and other bariatric surgeries to treat extreme obesity may resolve type 2 diabetes independently of weight loss, opening the door to discovery and to new therapeutic options for some individuals.**
- **Metabolically active brown fat has been detected in adults and may prove therapeutically useful in obesity prevention or treatment.**

## FUTURE DIRECTIONS FOR DIABETES RESEARCH

### Identification of High-Priority Research Goals

The promise of prevention, treatment, and cure for diabetes can only be realized through the vigorous support of scientific research efforts ranging from fundamental discovery research to clinical trials and translation of scientific findings into clinical practice. This Strategic Plan addresses important opportunities in 10 major diabetes research areas, as well as issues related to resource and infrastructure development for diabetes research.

The Strategic Plan was developed in a collaborative planning process led by the DMICC Chair and involving input from multiple stakeholders (see sidebar, “Process for the Development of the Strategic Planning Report of the DMICC”). Focused working groups of Federal staff, external scientists, and representatives from diabetes-related voluntary organizations identified forward-

looking, high-priority goals for research on diabetes and its complications within each research area. Broad input on Strategic Plan goals was also sought through a public comment period prior to publication. The major research areas and future directions for research, which are not listed in priority order, are summarized below\*.

### Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications

Type 1 diabetes, type 2 diabetes, obesity, and their complications have strong genetic bases that interact with environmental and behavioral factors. Identifying those factors that influence disease susceptibility is key to development of strategies for prevention and treatment of diabetes. Goals in this area span the following research needs and opportunities:

\* These summaries synthesize multiple research goals/suggested strategies to achieve goals, and are organized by subheadings used in the Future Directions section of the Strategic Plan chapters.

- **Genes and Pathways** – Understanding how candidate susceptibility genes contribute to a person’s risk and elucidating the interactions among those genes at a cellular level will help researchers discover common pathways of risk.
- **Detection of Rare Variants** – Fully characterizing susceptibility genes could be accelerated by sequencing the DNA of tens of thousands of individuals with type 1 diabetes, type 2 diabetes, or obesity to uncover the entire range of variations in DNA, from common to rare, that are linked to risk.
- **Gene-Environment Interactions** – Research on how genes or variants associated with risk interact with potential environmental factors, such as viral infections, nutrition, or gut microbes, to trigger disease will provide important insights to understand the development of diabetes, obesity, and complications.
- **Genetics and Health Disparities** – It will be especially important to identify genetic and environmental risk factors in high-risk, racial and ethnic minority populations in the United States that might explain the different rates of diabetes, obesity, and complications in those groups.
- **Epigenetic Contributions to Risk** – Environmental exposures may directly influence diabetes risk in part by interacting with the genome to alter how certain genes are expressed. Studying these interactions could explain how gestational diabetes contributes to the risk of diabetes and obesity in the offspring, or how a period of good glucose control early in the course of diabetes could reduce the risk of complications even years later.
- **Translation of Genetic Research from Bench to Bedside** – Increased knowledge of the causative factors of diabetes, obesity, and their complications

will open up new avenues of translational research to inform the design of innovative clinical trials for prevention or early intervention.

- **Pharmacogenetics/Pharmacogenomics** – Identifying genes and variants that influence positive and negative responses to diabetes therapies will open up prospects for personalized medicine, in which the use of specific pharmacologic agents can be tailored to individuals or populations based on their genetic profiles.

Research goals in this area of the Strategic Plan will guide future efforts to identify the genetic and other causes of diabetes, obesity, and their complications and use that knowledge to develop more effective strategies for prediction and intervention.

### Type 1 Diabetes and Autoimmunity

Preventing the onset of type 1 diabetes will require detailed knowledge of the causes and mechanisms of the autoimmune process that destroys pancreatic beta cells. Research goals in this area are aimed at understanding the immune system attack that destroys the pancreatic beta cells in people with type 1 diabetes and developing new therapeutic strategies to prevent or halt this harmful immune response. They focus on addressing gaps and opportunities in five key aspects of type 1 diabetes research:

- **Human Type 1 Diabetes Trials (Prevention/Reversal/Transplantation)** – Expanded clinical trials to test therapies to prevent or reverse type 1 diabetes would require recruitment of adequate numbers of well-characterized individuals who are at risk of or newly-diagnosed with the disease. Trials should capitalize on advances in new biomarkers of disease and improved models to

predict who is most likely to develop type 1 diabetes, in order to test promising prevention strategies.

- **Natural History and Pathogenesis of Human Type 1 Diabetes** – The development of prediction models and prevention strategies would be advanced by research to identify environmental factors that trigger autoimmunity in genetically susceptible individuals and that affect the rate of disease progression. Defining the natural history of type 1 diabetes would help researchers design intervention therapies that target specific stages in the progression of islet destruction.
- **Animal Models/Translational Efforts from Pathogenesis to Therapy** – New animal models of type 1 diabetes have opened up new research opportunities for therapeutic development and biomarker identification. The development of a mouse model with higher fidelity to human disease or computer-based models of type 1 diabetes would provide critical tools for research on disease progression and prevention.
- **Beta Cell Function in Type 1 Diabetes: Autoimmune Attack and Prospects for Recovery** – Research is needed to detect early signs of beta cell dysfunction, identify genes and mechanisms that protect beta cells from autoimmune destruction, and develop surrogate markers of beta cell recovery so that response to immune therapy can be evaluated.
- **Immune Mechanisms of Pancreatic Pathology** – Defining the roles of immune regulatory cell populations, including B cells, T cells, dendritic cells, and others, will be a key step in understanding the autoimmune destruction processes. Research to distinguish molecular pathways that are important in other autoimmune diseases from those that are unique to type 1 diabetes would inform decisions about whether to

test immune therapies that are in development for other autoimmune diseases in people with type 1 diabetes as well.

Pursuing opportunities outlined in this area of the Strategic Plan, ranging from basic studies to clinical trials, will advance knowledge of autoimmunity in type 1 diabetes and lead to new approaches for disease prevention and treatment.

## The Beta Cell

All major forms of diabetes share a common basis in loss of the insulin-producing pancreatic beta cells. Research on the normal development and function of beta cells will inform efforts to replicate, regenerate, or replace beta cells and restore normal insulin production. Goals in this area are aimed at elucidating the causes of beta cell dysfunction and on strategies to restore or replace insulin production and span the following research needs and opportunities:

- **Integrated Islet Physiology** – Understanding how the human beta cell functions in the context of the pancreatic islet would help scientists design scaffolds and other systems to improve the survival and function of transplanted beta cells and to develop drugs that can restore important signaling pathways within islets in people with type 2 diabetes.
- **Beta Cell Dysfunction and Failure** – Inflammation is now recognized as a factor in beta cell loss in type 2 diabetes as well as in type 1 diabetes. Identifying the signaling pathways involved in chronic islet inflammation could aid in the development of new anti-inflammatory agents to protect beta cells. Research to identify intracellular signaling

pathways that might be manipulated to protect beta cells, including the role of the intrauterine environment on islet development and function, could reveal mechanisms to preserve and restore beta cell mass and function.

- **Prevention and Treatment of Diabetes** – The development and testing of strategies to preserve and restore beta cell mass and/or function in people with pre-diabetes or diabetes are needed. Clinical research in this field would benefit from the identification of biomarkers to detect and monitor type 2 diabetes progression and remission.
- **Cellular Replacement Therapies for Diabetes** – Several lines of research hold promise for replacing beta cells lost in type 1 diabetes, including optimization of techniques for islet transplantation; stimulation of beta cell development from stem cells; reprogramming of non-beta cells into glucose-responsive, insulin-producing cells; and regeneration of beta cells in an individual's pancreas. New animal models will be needed to test potential beta cell replacement therapies.
- **Imaging the Pancreatic Islet** – The development of more accurate and reproducible techniques to image beta cells or islets in a living person would aid research in all areas of beta cell biology.

Collectively, the pursuit of Strategic Plan research goals related to the beta cell has the potential to transform diabetes treatment by advancing understanding of the cell that plays a critical role in all forms of diabetes.

## Type 2 Diabetes As a Multi-Dimensional Disease

In addition to beta cell failure, type 2 diabetes is marked by metabolic abnormalities in multiple organ systems, including muscle, liver, fat, and the brain. A systems biology approach could provide an unprecedented depth of understanding of the disease variability observed in people with type 2 diabetes and help identify pathways of disease development and progression. Research goals in this area integrate many different areas of type 2 diabetes research to achieve a comprehensive portrait of the disease, and address a variety of opportunities:

- **Insights into Gene and Environment Interactions in Type 2 Diabetes** – New tools and technologies are needed to facilitate research on these interactions, which might be mediated by factors such as microRNAs, epigenetic changes, or nutrients and xenobiotics.
- **Metabolic and Hormonal Regulation in Diabetes** – Defining the diverse molecular pathways of metabolic and hormonal regulation in diabetes could point to new therapies.
- **Inflammation and Endoplasmic Reticulum Stress—Impact on Insulin Signaling and Glucose Metabolism** – Research efforts are needed to understand the links between metabolism, chronic low-grade inflammation, and cellular stress and to identify potential targets for therapeutic intervention.
- **Mitochondrial Metabolism** – Studying the role of mitochondrial dysfunction in diabetes could clarify the relationship of obesity and overnutrition with the development of insulin resistance.



- **Nutrient Role in Glucose Homeostasis — Mechanisms of Overnutrition-Driven Tissue Dysfunction** – Identifying factors that regulate fat storage and mechanisms by which excess nutrient load damages organs would likewise help researchers understand the link between obesity and type 2 diabetes.
- **New Players in Control of Metabolism: Role of the Brain and the Gastrointestinal Tract** – A systems biology approach to research on diabetes should consider the role of the brain and the gastrointestinal tract, including the gut flora, in whole-body energy balance.
- **Defining the Subtypes of Type 2 Diabetes by Molecular Phenotyping** – A systems biology approach could be applied to characterizing in detail a large cohort of individuals across the range of normal metabolism to diabetes, to define subtypes of type 2 diabetes that might respond differently to specific prevention and intervention strategies.
- **Obesity, Inflammation, Insulin Resistance, and Macrophage Function** – Macrophages and inflammation appear to be activated by excess nutrients and subsequently play a role in eliciting insulin resistance as a consequence of obesity. Research is needed to clarify the mechanisms and outcomes of tissue-specific inflammation in obesity.
- **Mechanisms Underlying Energy Homeostasis: Impact on Obesity Pathogenesis and Treatment** – Untangling the complex networks of hormonal and neural mechanisms that control energy balance in the body could point to new therapeutic targets to prevent or treat obesity.
- **Central Nervous System Control of Thermogenesis** – New technologies are needed to facilitate study of the complex control of energy expenditure and how it contributes to weight maintenance and obesity in people.
- **Discovering Genetic and Intrauterine Determinants of Obesity Susceptibility That Predispose to Developing Diabetes** – Research on genetic factors that increase susceptibility to obesity could shed light on the molecular pathways involved in this disease. Likewise, studying the impact of the intrauterine environment on the offspring’s long-term risk of obesity, insulin resistance, and type 2 diabetes could reveal epigenetic modifications that affect the expression of obesity-related genes.
- **Adipose Tissue Biology** – Adipose tissue research is key to the development of treatments for obesity and type 2 diabetes. Understanding the mechanisms that regulate fat cell number, size, distribution, and signaling, and developing new technologies for studying adipose tissues, are urgent research goals.

Research goals identified for this area of the Strategic Plan build on and expand the perspective of diabetes as a disease that affects multiple systems in the body and that varies in both causes and outcomes among individuals.

## Obesity

Obesity is a major risk factor for type 2 diabetes and insulin resistance and is also a problem in people with type 1 diabetes receiving insulin therapy. Stemming the rising tide of type 2 diabetes will require research to understand the causes of obesity and overweight and to develop prevention strategies. Goals in this area are focused on opportunities to expand the understanding of molecular pathways, as well as behavioral, social, and environmental factors, that link obesity and type 2 diabetes:

- **Obesity Prevention and Treatment** – Behavioral strategies are needed to prevent inappropriate weight gain and promote or maintain weight loss in individuals across the lifespan, as well as in communities or large populations. The development and testing of such strategies would be supported by research on the non-biological determinants of obesity and obesity prevention and the use of technologies to tailor the delivery of interventions to individuals.
- **Improving Clinical Investigative Tools** – Progress in obesity research would be facilitated by the development of improved tools for clinical investigation, including advanced instrumentation to measure body composition, energy intake, physical activity, diet composition, and other parameters in a variety of laboratory and clinical settings.

Addressing Strategic Plan goals for obesity research is a critical component of public health efforts to reverse the rising epidemic of type 2 diabetes that is largely driven by the high rates of obesity in the American population.

### Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia

Maintaining blood glucose levels at near-normal levels has multiple long-term benefits for individuals with diabetes, but daily management of the disease is arduous for even the most diligent individuals. New technologies for glucose sensing and insulin delivery are needed that could help all people with diabetes easily and consistently manage their blood glucose at optimal levels and greatly reduce the burden of diabetes treatment. Goals in this area form a multi-pronged approach to meet complex research needs and opportunities in the quest for an artificial pancreas:

- **Glucose Sensors** – The development of a new generation of small, implantable, unobtrusive glucose sensors that report reliable and accurate data on glucose levels and warn of impending hypoglycemia could drastically reduce the number of daily finger sticks that people with diabetes who treat with insulin must endure, and could improve their metabolic control.
- **Algorithm Development-*In Silico*/Simulation Models** – To close the loop between glucose sensing and insulin delivery, glucose sensors will need to be linked to an automated insulin delivery device. Realizing this goal requires research to develop complex computer programs that account for numerous factors, including patient-to-patient variability and changes in a person’s behavior or environment.
- **Insulin—Improving Delivery and Formulation** – Research to develop novel insulin formulations or delivery methods—such as the development of a glucose-sensitive insulin molecule, or systems that integrate insulin pumps with glucose sensors into a single device—could lead to improvements in glucose control for many people with diabetes.
- **Telemedicine** – Telemedicine approaches that apply advances in information and communication technology, such as the Internet, mobile phones, and personal digital assistants, to diabetes management have the potential to improve outcomes, especially in younger age groups that are high users of telecommunication technologies and services.
- **Tissue Engineering for Replacement of Pancreatic Islets** – In addition to research on mechanical devices for diabetes management, bioengineering research to develop new

biomaterials could improve the efficiency and effectiveness of islet transplantation as a means to restore biologic regulation of glucose.

- **Impact of Closed-Loop Control on the Pathophysiology of Diabetes** – As work to close the loop between glucose sensing and insulin delivery progresses, a parallel research effort is needed to understand how these new technologies affect the pathophysiology of diabetes. Defining the impact of an artificial pancreas on brain metabolism, or determining the ability of mechanical devices to restore normal pathways for regulating glucose levels or reverse hypoglycemia unawareness, are some of the important research questions.
- **Behavioral Aspects** – Behavioral research could uncover factors that influence the adoption and effective use of new diabetes management technologies by people with diabetes and health care providers.
- **Design of Clinical Trials and Clinical Outcomes** – Clinical trials are needed to evaluate the optimal use of new technologies in populations that vary by form of diabetes, age, presence of complications, or other parameters.

Ultimately, pursuing research goals outlined in this area of the Strategic Plan could lead to the development of a fully automated, mechanical, artificial pancreas that could maintain blood glucose within a physiologic range with minimal input from the user, thus reducing the burden of disease management and improving quality of life for many people with diabetes.

### Clinical Research and Clinical Trials

Combating the diabetes epidemic requires a robust program of clinical research and clinical trials to identify, test, and compare approaches to the treatment

or prevention of diabetes and to translate research findings into effective therapies. Goals in this area address needs and opportunities in four key aspects of clinical diabetes research and could improve outcomes for all persons who are at risk for or are living with diabetes:

- **Preventing Type 2 Diabetes** – Landmark clinical trials in the past decade have demonstrated that type 2 diabetes can be prevented or delayed in individuals at high risk of developing the disease. More research is needed to understand how to better prevent or treat gestational diabetes, as well as to lower the associated long-term risk of type 2 diabetes in mothers with gestational diabetes and their offspring. In addition, research to widely disseminate the results of clinical trials for type 2 diabetes prevention has the potential to have a positive impact on public health.
- **Treatment** – Research efforts aimed at determining the optimal treatment of people with type 2 diabetes, especially early in the course of disease, could help to prevent or delay the onset of devastating complications and could inform efforts to develop individualized therapy for diabetes. Similarly, research to understand and reverse hypoglycemia could improve outcomes for people with type 1 diabetes.
- **Etiology of Diabetes and Its Complications** – Diabetes is a heterogeneous disease with multiple causes and a highly variable clinical course. Clinical research to define the genetic, metabolic, and environmental factors in diabetes is needed to fully understand the disease and its progression to complications in many people with diabetes.
- **Complications** – Identifying risk factors for diabetic cardiovascular disease and understanding how those factors differ between people with type 1

and type 2 diabetes could lead to better treatment strategies for all individuals with diabetes. The identification and validation of surrogate end points and biomarkers for vascular complications would greatly accelerate clinical trials to test new diabetes therapeutics.

Strategic Plan goals for clinical research and clinical trials in diabetes represent critical steps toward increasing the effectiveness of prevention and treatment strategies for diabetes and realizing maximal public health benefits from the diabetes research enterprise.

### Special Needs for Special Populations

Developing tailored approaches to diabetes treatment and prevention would reduce the burden of disease in specific populations, including children, older adults, pregnant women, people with other serious diseases and conditions, and minority populations that are disproportionately affected by diabetes. Goals in this area address the special needs and challenges related to the prevention and treatment of diabetes in these populations:

- **Ethnic and Racial Disparities** – Eliminating the disproportionate risks of diabetes and diabetes complications faced by certain ethnic and racial populations in the United States will require research to understand the genetic, behavioral, and biologic mechanisms that underlie ethnic and racial differences in diabetes susceptibility, as well as efforts to develop programs for lifestyle interventions that can target and reach large numbers of at-risk individuals.
- **Pregnancy and the Intrauterine Environment** – Research on the causes and consequences of diabetes in pregnant women and their developing fetuses could lead to new strategies

to improve long-term health outcomes in these women and their offspring.

- **Diabetes in Children and Youth** – The rates of type 1 diabetes, type 2 diabetes, and obesity or overweight are increasing in American children and youth. Research is urgently needed to understand the underlying triggers for these diseases in children, as well as to develop better diabetes management strategies that can improve long-term health outcomes and reduce the risk of diabetic ketoacidosis in the pediatric population.
- **Diabetes in Older Adults** – For older adults, research on behavioral approaches to help people make lifestyle changes that could prevent or better control diabetes could reduce the impact of diabetes in this vulnerable group, as could research that addresses age-related changes in metabolism and clearance of therapeutic drugs and therapy of diabetes in the context of multiple chronic diseases.
- **Diabetes and Psychiatric Disorders** – The mechanisms that link diabetes and psychiatric disorders and treatments are not well understood; research to uncover those mechanisms could point to novel strategies for diabetes screening and treatment in people with mental illness.
- **Secondary Diabetes** – Individuals with certain chronic conditions—such as cystic fibrosis, HIV infection, or organ replacement—often develop diabetes either as a result of their underlying disease or as a consequence of treatment. Research on secondary diabetes should focus on both understanding how these conditions or their treatment impair glucose metabolism and developing strategies to prevent diabetes and reduce the risk of cardiovascular disease and other complications.

By addressing the unique challenges posed by diabetes in different populations, Strategic Plan research goals in this area will ensure that the benefits of diabetes research are available to all individuals with diabetes.

## Diabetes Complications

Diabetes-related complications of the eyes, kidneys, nerves, heart, and other organs exact a significant toll on the personal health of individuals with diabetes and contribute significantly to the costs of health care in the United States. Goals in this area are aimed at reducing the considerable health burden caused by diabetes complications by spurring discovery in a variety of disciplines:

- **Metabolic, Biochemical, and Signaling Pathways** – Many gaps remain in the understanding of the molecular and cellular pathways that are disrupted in diabetes, eventually leading to organ and tissue damage. Research on the roles of mitochondria, inflammation, protein modification, and cellular self-digestion, among other biologic processes, could provide new insights into the pathophysiology of diabetes complications.
- **Genetics and Epigenetics** – Identifying the genetic and epigenetic factors that predispose or protect individuals from complications could reveal disease pathways and uncover targets for therapeutic development.
- **Tissue and Organ System Injury** – In addition to mapping general pathways that affect the development of complications, it will be important to study tissue-specific responses to diabetes. These lines of research would benefit from the development of *in vitro* models of vascular complications and the establishment of repositories of well-characterized human cells and tissues

representing all stages in the development and progression of complications.

- **Tissue Repair and Regeneration** – Research efforts to understand how diabetes impairs the body's normal repair and regeneration processes could also point to novel therapeutic strategies.
- **Biomarkers, Imaging, and Bioinformatics** – Focused development of effective biomarkers, noninvasive imaging techniques, animal and cell models that mimic human diabetes, and bioinformatics platforms would accelerate research on diabetes complications. Such tools and technologies could dramatically shorten the time required for development and testing of new drugs or other therapeutic strategies.
- **Therapeutic and Preventive Strategies** – Research on therapies for the prevention and treatment of diabetes complications needs to take a multi-pronged approach that includes the development of pharmacologic, nutritional, and behavioral strategies, as well as efforts to tailor interventions to individuals or to specific organs or cell types.

Achieving research goals for diabetes complications outlined in the Strategic Plan has the potential to enhance the lives and health of millions of people at risk for or living with the devastating complications of diabetes.

## Clinical Research to Practice: Translational Research

A key challenge in diabetes research is translating the important findings of controlled clinical trials for diabetes prevention or treatment into approaches that are effective, affordable, safe, and sustainable in real-world settings. Research goals in this area are aimed

at designing diabetes interventions to work in different populations and individuals and within discrete systems of care, and focus on needs and opportunities in five major aspects of this challenge:

- **Prevention of Type 2 Diabetes** – Translating the results of landmark clinical trials showing that type 2 diabetes could be prevented or delayed is critically important. Finding ways to accurately identify individuals who would benefit from prevention programs and developing approaches to prevent type 2 diabetes through integration of health care services or community programs could help stem the diabetes epidemic in adults and youth.
- **Diabetes Clinical Care** – The results of some clinical trials suggest that a standard approach to diabetes management might not be suitable for all people with the disease. The development of individualized approaches to diabetes clinical care would optimize the quality of life and health outcomes for all, including those in groups that have particular challenges with daily diabetes management, such as children and older adults.
- **Patient-Centered Care** – Research is needed to identify patient-specific factors that affect diabetes medical care or self-management.
- **Health Disparities** – Understanding why some populations, such as the poor, uninsured, or certain ethnic and racial minority groups, experience inferior quality of health care delivery, processes of care, and health outcomes is key to efforts to improve diabetes care. Research in this field must consider multiple factors at the level of the individual, provider, community, and health system while developing culturally appropriate interventions to improve health care and outcomes and reduce disparities.

- **Systems of Care** – Determining the optimal systems of care, both within and outside of the traditional health care system, as well as developing strategies to systematically improve the quality of diabetes care, are critical to the successful translation of diabetes research findings throughout the Nation.

Realizing Strategic Plan goals for translational research in diabetes is essential for improving public health and controlling the ever-growing costs of diabetes care.

## Resource and Infrastructure Needs for Diabetes Research

Diabetes and obesity are heterogeneous conditions with complex management needs and the potential for devastating complications. Much about the causes of these disorders and the most appropriate and effective means to treat them at the level of individuals, population groups, and health care systems remains to be discovered. All areas of diabetes research would benefit from efforts to encourage collaborative, multidisciplinary research, as well as the establishment of and broad access to shared resources and state-of-the-art technologies.

An eleventh working group was formed with representatives from each of the 10 research area working groups to consider resource and infrastructure needs for diabetes research. This group identified future directions for the development of research resources and infrastructure that would enable the successful implementation of this Strategic Plan for research and promote research progress towards reducing the medical, personal, financial, and societal burdens of diabetes.

- **Research Training and Human Resource Development** – Progress in diabetes research depends on the ongoing recruitment, training, and support of new researchers in basic and clinical research related to diabetes, including transdisciplinary approaches to research. Programs are needed to encourage the application of diverse fields of study, such as computational biology, engineering, nanotechnology, social sciences, and other disciplines, to diabetes research. Educating the medical community and the general public on clinical research would facilitate the implementation of clinical trials to understand pathophysiologic mechanisms and test new therapies for diabetes.
- **Diabetes Research Resources** – Research on diabetes and obesity would benefit from the establishment of central biobanks with annotated human tissue samples from individuals representing the entire disease spectrum, from healthy metabolism to complicated diabetes. Shared resources, such as biobanks, can improve the efficiency of research and allow scientists to evaluate novel hypotheses that depend on access to tissues that might be difficult for an individual laboratory to obtain. Support for longitudinal studies of individuals with type 1 diabetes or youth with type 2 diabetes could lead to new insights on the progression, treatment, and outcomes of these diseases. Mechanisms to encourage communication and collaboration among researchers and clinicians and between NIH-supported research centers would stimulate new hypotheses and facilitate translation of research findings into clinical practice.
- **New Technologies, Methodologies, and Measurements for Research** – The development and application of state-of-the-art technologies, methodologies, and measurements would open up significant new avenues of research on diabetes and obesity. Such tools and techniques include: advanced technologies for gene discovery, methods to analyze epigenetic processes, stem cell lines and technologies, proteomic and metabolomic methods, imaging techniques and reagents, bioinformatics resources, tools for measuring energy balance, methods for studying environmental influences, standardized measurements for translational research, methods for comparative effectiveness research, and emerging information and communication technologies.
- **Animal Models for the Study of Diabetes and Obesity** – Animal model research has contributed substantially to the understanding of diabetes and obesity, but these models exhibit substantial differences when compared to these diseases in humans. New small and large animal models, as well as *in silico* models, are needed that better represent the pathology and treatment of human diabetes and obesity. The development of standardized research protocols and definitions of abnormalities in mouse models of diabetes would facilitate comparison of research findings across research laboratories. Better methods to characterize mouse models in detail, including the application of advanced imaging technologies, would also improve research on diabetes, obesity, and their complications.

- **Distribution and Sharing of Human Data and Biosamples** – Mechanisms to disseminate information on available resources are needed to maximize access to and use of biosample collections, new technologies and methodologies, intervention programs, and other resources. Efficient sharing of clinical biosamples and data will rely on the development of policies that facilitate research while maintaining individuals’ right to privacy.
- **Public-Private and International Partnerships** – Building partnerships between NIH and other governmental agencies,

the pharmaceutical industry, the health insurance industry, private foundations, foreign research agencies or investigators, and community organizations can enhance diabetes research at all levels, accelerate the validation and approval of new therapies, and promote dissemination of research results to individuals affected by diabetes.

## IMPLEMENTATION: GUIDING FUTURE RESEARCH EFFORTS

This Strategic Plan reflects a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities for diabetes research are identified. The statutory DMICC will continue to play a key role by assessing progress toward the research goals described in this Plan, which was developed under its auspices. The NIH will also continue to solicit broad external

input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH, other DMICC member organizations, and the scientific community will use the research questions and future directions described in the Strategic Plan as a scientific guidepost to enhance fundamental understanding of diabetes, improve current treatment strategies, and identify ways to prevent or cure diabetes and its complications.



# PROCESS FOR THE DEVELOPMENT OF THE STRATEGIC PLANNING REPORT OF THE DMICC

## Origin

In 1999, the NIH published a comprehensive plan for diabetes research, entitled *Conquering Diabetes: A Strategic Plan for the 21st Century*. In the decade since that plan was released, major advances have been made in the understanding of diabetes, new tools and technologies have been developed, and strategies for diabetes prevention and treatment have been expanded. In 2006, the NIH published *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*, a report that described opportunities that would inform research on many areas of commonality between type 1 and type 2 diabetes, but with a primary focus on type 1 diabetes research. In 2008, the DMICC determined that the time was appropriate to update these plans by identifying the most up-to-date, high-priority opportunities for all areas of diabetes research that build on recent research advances and that can be accomplished in the next 5 to 10 years.

## A Collaborative Planning Process

The Strategic Plan was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing diabetes research. Working groups were assembled to address each of 10 scientific areas of important opportunity related to diabetes. An additional working group composed of representatives from each of the other 10 groups addressed overarching needs for scientific expertise, tools, technologies, and shared research resources. Each working group was

chaired by a scientist external to the NIH and was comprised of additional external scientific experts, as well as representatives of DMICC member organizations and diabetes voluntary organizations. Working groups met through conference calls and electronic exchanges to assess the state of the science and identify advances and emerging opportunities in their scientific areas.

An overarching Diabetes Research Strategic Plan Leadership Group was formed of the chairs of the 11 working groups and representatives from the government and diabetes voluntary organizations. This overarching working group met in person on July 7, 2009 to review progress of the scientific working groups and ensure that the Strategic Plan was comprehensive and addressed the most compelling opportunities for prevention, therapy, and cure of diabetes and its complications. A draft of the Strategic Plan was posted on the NIDDK website to provide an opportunity for broad public input prior to publication.

## Organization of the Strategic Plan

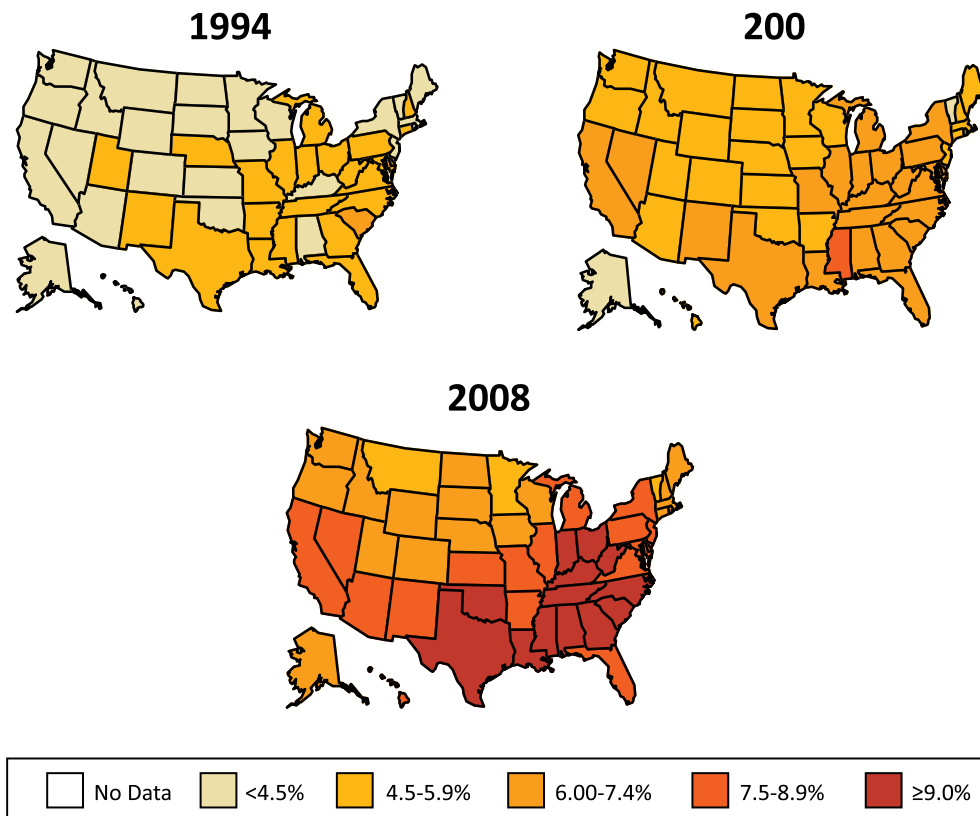
The Strategic Plan was framed around 10 major scientific areas representing important opportunities in diabetes research. These areas are overlapping but complementary in scope:

- Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications

- Type 1 Diabetes and Autoimmunity
- The Beta Cell
- Type 2 Diabetes As a Multi-Dimensional Disease
- Obesity
- Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia
- Clinical Research and Clinical Trials
- Special Needs for Special Populations
- Diabetes Complications
- Clinical Research to Practice: Translational Research

Each of the 10 chapters in the Strategic Plan addressing these areas of scientific opportunity includes an introduction, summaries of recent research advances, key questions and future directions (goals) for research, and a closing section describing how the research directions outlined in the chapter may transform the health of people with or at risk of diabetes. The Strategic Plan also includes a chapter that outlines resource and infrastructure development needs to support the implementation of the future directions for diabetes research identified by the working groups.





CDC statewide estimates of diagnosed diabetes in the U.S. in 1994, 2000, and 2008. The different colors represent the percent of adults 20 years of age or older with diagnosed diabetes in these years. These maps demonstrate the dramatic increase in prevalence of diabetes observed in less than two decades. (CDC's *Division of Diabetes Translation. National Diabetes Surveillance System* available at [www.cdc.gov/diabetes/statistics](http://www.cdc.gov/diabetes/statistics))

# INTRODUCTION

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Highlights of Diabetes Research Accomplishments

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NIH Diabetes Research Portfolio

Development of the Strategic Plan

Looking Forward: Future of Diabetes Research

## OVERVIEW

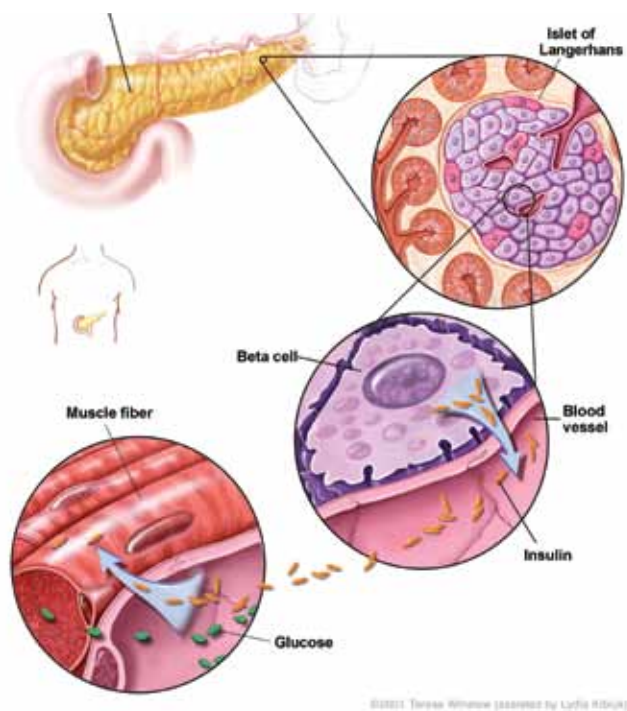
Diabetes affects an estimated 25.8 million people in the United States and is the seventh leading cause of death (1). Diabetes lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two- to four-fold, and is the leading cause of kidney failure, lower limb amputations, and blindness in working-age adult Americans (1,2). In addition to these human costs, the estimated total financial cost for diabetes in the U.S. in 2007—including costs of medical care, disability, and premature death—was \$174 billion (1). Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed (1). Moreover, another 79 million Americans are estimated to be at greatly increased risk of developing diabetes in the next several years (1). One in three American children born in 2000 are predicted to develop diabetes at some point in their lives (3). Globally, diabetes will affect an estimated 285 million adults in 2010, a figure that is predicted to rise to 438 million by 2030 (4). Diabetes thus presents an immense and complex public health challenge.

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of debilitating disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, due to a combination of resistance to the action of insulin and insufficient insulin production. Women can develop gestational diabetes, a risk factor for type 2 diabetes, during pregnancy. Many rarer forms of diabetes also exist.

### Type 1 Diabetes

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately 5 percent of adults and the majority of children and youth with diagnosed diabetes (1). While it most often develops during childhood, the disease may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the beta cells of the pancreas. These beta cells are found within tiny cell clusters called islets and produce the hormone insulin. If left untreated, type 1 diabetes results in death as muscle and other tissues are starved for glucose despite high levels of glucose in the bloodstream. Thus, people with type 1 diabetes require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels.

Despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for people with type 1 diabetes to achieve the precise level of regulation obtained by a healthy pancreas, which exquisitely senses and responds to insulin needs. Therefore, people with type 1 diabetes are susceptible to dangerous variations in their blood glucose levels, called hyperglycemia (high blood glucose) or hypoglycemia (low blood glucose). Both of these conditions can be life-threatening in extreme cases. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, as well as working on new beta cell replacement therapies meant to cure type 1 diabetes. Continued research to prevent type 1 diabetes in those at risk, restore insulin independence in people who are already diagnosed, and prevent the development



The pancreas is located in the abdomen, adjacent to the duodenum (the first portion of the small intestine). A cross-section of the pancreas shows one of the islets of Langerhans, or pancreatic islets. The islets are the functional unit of the endocrine pancreas. Encircled is a beta cell, the islet cell that synthesizes and secretes insulin. Beta cells are located adjacent to blood vessels and can easily respond to changes in blood glucose concentration by adjusting insulin production. Insulin facilitates uptake of glucose, the main fuel source, into cells of tissues such as muscle. (© 2001 Terese Winslow (assisted by Lydia Kibiuk).)

of disease complications, is crucial to reducing the burden of the disease and improving patients' quality of life.

## Type 2 Diabetes

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases among adults in the United States (1). Type 2 diabetes is strongly associated with obesity: more than 80 percent of adults with type 2 diabetes are overweight or obese (5). Type 2 diabetes is also

associated with aging, affecting an estimated 26.9 percent of Americans 65 years of age and older, and it occurs more frequently among racial and ethnic minority groups in the United States, including African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians and other Pacific Islanders (1). Other important risk factors include physical inactivity, a family history of diabetes, and a history of diabetes during pregnancy (gestational diabetes).

In type 2 diabetes, the body becomes resistant to insulin signaling, which can eventually result in impaired insulin production. Treatment approaches for controlling glucose levels include diet, exercise, orally administered medications that make tissues more sensitive to insulin or enhance insulin production, and, in some cases, injected insulin. There are also an estimated 79 million adults in the United States who have a condition called “pre-diabetes,” in which blood glucose levels are higher than normal, but not as high as in diabetes (1). This population is at high risk of developing type 2 diabetes. Fortunately, the Diabetes Prevention Program (DPP) clinical trial, spearheaded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with support by many components of the National Institutes of Health (NIH), as well as the Centers for Disease Control and Prevention (CDC) and the Indian Health Service (IHS), has shown that people with pre-diabetes can dramatically reduce their risk of developing full-blown type 2 diabetes with improvements in lifestyle or with drug treatment.

Type 2 diabetes was previously called adult-onset diabetes because it was predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and

adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. First, the onset and severity of disease complications correlate with the duration of diabetes; thus, those with early diabetes onset are at greater risk with respect to complications. Second, maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of diabetes in offspring. Thus, the rising rates of diabetes and pre-diabetes in young women could lead to 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 glucose level and thus prevent or delay the development of complications. Therefore, the advent of type 2 diabetes in youth has the potential to drastically worsen the enormous health burden that diabetes already places on the United States.

### **Gestational Diabetes**

Gestational diabetes is a form of glucose intolerance diagnosed during pregnancy. Gestational diabetes affects at least 7 percent and possibly as many as 18 percent of pregnancies in the United States (1,6) and occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians (1). It is also more common among obese women and women with a family history of diabetes. During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant. Immediately after pregnancy, 5 to 10 percent of women with gestational diabetes are found to have

diabetes, usually type 2 diabetes (1). Women who have had gestational diabetes have a 35 to 60 percent chance of developing diabetes in the next 10 to 20 years (1).

### **Other Forms of Diabetes**

Other types of diabetes result from specific genetic conditions, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus; surgery; medications; infections; pancreatic disease; and other illnesses. Such types of diabetes account for 1 to 5 percent of all diagnosed cases (1).

### **Complications of Diabetes**

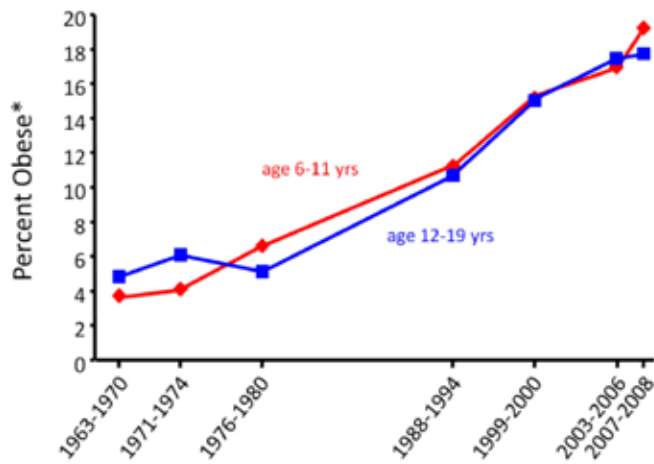
Persistent elevations of blood glucose levels, despite therapy, eventually damage nearly every organ in the body, including the eyes, kidneys, and cardiovascular system. Diabetes increases the risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurological problems, limb amputation, chronic wounds and skin ulcers, gum disease, and pregnancy-related problems. Overall, diabetes is estimated to lower average life expectancy by 15 years, due to these devastating disease complications (2). The good news is that NIH-supported research has demonstrated that life expectancy for people with type 1 diabetes is increasing, type 2 diabetes can be prevented or delayed in those at risk, and intensive control of blood glucose levels dramatically prevents or delays the development of diabetes complications.



## Costs of Diabetes

In addition to the toll diabetes takes on health, it places an immense cost burden on individuals and the health care system. The estimated total financial cost for diabetes in the U.S. in 2007—including costs of medical care, disability, and premature death—was \$174 billion: \$116 billion for direct medical costs and \$58 billion for indirect costs such as lost work productivity (1). After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures

would be in the absence of diabetes (1). One in 3 Medicare dollars is spent on people with diabetes (7). In addition to the eye, nerve, and kidney problems specific to diabetes, people with diabetes have worse outcomes after diagnosis of cancer and heart disease, require longer hospitalizations on average even for conditions unrelated to diabetes, are at increased risk of depression, and endure reduced quality of life and substantially increased personal medical expenses.



Trends in childhood overweight and obesity. The prevalence of obesity (see definition below) has increased steadily since the 1970s among 6-11 year old children. In older children (12-19 years), the rise in overweight prevalence was less gradual, with a sharp increase during the 1980s. These increases in weight have been accompanied by an observed rise in diabetes in youth. (\*Obesity is defined as equal to or greater than the 95th percentile of BMI-for-age and gender, based on 2000 Growth Charts from the Centers for Disease Control and Prevention. Sources for overweight/obesity data: NHES II & III, NHANES I, II, & III, NHANES 1999-2004; Ogden et al. JAMA 2002, JAMA 2006, JAMA 2008, JAMA 2010)

## HIGHLIGHTS OF DIABETES RESEARCH ACCOMPLISHMENTS

Over the past decade, research has led to major discoveries benefiting people with or at risk for diabetes.

Examples include:

- **Diabetes complications can be reduced by over half with intensive glycemic control early in the course of the disease.**
- **Weight loss in people with type 2 diabetes results in improved control of glucose, blood pressure, and cholesterol with less use of medications.**
- **Risk of developing type 2 diabetes can be dramatically reduced in people at high risk for developing the disease through diet and exercise to promote modest weight loss or by treatment with the diabetes drug metformin. Benefits persist for at least 10 years.**
- **Continuous glucose monitors improve glycemic control and reduce hypoglycemia in adults with type 1 diabetes.**
- **New genetic tests can identify infants with neonatal diabetes—a rare form of diabetes—who may be treatable with oral drugs (sulfonylureas) rather than insulin injections.**
- **Insulin independence has been achieved in people receiving islet transplants as treatment for severe type 1 diabetes.**
- **Residual insulin secretion has been found in many people with type 1 diabetes at diagnosis and beyond, spurring research on ways to preserve or expand this capacity.**
- **Insulin-producing cells have been generated in the laboratory from non-beta-cell sources, providing proof-of-principle for regenerative approaches to beta cell replacement.**
- **Many new susceptibility genes for type 1 and type 2 diabetes have been identified.**
- **New treatments for type 2 diabetes are available based on discoveries about how gastrointestinal tract hormones influence insulin secretion.**
- **Gastric bypass and other bariatric surgeries to treat extreme obesity may resolve type 2 diabetes independently of weight loss, opening the door to discovery and to new therapeutic options for some individuals.**
- **Metabolically active brown fat has been detected in adults and may prove therapeutically useful in obesity prevention or treatment.**
- **Women with gestational diabetes can lower their substantial risk for developing type 2 diabetes postpartum either through diet and exercise to induce weight loss, or with diabetes medication.**
- **Some people with diabetes and cardiovascular disease can do as well with medical management as with revascularization procedures.**
- **Intensive control of blood glucose during pregnancy can reduce birth defects, birth injuries, and the need for Cesarean section.**

- **Benefits of intensive control of glucose endure with reduced complications long after the period of good control. Good control of blood glucose, blood pressure, and lipids can reduce by half cardiovascular death in diabetes.**
- **Diabetes self-management training and improved health care delivery practices can improve diabetes outcomes.**
- **Affordable community-based approaches to lifestyle change for type 2 diabetes prevention have been developed.**

## GOALS OF DIABETES RESEARCH

The promise of prevention, treatment, and cure for diabetes can only be realized through the vigorous support of scientific research. This research must be conducted through a multi-pronged effort that addresses the complex challenges posed by diabetes, from dysfunctions in the most fundamental molecular and cellular processes, to the need for new approaches to translate scientific findings into improved health for people affected by the disease. This Plan addresses important opportunities in 10 major diabetes research areas.

- **Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications**
- **Type 1 Diabetes and Autoimmunity**
- **The Beta Cell**
- **Type 2 Diabetes As a Multi-Dimensional Disease**
- **Obesity**
- **Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia**
- **Clinical Research and Clinical Trials**
- **Special Needs for Special Populations**
- **Diabetes Complications**

- **Clinical Research to Practice: Translational Research**

None of this research can be pursued without trained investigators and research facilities, and this Plan also addresses the issues surrounding the technological and human resources needed to accelerate discovery in diabetes.

### **Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications**

Diabetes has a strong genetic basis that is modified by environmental factors. Powerful new tools, such as genome-wide association (GWA) studies, are accelerating gene discovery. Identification of key genes influencing risk for diabetes and its complications will not only help to predict who will develop the disease and aid in the development of new prevention strategies, but also identify key targets for the development of new molecular therapies and aid in individualization of therapy.

### **Type 1 Diabetes and Autoimmunity**

One way to attack type 1 diabetes is to stop it before it ever starts. Therapies based on modulating the immune system are already showing promise to slow loss of insulin-producing beta cells in the newly-diagnosed.

Increasing knowledge of what goes wrong with the immune system and identification of environmental factors that trigger the disease in those at risk will facilitate the discovery of novel ways to prevent autoimmunity, and thus prevent disease onset.

## The Beta Cell

All major forms of diabetes share a common basis in the loss of insulin-producing pancreatic beta cells. Thus, approaches to protect and/or increase the number of existing beta cells and to replace lost beta cell function are of critical importance. Understanding the steps in the normal development of beta cells coupled with advances in stem cell biology will yield approaches to replicate, regenerate, or replace beta cells and thus restore normal insulin production.

## Type 2 Diabetes As a Multi-Dimensional Disease

Systems biology may help to unlock the genetic and molecular complexity of diabetes. This new science attempts to integrate large data sets obtained by application of “omics” technologies—genomics, transcriptomics, proteomics, and metabolomics—to provide unprecedented depth of understanding of phenotypic variability and to identify novel pathways of disease development and progression.

## Obesity

Obesity is a major risk factor for type 2 diabetes and is also a problem in people with type 1 diabetes receiving intensive insulin therapy. Important new knowledge has emerged about the mechanisms by which fat tissue promotes harmful inflammation and insulin resistance, yielding new avenues for therapy. New therapeutic targets are also emerging from understanding of the powerful brain and body signals regulating appetite and energy balance. Successful approaches to sustained weight loss have demonstrated major benefits for those

with or at risk of type 2 diabetes. However, to stem the rising tide of type 2 diabetes, new approaches to prevention of overweight and obesity require research on many fronts, from fundamental studies to large clinical trials.

## Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia

Because it is proven to prevent complications, restoring glycemic control is a key goal in diabetes treatment. Devices for continuous glucose sensing and insulin delivery already provide valued treatment options for people who require insulin treatment, as well as the tantalizing near-term potential to link these technologies to create an artificial mechanical pancreas. Bioengineered insulin-releasing cells or molecules are other approaches to management of glycemia that could greatly reduce the treatment burden for people with diabetes.

## Clinical Research and Clinical Trials

Landmark NIH-supported clinical trials have provided proof that control of glucose, blood pressure, and cholesterol can dramatically reduce diabetes complications, and that the course of both type 1 and type 2 diabetes can be slowed. Yet, there is much to learn about the risks and benefits of diabetes therapies and about their comparative effectiveness. Combating the burden of diabetes requires a robust program of clinical research and clinical trials that can identify, test, and compare approaches to the treatment or prevention of diabetes and translate fundamental research advances into effective therapies for people living with or at risk for the disease.

## Special Needs for Special Populations

Increasingly, diabetes research has shown that one size doesn't fit all and that therapy and prevention approaches must be tailored for groups such as children and older adults, pregnant women, and people already battling other serious diseases and conditions. The disproportionate burden of diabetes in minority populations presents special challenges that need to be addressed by research.

## Diabetes Complications

Preventing diabetes-induced damage to eyes, kidneys, nerves, the heart, and other body tissues would go a long way to reducing the tremendous morbidity and mortality of this disease. Recognition of the phenomenon of "metabolic memory," with early aggressive glucose control yielding sustained benefits over the ensuing decades, highlights the importance of understanding the molecular mechanisms by which glucose damages blood vessels. Further research on the fundamental aspects of tissue and organ damage in diabetes will help pave the way to preventive and therapeutic strategies.

## Clinical Research to Practice: Translational Research

A huge gap exists between the levels of control of glucose, blood pressure, and cholesterol proven to reduce complications (and thus recommended in clinical practice guidelines) and the levels of control of these factors

achieved in actual medical practice. Further research to translate effective practices from the research setting to the population at large will help close the gap between the ideal and current real-world practice to improve health outcomes for people with or at risk of diabetes.

## Resource and Infrastructure Needs for Diabetes Research

Addressing the complexity of diabetes and its complications, and harnessing the new and emerging technologies that offer opportunities to understand, prevent, and treat diabetes, requires the collaborative efforts of fundamental and clinical scientists in a wide spectrum of disciplines, as well as the establishment of and broad access to shared resources and state-of-the-art technologies. Finding ways to leverage and further support resource and infrastructure development and promote multidisciplinary team efforts is critical to the successful implementation of plans for diabetes and obesity research.

## NIH DIABETES RESEARCH PORTFOLIO

The NIH is the primary source of Federal support for diabetes research. Diabetes research at the NIH is supported by regularly appropriated funds that the U.S. Department of Health and Human Services (HHS) receives for diabetes research through the Labor-HHS-Education Appropriations Committees. It is also supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which is a special appropriation to the Secretary of HHS to pursue research on type 1 diabetes and its complications. The NIDDK, on behalf of the Secretary, has a leadership role in planning, implementing, and evaluating the allocation and use of these funds.

While the NIDDK is the lead institute at the NIH for pursuing diabetes research and research training, diabetes research involves nearly every Institute and Center of the NIH, including the Fogarty International Center (FIC), National Center for Complementary and Alternative Medicine (NCCAM), National Cancer Institute (NCI), National Center for Research Resources (NCRR), National Institute on Minority Health and Health Disparities (NIMHD), National Eye Institute (NEI), National Human Genome Research Institute (NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute on Aging (NIA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Biomedical Imaging and Bioengineering (NIBIB), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute on Drug Abuse (NIDA),

National Institute of Environmental Health Sciences (NIEHS), National Institute of General Medical Sciences (NIGMS), National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), and the National Library of Medicine (NLM), as well as the Center for Scientific Review (CSR), the NIH Office of Research on Women's Health (ORWH), and the NIH Office of Behavioral and Social Sciences Research (OBSSR). In addition to the NIH, the CDC, Centers for Medicare & Medicaid Services (CMS), Food and Drug Administration (FDA), IHS, Veterans Health Administration (VHA), Department of Defense (DOD), Agency for Healthcare Research and Quality (AHRQ), Health Resources and Services Administration (HRSA), U.S. Department of Agriculture (USDA), and other governmental agencies conduct, support, or participate in diabetes research.

Also contributing to support of diabetes research are the two major diabetes voluntary organizations, the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA), as well as the pharmaceutical industry and some private foundations.

NIH funding for diabetes research in fiscal year (FY) 2009, including support from the *Special Statutory Funding Program for Type 1 Diabetes Research*, was \$1.03 billion (source: <http://report.nih.gov/rcdc/categories/>).\*

### Collaborative Planning Process

The statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC) provides a forum for

communication and collaboration to promote diabetes research. Its broad membership includes components of the NIH and other government agencies that support diabetes-related activities (see Appendix A). Through the DMICC, government agencies identify ways in which they can work together and build upon each other's expertise and resources. This approach helps ensure that Federal diabetes activities are coordinated and not duplicated, as well as stimulates collaborations where appropriate.

The collaborative planning process for diabetes research also involves the voluntary agencies, including the ADA and the JDRF, in an attempt to avoid duplication and enhance efficiency in providing resources. In addition, the NIH seeks input from the external scientific community, through venues such as scientific meetings and conferences, to inform its planning processes

### Examples of Major Current Diabetes Research Efforts

The NIH vigorously pursues and supports research on the understanding, prevention, and cure of diabetes. Because diabetes research spans such a broad range of disciplines, research efforts are under way in diverse areas, such as genetics, genomics, proteomics, immunology, developmental biology, obesity, cell biology, imaging, stem cell research, bioengineering, glucose sensing, and insulin delivery. Most fundamental research is accomplished through investigator-initiated regular research grants. To foster bench-to-bedside translational research, the NIH has developed consortia focused on specific goals such as understanding the development of the insulin-producing beta cell or the molecular events underlying pathogenesis of diabetes complications. Clinical trials test promising agents

and approaches for diabetes and its complications, as well as interventions to prevent diabetes onset. This section highlights a variety of major efforts the NIH has made to support and extend the investigator-initiated research portfolio and foster innovative approaches. Many of these efforts were undertaken in response to research priorities described in the 1999 strategic plan, *“Conquering Diabetes: A Strategic Plan for the 21st Century”*; strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research*; and the 2006 *“Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan.”* However, these examples—mostly major research consortia—are not a comprehensive list of the entire NIH diabetes research portfolio. The NIH supports investigator-initiated research projects and fosters development of research efforts in areas of particular importance and opportunity through solicitations for grant applications and research contract proposals, and the NIH will continue to strongly support these efforts.

### *Animal Models*

#### **Animal Models of Diabetic Complications**

**Consortium (AMDCC):** The AMDCC is an interdisciplinary consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The Consortium has already developed a number of promising models for complications involving the heart, kidney, and nervous system. Development of animal models is essential for pre-clinical drug development.

#### **Cooperative Study Group for Autoimmune Disease Prevention:** This research network is

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\*In addition to these funds, in FY 2009, funding from the American Recovery and Reinvestment Act enabled NIH to spend an additional \$121 million in support of diabetes research.

focused on finding ways to prevent type 1 diabetes and other autoimmune diseases by means other than broadly suppressing the entire immune system. The group's goals are to create improved models of disease pathogenesis and therapy to better understand immune mechanisms involved; to use these models to test and validate new tools that may be applicable to human studies; and to encourage research that can be quickly translated from animal to human studies, emphasizing the development of surrogate markers for disease progression and/or regulation that can be utilized in the context of clinical trials.

**Mouse Metabolic Phenotyping Centers (MMPC):**

The MMPC provides the scientific community with standardized, high-quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity and related disorders. Using state-of-the-art technology and on a fee-for-service basis, the MMPC provides a range of complex exams used to characterize mouse metabolism, blood composition including hormones, energy balance and physical activity, eating and exercise, insulin resistance, organ function, metabolic fluxes and morphology, physiology, histology, and measures of diabetic complications in heart, kidney, vasculature, eye, and other tissues and organs. Many tests are designed to elucidate subtle to complex traits that would define models of metabolic disease.

**Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG):**

This multi-institution study group was established to evaluate the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of kidney and islet transplantation. The program also supports research to understand the underlying molecular mechanisms of immune tolerance. Pre-

clinical research conducted by this group will help scientists move promising therapeutic agents from the laboratory into human clinical trials.

## *Genetics*

**Family Investigation of Nephropathy and Diabetes (FIND):**

The FIND consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease in people with diabetes, as well as their genetic susceptibility to retinopathy. These studies will help researchers understand the genetic underpinnings of kidney and eye complications of diabetes, which can, in turn, inform prevention and treatment strategies.

**Genetics of Kidneys in Diabetes Study (GoKinD):**

GoKinD was established to study the genetics of kidney disease in people with type 1 diabetes. The study group has collected DNA and other biological samples from over 1,700 adults with type 1 diabetes in the U.S. and Canada. Scientists will use these samples to identify genes that are important in the development of, or resistance to, diabetic kidney disease.

**Multi-ethnic Study of Type 2 Diabetes Genes:**

This research consortium was established to identify the causative variants for diabetes genes in multiple populations to allow for further research on their function and role in the development of diabetes. It will serve as a research pipeline to confirm and characterize the genetic associations for type 2 diabetes already identified from GWA studies, accelerating the analysis of this wealth of genetic information.

**Type 1 Diabetes Genetics Consortium (T1DGC):**

T1DGC is organizing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. The success of the T1DGC has led to an increase in the number of genetic elements identified



in association with this complex disease. With these exciting new insights, researchers may be able to identify individuals at risk for the disease, develop and test prevention-oriented strategies, and design more specific clinical trials to test interventions specifically tailored to people with similar risk profiles.

## *Epidemiology*

### **Epidemiology of Diabetes Interventions and**

**Complications (EDIC):** The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the Diabetes Control and Complications Trial (DCCT). The DCCT/EDIC research group has observed dramatic long-term benefits of intensive glucose control in preventing and delaying complications of the eyes, kidneys, nerves, and heart. These results have had a major impact on the clinical care of people with diabetes.

**SEARCH for Diabetes in Youth (SEARCH):** There are no comprehensive population-based estimates of diabetes burden among American youth. SEARCH is defining the prevalence and incidence of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. This study will help increase understanding of how diabetes strikes and unfolds.

### **The Environmental Determinants of Diabetes in**

**the Young (TEDDY):** The goal of TEDDY is to identify environmental causes of type 1 diabetes in genetically susceptible individuals. The study completed enrollment of at-risk newborns and is following them until they are 15 years of age. This long-term study is crucial to helping researchers understand the environment triggers that play a role in type 1 diabetes disease development.

## *Clinical Research and Trials*

### **Action to Control Cardiovascular Risk in**

**Diabetes (ACCORD):** ACCORD was designed to test three treatment approaches—intensive glucose, blood pressure, and lipid management—for decreasing the high rate of cardiovascular disease among adults with type 2 diabetes who are at especially high risk for heart attacks and strokes. ACCORD found that intensive metabolic control—aiming for near-normal hemoglobin A1c (HbA1c) values, goals below the ADA guidelines—could increase risk of death. Results from ACCORD and other clinical trials suggest that there is not a “one size fits all” approach for diabetes treatment, so patients may need individualized treatment strategies. In addition to cardiovascular disease, ACCORD is studying the effects of these therapies on diabetic eye, nerve, and kidney disease, as well as on rates of cognitive decline and structural brain damage.

### **Bypass Angioplasty Revascularization**

**Investigation 2 Diabetes (BARI 2D):** BARI 2D was designed to compare various treatment strategies for diabetes and heart disease to prevent early death, heart attack, and stroke. BARI 2D found that optimal medical therapy is as beneficial as elective revascularization procedures in patients with type 2 diabetes and stable coronary heart disease. Because heart disease is the leading cause of death in people with diabetes, findings such as these are important to help inform treatment choices by patients and health care providers.

### **Clinical Islet Transplantation Consortium (CITC):**

The consortium is developing and implementing a program of single- and/or multi-center clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this consortium aims to

make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

#### **Diabetes Prevention Program Outcomes Study**

**(DPPOS):** The landmark DPP clinical trial showed that type 2 diabetes could be prevented or delayed in people at high risk through a lifestyle intervention (diet and exercise) or treatment with the drug metformin. While both interventions were effective in all racial and ethnic groups, lifestyle was more effective in older adults and metformin was more effective in younger participants. The DPPOS is examining longer-term effects of the trial interventions on prevention of type 2 diabetes and its cardiovascular complications in DPP participants.

#### **Diabetes Research in Children Network**

**(DirecNet):** The focus of DirecNet is to investigate the use of technologic advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia that attends intensive insulin therapy. Goals of the network include assessing the accuracy, efficacy, and effectiveness of continuous glucose monitoring in children with type 1 diabetes, and determining the extent to which exercise contributes to the risk of hypoglycemia. Until cell replacement therapy is a viable treatment option for children with type 1 diabetes, research on glucose sensing and insulin delivery is crucial to improving quality of life and decreasing the number of hypoglycemic episodes.

#### **Diabetic Retinopathy Clinical Research Network**

**(DRCR.net):** Diabetes causes damage to the eyes and may lead to blindness. The DRCR.net conducts multi-center clinical research studies to test promising therapeutic agents for the treatment of diabetic retinopathy (eye disease), diabetic macular edema, and associated conditions. Because blindness is such a

severe and debilitating disease complication, research pursued through this network could dramatically improve quality of life for people with diabetes.

**HEALTHY:** This study was designed to target food service and physical education changes in schools and to promote healthy habits, in hopes of lowering risk factors for type 2 diabetes in middle school students. Identifying new strategies to prevent risk factors for diabetes is extremely important because recent data estimate that 1 in 14 children in the U.S. between 12 and 19 years of age has pre-diabetes (18)—and many of the children with pre-diabetes have risk factors for cardiovascular disease.

**Immune Tolerance Network (ITN):** This research network is evaluating new therapies that can selectively prevent or diminish specific harmful immune responses in type 1 diabetes, other diseases, and organ transplants, without disabling the immune system as a whole. ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. This type of research is critical to developing promising new strategies to cure type 1 diabetes by islet transplantation or reverse disease in new-onset patients.

#### **Look AHEAD (Action for Health in Diabetes):**

This long-term multi-center trial in over 5,100 participants is under way to determine if lifestyle intervention can improve cardiovascular outcomes in people who are obese and have type 2 diabetes. Encouragingly, first-year results of the trial have shown that while HbA1c, blood pressure, and LDL cholesterol improved in both the lifestyle intervention and control groups, participants in the lifestyle intervention group saw greater improvement.

**Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY):** Previously

considered a disease of adults, type 2 diabetes is now increasingly observed in children, particularly minority youth. Because type 2 diabetes is so new to children, physicians do not know how best to treat it in this young population. To address this gap in knowledge, the TODAY clinical study is comparing three different treatments for type 2 diabetes in youth.

**Trial to Reduce IDDM in the Genetically at Risk (TRIGR):** This multi-center, international study completed recruitment and is comparing the development of type 1 diabetes in genetically-susceptible infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, versus standard cow's milk formula. TRIGR could have a major impact on disease prevention if differences are observed between the two types of formulas.

**Type 1 Diabetes TrialNet:** TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent the disease in people at risk. TrialNet has launched several studies that are recruiting, and is in the process of evaluating several other therapeutic agents to test in the network. This type of collaborative network infrastructure is critical for facilitating clinical trials in type 1 diabetes, as well as for making real improvements in the health of people with the disease by identifying new therapeutic agents.

### *Translational Research*

**Beta Cell Biology Consortium (BCBC):** The mission of this consortium is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-

term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to people with diabetes. Towards this goal, the BCBC has created and distributed important reagents that will serve the scientific community at large.

**Translating Research Into Action for Diabetes (TRIAD):** TRIAD is a 10-year, six-center prospective study of managed care and diabetes quality of care, costs, and outcomes in the United States. TRIAD is the first and largest multi-center study of diabetes quality of care, quality of life, and factors affecting them. The overall goal of the study is to examine the influence of managed care structure on processes and outcomes of diabetes care.

**Translational Research for the Prevention and Control of Diabetes and Obesity:** This research program aims to translate recent advances in the prevention and treatment of diabetes and obesity into clinical practice for individuals and communities at risk. For example, one research study is building on the results of the DPP clinical trial to determine if a lifestyle intervention could be cost-effectively administered through the YMCA. Several other studies supported under this initiative involve communities with large minority populations disproportionately burdened by type 2 diabetes and obesity.

**Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID):** This cooperative program is designed to facilitate translation to the clinic of novel, scientifically meritorious therapeutic interventions. It does this by making available, on a competitive basis, resources for the pre-clinical development of drugs, natural products, and biologics. A partial listing of those services includes: high-throughput screening, studies in animal models, formulation, pharmacology and toxicology studies, and bulk substances acquisition.

## *Shared Research Resources*

**Diabetes Centers Program:** The Diabetes Centers Program administers two types of center awards, the Diabetes Endocrinology Research Centers (DERC) and the Diabetes Research and Training Centers (DRTC). While not directly funding major research projects, both types of center grants provide core resources to integrate, coordinate, and foster the interdisciplinary cooperation of a group of established investigators conducting research in diabetes and related areas of endocrinology and metabolism.

**Integrated Islet Distribution Program (IIDP):** Because of the substantial differences between human and rodent islets, it is essential that researchers studying the insulin-producing beta cells and other components of the pancreatic islets have access to human tissue. The major source of human islets is from

organs that are donated for islet transplantation but subsequently found to be unsuitable for transplantation. This contract-supported resource acquires these human islets from subcontracted islet isolation centers and distributes them to approved investigators to facilitate basic research on human islets. In addition, the program is focused on enhancing the quality of isolated islets and establishing appropriate viability test standards.

**NIDDK Central Repositories:** These three separate contract-funded components work together to store data and biological samples (including samples for genetic analyses) from significant, NIDDK-funded clinical studies, including landmark clinical trials in type 1 and type 2 diabetes. The purpose of the Central Repositories is to expand the usefulness of these studies by providing access to the biosamples and data to a wider research community beyond the end of the study.

## DEVELOPMENT OF THE STRATEGIC PLAN

### **Origin and Purpose of Plan**

It has been over 10 years since the last comprehensive diabetes research plan was released. That plan, “*Conquering Diabetes: A Strategic Plan for the 21st Century*,” was developed by the congressionally-established Diabetes Research Working Group and published in 1999. Opportunities described in that plan have led to many research advances described in this document. In the intervening time, however, major changes have taken place in the understanding of diabetes, new tools and technologies have been developed, and information on how to treat and prevent

diabetes has grown rapidly. In addition, significant data have emerged on the burden of pre-diabetes and on diabetes in special populations, such as type 2 diabetes in children. In 2006, the NIH published “*Advances and Emerging Opportunities in Type 1 Diabetes Research*.” Developed under the guidance of the DMICC, many of the opportunities described in that plan would inform all diabetes research—especially research on diabetes complications, which are common to type 1 and type 2 diabetes, as well as studies of the insulin-producing beta cell. However, the plan focused on opportunities most germane to type 1 diabetes. In light of all these

facts, the DMICC determined that the time was right to identify high-priority opportunities for all diabetes research that can be accomplished in the next 5 to 10 years. In many areas, the efforts undertaken to develop the current plan complement and extend opportunities described in the 2006 plan.

The purpose of this Strategic Plan is to serve as a scientific guidepost to the NIH, other Federal agencies, and to the investigative and lay community by identifying compelling research opportunities. These scientific opportunities will inform the priority-setting process for the diabetes research field and propel research progress on the understanding, prevention, treatment, and cure of diabetes and its complications.

### Collaborative Planning Process

The Strategic Plan was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing diabetes research (please see Appendix A). Participants included representatives from the NIH and other Federal agencies represented on the DMICC, scientists external to the NIH, and representatives from diabetes voluntary organizations.

The Strategic Plan was organized around the important opportunities in diabetes research as described previously. To formulate the Plan, working groups were convened to address each of 10 scientific areas of important opportunity. An additional working group composed of representatives from each of the other 10 groups addressed overarching needs for scientific expertise, tools, technologies, and shared resources. Each working group was chaired by a scientist external to the NIH, and was comprised of additional external scientific experts, as well as representatives of DMICC member organizations and diabetes voluntary organizations. The working group members were asked to survey the state of the science and develop a summary

of progress and opportunities relevant to each goal. Through conference calls and electronic exchanges, they assessed the advances and emerging opportunities relevant to their scientific areas.

In addition to the focused working groups, the Strategic Plan was informed by insights provided by an overarching Diabetes Research Strategic Plan Leadership Group comprised of the chairs of the 11 working groups and representatives from the government and from diabetes voluntary organizations. The overarching Leadership Group met in person on July 7, 2009, to assure that in aggregate the components developed by the focused working groups were comprehensive and addressed the most compelling opportunities for prevention, therapy, and cure of diabetes and its complications. They provided guidance on development and integration of the products of each working group into a final Strategic Plan that will serve the purpose of informing future priority-setting in diabetes research.

### Public Input To Inform the Planning Process

To solicit broad public input into the strategic planning process, the draft Strategic Plan was posted on the NIDDK Web site for comment prior to publication (<http://diabetesplan.niddk.nih.gov>).

### Organization of the Plan

Chapters focused on each area of important research opportunity include these key sections:

- **Introduction:** A brief description of the current state-of-the-science, and an overview of the importance of the chapter subject in propelling research progress in diabetes research.
- **Recent Research Advances:** Examples of major breakthroughs in diabetes research and related efforts that have made a significant impact on the

research field or people's health, particularly in the last 5 to 7 years.

- **Key Questions and Future Directions for Research:** Specific research questions and directions are described that can be pursued to advance research in the area described by the chapter. The future directions were identified by working group members as being critically important for overcoming current barriers and

achieving progress in diabetes research relative to the chapter's area of focus over the next 10 years.

This section also describes some immediate steps that can be taken to implement these research directions.

- **Importance of Research Goals and Strategies:** This closing section envisions how the research proposed in the chapter may transform the health of people with or at risk of diabetes.

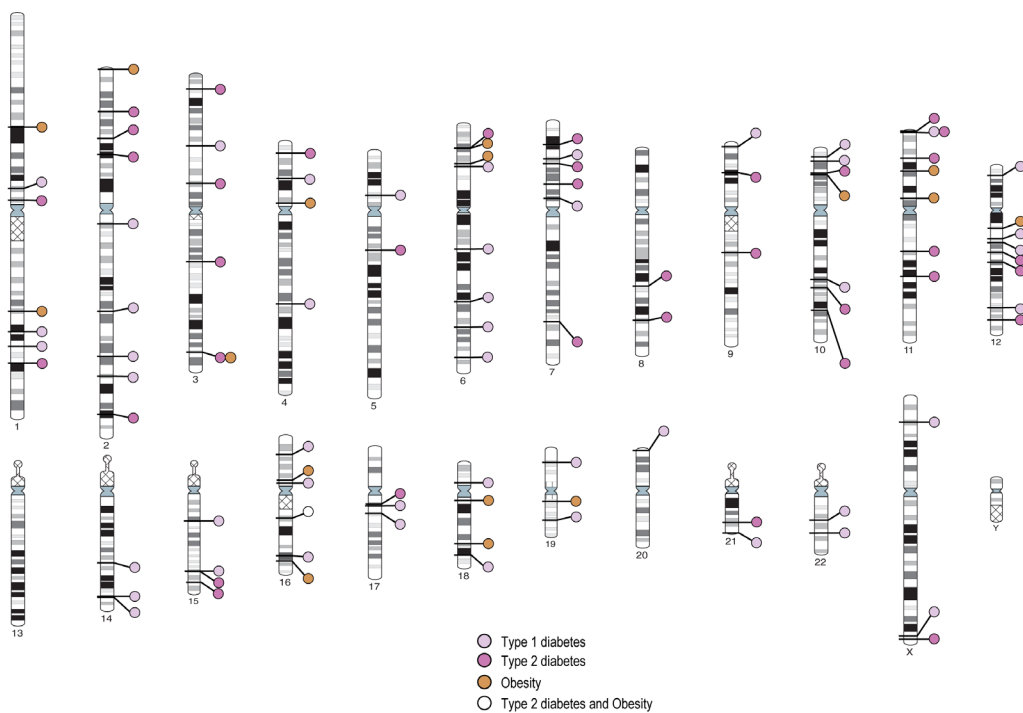
## LOOKING FORWARD: FUTURE OF DIABETES RESEARCH

Successful implementation of the research directions outlined in this Plan requires the collaboration of the multiple institutes and centers of the NIH, other government agencies represented on the DMICC, industry, and the diabetes research and voluntary community. It is only through the involvement and collaboration of these different entities that research progress will be realized.

Although this document, representing current research advances and future directions, is necessarily static, the strategic planning process is dynamic. Novel findings and new technologies can dramatically and positively

change the course of planned research. Therefore, for this Plan to be successful, it must periodically be assessed by scientific experts in the diabetes research field so that new and emerging opportunities can be identified. The DMICC will serve an important role by assessing progress toward attaining the objectives described in the Plan. The NIH will also continue to solicit the input of the broad scientific community through forums such as scientific workshops, conferences, and planning and evaluation meetings. This input will continue to be a valuable and necessary component of the NIH's strategic planning process for diabetes research.





Numerous candidate genes and genetic regions associated with type 1 diabetes, type 2 diabetes, and obesity have been revealed through genome-wide association studies. (Courtesy of Darryl Leja and Dr. Teri Manolio, [www.genome.gov/gwastudies](http://www.genome.gov/gwastudies), with modifications.)



# GENETIC BASIS OF TYPE 1 DIABETES, TYPE 2 DIABETES, OBESITY, AND THEIR COMPLICATIONS

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## INTRODUCTION

Type 1 diabetes, type 2 diabetes, obesity, and their complications are caused by the joint effects of many genetic, environmental, and behavioral risk factors. Genetic risk variants are present throughout the lifespan, and amenable to study at all times—before, during, and after the development of a disease or disorder. As a result, knowledge of genetic factors offers the potential for prediction, patient stratification, and insights into early precursors of these conditions when preventive therapies might be applied. Such studies contribute to the understanding of disease mechanisms and could also point to potentially modifiable environmental (encompassing behavioral) factors that might affect the initiation and progression of diabetes, obesity, and their complications.

Complex human diseases and disorders, such as diabetes and obesity, are associated with a spectrum of rare and common genetic variants with hundreds of contributing loci in the human genome. Researchers use a technique known as linkage studies to identify causal variants for diseases associated with a single gene—or, as in the case of diabetes and obesity, variants that are relatively rare in the general population but that might have large effects in families that are strongly affected by these serious health conditions (Figure 1). To find more common causal variants that have smaller individual effects on disease susceptibility, researchers turn to association studies (Figure 1). Previously, such studies were limited to the analysis of candidate genes that had been suggested by the biological functions of their gene products. Advances in genotyping and DNA sequencing technologies now permit investigators to search for disease genes throughout the entire human genome in an unbiased manner. Genome-wide

association (GWA) studies can be used to search for rare or common susceptibility genes in affected families or in large groups of individuals who do not have a family history of diabetes or obesity. Using these approaches, researchers have identified, to date, nearly 50 regions in the human genome that harbor risk variants for type 1 diabetes (Table 1), 38 for type 2 diabetes (Table 2), and 17 for obesity (Table 3). Much less is known about the genetic loci that influence susceptibility to diabetic complications.

Genetic factors—both known and those yet to be discovered—do not fully explain an individual's susceptibility to type 1 or type 2 diabetes, complications, or obesity, nor can genetics account for the increasing prevalence of these conditions in the last decade. Indeed, the risk of developing these complex medical problems is substantially influenced by environmental factors. Identifying such factors has been difficult due to the complexity and expense of long-term or cross-sectional studies in at-risk populations and the need to collect and store biosamples for future research to retroactively identify biomarkers of disease development. Nonetheless, researchers are exploring multiple, diverse factors that might play a role in diabetes and obesity, including viral infections and early exposure to cow's milk for type 1 diabetes, and reduced physical activity, increased consumption of manufactured and high-calorie foods, and stress for type 2 diabetes and obesity.

A critical unmet research need is the lack of genetic and environmental risk factor data in populations other than those of European origin, particularly those that are disproportionately affected by diabetes and obesity. The majority of candidate genes and causal variants for

diabetes and obesity have been identified in European-origin populations. The few studies of these genes in African American and Hispanic populations suggest that there may be differences in the importance of specific genes or causal variants from those identified in individuals of European origin. Targeted genomic and epidemiologic research is needed in order to better define the genetic regions of association and to reduce the rate of diabetes, obesity, and complications among high-risk minority populations.

Genetic and environmental factors interact in complex ways. For example, some individuals with high-risk variants in a particular gene might be at low overall risk for a disease (equivalent to the risk of the general population) because they carry variants in other loci that confer protection or because they live in a protective or low-risk environment. Environmental factors can also have a direct impact on genetic risk through direct modification of DNA, without change to the sequence, or through modification of DNA-associated proteins, in ways that confer persistent effects on gene expression—a phenomenon known as epigenetics. DNA marking by methylation or other biochemical reactions can occur during development or at any time throughout the lifespan and affect the way the marked gene is expressed even though the inherited gene sequence is not changed.

Exploring how epigenetic modification influences susceptibility to, and progression of, diabetes and obesity opens up the potential for new paradigms for predicting and treating these conditions.

The identification of genetic and environmental factors can lead to insights about disease pathogenesis. Based on the current collection of implicated genetic risk loci, it is obvious that multiple biochemical pathways are involved in diabetes and obesity, but not all of the pathways are likely to affect risk in the same way. Some may be associated with earlier or later ages of onset, slower or faster rates of beta cell mass loss, carbohydrate metabolism, apoptosis, or different patterns of antigen recognition in the autoimmune destruction of islets. The association may not be with diabetes and obesity per se, but rather with an intermediate phenotype or biomarker (autoantibody, metabolic profile, or related measurement), which, if under control of confirmed disease-associated variants, could be an early precursor of the disorder. By revealing which pathways are involved at different stages of diabetes or obesity, these data can help researchers identify new targets for therapeutic development and determine which people are most likely to benefit from specific interventions—an important step toward personalized medicine.

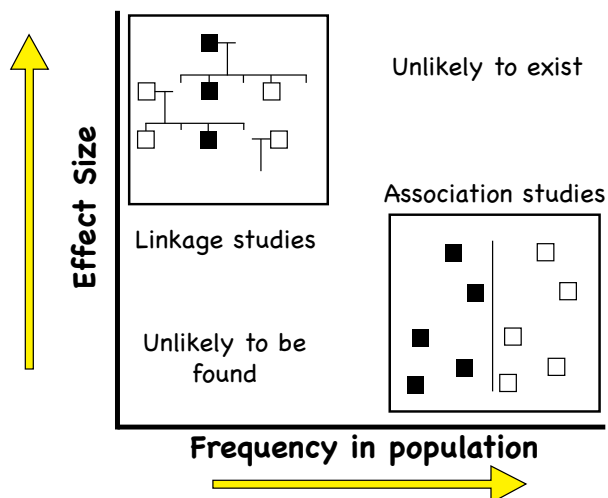


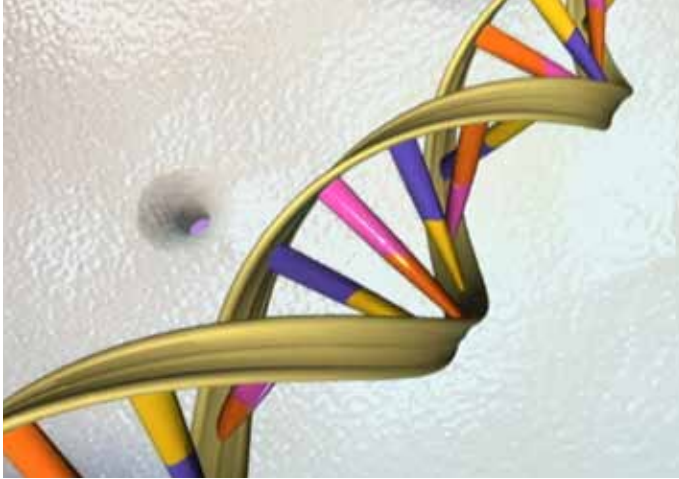
Figure 1. Hypothetical Characterization of Common and Rare Variants Contributing to Common Human Disease and Study Designs for their Discovery.

Low frequency variants with small effect size are unlikely to be found, while there also may be no high frequency variants with large effect size. Association studies are useful for detecting high frequency variants with small effect size, while linkage studies can detect lower frequency variants with large effect size.

**Table 1. Type 1 Diabetes Candidate Susceptibility Genes and Putative Function. Genes and gene regions associated with type 1 diabetes that have been identified and/or confirmed through GWA studies\* are listed here.**

Chromosome	Gene (suggested)	Gene Name	Possible Disease Mechanism
1	<i>PTPN22</i>	protein tyrosine phosphatase, non-receptor type 22	Negative regulator of T cell activation
1	<i>RGS1</i>	regulator of G-protein signaling 1	Regulator of G protein signaling
1	<i>IL10</i>	interleukin 10	Pleiotropic effects in immunoregulation and inflammation
2	<i>IL18RAP</i>	interleukin 18 receptor accessory protein	Enhances IL18 binding activity of IL18R1
2	<i>IFIH1</i>	interferon-induced helicase	Receptor for dsRNA from viral infections
2	<i>CTLA4</i>	cytotoxic T lymphocyte antigen 4	Inhibitory signal to T cells
2	<i>STAT4</i>	signal transducer and activator of transcription 4	Transcription factor for IL12, IL23, and IFN
3	<i>CCR5</i>	chemokine (C-C motif) receptor 5	Chemokine receptor
4	-	-	Unknown
4	<i>IL2</i>	interleukin 2	Proliferation of T and B lymphocytes
5	<i>IL7R</i>	interleukin 7 receptor	Regulation of lymphopoiesis
6	<i>HLA-A, HLA-B, HLA-DRB1, HLA-DQB1</i>	major histocompatibility complex, class I, A major histocompatibility complex, class I, B major histocompatibility complex, class II, DR beta 1 major histocompatibility complex, class II, DQ beta 1	Antigen presentation
6	<i>BACH2</i>	BTB and CNC homology 1, basic leucine zipper transcription factor 2	Maintain IL-2 production
6	<i>C6orf173</i>	centromere protein W	Transcription regulator family
6	<i>TNFAIP3</i>	tumor necrosis factor, alpha-induced protein 3	Inhibit NF-kappa B activation as well as TNF-mediated apoptosis
6	<i>TAGAP</i>	T-cell activation RhoGTPase activating protein	T cell activation
7	<i>SKAP2</i>	src kinase associated phosphoprotein 2	Essential role in the src signaling pathway
7	<i>COBL</i>	cordon-bleu homolog (mouse)	Central nervous system development
9	<i>GLIS3</i>	GLIS family zinc finger 3	Development of pancreatic beta cells
10	<i>IL2RA</i>	interleukin-2 receptor alpha chain	T cell activation
10	<i>PRKCQ</i>	protein kinase C, theta	T cell activation
10	<i>RNLS</i>	renalase, FAD-dependent amine oxidase	Unknown
11	<i>INS</i>	insulin gene	Involved in glucose uptake
12	<i>CD69</i>	CD69 molecule	Role in proliferation, transmit signals in natural killer cells and platelets
12	<i>ERBB3</i>	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Role in cell proliferation or differentiation
12	<i>KIF5A</i>	kinesin family member 5A	Intracellular organelle transport
12	<i>SH2B3</i>	SH2B adaptor protein 3	T cell activation
14	<i>DLK1</i>	delta-like 1 homolog ( <i>Drosophila</i> )	Unknown
14	<i>C14orf181</i>	chromosome 14 open reading frame 181	Unknown
14	-	-	Unknown
15	<i>CTSH</i>	cathepsin H	Degradation of lysosomal proteins
15	<i>RASGRP1</i>	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	T cell receptor signalling
16	<i>CLEC16A</i>	C-type lectin domain family 16, member A	Possible effects on T cell helper function
16	<i>IL27</i>	interleukin 27	CD4+ T cell differentiation
16	<i>CTRB2</i>	chymotrypsinogen B2	Involved in digestion and proteolysis
17	<i>ORMDL3</i>	ORM1-like 3 ( <i>S. cerevisiae</i> )	Involved in protein folding
17	<i>SMARCE1</i>	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	Critical modulator of the androgen receptor
18	<i>PTPN2</i>	protein tyrosine phosphatase, non-receptor type 2	Regulates cell growth, differentiation, mitotic cycle, and oncogenic transformation
18	<i>CD226</i>	CD226 molecule	Positive regulation of Ig-mediated immune response, mast cell activation, NK T cell-mediated cytotoxicity
19	<i>ICAM1, 4, 5</i>	intercellular adhesion molecule 1, intercellular adhesion molecule 4 (Landsteiner-Wiener blood group), intercellular adhesion molecule 5, telencephalin	Involved in adhesion
19	<i>PRKD2</i>	protein kinase D2	Regulates protein kinase C activity
20	<i>SIRPG</i>	signal-regulatory protein gamma	Negative regulation of receptor tyrosine kinase-coupled signaling processes
21	<i>UBASH3A</i>	ubiquitin associated and SH3 domain containing A	Negative regulator of T cell activation
22	-	-	Unknown
22	<i>C1QTNF6</i>	C1q and tumor necrosis factor related protein 6	Unknown
X	<i>TLR8</i>	toll-like receptor 8	Single-stranded RNA recognition
X	<i>GAB3</i>	GRB2-associated binding protein 3	Facilitate macrophage differentiation

\*As of June 2010



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DNA double helix. The four basic units of DNA, or bases, termed “A,” “T,” “C,” and “G,” form sequences of base pairs indicated in blue-yellow and pink-orange. The human genome contains 3 billion base pairs. Variations in the sequences of these base pairs is at the foundation of human diversity—including differences in susceptibility to diabetes, obesity, and their complications. *(Image credit: National Human Genome Research Institute.)*

Knowledge of gene variants and their interactions with environmental risk factors can also inform strategies to predict which individuals are most likely to develop disease over time. In diseases such as type 1 diabetes for which there are no proven prevention methods, identifying genetically at-risk children can lead to earlier detection of disease onset and reduction of the risk of adverse events like diabetic ketoacidosis, which can be fatal if undiagnosed and untreated (see the “Special Needs for Special Populations” chapter). Identification of at-risk children is also essential for research studies testing approaches to prevent disease or to identify environmental triggers. In type 2 diabetes and obesity, the development of prediction models based on genetic, biochemical, and environmental factors can be used to identify high-risk individuals who would most benefit

from lifestyle or pharmacologic interventions that have been shown to prevent or delay their onset. With several proven prevention approaches for type 2 diabetes, genetic risk factors may allow individual tailoring of preventive treatments.

As causal genes, their risk variants, and environmental triggers of diabetes, diabetic complications, and obesity are identified and characterized, their functional utility will become clearer. This chapter on the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” describes how state-of-the-art technologies and resources can be applied to accelerate research on prediction, prevention, and treatment of these complex conditions.

**Table 2. Type 2 Diabetes Candidate Susceptibility Genes and Putative Function. Genes and gene regions associated with type 2 diabetes that have been identified and/or confirmed through GWA studies\* are listed here.**

Chromosome	Gene (suggested)	Gene Name	Possible Disease Mechanism
1	<i>NOTCH2</i>	Notch 2	Beta cell development
1	<i>PROX1</i>	prospero homeobox 1	Beta cell development
2	<i>THADA</i>	thyroid adenoma associated	Unknown
2	<i>IRS1</i>	insulin receptor substrate 1	Insulin signaling
2	<i>GCKR</i>	glucokinase (hexokinase 4) regulator	Glucose metabolism
2	<i>BCL11A</i>	B-cell CLL/lymphoma 11A (zinc finger protein)	DNA binding
3	<i>PPARG</i>	peroxisome proliferator-activated receptor gamma	Insulin sensitivity
3	<i>ADAMTS9</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 9	Metalloprotease
3	<i>IGF2BP2</i>	insulin-like growth factor 2 mRNA binding protein 2	Growth factor regulation
3	<i>ADCY5</i>	adenylate cyclase 5	Insulin secretion
4	<i>WFS1</i>	Wolfram syndrome 1 (wolframin)	Beta cell function
5	<i>ZBED3</i>	zinc finger, BED-type containing 3	DNA-binding
6	<i>CDKAL1</i>	CDK5 regulatory subunit associated protein 1-like 1	Cell cycle regulation
7	<i>JAZF1</i>	JAZF zinc finger 1	Transcription factor
7	<i>KLF14</i>	Kruppel-like factor 14	Transcription factor
7	<i>GCK</i>	glucokinase (hexokinase 4)	Glucose metabolism
7	<i>DGKB/TMEM195</i>	diacylglycerol kinase, beta 90kDa/ transmembrane protein 195	Insulin signaling
8	<i>SLC30A8</i>	solute carrier family 30 (zinc transporter), member 8	Beta cell zinc transporter
8	<i>TP53INP1</i>	tumor protein p53 inducible nuclear protein 1	Unknown
9	<i>CDKN2A/2B</i>	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)/ cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	Cell cycle regulation
9	<i>CHCHD9</i>	coiled-coil-helix-coiled-coil-helix domain containing 9	Unknown
10	<i>CDC123/CAMK1D</i>	cell division cycle 123 homolog ( <i>S. cerevisiae</i> )/ calcium/calmodulin-dependent protein kinase ID	Cell cycle regulation
10	<i>HHEX/IDE</i>	hematopoietically expressed homeobox/ insulin-degrading enzyme	Transcription factor/insulin regulation
10	<i>TCF7L2</i>	transcription factor 7-like 2	Beta cell transcription factor
11	<i>KCNQ1</i>	potassium voltage-gated channel, KQT-like subfamily, member 1	Beta cell potassium channel
11	<i>KCNJ11</i>	potassium inwardly-rectifying channel, subfamily J, member 11	Beta cell potassium channel
11	<i>MTNR1B</i>	melatonin receptor 1B	Circadian regulation/insulin secretion
11	<i>CTCF-binding site</i>	CCCTC-binding factor (zinc finger protein) binding site	Imprinting
11	<i>CENTD2/ARAP1</i>	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1	Unknown
12	<i>TSPAN8/LGR5</i>	tetraspanin 8/ leucine-rich repeat-containing G protein-coupled receptor 5	Unknown
12	<i>HMGA2</i>	high mobility group AT-hook 2	Unknown
12	<i>HNF1A</i>	HNF1 homeobox A	Transcription factor
15	<i>ZFAND6</i>	zinc finger, AN1-type domain 6	DNA binding
15	<i>PRC1</i>	protein regulator of cytokinesis 1	Cell cycle
16	<i>FTO</i>	fat mass and obesity associated	Altered BMI
17	<i>TCF2/HNF1B</i>	HNF1 homeobox B	Beta cell transcription factor
21	<i>KCNJ15</i>	potassium inwardly-rectifying channel, subfamily J, member 15	Beta cell potassium channel
X	<i>DUSP9</i>	dual specificity phosphatase 9	Signaling

\*As of June 2010

## RECENT RESEARCH ADVANCES

Recent advances in molecular, statistical, and computational technologies have rapidly increased knowledge of the genetic contributions to common multi-factorial diseases and disorders, including type 1 diabetes, type 2 diabetes, and obesity. Major examples of these advances are described below.

### Human Genome Sequence, HapMap, and Genome Structure:

The Human Genome Project, a 13-year effort coordinated by the U.S. Department of Energy, the NIH, and the Wellcome Trust, was completed in 2003. The Project goals were to identify all genes in human DNA, determine the sequences of the 3 billion base pairs (bp) that make up human DNA, store this information in databases, improve tools for data analysis, transfer related technologies to the private sector, and address the ethical, legal, and social issues that might arise from the project.

Sequencing the human genome permitted the construction of a more detailed and user-friendly map of genetic variation. The resulting HapMap, a catalog of common genetic variants that occur in humans, describes the type and location of the variants, their size and distribution among and within populations, and their frequency in different populations. The HapMap is based on the fact that genetic sequences between individuals differ at about one in every 1,200 bases, resulting in a genetic variant (also referred to as a marker or polymorphism). The HapMap assists researchers in mapping genetic variants for diseases or phenotypes in a way that can provide increased genomic coverage and pinpoint more discrete areas for follow-up study. Because genetic variants that are near each other tend to be inherited together (forming haplotypes), a

small number of haplotypes can account for the majority of the common genetic variation. The International HapMap Project has identified common haplotypes in four populations as well as “tag” single nucleotide polymorphisms (SNPs) that uniquely identify these haplotypes. The methods now employed for GWA studies use these tag SNPs, which represent a subset of less than 1 million—far fewer than the 10 million common SNPs in the genome—thus avoiding redundant genotyping of millions of common SNPs in genetic studies.

In addition to single nucleotide polymorphisms, every individual's genome has regions that are inserted, deleted, inverted, and duplicated. These rearrangements are in the class of structural variants called copy number variants (CNV). It is estimated that approximately 8 percent of individuals have a 500,000 bp deletion in their genome, a span that is large enough to contain multiple genes. Specific regions in the



Genes play a central role in risk for developing diabetes, obesity, or complications—and can also affect how well a person responds to therapy. Solving the puzzle of how genetic factors interact within cells and with the environment in ways that promote or protect against disease is a critical goal for diabetes research. (Image credit: Erwin Solbach, The Scientific Consulting Group, Inc.)

genome contain duplicated sequences that are prone to recombination and are polymorphic in the population. These regions have been cataloged so they can be studied for their contribution to disease.

Structural variation and its effects on human disease represent a recent development in human genetics research, although large structural changes have long been recognized cytogenetically in rare syndromes. Recent studies suggest that CNV loci are widespread in the human genome and highly variable in size and frequency, with smaller CNVs being more frequent than larger ones. Current estimates, based on available re-sequenced genomes, suggest that each diploid human genome harbors approximately 3,000 CNVs greater than 100 bp, but these estimates are being refined. Two ongoing projects are expanding knowledge of human genome structural variation. The Genome Structural Variation (GSV) consortium ([www.sanger.ac.uk/humgen/cnv/42mio/](http://www.sanger.ac.uk/humgen/cnv/42mio/)) has designed a high-density tiling array across the entire genome to type HapMap samples from 20 participants of Caucasian ancestry from Utah and 20 participants of African ancestry from the Yoruba of West Africa. In parallel, the 1000 Genomes Project ([www.1000genomes.org](http://www.1000genomes.org)) is rapidly expanding the catalog of common CNVs, thus providing another source for CNV discovery and assessment of their linkage disequilibrium (non-random association) with flanking SNPs and small insertion/deletions (indels). Current estimates suggest that dense DNA re-sequencing allows calling of approximately 2,000 deletions greater than 150 bp per densely sequenced diploid genome, in addition to 500-1,000 duplications.

**Genome Architecture:** In addition to providing a new understanding of gene sequences, the Human Genome Project has elucidated many other features of the genome that regulate gene expression. The genome contains sequence elements that serve as regulatory

regions and bind both enhancers and repressors of gene expression, many times in overlapping binding sites so that the binding of an enhancer will interfere with the binding of a repressor. Regions have been identified that insulate genes from the regulatory signals of neighboring genes. Other regions direct the binding of histones that form higher-order chromatin structure. One of the most significant recent findings was the discovery of microRNAs (miRNAs) that are encoded in the genome and are important for coordinating the expression of genes for cellular developmental programs.

**High-Throughput Genotyping:** The Human Genome Project and the International HapMap Project provided a mechanism for characterizing the variation and structure in the human genome that could be used for detecting association between genotype and disease or risk phenotype. Realizing the full potential of these new resources required the development of high-throughput genotyping, a major technological advance. Prior to the HapMap, most genetic studies were performed by genotyping a single (or few) variant on individual samples that would often cost \$1/genotype/sample. A robustly powered study involved thousands of samples and at least 100,000 SNPs had to be genotyped to provide genome-wide coverage. The development of high-throughput genotyping technologies not only dramatically reduced the cost of genotyping (to under \$0.01/genotype/sample) but also reduced the time for completing the experiment to a few weeks. Thus, the same project that previously would cost \$500 million and require a year to complete could be accomplished (with 1 million SNPs) for \$2.5 million in 3 months time.

**Bioinformatics and Sharing Resources:** The volume of data from the Human Genome Project, the International HapMap Project, the 1000 Genomes Project, and individual laboratories has been growing at almost exponential rates over the past 5 years.



The National Center for Biotechnology Information established the Single Nucleotide Polymorphism database (dbSNP) in 1998 ([www.ncbi.nlm.nih.gov/projects/SNP/](http://www.ncbi.nlm.nih.gov/projects/SNP/)) to provide an easily accessible, curated catalog of human genetic variation for use in ongoing research. dbSNP serves as a central public repository for genetic variation and classifies SNPs, insertion/deletions, invariant regions, microsatellite repeats, named variants, and other uncharacterized heterozygous assays. The entries in dbSNP include disease-causing clinical mutations, as well as non-functional (neutral) polymorphisms. The database of Genotypes and Phenotypes (dbGaP) was developed to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype ([www.ncbi.nlm.nih.gov/gap](http://www.ncbi.nlm.nih.gov/gap)). dbGaP provides a repository of genetic results from published studies, including GWA studies, medical sequencing, molecular diagnostic assays, and studies of association between genotype and non-clinical traits.

The NIH also capitalized on major clinical studies to develop shared resources over the past several years that could accelerate genetic discovery in diabetes and obesity. For example, to expand the usefulness of clinical studies by providing access to the biosamples and data to a wider research community, the NIDDK established three Central Repositories for biosamples, data, and genetic information collected in these studies. Materials are available or expected to be repositied from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications Study (EDIC), Genetics of Kidneys in Diabetes Study (GoKinD), Family Investigation of Nephropathy in Diabetes (FIND), Type 1 Diabetes Genetics Consortium (T1DGC) (which also provides summary association results for type 1 diabetes at [www.t1dbase.org](http://www.t1dbase.org)), and other studies. Other NIH clinical

trials and studies, such as the NHLBI-led Framingham Heart Study, have also provided shared resources important for genetic studies.

**Resequencing, the Human Exome Project, and the 1000 Genomes Project:** The International HapMap Project has catalogued more than 1 million SNPs, most of which do not directly influence gene function, in the genome sequences of 269 people drawn from four diverse human populations. Once a candidate gene has been identified, a comprehensive approach to discovery of disease-causing variants is “population resequencing.” In this approach, candidate genes are totally or partially sequenced, and the frequencies of variants are compared between those with and without disease and controls to identify genetic variations that may contribute to disease. One aspect of medical resequencing is developing a catalog of common and rare variation within genes in selected disease entities, such as diabetes and obesity. The Human Exome Project is expanding the content of the catalog by discovering genetic variation in all genes in the general population—not just patients and controls—that can potentially affect gene function directly. The 1000 Genomes Project represents an international consortium to create the most detailed map yet of human genetic variation by sequencing the entire genomes of approximately 2,000 individuals. Interrogation of the 1000 Genomes Project database will provide a means for identifying the full list of SNPs and short insertions/deletions in regions associated with complex human disease, whether they are coding, intronic, or intergenic. Together, the data from the Medical Resequencing Project, the Human Exome Project, and the 1000 Genomes Project are providing resources previously unimagined for genetic research in diabetes, obesity, and related phenotypes.

## GWA Studies and Statistical Developments:

Analysis of the large volume of genetic marker data being generated required improvements in computing and analytic methods. With the number of SNPs approaching 1 million on each individual, strict criteria were required to achieve genome-wide levels of statistical significance. In addition, the increased depth of genetic information permitted more direct evaluation of a primary concern of GWA studies—the effect of bias due to unrecognized population stratification. With the advent of the HapMap and high-throughput genotyping, estimates of admixture and population structure could be made. The results of these advances in detecting and correcting for population heterogeneity improved disease gene detection at an analytic level over the genome.

Several approaches to analysis of genome-wide information have been used. The analysis of single SNPs and structural variants in a single population has been extended in order to pool information across multiple studies or across multiple strata within a single study. Although 1 million SNPs provides excellent coverage of the human genome, gaps remain that could be important. In order to assess the evidence of a candidate region existing in “un-genotyped” regions, an alternative approach to genotyping was developed in recognition that the HapMap contains the relevant information to permit “imputation” on the basis of the candidate region being near a SNP that is in the same haplotype block. Thus, the analytic approach of imputation permitted a statistical approach to provide probabilistic genotypes in regions that are not genotyped in the study, often increasing the information in the genome from less than 500,000 genotyped markers to over 2 million genotyped and imputed markers.

The genetic advances outlined in this chapter greatly increased understanding of the genome sequence, human variation, genotyping, and analytic approaches that have culminated in the discovery of a large number of candidate loci for type 1 diabetes, type 2 diabetes, obesity, and complications as detailed below:

**Type 1 Diabetes:** Ten years ago, only three gene loci had been identified for type 1 diabetes and replicated in many studies: *HLA*, *INS*, and *CTLA4*\*. Approximately 40 to 50 percent of the risk for type 1 diabetes can be attributed to alleles of the *HLA* class II loci in the major histocompatibility locus (MHC). The VNTR (variable number of tandem repeats) in the promoter of the insulin gene (*INS*) had also been shown to be associated with type 1 diabetes. This common variant is thought to influence the expression of insulin in the thymus, thereby affecting the ability of T cells to recognize this protein. The third locus, *CTLA4*, which encodes an inhibitor of T cell signaling, was identified using a functional candidate approach.

More recently, candidate gene studies identified two additional loci, *PTPN22* and *IL2RA*, which also modulate T cell activity. The *CTLA4*, *IL2RA*, and *PTPN22* genes have also been shown to be associated with other autoimmune diseases. The application of genome-wide SNP typing technology to large sample sets and comparisons with results from other diseases have identified new loci for type 1 diabetes, including *IFIH1*. The Wellcome Trust Case Control Consortium (WTCCC) studied 2,000 cases from the JDRF/WT British case collection and 2,500 controls from the British 1958 Birth Cohort (B58BC). In addition, a GWA study conducted on the type 1 diabetes cases from the GoKinD study of diabetic nephropathy added power to

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\* Names of genes/loci associated with type 1 diabetes, type 2 diabetes, and obesity are provided in the Tables.

detect additional loci. The T1DGC studied an additional 4,000 cases from the JDRF/WT British case collection and 2,500 controls from the B58BC. Combining results from these studies and replicating these in further case-control sample sets from Great Britain, Denmark, and the T1DGC families has confirmed nearly 50 genes/loci for type 1 diabetes at genome-wide significance (Table 1). Most of the newly-identified genes seem to affect T cell function and the immune system.

**Type 2 Diabetes:** Although many genes have been identified for rare Mendelian forms of diabetes, no genes were known for the most common form of the disease until 10 years ago. Association studies looking at candidate genes identified two genes associated with type 2 diabetes: *PPARG* and *KCNJ11* (*kir 6.2*). Both genes were selected as candidates because they were targets for diabetes drugs. A SNP genotyping project following linkage mapping studies found an association with *TCF7L2*, a gene coding for a transcription factor. Although variants in this gene confer a 40 percent increased risk of developing diabetes, it is not clear how this factor contributes to the pathophysiology of diabetes. Five groups around the world conducting GWA studies in European-origin populations identified an additional 12 genes for type 2 diabetes. A similar GWA study in Japan identified yet another gene, *KCNQ1*, which encodes a potassium channel subunit. Replication of the top associations from these studies in additional individuals, plus meta-analysis of data from multiple GWA studies, has increased the number of confirmed type 2 diabetes genes/regions to nearly 40 (Table 2). The candidate genes identified to date have modest effects on the disease, and many of them seem to affect the ability of the beta cell to secrete insulin.

**Obesity:** Several genes have been reported to be associated with obesity. GWA studies of individuals with type 2 diabetes identified the gene *FTO*, but its

effect on diabetes was mediated by body mass index (BMI). In addition, the gene *MC4R*, which causes a monogenic form of obesity, has also been associated with common obesity. The Genomewide Investigation of ANthropometric measures (GIANT) consortium combined results from 15 GWA studies for BMI associations in over 32,000 individuals and identified 17 genes that affect BMI (Table 3). Many of the genes, including *MC4R*, are known to act in the central nervous system, consistent with a role in regulating eating behavior and body weight.

**Complications:** Familial clustering of diabetic kidney disease has been identified and replicated in multiple studies using sib-pair and cohort designs. GWA studies have been completed on type 1 diabetes cohorts from the EDIC and GoKinD studies. In addition, the FIND study has used an admixture approach and a GWA study to identify genes predisposing to kidney complications. Several candidate genes have been suggested by these association studies, including those encoding angiotensin-converting enzyme (*ACE*), FERM domain containing 3 (*FRMD3*), cysteinyl-tRNA synthetase (*CARS*), Carnosinase, engulfment and cell motility protein 1 (*ELMO1*), superoxide dismutase 1, soluble (*SOD1*), and vascular endothelial growth factor (*VEGFA*), but no single locus has been convincingly established.

### Gene Expression Using Microarrays and Expression Quantitative Trait Loci Analysis:

DNA microarrays can be used to measure changes in gene expression levels, to detect SNPs, or to sequence genomes. In typical gene mapping approaches, a gene (locus) is detected that contributes to variation in a quantitative trait, such as fasting glucose or BMI—thus termed a quantitative trait locus (QTL). In contrast to traditional QTL mapping, expression QTL (eQTL)

**Table 3. Obesity Candidate Susceptibility Genes and Putative Function. Genes and gene regions associated with obesity that have been identified and/or confirmed through GWA studies\* are listed here.**

Chromosome	Gene (suggested)	Gene Name	Possible Disease Mechanism
1	<i>NEGR1</i>	neuronal growth regulator 1	Neuronal outgrowth
1	<i>SEC16B/RASAL2</i>	SEC16 homolog B ( <i>S. cerevisiae</i> )/ RAS protein activator like 2	Unknown
2	<i>TMEM18</i>	transmembrane protein 18	Neuronal development
3	<i>ETV5</i>	ets variant 5	Unknown
4	<i>GNPDA2</i>	glucosamine-6-phosphate deaminase 2	Unknown
6	<i>PRL</i>	prolactin	Hormone regulation
6	<i>NCR3, AIF1, BAT2</i>	natural cytotoxicity triggering receptor 3, allograft inflammatory factor 1, HLA-B associated transcript 2	Unknown
10	<i>PTER</i>	phosphotriesterase related	Unknown
11	<i>BDNF</i>	brain-derived neurotrophic factor	Regulated by nutritional state
11	<i>MTCH2</i>	mitochondrial carrier homolog 2 ( <i>C. elegans</i> )	Cellular apoptosis
12	<i>FAIM2</i>	Fas apoptotic inhibitory molecule 2	Adipocyte apoptosis
16	<i>SH2B1</i>	SH2B adaptor protein 1	Neuronal role in energy homeostasis
16	<i>MAF</i>	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	Adipogenesis and insulin-glucagon regulation
16	<i>FTO</i>	fat mass and obesity associated	Altered BMI
18	<i>NPC1</i>	Niemann-Pick disease, type C1	Intracellular lipid transport
18	<i>MC4R</i>	melanocortin 4 receptor	Hypothalamic signaling
19	<i>KCTD15</i>	potassium channel tetramerisation domain containing 15	Unknown

\*As of June 2010



Effect of epigenetic changes. This image shows mice that have an identical DNA sequence in a gene that both determines the color of their fur and, when not properly regulated, also promotes obesity. Their different coat colors and body size arise from variation in the chemical modification (methylation) of this gene. Therefore, even though the mice have the same DNA sequence, these epigenetic marks have a dramatic effect on their physical appearance. Moreover, the degree of this chemical modification can be influenced during development by factors such as maternal diet. Regulation of gene activity by epigenetics plays an important role in diabetes, obesity, and their complications. (Image courtesy of Dr. Robert A. Waterland and reprinted from *Journal of Pediatrics*, 149, Waterland RA, *Epigenetic mechanisms and gastrointestinal development*, S137-S142, Copyright 2006, with permission from Elsevier.)

mapping identifies regions of the genome that contribute to variation in gene expression. In eQTL studies, thousands of expression phenotypes are characterized on microarrays and, as a result, thousands of QTLs will be proposed. A major feature of eQTL analysis, therefore, is to study the relationship between the variation in the genome contributing to the quantitative trait and the expression of a gene (the transcriptome). In principle, a massive amount of genome annotation (QTL analysis) can be superimposed onto eQTL information for detection of genetic contribution to expression that may be near (cis) or distant (trans) to the functional gene. Gene expression microarrays have been used in numerous applications, including identifying novel genes associated with certain cancers, classifying tumors, and predicting patient outcome, although much more work needs to be conducted before these techniques can be used clinically. These techniques have begun to be applied to diabetes and obesity and, in the future, could yield clinically relevant information.

### Identification and Treatment of Neonatal

**Diabetes Mellitus:** Neonatal diabetes mellitus (NDM) is a rare genetic condition that usually occurs in the first 6 months of life. Most people with NDM are mistakenly

identified as having type 1 diabetes and treated with insulin injections. Research has allowed attribution of NDM in about 50 percent of individuals to dominant mutations in *SUR1*, *KCNJ11*, or *INS*, or recessive mutations at the gene encoding the enzyme glucokinase, *GCK*. The *SUR1* and *KCNJ11* genes encode the two protein subunits of a potassium ion channel that regulates insulin secretion; the mutations prevent the normal release of insulin from pancreatic beta cells. Genetic testing can be used to identify people who have these mutations and is now recommended for all diabetes diagnosed before the age of 6 months. Recent studies have shown that many of these infants' diabetes can be managed with the oral drug sulfonylurea. Not only is this drug less burdensome than insulin therapy, which requires injections and monitoring of blood glucose, but it also results in improved control of diabetes and less hypoglycemia in children with NDM.

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The last decade has seen major advances in knowledge of the human genome, the development of technologies to probe the genome in a rapid, unbiased, and detailed manner, and the identification of many, though by no means all, causal genes and environmental determinants of diabetes, complications, and obesity. This section builds on these findings by defining key questions and future research directions that aim to identify all causal genes/variants and environmental determinants, understand how these factors interact to cause onset or progression of these conditions, and use this knowledge to better predict, prevent, and treat diabetes, diabetic complications, and obesity.

### Genes and Pathways

Although great progress has been made in discovery of genomic regions that contribute to risk of type 1 diabetes, type 2 diabetes, and obesity, relatively few causal genes have been definitively identified. Moreover, a catalog of causal variants in those genes has not been developed, particularly in populations not of European origin. As researchers continue to discover the candidate genes and causal variants in the regions of interest, it is becoming clear that evaluation of single genes is unlikely to explain the complex biology of diabetes. To address these issues, an integrated approach is needed to identify the sets of genes and gene products that are involved in the biochemical pathways related to diabetes. These pathways could include “known” pathways, such as those involved in immune response, apoptosis, insulin signaling, and insulin action, or might require discovery of previously unrecognized pathways. The resulting

information can be used to create a highly annotated and interactive public database that is specific to diabetes- and obesity-related phenotypes. In this fashion, the genetic architecture of diabetes and obesity at the DNA level can be correlated with the function of genes/variants at the expression and protein levels. This information would provide an “anatomy” of diabetes and obesity genetic susceptibility.

### Key Questions

- **What are the causal genes and variants influencing or residing within each candidate susceptibility locus?**
- **Are the candidate genes/regions identified in European-origin populations (where most of the studies have been performed) also operative in other, ethnically diverse populations?**
- **Do candidate genes/risk variants interact to modify risk, and how is the penetrance of disease alleles affected by environmental factors?**
- **Are there subsets of genes that, taken together, represent a causal pathway that could define a therapeutic target?**
- **What are the effects of identified genetic variants and the integration of genomic, expression, and proteomic profiling on disease risk?**
- **Can genetic variation be coupled with gene expression profiles at the RNA and protein levels to catalog target tissues at the**

**population, individual, and cellular levels for both humans and animal models?**

- **Can model organisms be utilized to advance research from human genetic studies, and can results from model organisms direct targeted human studies?**

## **Future Directions**

- **Develop standardized and emergent protocols for assessing phenotypic characteristics of populations, both clinical and epidemiologic, for use in genetic studies.**
- **Understand how candidate genes contribute to disease risk.**
- **Elucidate the interactions among genes at the cellular level and discover common pathways of risk.**

Numerous attempts have been made to link various genes and environmental factors to diabetes and obesity risk, in order to identify a genetic network or pathway that could be specifically involved in susceptibility. Whether specific subsets of genes and causal variants or pathways of genetic risk factors are important and whether those interact with specific environmental factors in a population have yet to be determined. Addressing these questions requires new and expanded resources and research tools. Studies of large samples will enable researchers to conduct better-powered genomic analysis of targeted candidate genes. Similarly, analysis of diverse populations from multiple ethnic groups with extensive biospecimens and DNA collections will help determine whether genes and pathways identified largely in populations of European origin are broadly applicable. This line of research would be accelerated by ready access to state-of-the-art technologies, such as high-throughput, low-cost DNA sequencing, expression profiling using microarray

technologies and direct DNA sequencing, highly sensitive immunoassays, improved mass spectrometry approaches, such as stable isotope labeling with amino acids in cell culture (SILAC), and the development of accurate animal models with tissue-specific manipulation of variants in candidate genes. High-performance computing and mathematical modeling approaches are needed to conduct pathway analyses that incorporate multiple sources of data. (See also the chapter on “Resource and Infrastructure Needs for Diabetes Research.”)

## **Detection of Rare Variants**

To fully characterize genes associated with diabetes and obesity, large-scale DNA sequencing technologies need to be employed to make human sequencing a tool for both research and medical practice. Human DNA sequencing in large populations would enable identification of both common and rare variants that reside in genes and in intragenic regions. Identifying variation and determining how it influences risk of diabetes and obesity must be developed at both the molecular and the analytic level. The normal range of human variation present in populations may be extensive, and disease may manifest only in the presence of specific environmental or behavioral factors. Thus, characterization of human sequence variation provides a basis for understanding how specific environmental exposures can result in disease. Sequence-based strategies need to be efficiently scaled with developing technology to be complementary with efforts to obtain increasingly precise and reproducible phenotypic data. As more is learned from sequencing about the genomic contribution to diabetes, obesity, and complications, and as the cost of obtaining sequence information decreases, these data will become increasingly important for estimating future disease risk, improving prevention

and diagnostic tools, and treating disease, including prevention of complications.

## Key Questions

- **How can sequence variation that is rare in populations, yet accounts for familial risk of disease, be identified?**
- **Can genomic sequence data from many individuals with known phenotypes provide insight into the effect that natural variation in genome structure has on susceptibility to diabetes and obesity?**
- **What is “normal” sequence variation compared to “risk” variation in the context of environmental triggers that lead to diabetes and obesity?**
- **Can population-specific DNA sequences be identified that are associated with disease risk and that are predictive of response to therapies?**

## Future Directions

- **Perform DNA sequencing in tens of thousands of participants with type 1 diabetes, type 2 diabetes, and obesity to detect all sequence variants that may be associated with risk of these conditions.**
- **Correlate sequence variants with the level of risk for development of diabetes, obesity, and their complications.**

Distinguishing normal and risk sequence variation demands high-throughput, cost effective resources and accessible tools, including: catalogs of sequence variation at all disease-related gene sites for use in comparison across samples and studies; detailed biosample and DNA

collections from large numbers of individuals for the characterization of sequence variation in multi-ethnic populations; access to high-throughput, low-cost DNA sequencing using “next generation” technologies; and Web-based data repositories and bioinformatics and biostatistics tools that can incorporate common and rare sequence variants with existing epidemiological data to model disease risk. The current volume of DNA sequence data has been limited and restricted to “normal variation.”

## Gene-Environment Interactions

Diabetes and obesity are complex human traits that result from both genetic and environmental factors. One factor in type 1 diabetes is thought to be viral infections that, in genetically susceptible individuals, trigger an innate autoimmune process, leading to destruction of the insulin-producing pancreatic beta cells. In type 2 diabetes and obesity, behavioral factors contribute to weight gain, resulting in progressively dysfunctional metabolism of glucose or fat in genetically susceptible individuals. Early functional studies of the *FTO* gene indicate that mutations/variants in this gene alter behavior in a way that can lead to obesity. Thus, the interaction of genetic factors with environmental factors likely explains much of the risk for diabetes and obesity. Diabetic complications also have strong genetic and environmental components. For example, while predisposition to diabetic kidney disease is clearly heritable, poor glycemic control is known to increase the risk of this and other complications. Importantly, the risk factors that trigger disease could be context-specific, meaning that an individual with a genetic variant would also need to be exposed to a specific environmental trigger for the greatest risk to occur. Identification of these interacting partners should provide important insights for risk prevention and early detection of disease.



## Key Questions

- **What kinds of sample and data resources are needed for analyzing genetic variation in groups of participants with diabetes and obesity or in healthy populations before they develop complications, so that environmental triggers can be identified in those at high genetic risk?**
- **How and to what extent will information be collected on environmental triggers, especially unknown/potential triggers for diabetes, obesity, and their complications?**
- **Can research tools used in mouse models of disease be used to identify potential modifier effects in human genetic data?**
- **How can genetically determined epidemiologic risk factors be identified and monitored as biomarkers of exposures that interact with genetic risk variants?**
- **What recent changes in human exposures, diets, or social, cultural, and behavioral activities contribute to onset of disease in genetically predisposed individuals? Can any of these factors be modified to lower risk?**

## Future Directions

- **Determine how candidate genes or sequence variants interact with environmental risk factors that can lead to disease outcome.**

The complexity of the environment is greater than that of the genome, and a personal environment can change regularly. Thus, for each candidate gene/disease variant, many potential interactions with environmental risk factors are possible. As diabetes and obesity develop

over time, the coordinated tracking of exposures with subclinical markers of disease is necessary to characterize the interactions of genes with environments that increase risk. Biomarkers or surrogate environmental predictors are needed to identify agents that trigger disease progression. Environmental factors that might influence the risk of diabetes and obesity include nutrition, stress, physical activity, infections, and the human microbiome, which could influence susceptibility to both major forms of diabetes as well as obesity.

- **Develop resources and technologies to study gene-environment interactions.**

A critical component of genetics research is the development of novel resources and technologies to identify gene-environment interactions. Large, ethnically and geographically diverse cohorts of individuals need to be ascertained to establish research biobanks. Collection of specimens, genotyping for disease variants, and prospective follow-up of participants will help to identify those who are at risk for developing diabetes, complications of diabetes, and obesity, so that they can be asked to participate in detailed phenotypic and behavioral studies. Evaluation of the collected exposure data and biomarkers in the context of genetic risk should enable the identification of factors that are precursors of these complex medical problems and may help predict their outcome.

## Genetics and Health Disparities

A significant level of disparity in the burden of diabetes, obesity, and diabetes complications exists among different ethnic and racial populations living in the United States. African Americans and Hispanics born in 2000 in the United States are estimated to have over a 40 percent lifetime risk for diabetes, a rate that is almost twice that of Americans of recent European origin (3).

They also have a younger age of onset, contributing to their greater risk of complications. From 1980 to 2006, the age-adjusted prevalence of diabetes almost doubled among African Americans, while the age-adjusted prevalence from 1997 to 2006 among Hispanics increased about 20 percent (8). American Indians have the highest prevalence of type 2 diabetes in the United States—after adjusting for population age differences, the rate of diagnosed diabetes in American Indians aged 20 and older is 16.1 percent (1). Obesity is much more prevalent in African Americans than those of European origin. Diabetic complications also disproportionately affect African Americans and Hispanics. In 2006, African Americans with diabetes were more than twice as likely to be diagnosed with end-stage kidney disease due to diabetes as those of European origin; similarly, there was almost a 70 percent greater likelihood of this diagnosis among Hispanics, after adjusting for population age differences (9). Ethnic differences, such as diet, life factors, and disease risk, appear to be present from conception through the entire lifespan.

## Key Questions

- **Are genes and risk variants for diabetes and obesity in ethnic and racial minority groups in the United States, such as African American, Hispanic, Asian, and American Indian populations, the same as those found in populations of European origin?**
- **Are genetic variants identified in ethnic and racial minority populations for diabetes and obesity risk also predictive of pre-clinical disease, and do these variants interact with non-genetic risk factors similar to those identified in populations of European origin?**
- **Do genetic factors in minority populations**

**predict outcome of treatment and complication risk?**

## Future Directions

- **Identify the genetic and environmental bases of differences in diabetes onset, progression, and response to treatment in high-risk, minority populations.**

Research in genetics, social structures, cultural factors, behavior, and risk modification should focus on populations not of European origin that are at greatest risk to develop diabetes and obesity. Genetic research can aid in prediction and prevention of diabetes, obesity, and their complications in high-risk groups. Research is needed not only to screen minority populations for genes identified in populations of European origin, but also to search for evidence of novel genetic susceptibility factors in diverse populations. This knowledge could point to new methods for early screening and treatment of diabetes and obesity using genetic-risk-based approaches. Identification of genetic factors that predict outcome to treatment and complication risk could improve diabetes care and treatment of major complications. Finally, the ability to identify individuals with high genetic risk for developing type 2 diabetes and obesity would inform the design of clinical trials to prevent their onset in racial and ethnic minority populations in the United States. Working with minority communities in an integrated approach could be beneficial for advancing research on the genetic and environmental triggers of diabetes and obesity.

## Epigenetic Contributions to Risk

In addition to genetic factors, disease susceptibility may be determined, in part, by environmental influences

that occur during development. It is possible that single nutrients, toxins, behaviors, cultural factors, environmental exposures, or combinations of these factors can alter the expression of genes. These genes may be already recognized as containing sequence variants that influence risk for diabetes, diabetic complications, and obesity, or they may be unknown but important once modified. This process, known as “metabolic imprinting,” can affect the establishment of gene regulation during development, providing a potential biologic mechanism for disease susceptibility. Epigenetics is the study of persistent changes in gene expression that are not due to DNA sequence variants. Animal studies have suggested that epigenetic variation can contribute to obesity and, perhaps, diabetes. Epigenetic changes may help explain how gestational diabetes contributes to the long-term risk of diabetes and obesity in the offspring of affected pregnancies. Studying these changes may also contribute to understanding how a finite period of good glucose control early in the course of diabetes can slow the development of diabetes complications decades after the limited period of intensive management. Although the mechanism of this “metabolic memory” remains to be established, epigenetic changes provide a possible explanation. (See also the “Diabetes Complications” chapter for discussion of metabolic memory.) Changes in the environment (e.g., diet, exposures to various agents, stress) that induce epigenetic modification could account for much of the increased prevalence of diabetes and obesity in the United States.

### Key Questions

- **Do DNA methylation and other aspects of epigenetic modification contribute to inter-individual variation in the risk of diabetes, obesity, and diabetes complications?**

- **Do epigenetic mechanisms correlate with risk and serve as therapeutic targets?**
- **What is the potential interaction between epigenetic modification and a pro-inflammatory environment and oxidative stress, and how does this interaction affect the risk of diabetes and obesity?**

### Future Directions

- **Identify epigenetic markers that influence susceptibility to diabetes, obesity, and/or diabetes complications.**

Environmental exposures at any time from fetal development through adulthood may trigger a chemical change, such as a methyl group binding to a base in a gene or in a gene regulatory sequence, resulting in aberrant gene silencing or activation. In this manner, diet (i.e., nutrients), metabolic change (i.e., activity, glucose or lipid levels, inflammation), or exposures to pathogens (infection, toxins) can result in biochemical changes in specific target genes that may affect the risk of diabetes, obesity, or response to therapy. Research is needed to determine the role of specific exposures on embryonic or fetal development and correlate those exposures with clinical phenotype. The impact of social (stress), behavioral (maternal care), and environmental (pesticide, toxins, synthetics) factors on epigenetic changes and risk of diabetes, obesity, and diabetes complications must be considered with respect to health disparities. Existing biosamples and DNA can be used to detect epigenetic changes related to known diabetes and obesity genes or to environmental exposures. With enhanced knowledge of the impact of epigenetic changes on disease susceptibility, researchers can explore the potential for de-methylation therapies using dietary (e.g., vitamins, nutrients) and pharmacological

approaches to prevent or reverse risk for diabetes and obesity.

## Translation of Genetic Research from Bench to Bedside

Diabetes and obesity are characterized by an extended pre-clinical period during which change in normal function escalates into subclinical and clinical disease. In the case of type 1 diabetes, autoimmune destruction depletes beta cells and reduces the capability to secrete insulin and maintain glucose homeostasis. In type 2 diabetes, insulin resistance and beta cell dysfunction play important roles in progression of the disease as well as in deterioration of glycemic control and risk of complications. Obesity is often marked by long-term weight gain with concomitant increase in caloric intake, decrease in physical activity, and linked risk of type 2 diabetes. Each biological process, therefore, exhibits a pre-clinical period that provides a window for interventions. These interventions could act to prevent overt disease by slowing or halting the progression of immune or metabolic dysfunction. Similarly, diabetic complications develop over the course of the disease, offering the opportunity to intervene to delay or avert their onset.

Scientific discoveries must be translated into practical applications to reduce risk of diabetes and obesity. This bench-to-bedside approach to translational research requires that basic scientists provide clinical researchers with new tools for use in patients and for assessment of their impact. Simultaneously, clinical researchers need to make novel observations about the nature and progression of treatments in order to stimulate new basic research. Translational research has proven to be a powerful process that drives the clinical research engine. However, a stronger research infrastructure could strengthen and accelerate this critical part of the

clinical research enterprise with respect to diabetes and obesity in all populations.

## Key Questions

- **How can the development of diabetes and obesity investigators who are well-trained, multidisciplinary and interdisciplinary, and able to form research teams be fostered?**
- **Can an incubator be created for innovative research tools and information technologies focused on translational and behavioral research in diabetes and obesity?**
- **Will current guidelines on human participants research permit synergism of multidisciplinary and interdisciplinary clinical and translational research to facilitate the application of new knowledge and techniques in clinical practice?**
- **Can opportunities be developed to bring physiologists (both animal and human) into a productive collaboration with geneticists to bridge research gaps?**
- **What methods can be developed to translate novel techniques of prediction, prevention, and treatment into the general community?**

## Future Directions

- **Optimize the use of genetic and environmental risk factor data in the design of translational and clinical research programs for diabetes and obesity.**

The design of translational research paradigms and development of clinical trials requires very careful risk/benefit analysis that puts a premium on prediction of disease risk and potential outcome. As part of optimizing both the collection and use of data in these

studies, they should be designed to provide access to all individuals interested in participation and not restricted to any one group (defined by ethnicity, socioeconomic status, etc). Similarly, application of new technologies for the treatment, prevention, and prediction of diabetes and obesity should be open and transparent to all individuals. Innovative processes are needed for recruitment and retention of high-risk populations for diabetes and obesity. Therapies identified from research protocols with higher risk of adverse effects should be matched to participants with higher predicted risk of developing diabetes or obesity. Risks should be proportionate to potential benefit, and risks to children should be limited. The ability to provide novel therapies for diabetes and obesity would be advanced by the development of regional, centralized provider networks that can provide these therapies at high volume and distribute them rapidly to health care providers and researchers for application to all populations. Biomarkers that could more accurately predict response to specific types of therapies would increase the efficiency of trials and enable potential earlier intervention, at a stage where pre-clinical intervention may improve outcomes.

## Pharmacogenetics/Pharmacogenomics

Pharmacogenomics, the branch of pharmacology and genetics that studies the influence of genetic variation on drug response, is performed by correlating SNP and/or gene expression data with a drug's efficacy or toxicity. Pharmacogenomics (on a genome-wide level) attempts to develop rational means to optimize drug therapy, with respect to a person's genotype, to ensure maximum efficacy with minimal adverse effects. As more genes and pathways that contribute to disease

are identified, the same technologies can be used to personalize the prediction of response to treatment. One use of this growing genetic technology is to identify individuals whose response to particular drugs is determined, in part, by their genes. GWA studies and candidate pathway approaches have identified genes in populations that lead a person to respond to lower doses of drugs, experience adverse drug effects, or not respond to a particular drug at all. For example, the FDA has approved a genetic test to help assess warfarin sensitivity, as one-third of people metabolize this anti-coagulant medication more slowly than the general population and, therefore, experience a higher risk of bleeding. In this case, some of the previously unexpected response to warfarin depends on variants of two genes, the cytochrome P450 2C9 gene (*CYP2C9*) and the vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*). Some of these genetic differences are responsible for individual differences in drug metabolism. Currently, studies are under way to examine genetic differences that lead to different responses to drugs in people with or at risk of type 2 diabetes. In the NIH-led Diabetes Prevention Program clinical trial, which tested interventions to prevent or delay type 2 diabetes in people at high risk, treatment with metformin reduced the risk of developing diabetes by 31 percent among participants in that arm of the study relative to the control group. However, further analysis revealed that metformin was not effective in study participants carrying a lysine at a particular position in the protein encoded by *KCNJ11*, while it was effective in participants with a glutamate at that position. One of the first uses of genetics for personalized medicine may be to test individuals to determine which drug regimen would be most effective.

## Key Questions

- **What are the genes and variants that predict response to specific treatments of diabetes and obesity?**
- **Do genes that are identified for treatment response correlate with genes that predict risk of complications?**
- **Are genetic variants for response to treatment the same in different ethnic and racial populations, and do these variants interact with similar non-genetic risk factors?**
- **Is the use of genetic information in disease management cost effective? Does it lead to better patient outcomes?**

## Future Directions

- **Identify the genetic and environmental bases of differential response to pharmacologic treatment of diabetes and obesity, as well as their relationship to progression and complications of disease.**

Research in pharmacogenomics should focus on the relationship between inherited predictors of response to pharmacologic agents used in the treatment of diabetes (type 1 and type 2), obesity, and diabetic complications. Differential response to drugs used in treatment of these diseases has been observed across all population and ethnic groups. While some of the variation in response can be attributed to factors related to health status, compliance, and other confounding factors, there is a clear role for genetic factors. Pharmacogenomics can be applied to the problems associated with treatment of disease and complications at several levels. Genes that are associated with successful treatment of diabetes

and/or obesity may identify a molecular mechanism that provides insight on the etiologic framework of the disease. Variants in genes that predict treatment response can influence drug design in ways that could improve efficacy of the compound. Differential effects of genes across populations, including the interaction of genes with environmental risk, can be used to stratify populations in early efficacy studies or trials to improve the quality of clinical decision making and treatment options. Importantly, the identification of genes associated with adverse drug effects can greatly improve quality of life and reduce pharmacologically mediated morbidity and mortality. Thus, pharmacogenetic research will be of key importance to developing strategies to individualize diabetes prevention and therapy.

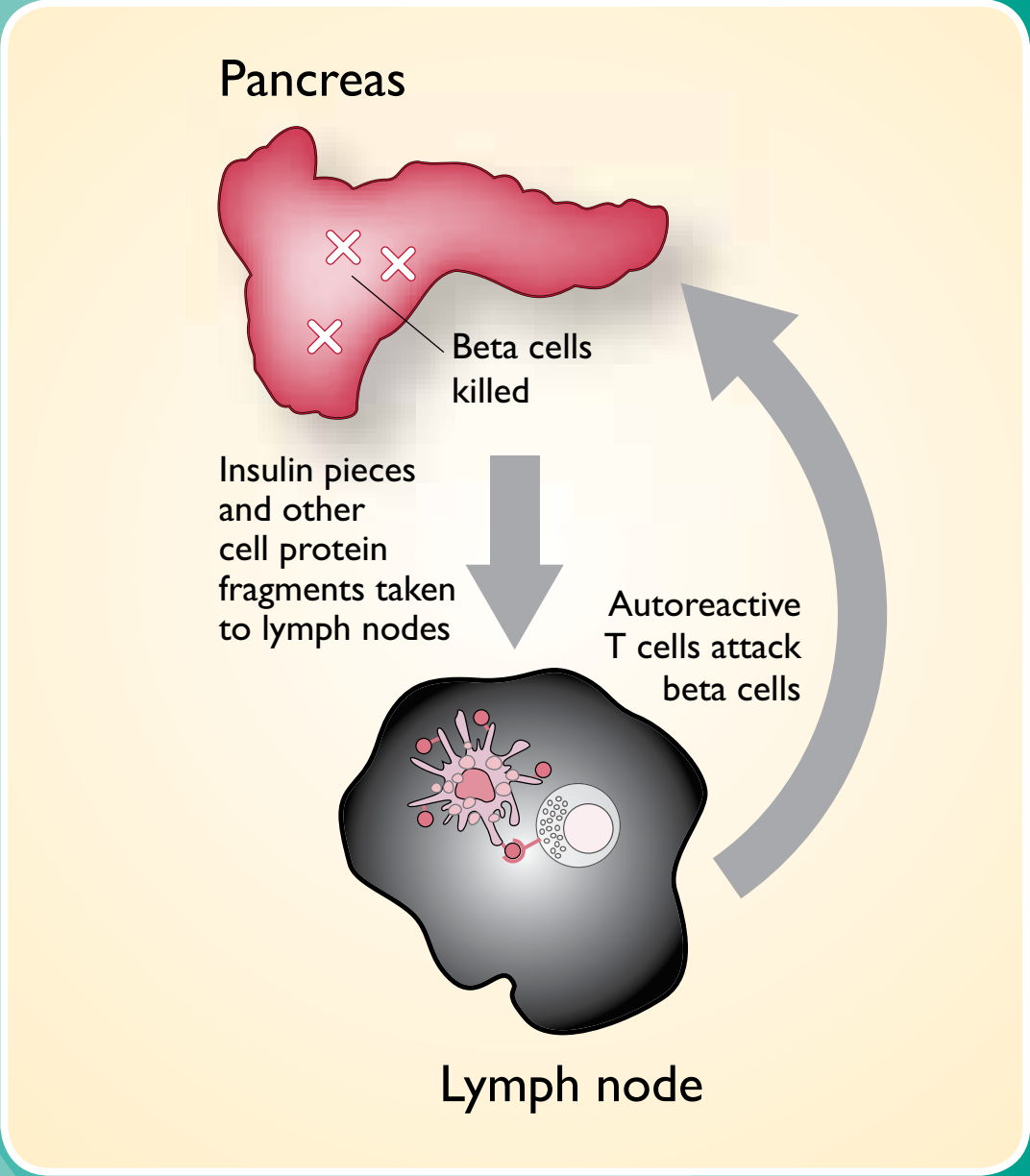
- **Evaluate the utility of genetic information from a public health perspective.**

Direct-to-consumer commercial companies are marketing genetic tests to the population; yet, whether these tests lead to better patient outcomes or improve health at the population level is unknown. Behavioral research into motivational strategies that improve patient behavior, outcomes research that validates the use of genetic results, and economic research that evaluates the feasibility of deploying point-of-care genetic testing must be carried out. As genetic information emerges, there is a need for trials that specifically address the question of whether *a priori* knowledge of genetic information 1) affects patient or practitioner behavior, 2) leads to better patient outcomes, and 3) is cost effective. Some of these studies can be initiated before a comprehensive set of genetic determinants associated with type 1 diabetes, type 2 diabetes, and obesity is compiled.

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

Both genetic and environmental exposure data can provide important leads into new therapeutic strategies, identify new treatment targets, and define the utility of many forms of treatment for diabetes, diabetic complications, and obesity. For example, therapy of children with a rare neonatal form of diabetes has been transformed by the identification of the genetic basis of the disorder and use of targeted therapy. Despite the complexity of the more common forms of diabetes, there has been substantial progress in the ability to identify individuals at increased genetic risk. Important new information about how genetic variation affects disease risk and response to therapy is emerging that will create opportunities to improve the health of people who are

living with these diseases or at risk of developing them. Genetics research could be used to identify people who are at high risk of developing diabetes or obesity so that they can be enrolled in prevention programs, where available, or closely monitored for disease development so that appropriate treatment can begin immediately at disease onset. Genetics information could also help clinicians identify which people are most likely to benefit from specific therapies and which have an elevated risk for adverse events. Assembling interactive, multidisciplinary teams of investigators will facilitate greater translation of genetics research into the clinical arena and public health.



The cycle of autoimmune attack in type 1 diabetes. Incited by various signals, immune T cells launch a misguided attack on beta cells in the pancreatic islets. Destruction of beta cells releases proteins, including insulin, that reinforce the autoimmune response. (Image courtesy of Focus, Harvard Medical School.)



# TYPE 1 DIABETES AND AUTOIMMUNITY

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## INTRODUCTION

Each year, thousands of children and young adults are diagnosed with the autoimmune disease type 1 diabetes—usually without warning. By the time they are diagnosed, their insulin-producing beta cells have been partially or completely destroyed. Without insulin, patients lose the ability to regulate uptake of dietary glucose into cells and tissues—effectively starving the body while blood glucose levels continue to rise. Patients are faced with a lifetime of insulin replacement therapy, administered via shots or an insulin pump, to control blood glucose levels; bouts of dangerously low or high blood glucose; and the threat of long-term health complications. While research supported by the NIH, other Federal agencies, voluntary organizations, and industry has made it possible for people with type 1 diabetes to live longer and healthier lives, the overarching research challenge remains to elucidate the disease, thwart its development and progression, and ultimately arrive at a cure. Fostering discovery in type 1 diabetes diagnosis, development, and the role of the immune system remains key to overcoming this research challenge.

When the symptoms of type 1 diabetes strike, it is a late stage event in a progressive, misguided destruction of the beta cells by the immune system—a process called autoimmunity. Normally, the immune system protects the body against infectious disease and cancer by destroying pathogens and tumor cells. In autoimmunity, a sub-population of the immune system T cells escapes a natural process of elimination by the body and instead can go on to incite tissue damage and disease. In persons who are genetically susceptible to developing type 1 diabetes, these rogue cells migrate to the pancreas, zeroing in on the cell clusters called islets

where beta cells reside. There, they can spark an immune system response that eventually destroys the beta cells, resulting in the need for insulin replacement therapy.

The misguided destruction sparked by autoreactive T cells in type 1 diabetes targets insulin and other normal, “self” beta cell proteins as if they belonged to dangerous microbes. For example, antibodies generated by the autoimmune response (autoantibodies) neutralize healthy beta cells bearing target protein(s) (antigen). A key objective of research to prevent or reverse type 1 diabetes involves finding a way to re-instill immune tolerance—the process by which the immune system considers a protein or other molecule as self, and does not mount a destructive response against cells or tissues containing that protein. This could require, for example, removing the rogue T cells, or forcing them into a non-reactive state. Several NIH-funded multi-center clinical trial networks are involved in major research efforts focused on solving this problem, including, but not limited to, the Immune Tolerance Network (ITN), the Type 1 Diabetes TrialNet, and the Cooperative Study Group for Autoimmune Disease Prevention. The induction of tolerance could, in theory, block the autoimmune process underlying type 1 diabetes. Thus, tolerance has been at the basis of design of many promising, new strategies to combat this disease.

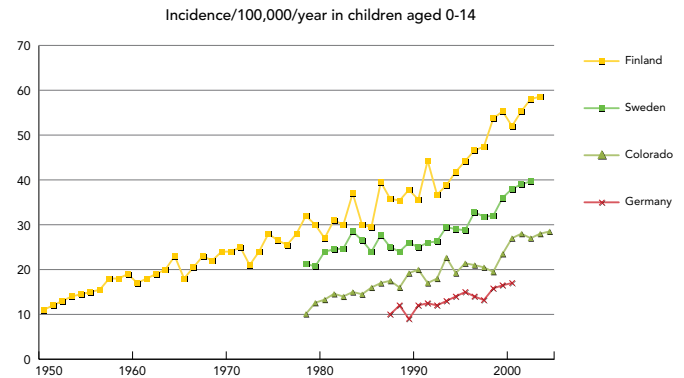


Testing blood glucose. Although it can strike at any time, type 1 diabetes most often strikes in youth and young adulthood, leading to a lifetime of blood glucose testing and insulin administration, via shots or a pump, to manage the disease and prevent or delay serious health complications. (Photo credit: © iStockphoto.com/MarkHatfield)

Indeed, a series of cell- or drug-based therapies, some of which are already in use for other medical conditions, are being tested both alone and in combination. Because people with type 1 diabetes are prone to developing other autoimmune diseases as well, researchers are also seeking clues to type 1 diabetes in the overlap and distinctions between these diseases.

Ideally, effective therapies to induce tolerance should selectively halt harmful immune processes without requiring lifelong suppression of a patient's entire immune system. For this reason, researchers are working toward so-called "antigen specific therapies," which would disrupt a particular defect in the immune system (e.g., a misguided response to a protein or other molecule), and are also designing studies to determine whether short-term immune suppression will allow resetting of the body's immune regulation and thus amelioration of beta cell destruction over time. Such efforts are the focus, for example, of the Type 1 Diabetes TrialNet multi-center clinical trials network. Although T cells are generally considered to represent the primary mediators of type 1 diabetes, clinical trials are also

testing treatments that target the immune system's B cells—e.g., anti-CD20 therapy—as there is increasing evidence that these cells play a role in promoting disease.



Incidence of type 1 diabetes in children, from neonates to age 14 years, is rising 3 to 5 percent per year. NIH-funded research studies, such as TEDDY, are being pursued to identify the environmental factors responsible. (TEDDY Study Group (2008). *The Environmental Determinants of Diabetes in the Young (TEDDY) Study*. *Ann NY Acad Sci* 1150:1-13. © 2008, John Wiley and Sons. Reprinted with permission.)

While such trials are under way, research on the causes of type 1 diabetes is also moving forward. Scientists are striving vigorously to understand the interactions between the environment and the immune system, as well as the means by which genes influence immune responses resulting in autoimmunity. The ongoing The Environmental Determinants of Diabetes in the Young (TEDDY) study is an important part of this effort. Interest has also grown in terms of identifying the roles that more "primitive" or less specific arms of the immune system, including innate immunity and inflammation, may play as contributors to the complex pathogenesis of this disease (see sidebar, "Inflammation and Immunity: Reaching into All Diabetes"). For example, evidence is growing for the role of inflammatory cells, such as mast cells and neutrophils, and cells of the innate immune system, such as NK or natural killer cells, in type 1 diabetes pathogenesis. Interest has also been sparked in the possible role of a small population of cells of the

immune system that seem to bridge non-specific and specific immunity (the natural killer T cells, or NKT cells). At the same time, scientists are studying the role of other important immune system cells, including dendritic cells, which are specialized antigen-presenting cells that can either activate immunity or induce self-tolerance. The target tissue for the destructive process, the pancreas, has also seen a marked renewal in research interest after lying fallow for a period of decades. This effort has provided much in the way of understanding the natural history of beta cell destruction in the disease and, when combined with the efforts in cell biology on beta cell regeneration

(see “The Beta Cell” chapter), provides hope for novel avenues of reversing type 1 diabetes in those with established disease.

The multi-faceted research efforts already under way to help bring about an end to the burden of type 1 diabetes continues to be shaped by new knowledge and discovery. The remainder of this chapter focuses both on major research advances and on new and emerging opportunities for research on type 1 diabetes and autoimmunity that could lead to achieving this important goal.

## RECENT RESEARCH ADVANCES

In just the past several years, scientists have learned a great deal about the immune system and how its normally protective functions go awry in type 1 diabetes and other autoimmune diseases. Technological developments have enabled scientists to image cells and tissues in living organisms. These advances have accelerated other, clinical efforts to develop therapeutic approaches to prevent, reverse, or treat type 1 diabetes. The following are some major examples of research that has advanced understanding of type 1 diabetes and autoimmunity.

**Islet Cell Transplantation To Reverse Long-Standing Type 1 Diabetes Continues To Show Promise:** After years of attempts, reproducible insulin independence has been achieved in humans receiving islet transplants as treatment for type 1 diabetes. Indeed, studies published a decade ago, emanating from Edmonton,

Canada, suggested that long-term (more than 2 years) islet survival and maintenance of function could be achieved. A key part of this early success was the adoption of treatment with agents that showed promise in preventing rejection and recurrent autoimmunity without suppressing or altering beta cell function. Even partial graft function allows for maintenance of improved metabolic control in clinical recipients. The so-called “Edmonton protocol” paved the way to many new approaches in islet transplantation currently under study to provide for better safety and glycemic control (e.g., new enzymes and procedures for islet isolation, novel drug regimens, and insulin independence following transplant with islets from a single organ donor). For example, a variety of drug regimens are being tested in clinical trials (see Table 1). Researchers are also testing the use of agents that interfere with inflammation and coagulation in the early post-transplant period

to determine if they can augment islet engraftment and survival. Such trials will also inform attempts to interfere with pathogenesis just before or just after diagnosis, as it is expected that agents that interfere with re-emergence of autoimmunity in the transplant could also be used to treat the primary autoimmunity underlying type 1 diabetes.

### New Studies of Promising Therapeutics Spurred by Clinical Trials that Assessed Safety and Efficacy of Treatments To Prevent or Delay Type 1 Diabetes:

Multiple agents have been tested in people at risk for developing type 1 diabetes to examine their effect on preventing or reducing the incidence of the disease. Completed trials include tests of nicotinamide, as well as injectable, nasal, and orally delivered insulin.

While some of these agents failed to show a direct beneficial effect overall, the oral insulin trial within the Diabetes Prevention Trial-Type 1 (DPT-1) conducted an *ad hoc* analysis of a subpopulation of treated participants who had higher levels of autoantibodies against insulin and found a significant (4 year) delay, on average, in diabetes onset in these patients—a finding currently being replicated in a trial conducted by the Type 1 Diabetes TrialNet. Furthermore, in people with newly-diagnosed type 1 diabetes, therapeutic agents have been found that preserve beta cell function, as evaluated by measurement of C-peptide (a by-product of insulin production). These findings are leading the way to new trials to prevent or delay the disease in people at risk for type 1 diabetes (see Tables 2 and 3).

**Table 1: Drug Trials in Islet Transplantation. A selection of ongoing or recently completed trials. Please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for more information.**

Agent	Mechanism/Target (if known)	Clinical Trial Phase for Islet Transplantation Use
Anti-LFA-1, efalizumab (Raptiva®)	Monoclonal anti-CD11a	I-II
Anti-CD3, teplizumab	Monoclonal anti-CD3	I-II
Mutant CTLA-4Ig, belatacept	Co-stimulatory blockade	II
Extendin-4 (Byetta®)	GLP-1 like activity for beta cell protection/growth	I-II
CD34 <sup>+</sup> cells	Stem cell immune modulation	I-II
TNF alpha antagonist		
1. Infliximab (Remicade®)	1. TNF alpha monoclonal antibody	1. I-II
2. Etanercept (Enbrel®)	2. TNF receptor 2-human IGG1 fusion protein	2. I-II, III
Anti-CD52, alemtuzumab (Campath-1H®)	Monoclonal T-cell depleting antibody	I-II
Anti-thymocyte globulin (Thymoglobulin®)	T cell depletion	I-II, III
Deoxyspergualin, gusperimus	Anti-inflammatory and immunosuppressive through inhibition of NFkappa B signaling and T/B cell antigen presenting cell differentiation	II
Anti-CD20, rituximab (Rituxan®)	B cell depletion	II
Sirolimus (Rapamune®)	mTOR inhibitor	I-II, III
Tacrolimus (Prograf®)	Calcineurin inhibitor	I-II, III
Mycophenolate mofetil (CellCept®)	Inosine monophosphate dehydrogenase inhibitor	I-II, III
Cyclosporine A (Neoral®)	Calcineurin inhibitor	I-II, III
Mycophelolate sodium (Myfortic®)	Inosine monophosphate dehydrogenase inhibitor	I-II, III
Daclizumab (Zenapax®)	Monoclonal anti-IL-2 receptor antibody	I-II, III
Basiliximab (Simulect®)	Monoclonal anti-IL-2 receptor antibody	I-II, III
Abatacept (Orencia®)	Co-stimulatory blockade	I-II
Lisofylline	Anti-inflammatory	II
Everolimus (Certican®)	mTOR inhibitor	I-II
Low dose corticosteroids	Anti-inflammatory	I-II, III
Low molecular weight dextran sulfate	Innate immune response inhibitor	II
IL-1-antagonist IL-1 Ra, anakinra (Kineret®)	IL-1 receptor antagonist	I-II
Anti-CD2, alefacept (Amevive®)	Anti-CD2 (memory T cells and NK cells)	I

**Table 2: Agents Under Study for Reversal of Type 1 Diabetes. Listed in the table is a selection of ongoing or recently completed trials. Please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for more information.**

Agent	Mechanism/Target (if known)	Clinical Trial Phase
Anti-CD3, teplizumab and oteplizumab (Tolerx®)	T cell immunomodulation	II-III
GAD alum (Diamyd®)	Antigen-specific tolerance vaccination	II-III
HSP60 (DiaPep277®)	Antigen-specific tolerance vaccination	II-III
Anti-CD20, rituximab (Rituxan®)	B cell depletion	II
CTLA4Ig, belatacept	Costimulation blockade	II
Anti-thymocyte globulin (Thymoglobulin®)	T cell depletion	II
Interleukin-1 (IL-1) pathway antagonist, anakinra (Kineret®)	Anti-inflammatory and improve beta cell survival	II
Alpha-1-antitrypsin (Aralast®)	Anti-inflammatory	II
Adult human mesenchymal stem cells (Prochymal™)	Impart immune regulation	II
GAD alum (Diamyd®), lansoprazole (Prevacid®), sitagliptin (Januvia®)	Enhancing GLP-1 and gastrin function for beta cell protection/growth, antigen specific immunomodulation	II
Closed-loop metabolic control at diagnosis	Intensive glucose control spares beta cell function	II
Imatinib (Gleevec®)	Protein tyrosine kinase inhibitor	II (pending)
Insulin B-chain	Antigen-specific tolerance vaccination	I-II (pending)
Statin, atorvastatin (Lipitor®)	Anti-inflammatory and lipid modulation	I
T regulatory cell therapy	Augment regulatory T cell numbers	I (pending)
Autologous dendritic cell therapy (with and without peptides from beta cell antigens)	Tolerogenic vaccine	I
Interleukin-2 (IL-2) (Proleukin®) and sirolimus (Rapamune®)	Downregulates T effector while sparing T regulatory function	I
Umbilical cord blood infusion	Enhance T regulatory cell numbers	I
Granulocyte-colony stimulating factor (Neulasta®)	Enhance T regulatory cell numbers	I
Anti-thymocyte globulin (Thymoglobulin®), granulocyte-colony stimulating factor (Neulasta®) “PowerMix” (Mixture of two Ig-cytokine fusion molecules, one an IL-2 agonist the other an IL-15 antagonist)	T cell depletion, enhance T regulatory cell numbers	I-II
Interleukin-1 (IL-1) receptor, canakinumab (Ilaris®)	Suppression of T effectors while sparing T regulatory function	Pre-clinical/ I
Interleukin-1 (IL-1) receptor, canakinumab (Ilaris®)	Anti-inflammatory	II (pending)
Bayhill’s DNA vaccine 3021 (proinsulin)	Antigen-specific tolerance or regulation induction	I-II
Anti-CD2, Alefacept (Amevive®)	Anti-CD2 (memory T cells and NK cells)	I-II (pending)
Inhibitor of interleukin-1beta, XOMA 052	Anti-inflammatory	II

## New Markers Discovered for Identifying Type 1 Diabetes-Susceptible Individuals Prior to Disease Onset:

Scientists recently discovered a new autoantibody that is an excellent additional marker for identifying pre-clinical type 1 diabetes, and improves the ability to predict disease when combined with previously known autoantibodies. With the discovery of this fourth major autoantibody (Zinc Transporter 8 (ZnT8) autoantibody), and analysis of large cohorts of children, autoantibody prediction of type 1 diabetes risk continues to gather strength, with increasing evidence for its feasibility both for relatives of people with type 1 diabetes and, more importantly, for the general population. Approximately 1 million Americans express

multiple autoantibodies targeting islet proteins (i.e., rate of 1/300) and are at high risk of progression to type 1 diabetes. Prediction using autoantibodies, combined with increasing refinement of genetic and metabolic prediction, sets the stage for prevention trials at multiple stages of the disease.

## Identification of Key Self-Antigens in Type 1 Diabetes:

Scientists have learned that insulin is a critical antigen for the development of type 1 diabetes in non-obese diabetic (NOD) mice, and have identified several other antigens recognized by autoreactive CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, or by autoantibodies in mice or humans (several of them shared between the two

**Table 3: Agents Under Study for Prevention of Type 1 Diabetes.** Listed in the table is a selection of ongoing or recently completed trials. Please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for more information.

Agent	Mechanism/Target (if known)	Clinical Trial Phase
Oral insulin	Oral antigen specific tolerance	II
Omega-3 fatty acids	Anti-inflammatory	Pilot
Hydrolyzed milk	Unknown	II
Nasal insulin	Mucosal antigen specific tolerance	II
Oral and nasal insulin	Oral and mucosal antigen specific tolerance (prePOINT study)	Pilot
Anti-CD3, teplizumab	Monoclonal anti-CD3	II

species). Other proteins resident to beta cells, including islet-specific G6Pase-related protein (IGRP), glutamic acid decarboxylase (GAD), and ZnT8, continue to garner much research interest for the potential roles they may have in disease development, as well as in the design of antigen-specific therapies to prevent and/or cure the disease. Indeed, one of these molecules (GAD) is undergoing phase III testing in both the United States and Europe for its ability to prevent or reverse type 1 diabetes when administered as a vaccine. In addition, recent studies suggest the immune system’s responses to these antigens—in particular, autoantibody profiles in humans—correlate well with disease parameters, encouraging their expanded use in clinical trials as a means to monitor and define success.

### Continued Improvement in Understanding Natural History of Type 1 Diabetes in Humans:

Multiple studies in children and adults have provided insights into how type 1 diabetes develops. Hundreds of thousands of children have now participated in prospective studies across the world identifying genetic and autoantibody risk for type 1 diabetes, with highest risk children then followed to development of diabetes. Children participating in these clinical studies have benefited by being diagnosed earlier and having lower rates of a life-threatening condition called diabetic ketoacidosis at type 1 diabetes onset. Increasing numbers of younger children are being enrolled into clinical trials and studies, mostly from families with

prior incidence of the disease (see the “Special Needs for Special Populations” chapter); the larger number of young children in trials creates a special challenge, as efforts seeking to prevent type 1 diabetes in young children require the highest ethical standards for safety. On the cellular level, many T cell and cytokine abnormalities evident prior to diabetes and correlated with pathogenesis have been defined. While research continues in that area, it is also now clear that a subset of patients with type 1 diabetes preserves some beta cells for decades—some have distinct and poorly characterized forms of type 1 diabetes, and others have immune-mediated type 1 diabetes that is either progressing slowly or in whom the process of beta cell destruction has naturally halted. Finally, findings from genetic studies highlight the fact that many susceptibility genes for type 1 diabetes are shared with other autoimmune diseases (e.g., thyroid disease, multiple sclerosis, celiac disease), which has important implications for pathogenesis and therapy (see also the chapter on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications”).

### Recognition of the Importance of Innate and Adaptive Immunity in both Type 1 and Type 2 Diabetes:

Scientists have gained a greater understanding of certain immune cells, called alternatively activated macrophages, that may play a role in type 1 diabetes, as well as in the obesity-induced inflammation and insulin resistance associated with

type 2 diabetes. The chemical signals (cytokines) that some of these cells produce may be protective against disease. In addition to the protective role of macrophages and other cells of the innate immune system, there is a growing interest in understanding the role of the adaptive immune system in pathogenesis of type 2 diabetes. The adaptive immune system involves the T cell and autoantibody responses to “self” molecules. Researchers have now observed that as many as 10 percent of individuals with type 2 diabetes have evidence of adaptive immune system activity. These are just two examples of a growing appreciation of the importance of immune responsiveness in type 2 diabetes, and how it may form the basis for future areas of therapeutic intervention. The potential importance for innate immunity in type 1 diabetes also derives from recent studies of the gut microbiome, the microbial communities that line the intestine. Studies in animal models have shown the pronounced ability for gut bacteria to influence innate immune responses that may have an impact on type 1 diabetes.

### **Animal Models Advance Understanding of Type 1 Diabetes and Testing of New Therapies:**

The spontaneously diabetic NOD mouse has provided abundant insights into the pathogenesis of type 1 diabetes. Studies of NOD mice have led to the identification of many of the targets of the autoimmune response, as well as the cell populations that mediate destruction of the insulin-producing beta cells. These insights have led to identification of similar targets and destructive cell populations in humans with type 1 diabetes. The NOD mouse model has also been valuable in understanding how diabetes-susceptibility genes and genetic networks common in mice and humans affect the immune response that leads to disease. Moreover, for a limited but growing number of therapeutics, reversal of diabetes in new-onset, spontaneously diabetic NOD

mice is possible. As a result, early diabetes reversal in NOD is increasingly used as a model for testing the potential efficacy of therapeutics in clinical trials. In the NOD mouse, reversal has been found to depend on intervention soon after diabetes onset, when there is still enough residual functional beta cell mass able to recover if the autoimmune process is halted. While not all therapies that work in animal models show such an effect in humans, others (e.g., anti-CD3 and oral insulin) do appear promising. Hence, animal models have clearly proven themselves useful for finding strategies to reverse disease in people with type 1 diabetes.

### **Development of Sophisticated Mouse Models of Human Disease for Study of Type 1 Diabetes:**

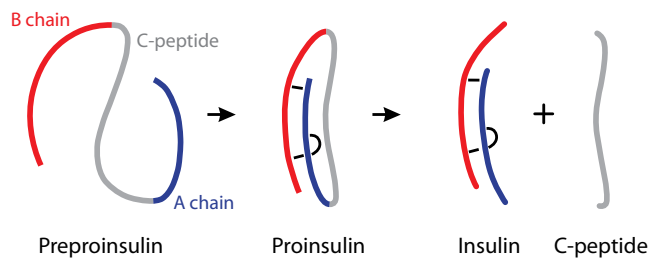
Increasingly sophisticated stocks of mice modeling human disease have been developed that are now providing the means to understand clinically relevant components of type 1 diabetes pathogenesis. These include mice that are either engrafted with functional human cells or tissues, genetically engineered to express human genes, or both, and can recapitulate aspects of the pathogenic process. These mice have been used to identify targets of the human immune response against transplanted islets, and have led to insights into the destructive cell populations that are important to this process. Mice engrafted with functional human immune systems may permit certain human immune responses, including autoimmune responses, to be manipulated in small animal models. As these types of studies cannot be done in people, such mouse models could facilitate the conduct of important translational research, providing insights into safety and efficacy before enrolling participants in clinical trials.

### **Beta Cells Still Present at Onset of Type 1 Diabetes:**

In contrast to earlier assumptions, researchers have found that, at diagnosis, a majority of



people with type 1 diabetes have circulating C-peptide, a marker of insulin production by the pancreas. While C-peptide levels are reduced in comparison to people without the disease, the measurable and inducible C-peptide is very suggestive of functional beta cell mass. This observation is important for future therapies as the positive benefit of immune modulation in the NOD mouse is best realized when a pancreatic beta cell mass capable of promoting euglycemia is present. Moreover, in humans the presence of C-peptide has been associated with improved control of diabetes and less risk of life-threatening hypoglycemia. Thus, preservation of C-peptide, as well as expansion of beta cell mass in new-onset type 1 diabetes, is a major focus of therapeutic investigation.



The hormone insulin is formed by chemical modification and cleavage of a precursor molecule. The cleaved “C-peptide” is useful for monitoring residual beta cell function in people with diabetes who are on insulin therapy.

### Beta Cells Can Resist Immune Mediated

**Destruction:** Scientists have defined some of the pathways by which beta cells are destroyed by the immune system. In addition, gene therapy and transgenic experiments in animal models have shown that beta cells can be protected from cytokine induced destruction as well as transplant rejection. This research has shed light on potential therapeutic strategies to preserve beta cell function that can be tested in people in the future.

### Elucidating Mechanisms Underlying Tolerance:

Type 1 diabetes is thought to arise from a defect in immune tolerance, the “normal” state in which the immune system is non-reactive to healthy cells and tissues. Scientists have learned much about the cellular and molecular mechanisms controlling tolerance induction in recent years. In particular, some gene expression regulators (transcription factors, e.g., forkhead box p3 (Foxp3)) are important for the proper function of regulatory T cells, which suppress misdirected immune responses, while other transcription factors (e.g., autoimmune regulator (Aire)) function to allow the removal of autoreactive T cells during development. Other factors known to be important for tolerance induction or maintenance include those involved in immune cell signaling or modulating immune responses (co-stimulatory molecules and cytokines); the biology of regulatory T cells; and the function of dendritic cells, a type of antigen presenting cell, in the process. This knowledge has enabled the design of several successful strategies for imposing a state of tolerance, for example, to transplantation antigens in normal rodents, but this has proven to be much more challenging for restoring self-tolerance in rodent models of diabetes. Numerous observations suggest that similar deficiencies in tolerance induction play an important role in human type 1 diabetes, including the association between alleles of the gene encoding insulin (*INS*), their expression level in the thymic stroma (where removal of autoreactive T cells takes place), and diabetes incidence; the development of diabetes in patients with mutations in the genes encoding Aire (*AIRE*) and Foxp3 (*FOXP3*); and the observations of defective regulation of activated T cells by regulatory T cells in type 1 diabetes patients. These findings are helping pave the way to

future approaches that could restore a state of immune tolerance in people with type 1 diabetes.

### **Understanding Mechanisms Contributing to the Initiation of Insulinitis in Type 1 Diabetes:**

Scientists have made progress in elucidating the molecular mechanisms underlying insulinitis in animal models of type 1 diabetes. Insulinitis, the inflammation of the pancreatic islets that leads to beta cell destruction, is marked by the appearance of white blood cells (T cells, B lymphocytes, and others) in the islets. Studies in several rodent models have now established that potentially diabetogenic T cells circulate innocuously through the blood and lymphoid organs until a poorly understood event early in life provokes islet beta cell death, releasing antigens that stimulate the islet-antigen-reactive T cells and cause them to be retained in the pancreas, where they create structures resembling lymphoid tissue. It is not yet known to what extent this scenario is followed in humans, although insulinitis similar to that of rodent models has been observed in sections of pancreata from at least some people with type 1 diabetes. These findings in rodent models could help researchers identify the initial steps that activate the T cells responsible for launching autoimmune destruction of beta cells in humans and lead to new targets for intervention.

### **Discovery of Multiple Cellular Factors That Contribute to Progression to Diabetes:**

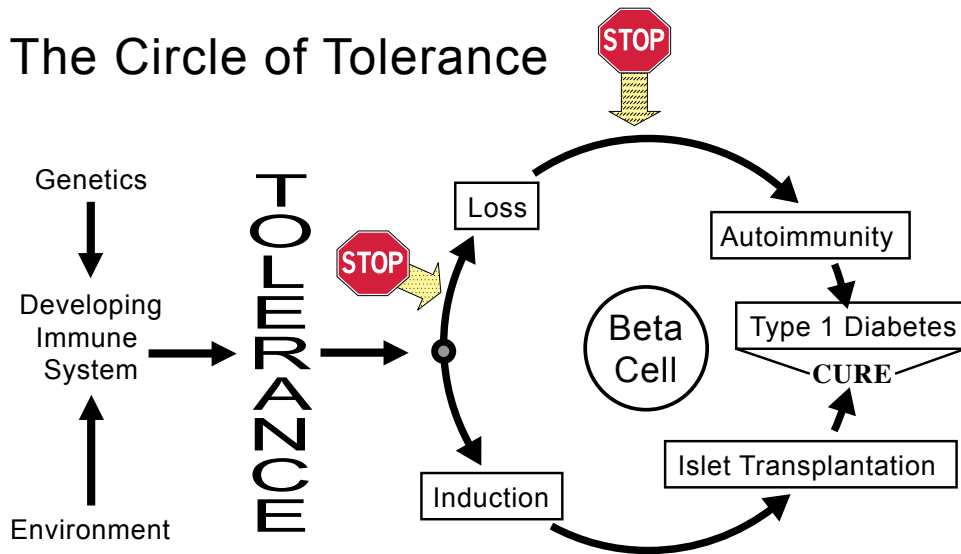
The major culprits in type 1 diabetes pathogenesis in rodents are “helper” T cells (CD4<sup>+</sup> T cells) that promote immune system activity and/or cytotoxic T cells (CD8<sup>+</sup> T cells) that actually destroy beta cells. There is evidence

that this is also true for human type 1 diabetes, because patients have responded to treatment with therapeutic agents directed against T cell activity, such as cyclosporine-A and anti-CD3 monoclonal antibody. Nonetheless, there has been increasing appreciation of the importance of other cellular players, notably macrophages, dendritic cells, B cells, natural killer (NK) cells, and NKT cells. Recent years have also brought an increasing understanding at the molecular level, particularly regarding the role of co-stimulatory molecules that transmit either stimulatory or inhibitory signals to T cells (e.g., CD28, CTLA-4, PD-1) and the role of cytokines (e.g., type-1 and -2 interferons, IL-2, IL-21, IL-15, IL-10, IL-17). However, more remains to be learned, as scientists have not yet been able to integrate the various cellular and molecular elements into a coherent disease scenario. In particular, although a number of candidate cells and molecules have been identified, there is no consensus on what agents ultimately destroy the beta cells, perhaps because different mechanisms come into play in different models and in different patients. The discovery of multiple factors that could play a role in type 1 diabetes is important for people with the disease, as these factors may represent additional targets for therapeutic intervention.

### **Immunoregulation—Understanding Cellular**

**Controllers:** It has become clear that type 1 diabetes is a regulated disease: initiation of insulinitis and the time between insulinitis and conversion to overt diabetes

## The Circle of Tolerance



The circle of tolerance. Tolerance denotes the absence of a detectable, functional immune response in the absence of immunosuppression. Loss of tolerance is at the root of autoimmunity. In type 1 diabetes, preventing this loss of tolerance (dotted “stop”) is the ultimate goal, to prevent disease. Current efforts are also aimed at interfering with T cell function after the loss of tolerance (striped “stop”), e.g., with immunosuppressive agents or other means. Strategies to induce tolerance are also needed to aid success of islet transplantation and potentially provide a cure. (Image courtesy of Dr. Aldo A. Rossini. Adapted from *Diabetes*, Vol. 53, 2004; 267-275. Copyright 2004 American Diabetes Association. Reprinted with permission from the American Diabetes Association.)

are both subject to immunological control. In recent years, immunologists have identified and characterized a number of cellular controllers. The most well-studied are regulatory T cells (also called “Tregs”) expressing the *Foxp3* protein marker, but appreciation is growing for the activities of regulatory B cells, monocytes, and other T cell populations. The importance of *Foxp3*-expressing regulatory T cells in regulating diabetes progression has been established in a number of rodent models. Precisely when, where, and how these cells act is still actively debated. The fact that people who

have a rare disease called “immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome” (IPEX), caused by a mutant *FOXP3* gene, rapidly develop severe type 1 diabetes, argues for the importance of regulatory T cells in controlling human diabetes. It remains controversial whether or not people with classical type 1 diabetes have a defect in regulatory T cell-mediated immunoregulation. In either case, modulating regulatory T cell activity represents an interesting therapeutic strategy that is being actively pursued.

## INFLAMMATION AND IMMUNITY: REACHING INTO ALL DIABETES

Imagine receiving a diagnosis of type 2 diabetes. The symptoms seem to add up—fatigue, dizziness, thirst—and medical tests reveal high blood glucose, but apparently no need for insulin. Middle-aged and a bit overweight, the diagnosis seems clear, and you start a standard program of control with diet and exercise plus oral agents. Although your diabetes is initially well-controlled, within a few years your glucose levels have become high again. Frustrated, you seek new tests—and receive a new diagnosis, one of autoimmune diabetes that now must be treated with insulin. As it turns out, distinguishing different forms of diabetes can be less straightforward than commonly thought, and autoimmune diabetes can strike at any age. At the same time, research is revealing that type 1 and type 2 diabetes may have more in common than previously thought, an observation that is opening up new avenues to therapy.

Traditionally, doctors have distinguished between type 1 and type 2 diabetes according to certain clinical signs or symptoms. The autoimmune disease type 1 diabetes is more likely to be suspected in children and youth, and diagnosis is confirmed if a person has autoantibodies and is insulin-dependent at diagnosis. Conversely, people who are middle-aged and older and/or obese are more likely to be diagnosed with the non-autoimmune disease type 2 diabetes, which is characterized by insulin resistance that at first can generally be treated with diet, exercise, and oral medication. In recent years, however, some of the traditional lines between type 1

and type 2 diabetes have blurred. More children have been developing type 2 diabetes, associated with the epidemic of obesity. In addition, given the increases in obesity in the population, many children with type 1 diabetes are overweight at diagnosis—making it difficult to distinguish between type 1 and type 2 diabetes in youth based on weight alone.

Furthermore, in between these two classic types of diabetes lies a grey area, populated largely by people diagnosed as adults. Some people may experience an unusual, late onset of type 1 diabetes, requiring immediate treatment with insulin. Others show signs of both type 1 and type 2 diabetes, a condition called latent autoimmune diabetes in adults, or LADA. While people with this form of diabetes are often diagnosed with type 2 diabetes because they don't need insulin initially, they are actually suffering from an autoimmune process that damages and destroys the insulin-producing beta cells. Fortunately, once suspected, this confusion can be resolved with testing for islet autoantibodies. As many as 10 percent of newly-diagnosed, non-insulin-requiring adults with diabetes may have this form of diabetes. Similarly, autoantibodies are sometimes found in children and youth thought to have type 2 diabetes (latent autoimmune diabetes of youth—LADY), but less is known about how many people are affected in this age group.

Clinicians, patients, and researchers alike struggle with this apparent overlap of types of diabetes. For patients and clinicians, obtaining a correct diagnosis

can be a challenge, and there are still therapeutic hurdles once a diagnosis is achieved—for example, there is still debate about the optimal management strategy for LADA. For researchers, an important goal is to better understand why some people develop classic type 1 diabetes in youth, others when they are adults, and what are the underlying causes of differences in disease course in older and younger people with classic type 1 diabetes and in people with LADA and other hybrid forms of diabetes. There may, in fact, be a spectrum of autoimmune diabetes, of which classic type 1 diabetes is the most extreme form. Genes, age, differences in production of autoantibodies, and environmental factors may all play a role. People with diabetes would benefit from an improved classification of type 1 diabetes that would highlight differences and potentially lead to more tailored approaches to therapy.

Encouragingly, new studies of how diabetes develops and progresses are uncovering shared features between type 1 and type 2 diabetes that may also help explain some intermediate forms of the disease. At the heart of these studies are inflammation and immunity. Inflammation is a complex mixture of cellular and chemical responses the body deploys in reaction to perceived cell and tissue injury, such as a bacterial infection. While useful to help control infections and promote tissue repair, inflammation is a blunt instrument that can also inflict harm on healthy tissues, especially if it is misdirected or

becomes chronic. Different types of inflammatory reactions have been linked to different types of diabetes, but now there is evidence that these lines may not be so distinct. For example, inflammation of the islets (insulinitis)—the hallmark of type 1 diabetes—is not exclusive to type 1 diabetes and may contribute to loss of beta cells in type 2 diabetes. Conversely, low-grade systemic inflammation and insulin resistance contribute to type 2 diabetes, but may also play a role in type 1 diabetes, exacerbating the dominant autoimmune process that is destroying beta cells. Inflammation is also implicated in the development of diabetes complications.

Cells of the immune system both promote inflammation and are vulnerable to its effects. Scientists suspect that some of the clues to variations in diabetes lie in a complex interplay among cells involved in inflammation, those implicated in autoimmunity, and inflammatory signals themselves. These interactions, in turn, will be affected by genetic and environmental factors. Learning more about how inflammation is regulated by the immune system in the context of diabetes could reveal more about the similarities and differences between type 1 and type 2 diabetes and their complications, potentially reveal more about mechanisms underlying hybrid forms of diabetes, and lead to more specific therapeutic approaches that could benefit people with different types of diabetes.

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the importance of understanding the immune system in winning the battle against type 1 diabetes. Since the publication of that roadmap for diabetes research, recommended steps—including exploiting important discoveries from the fields of immunology and cell and molecular biology in order to find ways to prevent or block development of diabetes, and establishing multi-center clinical trials networks to test new therapies—have led to new insights into ways to prevent, treat, or potentially reverse type 1 diabetes. To help speed progress, these efforts have been bolstered and updated through strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research* and through the 2006 “*Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan.*” However, the incidence of type 1 diabetes has continued to rise during the past decade, and as prospects for extended life with diabetes improve so does the threat of long-term complications—lending urgency to closing the gaps in the fundamental understanding of type 1 diabetes and autoimmunity while still leveraging what has already been learned. Moreover, the pronounced increases in obesity rates across the age spectrum have led type 1 and type 2 diabetes to become less compartmentalized as diseases in the population (see the “Obesity” chapter), creating an additional challenge to understanding and treating type 1 diabetes. Described below are research questions and opportunities to pursue in the next decade to reach the goal of meeting these challenges.

### Human Type 1 Diabetes Trials (Prevention/Reversal/Transplantation)

Based on continuing research advances over the last decade, major expansions have occurred in efforts designed to prevent or reverse type 1 diabetes, which may in turn lead to effective new therapeutic strategies. Ongoing prevention trials include a pilot study to test orally administered insulin in genetically at-risk people and studies testing nutritional interventions (e.g., vitamin D, fish oil, highly hydrolyzed milk formula, delay in introduction of gluten). Additional clinical trials are planned in this arena, especially to capitalize on agents found to be effective in slowing beta cell loss in new-onset type 1 diabetes by studying their use earlier in the course of type 1 diabetes development and before the diagnosis of disease. Such studies capitalize on new biomarkers of disease and improved predictive models. Clinical trials networks and research consortia have been organized to facilitate collaborations between basic and clinical investigators, promote bench-to-bedside translational research, and test new approaches for preventing the onset of type 1 diabetes, reversing disease, and improving islet transplantation as a treatment option (see also “The Beta Cell” chapter regarding ways to advance islet transplantation). Researchers will benefit from the opportunities presented by these collaborative efforts in developing new studies to answer key clinical questions in type 1 diabetes.

## Key Questions

- Will additional information about genetic underpinnings of type 1 diabetes allow therapies to be targeted to homogeneous populations, thus increasing their effectiveness?
- Will antigen-specific versus non-specific tolerance induction protocols be safe and effective in preventing progression to overt type 1 diabetes in individuals deemed to be at high future disease risk?
- How can combination therapies using short-course immunosuppressants, cellular mobilization agents, insulin sensitizers, anti-inflammatories, islet antigens, and/or molecules capable of inducing beta cell replication *in vivo* be tested?
- How can multi-center, international collaborative trials that support biomarker and discovery studies best be accomplished?
- How can very long-term follow-up (i.e., beyond the 1 to 2 year standard for current studies), including metabolic and mechanistic studies, as well as monitoring of adverse events of patients in trials for the prevention of beta cell loss, be accomplished?
- Can biomarkers be developed to stratify patients for trials and to obtain an early indication of therapeutic effectiveness?
- Will drugs designed for the treatment of other disorders, especially autoimmune disorders, and possessing a highly

favorable safety profile, prove efficacious as treatment(s) for type 1 diabetes?

- Is it possible that intervention may provide a clinical benefit in patients months or even years after diagnosis?
- Could the principles of “disease staging,” often used in oncology, be applied to settings of type 1 diabetes both prior to and well beyond the diagnosis of this disease?

## Future Directions

- Conduct coordinated clinical trials to test therapies to prevent or reverse type 1 diabetes.

Because type 1 diabetes is not a highly prevalent disease, screening of large populations is required to identify an adequate number of persons at risk for the disease and amenable to clinical intervention trials. Clinical trials in people newly-diagnosed with the disease also require a multi-center effort because at present, most (but not all) studies require that people must be recruited within 3 months of onset. Thus, clinical trials in type 1 diabetes require a large cooperative network, which is complex to operate. Coordinated efforts by regulatory agencies (FDA), clinical trial sponsors (NIH and pharmaceutical companies), and participating researchers (institutions) are needed to accomplish trials using combination therapies, which will require many more people than single-agent trials. To facilitate this coordination, more centralization of Institutional Review Boards (IRBs) is needed to allow associated biomarker studies and easier implementation of multi-center trials, and barriers to conducting collaborative, international trials should be addressed.

Bold initiatives are needed to address many of the key questions. For example, early results from disease etiology studies could suggest it would be feasible to perform prevention trials, using benign interventions (e.g., probiotics or other “generally regarded as safe” (GRAS) agents), in very young children, and using surrogate end points and biomarkers of pathogenesis. Such an undertaking would likely require large-scale screening of the general population, combined with registries, in order to help recruiting for prevention trials and to ensure that the results obtained are applicable to the broadest population.

In addition, it is important to note that the design of future clinical trials will need to take into account any beneficial therapies that arise in the interim, which could limit use of placebo controls and complicate trial operations, as well as increase the overall adverse event burden. With this, clinical trials which add therapeutic arms (“rolling”) may be needed to efficiently cope with the fast pace of new immunomodulatory drug discovery and rapid drug approvals. This approach could increase the difficulty in recruiting participants for testing newer agents.

## Natural History and Pathogenesis of Human Type 1 Diabetes

Researchers have made progress over the past decade in understanding genetic risk factors and development of type 1 diabetes, but much remains to be learned about how—and why—anti-islet autoimmunity takes hold and flourishes in some individuals and not others, especially not in those individuals who carry a protective *HLA* allele, such as *HLA DQB1\*0602*. The mechanism by which this allele confers dominant protection is under investigation. The role of environmental factors in the genesis of type 1 diabetes is an area of increasing focus, as understanding these factors and their interaction

with individual susceptibilities could lead to new preventive strategies (see the chapter on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications”). Recent technological developments and large-scale collaborative research efforts already established by NIH will afford scientists the opportunity to meet many of these research challenges in the years ahead.

### Key Questions

- **What is the natural history of type 1 diabetes, including the precise sequence of events leading to the initiation of insulinitis, and continuing on to clinical diabetes?**
- **Why is type 1 diabetes increasing in incidence and occurring more often at younger ages?**
- **What is the basis of the observed heterogeneity in type 1 diabetes and is there additional heterogeneity yet to be discovered?**
- **Is noninvasive imaging of beta cell mass and associated insulinitis achievable?**
- **Can autoimmune pathogenesis at the islet, whether in people in pre-clinical stages of pathology or in autoimmune recurrence in transplant recipients, be measured indirectly in the blood, for example by a measurement of T cell responses to diabetes-relevant antigens? Can such biomarker assays be developed to enhance prediction of type 1 diabetes, facilitate studies of natural history, and serve as surrogate markers in therapeutic trials?**
- **What is the role of the gut microbiome in disease etiology?**



## Future Directions

- **Discover triggering factors for islet autoimmunity and environmental factors responsible for the recent increase in incidence of type 1 diabetes.**

Scientists have very little knowledge of the events that initiate anti-islet autoimmunity in humans; knowledge is also limited in animal models that spontaneously develop the disease. In particular, several questions regarding environmental triggers remain unanswered: Is there a specific environmental factor that triggers islet autoimmunity in humans or are there thousands of factors? Is the factor dietary or infectious? Is a triggering factor needed at all? What is the role for the microbiome in the pathogenesis of this disease? These questions represent fundamental gaps in knowledge, but are crucially important to answer because defining triggering factors may permit scientists to design safe strategies for type 1 diabetes prevention. It is likely that the safest prevention of type 1 diabetes on a population basis will come from identifying key environmental factors. Ongoing large NIH studies, such as TEDDY, are screening approximately 400,000 newborns and following those who are genetically susceptible. TEDDY and other studies will hopefully provide the resources for the discovery of key triggering and modulating environmental factors. Depending on the timing and mechanism of triggering, however, even these studies with follow-up of high-risk children at 3 month intervals may not define all the triggering factors. Development of innovative technology and study designs to enhance the ability to define triggers of autoimmunity that may occur over a course of days should be encouraged both as proof of principle in animal models and studied in humans.

- **Better define the heterogeneity and diagnosis of type 1 diabetes and foster the development**

## **of therapies specific to different forms of the disease.**

Approximately 15 percent of children at onset of type 1 diabetes lack all islet autoantibodies and, when taken together with studies examining the natural history of type 1 diabetes (i.e., investigations of individuals before hyperglycemic onset), a new appreciation has emerged for the heterogeneity of what is commonly referred to as type 1 diabetes. Some of these children have autoimmune type 1 diabetes, but antibody tests are currently inadequate; some have monogenic forms of diabetes that require tailored therapy; some have forms of type 2 diabetes that are difficult to diagnose; and some are likely to have yet to be discovered genetic forms of diabetes. In addition, heterogeneity may be uncovered only after diabetes diagnosis (see sidebar, “Inflammation and Immunity: Reaching into All Diabetes”). For example, some children may lose residual beta cell function and insulin production more rapidly than other children. Systematic studies of diabetes heterogeneity in children are needed to allow the development of specifically targeted care and to delineate natural history without mixing fundamentally separate disorders. A better understanding of the heterogeneity in the disease at or before diagnosis, as well as after diagnosis, is vital. Indeed, research should address the importance of differences among people in the rate of loss of C-peptide production, and their influences on the rate of developing complications, which could also be influenced by the autoimmune state.

- **Delineate the natural history, or histories, of type 1 diabetes.**

At multiple stages in the development of type 1 diabetes, current knowledge is inadequate for the optimal design of preventive therapy. As more is learned about the genetic determinants of type 1 diabetes, this developing

knowledge needs to be evaluated in terms of how well it may predict development of islet autoimmunity and natural history of progression. Triggering factors are unknown; their identification will almost certainly depend upon being able to define when islet autoimmunity is initiated in a genetically susceptible individual or animal model. Although high rates of progression to diabetes have been demonstrated among multiple-autoantibody-positive individuals, the natural history of long-term progression (more than a decade of follow-up) is unknown. If a subset of individuals escapes progression to diabetes, the existence of “natural escape” will influence therapeutic choices, and the determinants of this state will be important to define. Methods to accurately define beta cell mass in people are needed to improve disease prediction and to define the fundamentals of beta cell loss. Better assays are also needed to define T cell mediated autoimmunity during the period prior to development of type 1 diabetes, when patients are experiencing non-specific symptoms (prodrome), as well as all other phases of pathogenesis. Improved metabolic and physiologic understanding is needed during both the prodrome and post-onset of diabetes, as well as during further loss of beta cells.

► **Elucidate the impact of environmental or other non-genetic factors on development of type 1 diabetes.**

Not all individuals with genetic susceptibility get insulinitis, and not all individuals with autoantibodies get diabetes. In fact, the identical twin of a person with type 1 diabetes can take as long as 40 years to develop the disease. Both the age at which islet autoimmunity appears and the rate of progression from autoimmunity to overt diabetes differ for identical twins, with a greater discordance in rate for siblings, and even greater discordance among unrelated

individuals in the general population. Type 1 diabetes occurs at all ages, suggesting that precipitating events can occur throughout life. There may also be environmental factors that inhibit rather than promote progression to type 1 diabetes in those at risk for the disease. Innovative application of available technologies, including “next generation sequencing” (e.g., unbiased pathogen detection, intestinal flora, T and B cell receptors, and mutational analysis), messenger microarray, epigenetic analysis, proteomics, metabolomics, and systems biology integration, should be applied to better understand the environmental triggers of type 1 diabetes. Environmental impacts notwithstanding, genetic impacts on the age of onset are strong, as shown by single gene mutations that remove regulatory T cells leading to diabetes in the first week of life, and by the observation that people with adult-onset type 1 diabetes often do not have the high-risk genetic variants (e.g., *HLA* alleles) borne by people who develop the disease as children.

► **Study role of innate immunity in diabetes.**

Although analysis indicates that type 1 and type 2 diabetes do not share many genetic risk factors, research has demonstrated that multiple cytokine pathways are dysregulated and innate immunity may be important for beta cell loss and complications in both diseases. For example, the cytokine IL-1 and the opposing IL-1 receptor agonist (IL-1Ra) are being studied as a therapeutic in both type 1 and type 2 diabetes. In addition, IL-1 beta antagonists are also being actively studied in basic and clinical research. Research should be pursued to further examine this possibly shared disease pathway.

## Animal Models/Translational Efforts from Pathogenesis to Therapy

New animal models of type 1 diabetes and autoimmunity are opening up research opportunities that were not possible before. In particular, mouse models with greater fidelity to human disease are becoming increasingly useful research tools for studying underlying mechanisms of disease and for testing new therapies. Researchers will soon be able to capitalize on the development and availability of these resources and related tools to expand fundamental understanding of the disease and to assist in translation of promising pre-clinical findings into treatments for patients and people at risk for type 1 diabetes.

### Key Questions

- **Can higher fidelity mouse models of human disease be developed that will improve the ability to predict the efficacy of new therapies in patients?**
- **Can NOD mice (and/or higher fidelity mouse models of human disease) be used to:**
  - **Perform systematic screening of small molecules or other potential therapies for prevention or reversal of type 1 diabetes?**
  - **Identify environmental agents that precipitate or prevent type 1 diabetes?**
  - **Identify biomarkers in the blood that can monitor islet cell mass or autoimmunity?**
- **Can the function of human diabetes susceptibility or protective genes be effectively studied in mouse models?**

- **Can common pathogenic mechanisms be identified among different autoimmune diseases and in different disease models that may inform the search for new therapeutic targets and strategies?**

### Future Directions

- **Rapidly translate new findings on disease pathogenesis in animal models into potential therapies.**

Although findings in NOD mice led to clinical trials testing insulin, anti-CD3, and other agents, it will be important to use animal models to move beyond these approaches to the next generation of immunomodulatory therapeutics. New targets should be identified and rapidly validated in animal models, and the mechanism of action determined to facilitate their translation to humans. New approaches, such as cellular therapy using stem cells, regulatory T cells, or modulation of novel cell targets (e.g., NK cells, NKT cells, B cells) may be modeled in animals and translated into the clinic.

- **Use animal models to identify and validate biomarkers of type 1 diabetes.**

Animal models may provide key insights into biomarkers for human type 1 diabetes. Future research to identify and validate translatable biomarkers could possibly facilitate the ability to predict disease and to measure the efficacy of therapeutic intervention.

- **Develop a higher fidelity mouse model of human disease that develops type 1 diabetes.**

A mouse that has a functional human immune system and that develops type 1 diabetes may provide an ideal

pre-clinical model for studying human type 1 diabetes without putting patients at risk. Ideally, such a model(s) would advance research into the pathogenesis of human disease, and would enable the identification of genes, environmental agents, and therapeutics that are directly relevant to people with type 1 diabetes. A current barrier to research progress is that many therapeutic agents being tested in the clinic are specific for humans and cannot be adequately tested in mice. Thus, such a mouse model would be an extremely valuable tool for evaluating these types of agents before they are tested in people. In addition, development of higher fidelity mouse models of human type 1 diabetes could provide a battery of models of type 1 diabetes that more closely reflect the genetic heterogeneity of humans. Having models of disease that can accommodate the natural diversity of the human population, rather than relying on the response of a single inbred strain of mice with a single set of diabetes susceptibility and resistance genes, would dramatically expand the ability to identify mechanisms of pathogenesis and surrogate markers of active/inactive diabetes that are uniquely human. Development of such sophisticated mouse models of human disease to support research in type 1 diabetes will be very challenging, and likely will require extensive genetic manipulations to replace species-specific molecular systems (e.g., cytokines, receptors, signaling molecules, adhesion, and trafficking) to create the appropriate environment for modeling the human disease process.

➤ **Develop *in silico* models for type 1 diabetes.**

There has been progress in developing *in silico* (computer) models for the study of multiple diseases, including type 2 diabetes. These *in silico* models permit hypotheses to be tested rapidly and help to inform the design of experiments to further test and validate hypotheses *in silico* and in biological systems. The development of *in silico* models for type 1 diabetes

would greatly accelerate progress in understanding the pathogenesis of type 1 diabetes, as well as in identifying and modeling the potential of various therapeutics prior to pre-clinical testing in animal models and testing in clinical trials.

## **Beta Cell Function in Type 1 Diabetes: Autoimmune Attack and Prospects for Recovery**

Although many questions remain, recent research findings about beta cells and autoimmunity are improving prospects for developing strategies to preserve and enhance beta cell function that may delay or prevent progression of type 1 diabetes. Efforts to understand fundamental beta cell biology, described in “The Beta Cell” chapter, will be key to developing these strategies as well.

### **Key Questions**

- **What is the beta cell mass/function at onset of type 1 diabetes?**
- **How much residual beta cell mass/function is required for reversal after immunotherapy? Does it differ with different treatments?**
- **Can mechanisms that protect mouse cells from autoimmune destruction also protect human islets from autoimmune attack?**
- **Why is pancreas volume greatly reduced in people with type 1 diabetes? Does this reduction have an influence on disease parameters? Can it be used as a biomarker of disease development or potential for success in therapeutic intervention?**
- **Are there diabetes-susceptibility genetic variants that determine the ability of**

**beta cells to resist autoimmune attack, or to regenerate or recover function once autoimmunity is controlled?**

## **Future Directions**

- **Develop metabolic tests to detect early signs of beta cell dysfunction.**

Additional metabolic tests that detect more subtle dysfunctions in genetically-defined at-risk populations than is currently possible could be used to determine whether the known autoantibodies precede metabolic disturbance or are the result of beta cell dysfunction. Metabolic changes could potentially also be used to improve disease onset prediction during the prodromal phase.

- **Examine the effect of insulin resistance on the development of type 1 diabetes.**

It has been hypothesized that some type 2 diabetes phenotypes, such as insulin resistance, can accelerate the onset of type 1 diabetes, at least in a subset of individuals. If true, this could be used to better predict risk and timing of onset, and could provide an explanation for the increased incidence of type 1 diabetes in puberty—a time period when insulin resistance is higher.

- **Identify genes and mechanisms that protect beta cells from autoimmune dysfunction and/or destruction, in animal models or in humans when possible.**

Beta cell biologists are developing an increasingly detailed understanding of the effects of inflammation, hyperglycemia, and other stressors on beta cell function, survival, and replication, especially in the context of type 2 diabetes. More detailed understanding is needed

of how autoimmunity in type 1 diabetes affects the beta cell and whether opportunities exist to protect the beta cell from autoimmune damage. Part of the difficulty arises from the rapid timescale of autoimmune destruction and the inability of beta cell biologists to access the pancreas during this critical time frame. Therefore, better tools are needed to allow dissection of the effects of autoimmunity on the beta cell.

- **Define specific and sensitive surrogate markers of physical and/or functional beta cell recovery in response to immunotherapy and determine if beta cell mass can regenerate without reactivating autoimmunity.**

As noted previously, a growing body of evidence has suggested that researchers are getting closer to identifying a means to halt the autoimmune process underlying beta cell destruction. If this hope becomes reality, the benefits to the diagnosed patient are likely to be indirect at first (e.g., a reduction in daily exogenous insulin usage, production of some endogenous C-peptide which could help overall glucose control). The longer-term goal would be to stimulate beta cell regeneration with the halt of autoimmunity. Therefore, sensitive and specific markers are needed that reflect not only the degree of beta cell mass that exists at the time immune intervention occurs but, in addition, those that may reflect any recovery that beta cells see following attenuation of the autoimmune response. Indeed, researchers actively question to what degree beta cells are capable of self-regeneration and, beyond this, whether such regeneration would once again initiate or rekindle a destructive autoimmune response.

## Immune Mechanisms of Pancreatic Pathology

To understand the pathogenesis of type 1 diabetes and the autoimmune destruction of pancreatic beta cells, better basic information and research tools or systems for analysis are needed. For example, questions remain as to how effector or pathogenic autoimmune T cells are created or maintained, and through what basic mechanisms they are controlled by other cells, including the regulatory T cells that are known to dampen pathogenic responses. It is also important to understand the role of B cells as autoantibody producers, as well as antigen presenting cells, in the pathology of type 1 diabetes.

### Key Questions

- **How diverse are the T and B cell responses to individual diabetogenic antigens, and how can the dominant effect of major histocompatibility complex (MHC) sequence on diabetes susceptibility be explained?**
- **What are the respective roles of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, as well as other immune cell subsets (e.g., B cells, NK cells, dendritic cells, and mast cells), in pathogenesis?**
- **What is the role of regulatory cell populations in diabetes pathogenesis or protection?**
- **What is the relationship between autoimmunity and inflammation in type 1 diabetes, and what are the roles of other organs such as gut, liver, fat, or others?**
- **What underlies the variability of attack on different islets within the same pancreas,**

**and can that understanding be used to interdict the disease process?**

### Future Directions

- **Identify the range of tolerance mechanisms defective in type 1 diabetes models and patients (e.g., genetic polymorphisms in immune system genes) and delineate precisely where the cellular and molecular defects lie.**

Over the last decade, the list of immune system components in people with type 1 diabetes that could be defined as defective, due to their inability to impart tolerance to beta cells, has grown in number. At the same time, as noted in the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter, the number of genetic loci considered to modulate susceptibility to type 1 diabetes has seen marked expansion—nearly 50 genes or genetic regions have been identified—the majority of which have potential to be involved in the immune system. As a result, the research community needs to establish a blueprint for the nature and order of these immune system defects (i.e., which ones could be considered primary, and which ones represent downstream effects of earlier defects) and determine how genetic differences impart these immune system defects. Pursuing such research has the potential to better explain the pathogenesis of type 1 diabetes, lead to improved disease prediction, and allow for the development of better targeted therapeutics.

- **Define how auto-inflammatory infiltrates and beta cells communicate with each other in controlling type 1 diabetes progression.**

A better understanding of autoimmunity-relevant changes within the beta cells, such as upregulation of molecules that present antigens to cytotoxic T cells (MHC class I molecules), or induction of inflammatory antigen processing machinery, could provide new therapeutic options. Research should also be pursued to understand how cross-talk between beta cells and cells of the innate and adaptive immune systems impinges on the progression and treatment of diabetes. For example, inflammatory and autoimmune processes (including local cytokine production) could directly alter beta cell function, which could in turn activate more inflammation or autoimmunity. This understanding could form the basis for new combination therapies. If beta cell regeneration is feasible in humans, it will be important to define the physiological stimuli that elicit beta cell regeneration in response to acute beta cell ablation and to establish how chronic autoimmune inflammation interferes with the induction and/or effector function of these stimuli. If in the end it is a kinetic issue—i.e., more beta cells are lost than are being regenerated—therapies can be developed to target that issue.

► **Understand the repertoires of responding lymphocytes, including T cells and B cells.**

For many years, scientists believed that the immune system cells infiltrating the pancreatic islets and rendering the damage that results in type 1 diabetes not only saw multiple antigenic targets, but were themselves diverse in their expression of certain surface markers (i.e., in the case of T cells, their T cell receptor molecules). That hypothesis has changed recently, as data from animal models, as well as very limited information from human pancreata, suggest that the repertoire of T cells entering the islet may be much more focused. This concept, however, remains preliminary in nature, as its proof will rely on the availability of pancreatic

tissue specimens obtained from individuals collected throughout the natural history of type 1 diabetes (i.e., before disease onset, at onset, and continuing until long after disease onset). Addressing this question could dramatically improve understanding of why type 1 diabetes develops and could also help guide the development of a highly specific means to prevent the disease.

► **Identify the range of regulatory cell populations potentially defective in type 1 diabetes and learn which regulatory populations—defective or not—provide good therapeutic opportunities.**

A complete catalog of the cells involved in the body's misguided attack on its own beta cells would likely accelerate opportunities for therapy—any important player could provide insight and opportunity for a successful intervention. Research should be pursued to define the roles of T cells, B cells, NK cells, dendritic cells, mast cells, and others in type 1 diabetes pathogenesis. A large body of literature also suggests an important role for cells that, based on their properties, would be considered regulatory. Indeed, a greater understanding of regulatory T cell populations could provide insight into how to manipulate “master switches” in the immune system and soften or mute the attack on pancreatic beta cells. In addition, studies should define methods to isolate and expand these cells outside of the body so that they could be tested for safety and therapeutic benefit upon re-introduction into a person with type 1 diabetes, alone or in combination with novel or existing drugs.

► **Define which pathways are shared by different autoimmune diseases and which are disease-specific.**

One of the major recognitions in type 1 diabetes research over the past decade was the discovery that a small but appreciable percentage (approximately 5 percent) of people with type 1 diabetes also has another autoimmune disorder, celiac disease (10). The finding of autoimmune disease in association with type 1 diabetes is not new. For example, it has been known for decades that people with the disease are also at increased risk for autoimmune thyroid disease. These situations nonetheless form remarkable opportunities to define disease-specific mechanisms (both genetic and immunologic) by performing studies in people having only one disease, versus those who have disorders in combination with each other. This information will help the field make informed decisions about the applicability to type 1 diabetes of particular immunotherapies that are being tested or used in more prevalent autoimmune diseases.

► **Extend and preserve existing pancreas repositories and data banks, which are critical for direct examination of pancreatic pathology.**

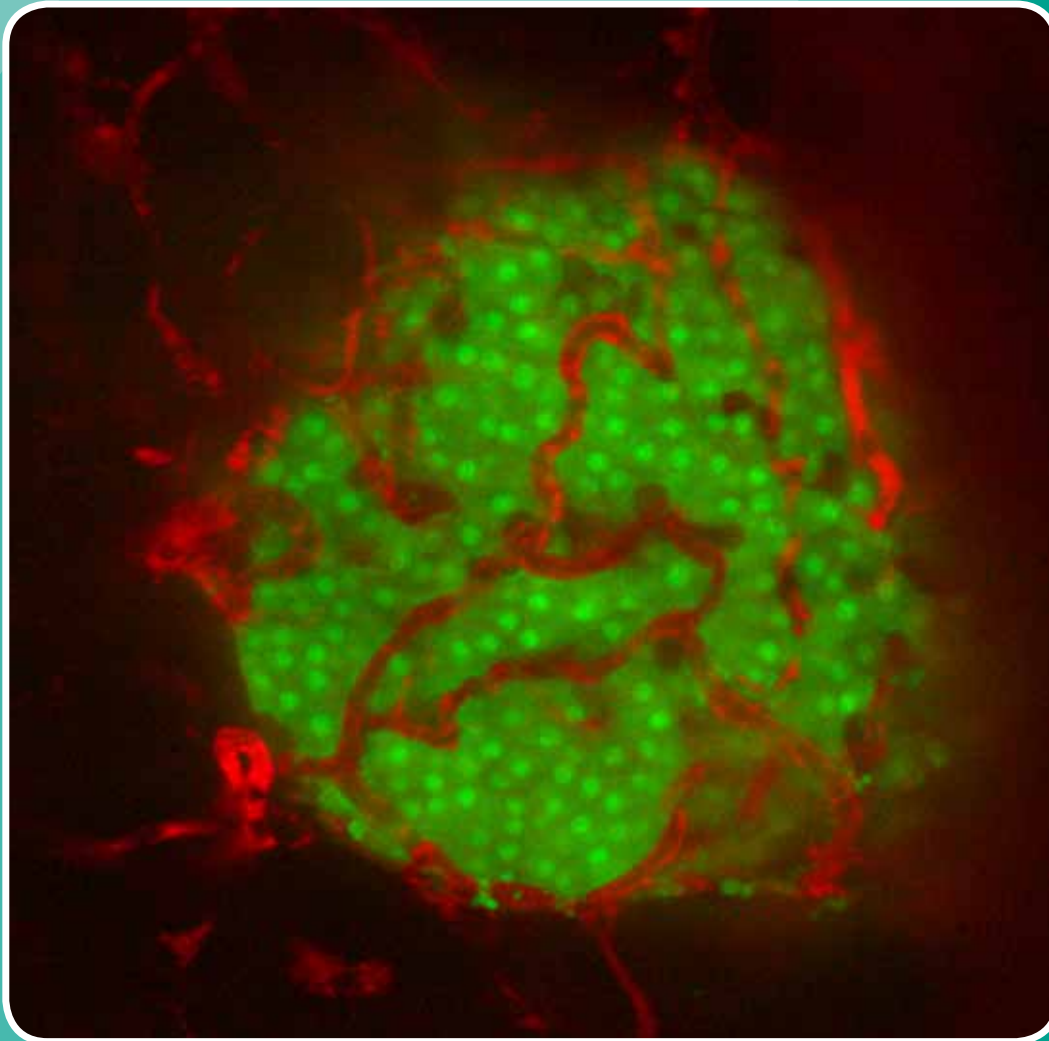
The value of these resources for type 1 diabetes research is clear. For example, pancreatic tissues could be probed for viruses which could then be candidates for triggering infections and studied using the resources of samples from human populations at risk for type 1 diabetes. In addition, the pancreatic and draining lymph node samples banks could be used to define number and specificity of autoreactive T cells in human and mouse islets and to understand their heterogeneity (in terms of T cell receptor usage and antigen recognition). Information gained from pancreas pathology could also possibly be used to help recreate the human islet using stem cells.



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

Overcoming type 1 diabetes will rely on multiple and diverse research efforts, from basic research to clinical trials and epidemiological studies. Bolstering coordination among clinical researchers, government agencies, and industry should aid the flow of candidate interventions into clinical testing—such as that seen in the NIH-supported Type 1 Diabetes TrialNet—and facilitate rapid redirection or addition of efforts in light of new scientific findings. These efforts, in turn, will rely on greater understanding of how type 1 diabetes develops, both through studies in people to uncover genetic, environmental, and other contributing factors, and through improved animal models of the disease. Animal models will also play a crucial role in

the identification and testing of interventions for their potential utility in combating type 1 diabetes and its complications. Biomarkers that are accurate predictors of early pathogenesis in people will be critically important for enabling effective disease prevention. Similarly, biomarkers of autoimmune pathogenesis or beta cell destruction or recovery will be needed to monitor the efficacy of interventions designed to reverse the disease or its complications after onset. Results from fundamental studies of normal immune mechanisms and autoimmunity could help explain the onset, progression, and heterogeneity of type 1 diabetes, and potentially point the way to new approaches to prevent, reverse, or treat the disease.



Mouse pancreatic islet imaged with confocal microscopy. This image reveals how beta cells (green) and other cells in the islet are surrounded by a dense vascular network (red), and was produced using a technique that allows researchers to follow the pattern of blood flow in the islet, which may be perturbed in diabetes. Advances such as these will help researchers better understand islet structure and function in health and disease, aiding efforts to replace islets lost to diabetes. *(Image courtesy of Dr. Lara Nyman and Dr. Alvin C. Powers, Vanderbilt University.)*

# THE BETA CELL

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

## INTRODUCTION

Beta cells, which are found in the pancreas within tiny cell clusters called islets, are the body's sole source of the essential hormone insulin. Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, and results in the inability of the body to absorb and use glucose as a cellular fuel. These defects result in a persistent elevation of blood glucose levels and other metabolic abnormalities, which, in turn, lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the immune system launches a misguided attack, destroying the beta cells of the pancreas, and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production. While the causes of beta cell loss or failure differ, all major forms of diabetes share a common bond in the pancreatic beta cell.

This chapter highlights basic and clinical science focused on the beta cell that will allow the development of strategies to prevent, treat, and cure diabetes. More

broadly, an understanding of integrated islet physiology at the cellular and biochemical level could allow researchers to develop a means of increasing insulin secretion and enhancing beta cell mass. Determining the molecular mechanisms underlying beta cell dysfunction and failure could identify new targets for pharmacological intervention in diabetes. Efforts to optimize islet transplantation sites and improve islet survival are needed to overcome some of the obstacles that impede the widespread implementation of islet transplantation as a treatment for diabetes. Advances in basic stem cell biology and regenerative medicine will need to be harnessed if the promise of new cellular therapies for type 1 and type 2 diabetes is to be realized. The development of novel methods to accurately assess the post-transplant islet mass will be necessary not only to monitor long-term changes at the transplant site, but also to assess the effectiveness of future therapeutic strategies directed at replacing and regenerating beta cells.

## RECENT RESEARCH ADVANCES

**Generation of Insulin-Producing Cells from Human Embryonic Stem Cells:** Taking cues from developmental biology, it has been possible to obtain insulin-producing cells using a step-wise protocol to direct the differentiation of human embryonic stem (ES) cells\*. The process was designed to mimic how the pancreas forms during fetal development by directing cells through

stages resembling this process (i.e., definitive endoderm, gut-tube endoderm, pancreatic endoderm, and endocrine precursors). Some of the human ES cell-derived insulin-producing cells have insulin content approaching that of adult beta cells. Similar to fetal beta cells, these cells release C-peptide in response to multiple secretory stimuli; however—unlike the adult beta cells they need to

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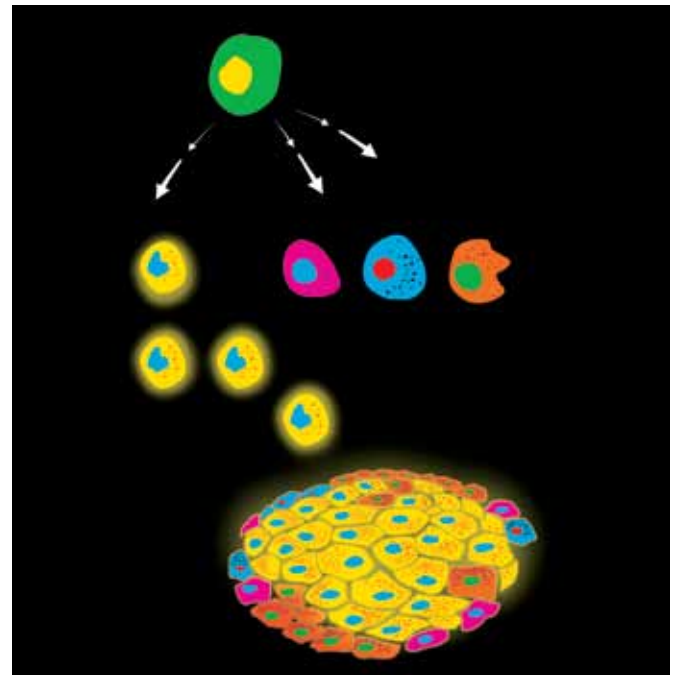
\*The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.

replace—they are not very responsive to glucose. Although these cells do not yet display regulated insulin secretion, nor is the process to produce them highly efficient, this major achievement provides proof-of-principle that it is possible to recapitulate, *in vitro*, the steps leading to the production of insulin-producing cells—a significant leap forward toward the goal of developing beta cell replacement therapies to cure type 1 or severe type 2 diabetes.

**Induced Pluripotent Stem Cells:** In addition to ES cells, there is now evidence that induced pluripotent stem (iPS) cells can be coaxed to differentiate into insulin-producing cells. Although such cells share the main shortcomings of ES cell-derived insulin-producing cells, their derivation raises the possibility of obtaining immunocompatible or even patient-specific insulin-producing cells.

**Adult Mouse Cells Reprogrammed To Become Insulin-Producing Cells:** Research performed in diabetic mice has shown that introducing expression of just three genes is sufficient to reprogram non-insulin-producing adult pancreatic cells (and potentially other cell types) into beta-cell-like insulin-producing cells. The reprogrammed cells lowered blood glucose in diabetic animals—important progress towards harnessing regenerative medicine to treat diabetes. The reprogrammed cells were shown to be stable and effective for the life of the mice. A common technique, called viral gene transfer, was used to introduce the three genes into mouse cells. Future research that could lead to possible applications of this technology to people with diabetes includes achieving similar results without using a virus to carry the genes, testing the approach in other cell types, and replicating the findings in human cells. While much work remains to be done before this becomes a safe and effective therapy, the principle of adult cell reprogramming

is a major step forward and could serve as a model for other applications of regenerative medicine.



Stem cells can differentiate into a number of different cell types, a characteristic that may allow researchers to develop therapies for diabetes to replace destroyed, damaged, or malfunctioning beta cells and islets. (Image credit: Donald Bliss, Medical Arts and Photography Branch, NIH.)

**Demonstration that Beta Cell Mass Is Dynamically Regulated:** Surveys of human cadavers have shown that pancreata from people with type 1 diabetes exhibit a profound loss of beta cells and have low insulin levels, while the loss of beta cells in people with type 2 diabetes is less severe. However, in type 1 diabetes, beta cell depletion is often not absolute, and scattered insulin-immunoreactive cells may often be observed even after many years of disease. Studies in people with type 2 diabetes have also shown an intriguing correlation between duration of diabetes and decline of beta cell mass. Animal studies have shown that the progression from insulin resistance to type 2 diabetes is associated with an initial dynamic increase in beta cell mass to

accommodate the metabolic demand for insulin, followed by a progressive loss of beta cell mass. Similarly, animal studies of how changes in beta cell mass are regulated during pregnancy to meet increased insulin demands have rendered new insights that could help explain gestational diabetes. One of the difficulties in studying beta cell regeneration has been the lack of a robust, synchronized animal system that would allow the controlled destruction of beta cells and study of subsequent cell proliferation in the adult pancreas. Several new transgenic mouse models have been developed that permit the study of the dynamics of beta cell regeneration from a diabetic state. Lineage tracing analyses have indicated that enhanced proliferation of surviving beta cells, or perhaps other pancreatic lineages under extreme conditions of tissue damage, contributes to beta cell regeneration. These advances have enabled investigators to measure changes in beta cell proliferation and survival as a function of disease progression, leading to the hypothesis that diabetes is primarily the result of impaired beta cell mass, and that the seemingly irreversible course of the disease and its growing refractoriness to interventions reflect a deficit in the number of functioning beta cells.

**Advances in Whole Islet Biology:** Beta cells do not function in isolation. They are embedded in the pancreatic islets, which include several different endocrine cell types, blood vessels, and nerve endings. While it has been known for decades that hormone products of different endocrine cells have profound effects on neighboring islet cells (paracrine effects), the extent of regulation among islet cell types, the specific roles of neurotransmitters, and the molecular underpinnings of these interactions have only started to come to light in the last decade. Finally, a new cell type has been discovered in the pancreatic islet—the ghrelin-producing cell, which is thought to exert both autocrine (self) and paracrine effects. The ghrelin receptor (GHSr) is present not only on ghrelin-producing cells,

but also on beta cells and the glucagon-producing alpha cells. A better understanding of these complex intra-islet paracrine and autocrine regulatory roles could lead to novel therapeutic strategies to improve regulated insulin secretion and/or beta cell mass in type 2 diabetes.

### **Insulin As Beta Cell Growth Factor and Regulator of Islet Function:**

While the paracrine effects of other endocrine cell types on the beta cell are fairly well-documented, the autocrine effect of insulin on beta cell function remains a matter of debate. Historically, it has been suggested that insulin exerts a negative effect on beta cells, but recent data provide evidence for a positive role of insulin on beta cell function and survival. Moreover, insulin signaling, once thought to be exclusively important in peripheral target cells, has now been shown to be critical to maintain beta cell mass, and for compensatory islet growth in insulin-resistant states. This new understanding of the role of insulin will help investigators in efforts to replenish and maintain beta cells in the islet.

### **Extracellular Matrix and Cell-Cell Interaction:**

In humans and other vertebrates, the endocrine pancreas has developed into a complex network of cells. Signals that diffuse through the intercellular space of the islets interplay with signaling cascades that depend on membrane proteins and are concentrated at points of cell contact. These mechanisms mediate both indirect (e.g., neurotransmitter-, hormone-, ion-, nucleotide-mediated) and direct (e.g., cell adhesion molecule-, integrin-, receptor-, and junction-mediated) islet cell-to-cell communication. These cell-to-cell interactions combine to ensure key functions and properties of the pancreatic islet, such as synchronized insulin secretion in response to glucose, or maintenance of islet size and architecture. In recent advances, investigators have identified individual cell surface proteins involved in these integrated responses. These observations raise the exciting prospect

that proper expression of these proteins may help foster the development of novel cell sources that would retain, at least partially, the ability to respond properly to acute glucose stimulation—a function which depends on proper cell-to-cell communication. Practical applications that can be explored using this knowledge include improved islet transplantation protocols, novel strategies for islet repair or remodeling, pancreatic tissue engineering using stem or progenitor cells, and the design of three-dimensional scaffolds for the development of a bioartificial endocrine pancreas.

**Vascular Endothelium and Islet Function:** The pancreatic islets are one of the most vascularized tissues in the body, a characteristic that could inform efforts to restore islet function. Recent studies have demonstrated that islet endothelial cells that line the internal walls of capillaries feeding the islet—the microendothelium—are not only involved in the delivery of oxygen and nutrients to endocrine cells, but also induce insulin gene expression during islet development, affect adult beta cell function, promote beta cell proliferation, and produce a number of factors promoting blood vessel dilation/constriction and new growth, including vascular endothelial growth factor A (VEGF-A) and human growth factor (HGF). These islet endothelial cells also play a critical role in the early phase of type 1 diabetes by increasing the expression of surface leukocyte-homing receptors, thereby enabling immune cells to enter the endocrine tissue and cause beta cell destruction. These findings are important not only for understanding islet biology, but also for islet transplantation efforts, as the ability of transplanted islets to revascularize with host vascular elements may be of great importance for islet graft function and survival. Moreover, it has recently been shown that residual intra-islet endothelial cells in islets processed for transplant may also participate in revascularization of pancreatic islets subsequent to transplantation. Preservation

of intra-islet endothelial cell mass may improve long-term graft function by masking foreign antigens.

Together, these advances suggest an important role of the islet microendothelium in normal islet physiology and its possible involvement in type 1 and 2 diabetes pathogenesis, as well as in islet revascularization in transplantation settings.

### **Endocrine/Exocrine Cell-Cell Communication:**

The pancreas hosts two major tissue types, endocrine tissue (the islets) that secretes insulin, glucagon, and other hormones, and exocrine tissue that secretes digestive enzymes. The endocrine and exocrine tissues of the pancreas have traditionally been considered to be two separate entities, structurally and functionally. However, recent observations suggest that the pancreas is a functionally integrated organ in which endocrine and exocrine glands are structurally interconnected, with a continuous matrix supporting the microcirculation, and ductal function allowing for a well-orchestrated functional response. In rodent models and in humans with type 2 diabetes, a widening of the islet/exocrine interface has been observed as a result of a loss of the interstitial matrix and is associated with inflammatory cell infiltration and fibrosis in the islet/exocrine interface. This damage is thought to lead to a loss of cellular paracrine communication that may disrupt signals between the endocrine and exocrine pancreas and gut (i.e., inducing a dysfunctional insulin-acinar-ductal-incretin gut hormone axis), potentially explaining the pancreatic insufficiency and decrease in levels of glucagon-like peptide-1 (GLP-1)—a gut hormone that influences islet function and beta cell mass—known to exist in at least some individuals with pre-diabetes and overt type 2 diabetes.

**Cellular Nutrient Sensing and the Beta Cell:** A number of scientific advances have contributed to the understanding of the complex signaling pathways that are

essential to beta cell function. Transgenic mouse models of type 2 diabetes combined with detailed biochemical analyses have revealed that the cellular response to nutrients is mediated by the concerted action of a variety of key signaling pathways. These critical pathways include the adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway, which responds to changes in energy charge; the mammalian target of rapamycin (mTOR) pathway, which responds primarily to amino acids; the hexosamine pathway, which is responsible for the synthesis of O-linked N-acetylglucosamine, and which responds to amino acids, glucose, and products of fat metabolism; and pathways controlled by the sirtuins, a class of deacetylases that is dependent on nicotinamide adenine dinucleotide (NAD). In turn, these essential pathways interact with, and serve to modulate, homeostatic mechanisms such as insulin signaling, and the transforming growth factor-beta (TGF-beta) and mitogen-activated protein kinase (MAP kinase) signaling cascades. The principal job of the beta cell is to orchestrate the endocrine response to nutrients through these complex, interconnected signaling pathways. Deregulation of these pathways could lead to the beta cell pathology associated with diabetes.

**Endoplasmic Reticulum Stress Signaling in Pancreatic Beta Cells:** The endoplasmic reticulum (ER) is a cellular compartment specialized for folding and modification of nascent proteins. Disruption of ER homeostasis activates the unfolded protein response (UPR). In pancreatic beta cells, glucose-regulated insulin production requires an intact UPR. When the UPR in the beta cell is dysfunctional, ER stress ensues, and beta cells undergo cell death, or apoptosis. Genetic and biochemical evidence in humans and mice support a critical role for the UPR in preserving ER homeostasis and in preventing beta cell failure, mechanisms that are fundamental in the etiology of diabetes.

**Identification of Gene Mutations in Rare Forms of Diabetes Provides New Insights into the Beta Cell:** The rare syndrome of permanent neonatal diabetes mellitus (PNDM) has provided an opportunity to identify genes that regulate beta cell development and function. It was found that, in a subset of affected children, there are missense mutations in the insulin gene that in turn lead to the production of misfolded proinsulin molecules. These mutant proteins are thought to affect beta cell function by interfering with the processing of proinsulin to generate insulin and causing ER stress. While the relevance of these observations to more common forms of the disease is at this point unclear, other studies in experimental animals and transformed cell lines have shown that ER stress, the UPR, autophagy, apoptosis, premature senescence, and germane cellular biological abnormalities play important roles in beta cell failure in general—suggesting that the mechanistic foundation for these phenomena should be investigated in greater detail *in vivo*. Still other, more common forms of neonatal diabetes have been attributed to mutations in genes encoding the two protein subunits of a potassium ion channel that regulates insulin secretion; the mutations prevent the normal release of insulin from pancreatic beta cells (see the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter). This insight into beta cell function has also had the benefit of yielding genetic tests that can be used to identify people who have these mutations, many of whom can manage their diabetes with the orally administered drug sulfonylurea—a less burdensome therapy than insulin therapy.

**Multi-Pronged Approach to Preservation of Beta Cell Function in Human Diabetes:** Several recent studies have shown that type 2 diabetes is associated with a progressive decrease of functional beta cell mass.



Human and animal studies have also suggested that sulfonylureas, the main class of drugs used to treat beta cell dysfunction, may actually precipitate long-term beta cell failure. Recent laboratory discoveries and early clinical studies suggest that preservation or recovery of endogenous insulin secretion may be improved by the use of new (alternate) drugs or new, physiology-based, treatment regimens. Identification of genetic variants associated with beta cell abnormalities has been achieved by genome-wide association (GWA) studies in type 2 diabetes. In addition, rare, monogenic forms of non-autoimmune diabetes (such as PNDM and maturity onset diabetes of the young (MODY)) may provide insights into factors involved in failure of insulin secretion and help to explain why the loss of beta cell function described in epidemiologic studies is so variable. Limited studies investigating the striking improvements in glycemia some people with diabetes experience after bariatric surgery have highlighted the role of gastrointestinal (GI) hormones in modulating and sustaining insulin secretion. Drugs that act through a variety of mechanisms—including insulin sensitizers, such as metformin and thiazolidinediones; the incretins, such as GLP-1; and inhibitors of dipeptidyl peptidase 4 (DPP-4), which prolong action of GI incretins—provide opportunities for new treatment approaches that can enhance and potentially sustain endogenous insulin secretion in people with type 2 diabetes. Technological advances, such as development of continuous glucose monitoring and experimental semi-closed-loop systems to achieve and maintain normoglycemia with less risk of severe hypoglycemia, will enable treatment regimens that may reduce damage to endogenous beta cells and may enhance survival of transplanted islets by diminishing glucotoxicity.

**The Beta Cell Biology Consortium (BCBC):** The BCBC is a large international team of investigators whose research has focused on understanding pancreatic

developmental biology. Specifically, genes responsible for the establishment of the different pancreatic lineages have been identified, and the integrated cascade of interactions leading to the formation of the adult organ decoded. This knowledge has spawned studies of pancreatic beta cell regeneration, cell plasticity, and reprogramming. It has also laid the foundation for the successful generation of insulin-producing cells from human ES cells, and for the integration of complex signaling pathways in the pathogenesis of beta cell dysfunction. The BCBC is engineering beta cell ablation models into immunodeficient mouse strains to allow the assessment of human stem/progenitors in correcting diabetes. The long-term goal is to generate mouse models that will support the development of a human immune system so that human beta cell function can be evaluated in the context of human immunity and autoimmunity. The BCBC has generated many tools and reagents for the diabetes community, including new monoclonal antibodies that recognize human islet cells, and new transgenic mouse models that are being used to understand beta cell development and regeneration.

### **Infrastructure Creation To Improve Human Islet Isolation and Promote Basic Islet Research:**

For decades, most research concerning the factors that determine pancreatic beta cell mass has been derived from rodent animal models and/or cell lines. Although informative, more recent investigations have shown that human islets differ from their rodent counterparts with respect to the regulatory and metabolic milieu that affects their susceptibility to injury and their adaptive response for replication. It is now clear that the human islet is without a convenient laboratory surrogate for such studies, and evidence-based studies obtained from rodents may not extrapolate to the human. To facilitate basic research using human islets, the NIH established the National Islet Cell Resource Centers Consortium (ICRs),

which successfully prepared and distributed cadaveric human islets for fundamental research, using optimized shipping conditions that sustain viability, to more than 150 investigators in North America. The ICRs have been succeeded by the Integrated Islet Distribution Program (IIDP), a contract-supported resource that acquires human islets from subcontracted islet isolation centers and distributes them to approved investigators to facilitate basic research on human islets. Procurement, processing, and testing of the pancreas are costly. It has been critical to have human islets available at a greatly subsidized cost to assure the clinical relevance of fundamental research.



Human islets like these are isolated for research or for transplantation into patients. (Image courtesy of Dr. Camillo Ricordi, University of Miami, Diabetes Research Institute.)

**PET Imaging Agents Target the Pancreatic Beta Cell:**  $^{11}\text{C}$ -DTBZ ( $^{11}\text{C}$ -dihydrotetabenazine) is an imaging agent developed for positron emission tomography (PET) imaging of the dopaminergic neurons of the brain. Its target, the Vesicular Monoamine Transporter 2 (VMAT2) protein, was identified in gene array screens of islet cells. The imaging agent binds specifically to beta and pancreatic polypeptide-producing (PP) cells of the islet and has been used to visualize these cells in the human pancreas in healthy people and in people with diabetes. Currently, researchers are working

to modify the molecule in order to improve its imaging and binding characteristics to the point where it can be reliably used to monitor beta cell mass in people. Other research is ongoing to determine the specific location and expression of its molecular target in the pancreas. Additional highly promising imaging agents are being developed that target markers enriched in the beta cell, such as the GLP-1 receptor. Development of the imaging agent  $^{11}\text{C}$ -DTBZ has thus spurred noninvasive studies of beta cells.

### **Magnetic Resonance Imaging (MRI) Agents Hold Promise for Imaging Transplanted Islets:**

The current practice of transplanting islets into the liver of people with diabetes presents both challenges and opportunities for imaging. The liver takes up many of the molecular imaging agents in a non-specific way, and therefore tends to have a high background signal in most experiments. Considerable progress has been made by either labeling the islets themselves with iron-based contrast agents prior to transplantation, or by encapsulating the isolated islets in immunoprotective coatings that contain iron- or gadolinium-based contrast agents. Signals with these methods persist long after transplantation in rodent, porcine, and primate models, and correlate very well with islet survival. Human trials are under way using this approach.

**Ability To Image Islet Inflammation *In Vivo*:** The presence of islet autoantibodies, and perhaps metabolic changes as detected in the circulation, are the current standards to measure islet autoimmunity, but are an indirect measure. In preliminary experiments, the specific T cell populations that cause insulinitis have been directly visualized using molecular imaging approaches, but the most promising and least invasive approach is to take advantage of the vasculature “leakiness” that develops during inflammation. Large iron-based MRI contrast agents tend to remain in the bloodstream except in sites of

compromised vasculature, and a persistent signal in the pancreas due to islet inflammation has been successfully

monitored in type 1 diabetes mouse models and in people recently diagnosed with the disease.

## IMAGING: AN INSIDE LOOK AT BETA CELLS

Seeing is believing. Imaging scientists are working to find ways to visualize the processes that lead to diabetes and how the body responds to therapy. These new tools will further a better understanding about how the disease starts and progresses. Imaging techniques will provide insights into why, how, and when diabetes occurs, as well as point to new ways for treating the disease.

The secret to imaging diabetes is the use of drug-like imaging agents that selectively “light up” the cells or biological processes involved in disease. For instance, the metals iron and gadolinium change the signal in magnetic resonance imaging (MRI). Compounds that contain these metals can be designed to home in specifically on the insulin-producing beta cells in the pancreas, thereby permitting them to be counted. Similar compounds have been used to light up the inflammation in the pancreas that accompanies the autoimmune destruction of the beta cells and causes type 1 diabetes. Other imaging agents mimic nutrients or hormones and, when taken up by cells, reveal clues to their function and metabolism. These types of agents are commonly labeled with minute levels of radioactivity and detected by positron emission tomography (PET). Thus, they might allow researchers to distinguish

among active and distressed beta cells. Currently, considerable effort is focused on putting imaging labels on the isolated pancreatic islets used for transplantation into people with diabetes. This approach would enable doctors to actually watch the locations to which the transplanted tissues migrate once they are infused into people and to determine their fate—that is, to know how many survive to produce insulin, find out whether they grow in their new environment, and see what happens to those that die. Imaging might also disclose the formation of new blood vessels and nerves around the islets, as well as reveal the importance of these processes for insulin secretion.

Scientists have learned to incorporate into mice a family of proteins that either emit light (such as the luciferase/luciferin system from the firefly) or fluoresce (such as green fluorescent protein). These constitute a very powerful set of imaging tools that are used in basic animal research. For instance, fluorescently labeled insulin can be tracked by the microscope to uncover defects in insulin secretion that might be involved in diabetes. Fluorescently labeled beta cells are making possible novel studies of islet biology, such as viewing islet blood flow in live animals—an approach which could yield new information

about the dynamic relationships between cells in the islet. From identifying and monitoring precursor cells that become new insulin-producing beta cells, to assessing cellular activities important to islet function, it is hoped that these imaging tools will help researchers better understand the development and function of beta cells and islets.

Imaging may also one day help people to manage their diabetes or be used to identify individuals prone to diabetic complications before they

become clinically obvious. New, noninvasive ways to detect and monitor a variety of metabolic problems associated with diabetes may emerge. For instance, new glucose-sensitive imaging agents may make possible the continuous monitoring of plasma glucose without finger sticks. Such an advance would be enormously beneficial for people with diabetes. Therefore, scientists are working to bring emerging imaging tools to bear on all aspects of diabetes and its treatment.

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, highlighted research on the beta cell and islet replacement as key opportunities for advancing treatment of type 1 diabetes. Since that time, new discoveries have underscored the importance of beta cell loss in onset and progression of type 2 diabetes as well. The establishment of centers for islet transplantation research and of a national system for islet distribution, the creation of a collaborative group of beta cell biology research centers, and expansion of fundamental studies of beta cells and islets—all recommended steps from the DRWG’s roadmap for diabetes research, reinforced by subsequent planning efforts—have accelerated research progress in a way that will benefit prevention and therapy for the majority of people with or at risk of developing diabetes. The great promise of beta cell and islet replacement and regeneration, as well as the potential to protect and preserve a person’s own beta cells, merits continued focus on new and emerging opportunities to achieve these ends.

### Integrated Islet Physiology

The cohesive nature of the pancreatic islet, with its complex set of intra-islet cell communication and highly coupled physiological function, is required for the fine-tuning of insulin secretion in response to ever-changing blood glucose levels. Disruptions in the number of cells in a particular islet cell population, or in the interactions between islet cell types, can contribute to the development of diabetes. In addition, optimization of cell replacement strategies for the treatment of type 1 diabetes will probably require the assembly of islet

structures for engraftment that closely resemble the cellular composition, arrangement, and functionality of the normal human islet. In order to better understand the contribution of integrated islet physiology to the pathophysiology of type 1 and type 2 diabetes, and to use this knowledge for the development of new therapeutic strategies, a number of questions remain to be answered.

### Key Questions

- **What is the full communication network that exists between the five endocrine cell types regulated in the islet? What is its role in disease progression?**
- **Are novel receptors and paracrine factors present in the endocrine pancreas?**
- **What are the functional interactions among the exocrine, ductal, and endocrine cell types?**
- **How does islet vasculature affect islet function and engraftment after transplant?**
- **How is islet innervation established? Does it change over time and/or in response to physiological cues and disease states? How does it affect islet function?**
- **What is the integrated physiology of the human islet? How does this differ from regulation in rodent islets?**

### Future Directions

- **Investigate integrated islet paracrine regulation.**

A picture is emerging of the physiological cross-talk that exists between the various cell types in the pancreatic islet, but much remains to be done to understand both integrated islet paracrine regulation and the contribution of the different islet cells to disease progression and treatment. Further comprehensive studies are required to better understand how these cell populations influence each other's function, survival, and growth. In particular, appropriate lineage-specific transgenic mice should be used to manipulate genes of interest, such as the receptors mediating key paracrine pathways, in specific islet cell types.

► **Develop drug therapies targeting islet signaling pathways.**

Analogues of intra-islet signaling peptides are attractive drug candidates for the treatment of type 2 diabetes. Several cell membrane G-protein coupled receptors (GPCRs) of unknown function and their ligands are known to be expressed in the endocrine cells of islets. Orphan GPCRs have also been identified in various islet cell types. Much remains to be explored in relation to GPCR pharmacology and drug development for islet dysfunction in type 2 diabetes. This requires more basic studies with the use of pathophysiologically relevant models, as well as the development of assays and technology platforms for high-throughput screening. As other cell membrane proteins, such as channels and primary and secondary transporters, are identified in islet cells, they may also become important pharmacologic targets.

► **Develop scaffolds and other support systems for beta cells.**

Using knowledge of islet physiology to manipulate interactions between cell-adhesion proteins (integrins) and the extracellular “support gel” (extracellular matrix,

or ECM) is an attractive strategy for potentiating beta cell survival, and function. Chemical modulators of the ECM-integrin system could lead to the development of therapeutic agents that can improve islet endocrine function, survival, or growth *in vivo*. In the context of engineering a transplantable bioartificial pancreas, dissociated cells, such as purified beta cells, islet progenitor cells, or stem cells, would benefit from being provided with extracellular sites made of surrogate ECM materials for attachment prior to implantation, as these scaffolds could help to maintain viability and differentiated function, and aid in the formation of islet-like clusters. Innervation also supports the islets, and studies on how innervation is established and affects islet function will need to be pursued.

► **Increase understanding of human (versus rodent) islet physiology.**

The pancreatic islets in the normal adult account for about 1 to 2 percent of the total pancreas weight in humans and in rodent species. However, although human and rodent islets contain similar endocrine cells, the relative numbers and distribution of component cells are distinct. Rodent islets are distinguished by a large central core of insulin-producing beta cells, but in human islets the beta cells are more randomly dispersed, and glucagon-producing alpha cells are more abundant. Therefore, the human islet cellular composition/arrangement enables closer juxtaposition and communication between these two cell types that may influence complex metabolic processes, such as counter-regulation. Human islets also have a less dense capillary vasculature. These differences may have profound consequences for beta cell self renewal and adaptive expansion triggered by immune, viral, and metabolic assaults or by an increased insulin

demand. Maintenance or induction of the beta cell mass is less well understood in humans as compared to rodents. The apparent heightened adverse sensitivity to chronically high levels of blood glucose and lipid stimulation in human islets also needs to be better understood. Insights into the regulatory pathway of islet regeneration will require the availability of human islets to develop therapeutic strategies.

► **Determine the influence of the intrauterine environment on islet development and function.**

There is an increasing incidence of gestational diabetes and obesity during pregnancy. An understanding of how this altered intrauterine environment has an impact on the offspring, particularly as it affects islet development and function and subsequent diabetes, is critical. Studies should be pursued in animal models and in humans in order to elucidate the potential role(s) of intracellular signaling pathways, inflammatory cytokines, nutrient sensing pathways, and epigenetic imprinting, under both normal and dysfunctional metabolic conditions during pregnancy.

## Beta Cell Dysfunction and Failure

In the last decade, evidence has accumulated to suggest that the progressive clinical course of diabetes reflects primarily a decrease in beta cell function. However, this decrease is not merely due to a functional impairment, but also to actual loss of functioning beta cells. Genetically engineered mouse models of type 2 diabetes have revealed the complexity of disease progression and provided insight in determining the relationship between insulin resistance and impaired beta cell function in diabetes. Several potential mechanisms of beta cell failure have been explored, including the role of the UPR, the importance of numerous signaling

pathways in nutrient sensing (e.g., insulin, MAP kinase, mTOR, AMPK, hexosamine, and sirtuins), programmed cell death (apoptosis), autophagy, and premature senescence, as well the contribution of inflammatory mediators. Recent genetic and biochemical evidence in both humans and mice suggests a critical role for the UPR in preserving ER homeostasis and preventing the beta cell failure that may be fundamental in the etiology of diabetes. Chronic or overwhelming ER stress stimuli associated with metabolic syndrome can disrupt protein folding in the ER, reduce insulin secretion, invoke oxidative stress, and activate cell death pathways. Similarly, chronic inflammation in the beta cell environment leads to accumulation of factors (cytokines) that can impair beta cell function by initiating apoptotic signaling pathways, or that can promote beta cell damage or death by mediating changes in local vascular or immune cell constituents. Recent evidence suggests that chronic inflammation of the pancreas can adversely affect islet function in type 2 diabetes. This finding suggests the intriguing possibility that immune modulators may have therapeutic potential for slowing or reversing beta cell decline not only in type 1 diabetes but in type 2 diabetes as well.

### Key Questions

- **What are critical steps of UPR that could be manipulated to improve beta cell function and survival?**
- **Which of the nutrient sensing pathways contribute to beta cell loss?**
- **Which of the intracellular signaling pathways can be manipulated to preserve beta cell function and mass?**

- **What are the initiating events, participating cells, and destructive processes underlying the intra-islet inflammatory response?**
- **What are common features of immune-mediated damage in type 1 and type 2 diabetes, and how might this potential mechanistic overlap inform the development of new therapeutic approaches for both diseases?**

### **Future Directions**

- **Discover ways of modulating intra-islet inflammatory mediators in order to prevent insulinitis in type 2 diabetes.**

Immune modulation is important to efforts to avert beta cell loss in type 1 diabetes and thereby prevent or slow progression of the disease (see the “Type 1 Diabetes and Autoimmunity” chapter), but inflammation is increasingly recognized to play a role in pathogenesis of beta cell loss in type 2 diabetes as well. Based on the discovery that a pro-inflammatory state exists in type 2 diabetes and contributes to islet failure, it is important to conduct research on signaling pathways involved in maintaining the chronic islet inflammation, a preliminary to identifying therapeutic areas and modalities that can be safely engaged to protect beta cells against ongoing metabolic stress. There are extensive opportunities to leverage existing research and knowledge in other areas and longstanding experience with anti-inflammatory agents in a variety of disease contexts.

- **Develop pharmacological agents to modify key signaling molecules to preserve and protect beta cell function.**

Several new pathways leading to cellular dysfunction of beta cells have been uncovered. Taking advantage of the fact that these pathways appear to be of general relevance in multiple organ damage and different cell contexts, it is envisioned that therapeutic interventions designed to prevent, for example, polypeptide misfolding, oxidative damage, and/or UPR-induced cell death can also be used to improve beta cell function and/or survival in the treatment of diabetes. The use of modified chemical chaperones or delivery of specific pathway inhibitors, as well as agents known to promote cellular senescence and protect against apoptosis, are examples of the therapeutic approaches that can be used in this regard.

### **Prevention and Treatment of Diabetes**

If normal beta cell responses can be preserved or failure of endogenous insulin secretion can be reversed, major improvements in the outcome of diabetes treatment may be achieved. Even partial preservation of insulin secretion should be important because it is associated with less severe hypoglycemic episodes and may enable good glucose control to be achieved with simpler treatment regimens. In the last few decades, investigations began to reveal the underlying pathophysiology and identify potential strategies to prevent loss of beta cell function. Crucial information has become available in just the last 5 to 10 years, including definitive proof that the rate of progression from normal glucose metabolism to pre-diabetes to type 2 diabetes can be slowed. Much has also been learned about type 1 diabetes, and efforts are under way to find ways to suppress or stop the autoimmune destruction of beta cells. Clearly, people with diabetes could benefit from development of ways to preserve beta cell function, reverse functional failure of insulin



secretion, and increase beta cell mass. A program of studies will be needed to achieve these goals, starting with learning the key requirements to protect beta cells and their glucose-sensing and insulin secretion mechanisms from toxic metabolic stress. Multiple studies will be necessary to learn how to reliably improve beta cell function and mass, and to convert current knowledge into treatments that will produce long-lasting benefits. It will require collaboration of basic scientists, clinical investigators, epidemiologists, and clinical trial leaders to convert new knowledge into effective clinical therapies.

### Key Questions\*

- **What are the causes of the potentially reversible loss of beta cell insulin secretion in response to hyperglycemia?**
- **What are the best treatments to preserve endogenous insulin secretion? Should insulin secretion be stimulated or are lasting recoveries more likely if the demand for insulin secretion is temporarily reduced?**
- **Are combination therapies more effective than single drug (or behavior) therapy in preserving beta cell function in people with pre-diabetes or early diabetes?**
- **What are the best treatments to induce sustained recoveries of endogenous insulin secretion?**
- **What are the benefits (both short- and long-term) of partial preservation of endogenous insulin secretion in people who still will require long-term anti-diabetic drug therapy?**

- **Can biomarkers (genetic or metabolic) be identified that will enhance the ability to predict a) progression to diabetes from pre-diabetes, or b) recovery of insulin secretion in overt diabetes? Can biomarkers predict the rate of failure of endogenous insulin secretion or stabilization/improvement of beta cell function in response to intervention(s)?**
- **Does duration or severity of preexisting hyperglycemia alter the probability of recovery of endogenous insulin secretion in type 2 diabetes? Does the response to treatment vary by the type of therapy employed to induce “remissions” of type 2 diabetes?**

### Future Directions

- **Develop strategies to preserve and restore beta cell function in pre-diabetes and diabetes.**

A key goal for research is to improve underlying understanding of the pathophysiology of beta cell failure in humans. Studies are needed to define how to optimize beta cell preservation in both pre-diabetes and early diabetes and, in overt diabetes, how to optimize lasting improvement in insulin secretion. Differences in responses to different treatment strategies need to be documented. This information is critical for planning long-term clinical trials aiming to induce more long-duration preservation or enhancement of endogenous insulin secretion. Applications could be developed for short-term interventions, such as treatment regimens during immunotherapy for people with new-onset

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\*See the “Clinical Research and Clinical Trials” and “Special Needs for Special Populations” chapters for additional questions related to larger clinical trials and other studies designed to bridge the gap between clinical trials and translation of results into information that could be widely applied in clinical care and public health efforts.

type 1 diabetes or people receiving islet or pancreas transplants. Protecting beta cells will be critical to optimize results of future studies to stimulate an increase in endogenous beta cell mass.

➤ **Identify biomarkers for type 2 diabetes progression and remission.**

It will be critically important to identify biomarkers, either permanent (genetic markers, evidence of epigenetic alterations, etc.) or metabolic markers (isolated measures or patterns of change), that can easily and inexpensively improve prediction of a) progression from pre-diabetes to type 2 diabetes or b) ability to induce “remissions” with recovery of endogenous insulin secretion. Specific and sensitive markers would both simplify clinical research and provide a basis for eventual clinical application of new discoveries.

➤ **Conduct clinical studies of beta cell preservation in pre-diabetes.**

Additional studies employing strategies to enhance beta cell function are needed in pre-diabetes. These studies would capitalize on the remarkable success of type 2 diabetes prevention trials to further reduce the risk of progression to type 2 diabetes and potentially reverse pre-diabetes. Special opportunities exist to explore ways to reduce the risk of progression to established diabetes in women with gestational diabetes and people with hyperglycemia related to other sources of transiently increased demand on beta cell function (infection, high-dose corticosteroids, etc.).

➤ **Integrate mechanistic studies into clinical trials to improve understanding of the effects of long-term interventions on beta cell mass and function.**

It is important to design and carry out long-term clinical outcome studies demonstrating how different interventions, degrees of metabolic control, and classes of drugs affect development, regeneration, and loss of beta cell mass. Research is needed to establish a firm connection between beta cell mass serum markers or dynamic tests of beta cell function.

## Cellular Replacement Therapies for Diabetes

Strategies have focused on finding a way to replace the beta cells of the pancreas that are destroyed in type 1 diabetes by the immune system. One therapeutic strategy that has shown promise is islet transplantation. In this procedure, pancreatic islets are taken from a deceased human donor and transferred into an adult patient, most commonly in the liver. Once implanted, the donor islets make and release insulin in response to the recipient’s needs. Currently, the procedure remains experimental, and is reserved for adults with exceptionally brittle diabetes and recurrent hypoglycemia, or people with end-stage renal disease. Although the improvements in success rates with the therapy have brought tremendous hope for a cure, formidable obstacles impede widespread implementation of islet transplantation. One impediment is the toxicity associated with the immunosuppressive regimens that are required to prevent rejection of the transplanted islets. There are many research projects in progress that attempt to increase understanding of the impact of immune suppression on islet transplantation, as well as clinical trials to improve drug regimens for preserving islet grafts. Controlling the immune response to transplanted islets is critically necessary. In addition, a subset of patients who have received a transplant

will experience a return of autoimmunity even while on immunosuppressive therapy. Immunosuppressive drugs have serious side effects, which may include direct effects on regenerating beta cells, as has been observed in studies of mouse models. These issues are addressed in the “Type 1 Diabetes and Autoimmunity” chapter. Another impediment is the inadequate supply of donor pancreata for the number of potential recipients. Researchers are seeking ways to optimize both the organ procurement and the islet isolation processes from these precious and finite resources. Consonant with these efforts, research is in progress to determine whether cells from other sources—e.g., progenitor/stem cells or genetically modified pancreatic cells—can be directed to develop into islets or beta cells, and thus provide an unlimited source of cells for transplantation. Ongoing research in regeneration is also under way to determine if adult beta cells can be coaxed to form more beta cells (replication) or if other resident cell types can be directed toward a beta cell fate (transdifferentiation, transdetermination, or reprogramming).

### Key Questions

- **Are there ways to promote successful islet engraftment and survival so that people require fewer islets and/or transplants to produce sufficient amounts of insulin?**
- **Can researchers harness the information from a fundamental understanding of the developmental biology of the endocrine pancreas to generate fully functional beta cells from stem cells *in vitro*?**
- **Can iPS cells be generated safely for patient-specific cell replacement therapy, eliminating the concern of genome integration by the associated viral vectors?**

- **What are the underlying principles of cellular reprogramming, and under what physiological or pathophysiological conditions will transdifferentiation, transdetermination, and reprogramming occur?**
- **What are developmental and/or epigenetic factors that affect pancreatic endocrine fate?**
- **Given the number of ways to increase beta cell mass in rodent models, can these findings be translated into increasing beta cell mass in humans?**
- **What are common features in beta cell replication between rodents and humans at the physiological periods when replication is known to take place (neonate, puberty, and pregnancy)?**

### Future Directions

- **Improve islet transplant procedures by determining the optimal sites for islet transplantation and developing novel islet survival strategies.**

Early inflammation at the site of transplantation, and even the diabetic environment itself, is likely to contribute to the programmed cell death of beta cells. Currently, the liver is the preferred site for islet transplantation (islets are infused into the portal vein), but better sites need to be identified. In addition, information is needed to fully understand the effects of transplantation and associated transplant drugs on beta cell survival, proliferation, and function in humans.

- **Define a molecular signature for endogenous human beta cells, as well as for human stem cell-derived beta cells, and their progenitors.**

Defining such a standard is an essential benchmark for determining how closely the stem cell-derived beta cells resemble native pancreatic beta cells. The benchmarks could include physiological criteria, cell surface markers, transcriptome, and/or epigenetic status.

- **Discover late developmental pro-beta cell signals and use these signals to produce large numbers of functional human beta cells from stem/progenitor cells.**

These signals could be secreted factors, small molecules, extracellular matrix components, epigenetic regulators, and/or protein transduction approaches that would allow the prospective programming of human ES cells or iPS cells to become mature beta cells *in vitro*. Techniques that would facilitate the isolation, purification, and scale-up of defined progenitor populations and their endocrine pancreas progeny will be needed.

- **Generate large quantities of fully functional beta cells through the transdifferentiation or direct reprogramming of other adult or progenitor cell types *in vitro* and/or *in vivo*.**

The potential to redirect cell differentiation by the overexpression of genes suggests that it is possible to convert different cell types into pancreatic endocrine cells. Understanding the mechanisms of how this process occurs will form the basis for developing strategies for the *in vitro* and *in vivo* reprogramming of non-beta cells into regulated insulin-producing cells.

- **Develop animal models to test the engraftment, survival, and metabolic impact of human beta cells or islets derived in culture from stem/progenitor cells.**

Quantitative transplantation assays are needed to assess the efficacy of cell replacement therapies. Of particular importance, to enable safety testing, are non-human primate models or mouse models that are engineered to accept human cells. The development of appropriate animal models for testing potential cell replacement therapies is a critical step before human therapies can be realized.

- **Create new animal models of human diabetes.**

It may be possible to reconstruct human type 1 diabetes in a mouse model and observe how autoimmune diabetes is initiated and how the disease process unfolds. One approach is to develop iPS cell lines from people with type 1 diabetes. Protocols would be needed to direct differentiation of these iPS cell lines toward the pancreatic beta cell, hematopoietic stem cell, and thymic epithelium cell fates—all critical cellular components of the type 1 diabetic system. The generation of an optimal mouse recipient for engraftment with human hematopoietic cells, beta cells, and thymic epithelium would have to be generated. These new animal models could be useful in developing and testing new drugs for the treatment of diabetes.

- **Understand the cell types, signaling pathways, and genes that control islet cell mass and beta cell replication and are relevant to the regenerative capacity of the human islet.**

In humans, there is morphological evidence for beta cell regeneration, even in people with long-standing type 1 diabetes. There are clear differences between rodent and human islet physiology that have impeded the discovery of new therapies for enhancing beta cell mass in humans. While the use of animal models of beta cell regeneration is still the most efficient way to identify new signals and pathways, it will be necessary to validate this information in human islets.

## Imaging the Pancreatic Islet

The ability to measure pancreatic beta cell mass, function, outcome of transplantation, and inflammation would allow researchers and clinicians to monitor the natural history of type 1 and 2 diabetes and response to therapy, and to delve deeper into the mechanisms of beta cell failure and regeneration. This is a uniquely challenging goal, as the pancreatic beta cell poses all of the major challenges that could be ascribed to an imaging target. The islets in which the beta cells reside comprise a tiny fraction—1 to 2 percent—of an organ buried deep in the abdomen, where they are in constant motion. Although knowledge of the endocrine pancreas and its development is growing, there are still few, if any, completely unique and reliable cell markers, and little is known about the biology of those putative markers that have been identified. Human islet tissue is difficult to obtain and difficult to work with. Although many rodent models are available, they are also difficult to work with and imperfectly mimic the human situation. Despite all these challenges, a hallmark of beta cell imaging research, even in the very earliest studies, has been remarkable ingenuity and creativity accompanied by rigorous scientific standards. Novel imaging approaches have been applied to this problem virtually upon discovery, and new powerful imaging agents have been devised in service to this problem.

## Key Questions

- **What are the best technologies, reagents, and targets for noninvasive imaging of pancreatic beta cell mass and function? For islet inflammation?**
- **How best can transplanted islets be monitored *in vivo*? Can angiogenesis and neurogenesis in these islets be visualized directly, and can imaging be used to monitor the life cycle and common causes of loss of the transplanted tissues?**
- **How does beta cell mass change throughout the normal human lifespan? What are the effectors and natural history of cell loss in diabetes? What is the relationship between mass and function in health, pregnancy, obesity, insulin resistance, etc.?**

## Future Directions

- **Assemble interdisciplinary environments and teams to work on imaging the beta cell, and invite cross-pollination from related fields such as cancer and neuroimaging.**

Promising new imaging approaches should be quickly brought to bear on beta cell imaging. This requires rich environments with teams of creative people that have access to various forms of imaging and expertise in reagent production and labeling, diabetes, and islet biology. In order to most efficiently develop and understand the best application of new technology, safe beta cell imaging approaches that are validated in animal models should be tested as early as possible in humans, and results from these early clinical studies should drive new mechanistic experiments in animal models.

- **Identify cell-specific beta cell surface proteins as molecular imaging targets and use high-throughput methods to find or produce highly specific, tight-binding, small molecule or peptide imaging agents.**

Currently, the biggest hurdle for beta cell imaging is the lack of beta-cell-specific markers and highly specific, pure, highly labeled imaging agents. These marker proteins should be stable over time and disease states, accessible to exogenous ligands, and correlate well with beta cell mass or number.

- **Recruit chemists to design imaging agents for beta cell targets, or to improve the kinetic and imaging properties of existing promising agents.**

Reasonable success has been achieved by mining libraries of extant neuroimaging agents for the ability to bind beta cells. It is likely that these and other candidate reagents can be optimized for the human beta cell.

- **Develop novel, noninvasive technologies to monitor islet cell function, islet angiogenesis, nerve function and growth, and inflammation.**

Although the primary goal is to measure beta cell mass or number *in vivo*, there are many other properties of the islet that could serve as imaging targets and would be of

great benefit in understanding the life cycle of the islet and the pathogenesis of diabetes. A reliable marker for inflammation may allow identification and treatment of people at high risk for diabetes prior to clinical signs. If researchers could measure islet nerve action and perfusion, it might help in monitoring islet neogenesis and response to therapy, or perhaps in understanding if there are different mechanisms of diabetes in different populations.

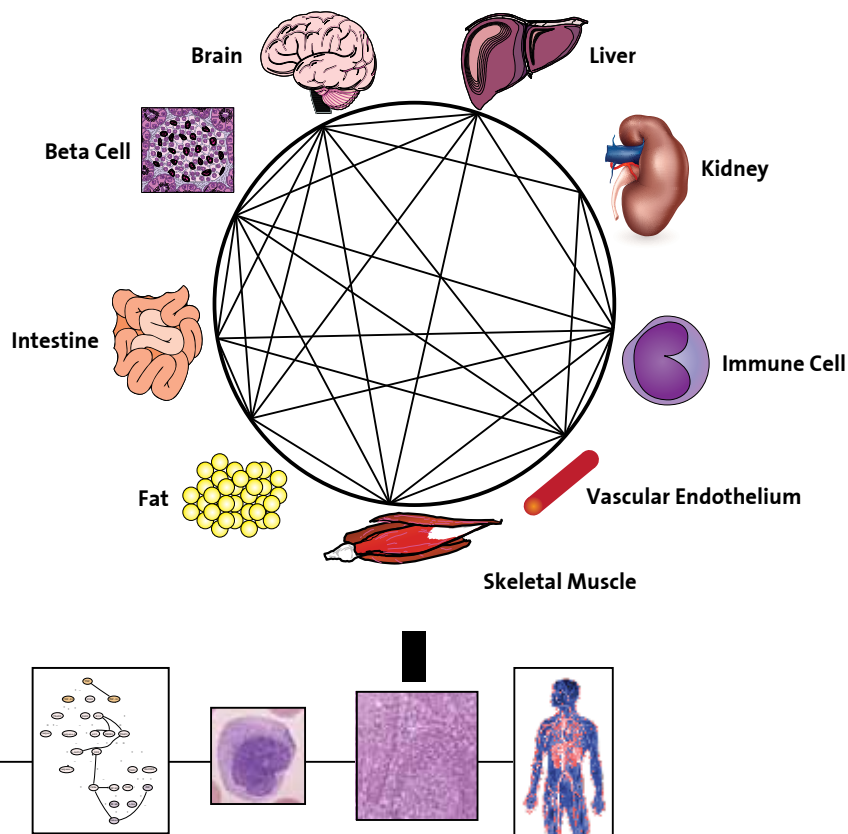
- **Define the biology of promising imaging agents and their cell targets, such as the expression in development and islet life cycle, cellular location during function, and other fundamental properties.**

Correct interpretation of imaging data requires a great deal of knowledge of the imaging approach, the reagents being employed, and the biological target. Studies should be pursued to define the specific location and concentrations of target molecules across the pancreas and in other gut organs, in various stages of development, and in health and disease, so that it is clear when a change in signal indicates a change in beta cell mass rather than a change in assessable target or some other biological event. Such studies will certainly uncover novel properties of the beta cell and the islet, as well as validate the imaging approach.

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

Research studies of beta cell function and islet biology have the potential to transform diabetes treatment. Armed with new knowledge of the factors governing how beta cells develop, grow, function, and die within the pancreatic islet, researchers may be able to develop new approaches to preserve or restore regulated insulin secretion. Already, scientists are reproducing some of the beta cell's insulin-producing capacity *in vitro*; continued progress in stem cell biology and cellular reprogramming holds out the hope of regenerative medicine as a treatment for diabetes. People with

diabetes should also benefit from islet research that leads to improved approaches to transplantation and maintenance of islets, and from advances in imaging technologies and techniques to detect both when beta cells are being lost to disease or injury and when they are successfully restored through medical interventions. In conjunction with research on ways to avert beta cell stress and destruction, these efforts hold promise to yield new ways to strike at the heart of diabetes and to improve outcomes for people living with this disease and those who are at risk.



From complex intercommunications that span molecules, signaling networks, cells, and tissues, and the whole human body (bottom) to the interplay of multiple organs and tissues involved in this disease (top), type 2 diabetes is a disease of many parts and many dimensions. Identifying all the changes that occur during development and progression of type 2 diabetes will be aided by systems biology approaches.

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# TYPE 2 DIABETES AS A MULTI-DIMENSIONAL DISEASE

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

## INTRODUCTION

Type 2 diabetes is not a single, “simple” disease. Rather, it is a constellation of disease syndromes, all leading to a final common diagnostic marker—hyperglycemia, or high levels of glucose in the blood. This heterogeneity and degree of complexity makes research on the causes of type 2 diabetes very challenging. Maintaining normal glucose levels (glucose homeostasis) requires a balance between insulin secretion from the pancreatic beta cells and insulin action in target tissues, which determines the rates of glucose production from the liver and glucose utilization by skeletal muscle and other tissues. Resistance to insulin action is a characteristic metabolic defect that precedes hyperglycemia in the great majority of people with type 2 diabetes and often defines a state called pre-diabetes. In people who develop hyperglycemia, the proximate cause is a decline in beta cell function, which in the face of insulin resistance leads to relative insulin deficiency.

It is important to recognize the significant interconnections among type 2 diabetes, metabolic syndrome, and cardiovascular disease. Insulin resistance is a central component in the pathogenesis of all of these conditions. More importantly, at a clinical level, both type 2 diabetes and metabolic syndrome are major predisposing factors for atherosclerosis and cardiovascular disease. Cardiovascular disease is the major cause of death in people with type 2 diabetes. Dissecting the pathogenesis of type 2 diabetes and finding new points to intervene with therapy can thus have a major impact on atherosclerosis and cardiovascular disease not just for people with diabetes, but for other at-risk individuals as well.

Multiple biological systems appear to be involved in the progressive pathogenesis of type 2 diabetes, including a variety of circulating hormones, nutrient pathways and intracellular molecular signals. These systems are controlled by a combination of genetic and environmental factors, creating numerous opportunities for disruption of function. Nearly 40 genetic loci are known to have an impact on the risk of developing type 2 diabetes. Diabetes incidence has increased dramatically in recent years, mainly as a result of environmental factors, including the current epidemic of obesity caused in part by widespread dietary changes and sedentary lifestyle. These environmental factors unmask the genetic susceptibility to diabetes that would go undetected in other environments. The complex pathogenesis of type 2 diabetes varies from person to person and reflects heterogeneous genetic and environmental triggers and metabolic abnormalities in multiple organ systems (e.g., muscle, liver, fat, beta cells, and brain). If optimal therapy is to be developed for individuals with type 2 diabetes, research approaches are needed that can systematically untangle the diverse contributors to this disease.

A systems biology approach to diabetes research recognizes this complex pathogenesis and the fact that diabetes reflects a disruption of energy homeostasis of the entire body. It takes advantage of established molecular, cellular and physiological technologies, as well as the many recently developed high-throughput discovery tools that collect and integrate large data sets obtained using “omics” technologies—genomics, transcriptomics, proteomics, lipidomics, and

metabolomics. Together, these approaches provide an opportunity to understand phenotypic variability at an unprecedented depth and to identify novel pathways of disease development and progression. With the complete sequencing of the mouse and human genomes and identification of a large number of single nucleotide polymorphisms (SNPs) that span these genomes at close intervals, disease phenotypes can now be mapped to specific regions on chromosomes. These technologies allow researchers to associate classical clinical markers of disease phenotype, such as blood glucose or insulin levels, with a much more detailed set of phenotypic variables, including tissue mRNA levels and circulating protein and metabolite concentrations. Like disease traits, transcript, protein, and metabolite levels can be used to map quantitative trait loci (QTLs) to specific regions of the genome. Ultimately, such a detailed multi-dimensional analysis could provide a roadmap for more

precise tailoring of diabetes therapies to individuals who have the disease.

This chapter focuses on the great promise of a systems biology approach for understanding mechanisms leading to type 2 diabetes, for sub-classification of different forms of diabetes to assist in tailoring of therapeutic strategies, and for more detailed evaluation of new drugs to treat the disease. Integrating different areas of type 2 diabetes research is key to this approach. These areas include cell biology of hormone action, mechanisms of obesity-associated metabolic dysfunction, inflammation and endoplasmic reticulum stress, mitochondrial metabolism, gene and environmental interactions, the role of the gut microbiome, the role of the central nervous system in metabolic regulation, and opportunities for translation of new scientific discoveries from the bench to the bedside.

## RECENT RESEARCH ADVANCES

**High-Throughput “Omics” Technologies Yield Detailed Molecular Phenotyping:** Researchers can now sequence the full expressed genome, as well as promoter regions, in large numbers of individuals and obtain measures of gene copy number and SNP maps for expression QTL assessment. Simultaneously, technologies have evolved to estimate gene function via expression of thousands of specific mRNAs at a high level of throughput and sophistication. Advances in proteomics make it feasible to simultaneously monitor several thousand tissue and plasma proteins. Disease state can influence post-translational modifications, such as protein phosphorylation, acetylation,

glycosylation and other changes that can also be measured in a high-throughput manner. Metabolomics, the simultaneous quantitative measurement of thousands of small molecules, has been integrated with genotyping and transcriptomic profiling in animal and human studies. For example, in the KORA study (a population-based study from Germany), significant associations were observed between SNPs and changes in specific metabolites. This finding allowed polymorphisms in four genes encoding metabolic enzymes to be linked to perturbations in the metabolic pathways in which the enzymes function. Thus, tools are now in place to describe an individual’s metabolic

state with molecular and transcriptional fingerprints and link it to the individual's genetic profile. These are important steps toward understanding the many genetic and environmental contributors to diabetes and developing personalized therapies.

### **Genetic Factors in Type 2 Diabetes Pathogenesis:**

Although a number of rare monogenic forms of type 2 diabetes have been identified, the common forms of type 2 diabetes appear to result from complex interactions among multiple genetic loci and environmental factors. While more than 50 genetic loci associated with type 2 diabetes and obesity have recently been identified using high-throughput genome-wide association (GWA) studies, family history for diabetes still conveys more information about diabetes risk than specific gene mutations, indicating that much remains to be learned. Continued investigation of these multiple genetic factors may point to new mechanisms involved in disease risk and potential strategies for therapy (see the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter for additional information about advances in diabetes genetics).

### **Environmental Factors in Type 2 Diabetes**

**Pathogenesis:** The most obvious environmental factors that lead to insulin resistance and the development of diabetes are a high-calorie diet, sedentary lifestyle, and obesity. It is not easy in the face of these strong risk factors to identify other, more subtle environmental risks. In addition, these factors are overlaid by cultural features that influence diet and exercise and how the individual interfaces with his or her environment. Clearly, these interactions exist and need to be identified. Conversely, regular exercise training has long been known to enhance insulin sensitivity in people with and without diabetes. In recent years, the discovery of exercise-response

genes has provided molecular insight into novel and conventional pathways that regulate glucose and energy homeostasis in health and diabetes. Exercise has acute effects to increase insulin sensitivity and enhance glucose and lipid metabolism, and training also modifies expression of genes involved in glucose homeostasis. Evidence is emerging that genetic or environmental factors may influence an individual's response to exercise and other environmental factors. Researchers have found, for example, that antioxidants may block the beneficial effect of exercise training on glucose metabolism. Proper integration of these factors is needed to define exercise training programs that promote the greatest health benefits, including enhanced insulin sensitivity in diabetic humans.

### **Intracellular and Extracellular Signaling Pathways That Integrate Growth Factor, Nutrient, and Energy Sensors:**

Elucidation of the role of receptors, G proteins, pathways of insulin and other hormone signaling, protein kinases and phosphatases, and histone acetylases and deacetylases has allowed for a more thorough understanding of signal transduction pathways that govern metabolism. Important advances include elucidation of pathways involving insulin receptor signaling, phosphatidylinositol (PI) 3-kinase, the serine/threonine kinase Akt, mitogen-activated protein (MAP) kinases, forkhead transcription factors, and sirtuins, as well as the mechanisms by which they are integrated, including transcriptional co-activators and co-repressors. Modern mouse genetic engineering has allowed the function of each of these molecules to be defined *in vivo*, as well as *in vitro*. In addition to hormones, nutrients have been shown to directly modify signal transduction pathways that regulate glucose and lipid metabolism through kinase cascades (the modification of proteins, lipids and other molecules by the addition or removal of phosphate groups). Recent

advances include the identification and characterization of protein kinase cascades, such as the AMP-activated protein kinase (AMPK) and the amino acid sensor mammalian target of rapamycin (mTOR), both of which are also regulated by hormones. These discoveries emphasize the important role of nutrients on cellular and whole body insulin action through an interplay between intercellular energy sensors and metabolic/gene regulatory events.

### **Tissue Crosstalk and Feedback in Controlling Energy Balance:**

Over the past decade, a whole new class of hormones has been discovered—the “tissuekines.” These circulating bioactive peptides are secreted from leukocytes (cytokines), different fat depots (adipokines), and muscle (myokines), for example, and act on liver, brain, and other tissues. The activities of these tissuekines revealed a previously unsuspected level of crosstalk between cell types throughout the body that contributes to metabolic regulation. Crosstalk between tissues is also mediated by nutrients and metabolites, particularly circulating lipid and carbohydrate species generated from liver and fat.

### **Transcriptional Mechanisms Regulating Hepatic Glucose and Lipid Metabolism:**

In addition to regulation of membrane receptors and transporters, hormones and nutrients can regulate cellular function through control of gene expression. Advances in the molecular biology of nuclear receptors and other transcription factors have furthered understanding of protein complexes involved in the regulation of gene expression in fat, liver, and muscle, as well as other tissues, that affect overall metabolic status and cellular functions in highly-differentiated cell types. Nuclear receptors involved in diabetes pathogenesis can be direct targets of steroid and thyroid hormones, as well as targets of nutrient signals and of xenobiotics—

chemical substances not normally found in the organism but introduced from the environment. A major part of insulin action also occurs by regulation of gene transcription by forkhead box O1 (FoxO1) and other transcription factors. These effects are further modified by co-repressors and co-activators, as well as covalent modification by acetylation/deacetylation, in response to external stimuli. Over the past decade, research on the contribution of transcriptional control to overall metabolic fuel homeostasis has provided important insights into fundamental mechanisms of hormone action, control of cell differentiation, and the biological clocks that govern many bodily functions.

### **Cell Biology of Protein Trafficking and When It Goes Wrong:**

Insights into the mechanisms that control protein trafficking among organelles in cells yield new information about hormonal regulation of glucose metabolism, particularly control of insulin secretion within the beta cell and control of glucose transport in muscle and fat cells. Scientists have identified many of the proteins and their interactions by which insulin regulates GLUT4 glucose transporter trafficking from intracellular regions to the cell membrane to stimulate glucose uptake. Defects in insulin-stimulated glucose uptake in muscle represent one of the earliest detectable lesions in humans with pre-diabetes.

The endoplasmic reticulum (ER) is a vast network of membranes in which all secretory and membrane proteins are assembled, and proper folding, maturation, storage, and transport of these proteins take place. ER stress has been detected in both experimental and human obesity and in states of insulin resistance, such as fatty liver associated with type 2 diabetes. In this condition, misfolded proteins or metabolic signals activate a complex series of events called the unfolded protein response (UPR)—an attempt to restore the

functional integrity of the ER. Inflammatory pathways involving the enzymes c-Jun N-terminal kinase (JNK) and I $\kappa$ B kinase (IKK), reactive oxygen species, and other nutrient sensing and pathogen response systems are also integrated with ER function. Molecular and chemical tools that can mitigate ER dysfunction have demonstrated some therapeutic efficacy in rodent models of obesity, insulin resistance, and type 2 diabetes. ER stress is implicated in beta cell dysfunction and viability, suggesting that it could also be an important feature of type 1 diabetes.

### **Inflammation and Metabolic Homeostasis:**

Experimental, epidemiological, and clinical evidence produced in the past decade has causally linked inflammation and the inflammatory response to the pathogenesis of obesity, type 2 diabetes, and metabolic syndrome, and their complications. Several important molecular mediators, including the stress kinases JNK and IKK, and the suppressors of cytokine signaling (SOCS proteins), have been identified and genetically validated in mouse models. Interventions that suppress or modify the inflammatory response systems have been shown to improve insulin sensitivity and glucose metabolism, demonstrating that inflammation as it occurs in diabetes participates in metabolic deterioration. Most recently, clinical studies have shown similar effects, providing evidence for a role of inflammation in human metabolic disease. It has also become clear that inflammation plays an important role in diabetes complications, particularly macrovascular disease, where the process can involve both vascular endothelial cells and smooth muscle cells.

### **Mitochondrial Activity and Insulin Resistance in Humans and Animal Models:**

Multiple studies in humans using noninvasive imaging and muscle biopsies indicate that impaired capacity for oxidative function

is present in type 2 diabetes and insulin resistance. Researchers observed that the insulin resistance present in people who have type 2 diabetes or are undergoing normal aging is associated with reduced activity of key mitochondrial pathways that use oxygen to generate adenosine 5'-triphosphate (ATP), the cell's "energy currency"—leading to the idea that muscle mitochondrial oxidative dysfunction may be an early defect in diabetes. Coordinated changes in expression of nuclear genes encoding mitochondrial proteins underlie these changes. Researchers can now explore a variety of mechanisms potentially linking impaired mitochondrial oxidative function to insulin resistance, including excessive lipid accumulation over time, particularly with ensuing energy excess, leading to lipotoxicity; reduced ATP synthesis for energy-requiring insulin signaling and insulin-stimulated glucose uptake; reduced ATP synthesis during exercise, potentially contributing to reduced aerobic capacity, muscle fatigue, and decreased voluntary exercise over time; and, in adipose cells, reduced insulin signaling and reduced secretion of adipokines.

### **Circulating Fatty Acids, Ectopic Lipid Storage, and Insulin Resistance:**

Chronic exposure of the liver to elevated fatty acids overwhelms the capacity for fatty acid oxidation, leading to esterification in triglycerides, increased production of very low density lipoproteins (VLDL), and generation of lipid-derived metabolites that interfere with insulin signaling. Similar events occur in muscle, where chronically elevated lipids increase fatty acid beta-oxidation enzymes. In sedentary humans and animals, the induction of the beta-oxidative machinery ultimately leads to the activation of enzymes that interfere with insulin action. It appears that elevated circulating lipids and inappropriate fat storage in peripheral tissues (ectopic fat) occur when the adipocyte cannot store all of the fat being produced.

The discovery that lipid droplet biogenesis proteins modulate insulin sensitivity reinforces the hypothesis that mechanisms that impair fat storage in adipocytes lead to insulin resistance. This hypothesis is further supported by findings of insulin resistance induced by infusion of exogenous lipid, as well as insulin resistance in lipodystrophy, a condition characterized by abnormal fat distribution.

### **Amino Acids Play a Role in Insulin Resistance and Glucose Homeostasis:**

Obese and insulin resistant humans have elevated levels of various amino acids, including the branched-chain amino acids (BCAA). One BCAA, leucine, interferes with insulin action via stimulation of the enzymes mTOR and S6K1 and modification of insulin receptor substrate (IRS) proteins. A comprehensive targeted metabolomics study in obese, insulin-resistant individuals and lean controls revealed that a BCAA metabolite signature was strongly related to insulin resistance in this cohort. These findings, coupled with rodent and human feeding and amino acid infusion studies, show that during high fat consumption, BCAA could contribute independently to development of obesity-associated insulin resistance. A study in mice, which correlated genetic loci, transcripts, and metabolites, identified a molecular network through which the amino acid glutamine regulates phosphoenolpyruvate carboxykinase expression and, therefore, glucose production in the liver. These studies illustrate how nutrients and metabolites can have broad effects on multiple metabolic pathways and point to the need for more careful dissection of the role of individual nutrients and metabolites in the pathogenesis and possible treatment of type 2 diabetes and other insulin resistant states.

### **Novel Locations and Functions of “Taste” Receptors and Their Potential Impact on Diabetes and Obesity:**

Novel nutrient receptors are being identified throughout the body. For example, the sweet and bitter taste receptors of the oral cavity that underlie taste quality perception are also distributed throughout the specialized endocrine cells of the gastrointestinal tract and pancreas. Recent studies have shown that the gut-expressed sweet taste receptor (and its associated signal transduction pathway) helps regulate intestinal uptake and metabolism of sweet compounds, and the release of insulin from the pancreas during digestion. In other studies, the oral taste cells have been shown to contain hormones previously found in gut endocrine cells that are known to regulate insulin release from the pancreas. These non-traditional functions of the oral and gut sweet receptors suggest a direct role for taste and taste receptors in diabetes and obesity, a role that is markedly different from the sensory function of the oral taste system. Research has also revealed an association between bitter taste receptors in the gut and glucose metabolism. Further study of the roles of nutrient receptors in diabetes and obesity is clearly warranted.

**Role of Brain in Carbohydrate Metabolism:** The last 10 years have provided tremendous advances in understanding central nervous system (CNS)-dependent control of metabolism. Initial studies in mice and rats with inactivation of the insulin signaling cascade in the brain revealed a critical role for neuronal insulin action in control of hepatic glucose production. Subsequent studies uncovered control of both hepatic glucose production and peripheral glucose disposal, as well as adipose tissue mass, by hormones acting via the CNS,

including leptin, insulin, ghrelin, glucagon-like peptide-1 (GLP-1), and others. The growing understanding of the primary neuronal target sites, their projection sites, and the intracellular signaling cascades mediating these effects provides promising novel avenues for the treatment of impaired glucose metabolism and associated disorders, such as dyslipidemia.

**Bench to Bedside and Back Again:** Research on the mechanism of action of drugs for type 2 diabetes treatment has yielded tremendous insight into basic biology, just as knowledge gained through basic studies has led to powerful new classes of drugs. Metformin, a biguanide insulin sensitizer, suppresses hepatic glucose production and lowers fasting glucose. This effect appears to be, at least partly, through the action of AMP-activated protein kinase, an important energy sensing protein kinase that regulates nutrient metabolism. The second class of insulin-sensitizing diabetes drugs, the thiazolidinediones, act by binding to the peroxisome proliferator-activated receptors (PPAR), primarily in the nucleus of fat cells, regulating insulin sensitive genes for nutrient metabolism and fat storage. Exenatide, or exendin-4, is a new peptide therapeutic that was approved to treat type 2 diabetes in 2005. This drug, which was obtained originally from the venom of the Gila monster, acts to stimulate secretion of insulin from the beta cell by mimicking the action of

the normal incretin GLP-1. Exendin-4 is more effective than GLP-1 itself because it resists degradation and has a much longer half-life in the circulation. However, now drugs are also available that inhibit the enzyme that normally degrades GLP-1, an enzyme called dipeptidyl peptidase-4 (DPP-4), and these serve as an oral alternative to the peptides, which require injection. These examples demonstrate the synergy between basic mechanistic research, discovery research, and drug development. They support the hope that additional drugs will be developed to target molecules involved in diabetes pathophysiology, and that biological pathways will be elucidated through the investigation of new bioactive molecules. The huge promise of a systems biology approach to diabetes research is that it has the potential to identify factors and pathways that can be targeted for a more holistic diabetes therapy.

**Gastric Bypass and Glycemic Control:** While initially aimed at the treatment of obesity, gastric bypass and other bariatric surgeries have been shown to produce a much greater improvement of glucose metabolism than expected from the obtained weight reduction. Diabetes is resolved in some cases after surgery but prior to significant weight loss. Identifying the molecular basis of the gut/CNS crosstalk responsible for these effects is expected to set the ground for the development of novel therapeutic strategies for diabetes.



## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, highlighted cell signaling and cell regulation as an important area of opportunity in understanding type 2 diabetes, and acknowledged the emergence of new technologies that were already propelling the field. Since then and with the support of the NIH, many of these new technologies have come to fruition so that now a true systems biology approach to type 2 diabetes is feasible. This will allow elucidation of the complex biological interactions involved in disease pathogenesis by integrating information about cell signaling pathways with genetic, transcriptional, metabolic, and environmental factors. Described below are research questions and opportunities focused on developing an integrated understanding of the molecular pathogenesis and consequences of type 2 diabetes.

### Insights into Gene and Environment Interactions in Type 2 Diabetes

The rise in diabetes incidence over the recent decades underscores the existence of environmental triggers that promote disease in people with a genetic predisposition. Researchers understand some of these triggers: the “unhealthy diet” and sedentary lifestyle that result in obesity are major risk factors for type 2 diabetes, and maternal obesity and gestational diabetes can result in metabolic abnormalities in the offspring. Unfortunately, in contrast to “omic” technologies that allow a relatively complete sampling of genetic, genomic, proteomic, and metabolomic variables, at present there is no similar unbiased approach available for identifying all of the environmental stressors that might contribute to

diabetes. However, recent studies have shown that epigenetic modifications of DNA structure can take place as a result of environmental factors that act in addition to the mutations found in inherited DNA sequences. Researchers have also begun to investigate how nutrients and exercise alter gene transcriptional programs, and explore novel transcriptional and translational regulatory mechanisms, such as noncoding microRNAs.

### Key Questions

- **What can a systems biology approach reveal about gene and environment interactions?**
- **Can a systems biology approach reveal the mechanisms whereby the identified diabetes genes and gene variants contribute to glucose homeostasis and type 2 diabetes pathogenesis?**
- **Do some genes and genetic variants contribute to diabetes only when a particular environmental factor is present?**
- **What is the mechanism by which diet, exercise, and other environmental factors affect insulin sensitivity, and what are the specific dietary and other environmental factors that are most important?**
- **How does the intrauterine and early postnatal environment influence diabetes risk?**
- **How do epigenetic modifications in gene expression profiles influence the metabolic response in type 2 diabetes?**

- **What other major regulatory mechanisms, such as miRNA, influence diabetes pathogenesis?**

## **Future Directions**

- **Develop new tools and technologies for complex genetic/genomic studies and metabolic profiling.**

Once established, core laboratories focused on the various “omic” technologies can take on the challenge of determining the role of changes at these levels in various metabolic and diabetic states. This service requires policies that ensure sufficient time and resources for continued technology development, which is critical for future new systems biology approaches. Advanced functional genomic platforms can help researchers characterize model organisms and animal models in search of specific gene-environment interactions that lead to loss of metabolic homeostasis and diabetes. Development of new tools and technologies for large-scale population genetics and the emerging interface between epidemiology and high-density genetic and molecular analysis will lead to better understanding of how genetic variation determines changes in gene networks and metabolic function in clinical populations. High-content molecular profiling technologies (metabolomics and proteomics) coupled with sophisticated computational and bioinformatics tools are needed to define novel pathways that can be exploited for drug discovery and diabetes therapy. Further development of computational tools for integration and interpretation of large, complex data sets emanating from different “omics” platforms should also be undertaken. Aligning these activities with educational and training opportunities in mass spectrometry, NMR, data analysis, and advanced computational methods will help scientists realize maximal benefit and impact from

application of these technologies to diabetes research.

- **Study the role of microRNAs in type 2 diabetes pathogenesis.**

Research is needed to discover and quantitate the universally present small non-coding RNAs or microRNAs (miRNAs) present in all tissues and cell types. Several studies have begun to provide evidence that small RNA species may play a role in the pathogenesis of type 2 diabetes and that either endogenous miRNA or their specific inhibitors may be exploited as targets for therapeutic intervention. The full impact of miRNAs and how they modify physiology and interact with other genetic factors remain to be defined.

- **Investigate the role of epigenetic changes in type 2 diabetes pathogenesis.**

Epigenetic changes in DNA have been noted in certain forms of cancer and during embryologic development. Accumulating evidence suggests that DNA methylation can be modulated by the environment. For example, glucocorticoid receptor gene methylation is modified in the hippocampus of rat pups in response to maternal grooming. This observation provides a direct example of how childhood environment may determine adult stress-responses. Dietary modification can also have a profound effect on DNA methylation and genomic imprinting. Graded methylation-driven silencing of an element that regulates coat color and the obesity phenotype of the agouti mouse has been shown in the offspring of mice fed diets with different amounts of folic acid. Environmental toxins, such as heavy metals, can disrupt DNA methylation. Estrogenic and anti-androgenic toxins that decrease male fertility can also alter DNA methylation, and these changes are inherited by subsequent generations. Thus, epigenetics may

provide a mechanism to link the changing environment to long-term effects on incidence of type 2 diabetes in individuals and families. Moreover, DNA methylation, histone acetylation, and deacetylation may introduce epigenetic changes in the intrauterine environment and throughout an individual's lifetime, which may influence age-related modifications in gene expression profiles that can contribute to metabolic disease. Identifying the enzymes that mediate modifications in DNA structure and transcription provides an opportunity for a more systematic approach to defining the role of epigenetic enzymes in control of metabolic regulation and diabetes pathogenesis.

- ▶ **Investigate how nutrients interact with different genetic backgrounds to influence diabetes development.**

In rodents, genetic background dramatically affects response to environmental stresses, such as high-fat diet, as well as to other genetic alterations that lead to insulin resistance or changes in beta cell function. A systems approach with measurement of transcript, protein, and metabolite levels allows the integration of both genetic background and environmental influences and the combined analysis of various “omics” information to discover regulatory pathways that may be relevant to disease progression. The identification of these pathways and distinct nutrient and energy “sensors” that control them may lead to the development of new prevention strategies for certain people in the pre-diabetic state through individualized diets that can enhance insulin action.

- ▶ **Identify xenobiotics and xenobiotic receptors that might act as environmental sensors and influence diabetes development.**

In addition to major dietary components, such as carbohydrates, fats, and protein, minor dietary

components (trace metals) and xenobiotics, i.e., other chemicals that enter the body, such as drugs and environmental pollutants (e.g., dioxins, polychlorinated biphenyls), may have important effects on pathogenesis of diabetes and its complications. While some candidate xenobiotics and xenobiotic receptors involved in metabolism have been identified, research is needed to discover more substances that can play a role and to understand their mechanisms of action at a cellular and molecular level.

## Metabolic and Hormonal Regulation in Diabetes

The loss of glucose homeostasis that defines diabetes is the clinical manifestation of the failure of an enormous system of homeostatic mechanisms involving many cell types and the huge number of intersecting signaling and metabolic pathways within each cell. Great strides have been made in understanding the cellular basis of this metabolic regulation. In addition to information gleaned from targeted molecular and cellular biology approaches, genomic, proteomic, and metabolomic approaches have revealed a number of new pathways, regulatory events, and modes of interactions among tissues, receptors, and processes. Physiological and cellular models of hormone action have revealed new molecules involved in receptor biology, protein trafficking, control of enzyme activities, and transcription. This progress has resulted in a new, integrated view and opened the door to exciting new therapeutic opportunities for diabetes.

### Key Questions

- **Are there unidentified hormones, or small molecules with hormone-like activity, that signal from tissue to tissue or communicate via the CNS to affect metabolism, and what are their functions? What are their sites of production and mechanisms of action?**

- **What is the full complement of molecular players involved in regulation of gene transcription and protein translation? How do they interact to effect different gene expression patterns?**
- **How do the many signaling pathways within cells interact to control metabolism, cell growth, and energy production?**
- **What are the dominant molecular mechanisms of insulin resistance in different tissues, and how do they differentially affect glucose, lipid, and amino acid metabolism?**
- **Is the mechanism of insulin resistance different in different pathological states, such as diabetes, obesity, polycystic ovarian disease, and related conditions?**
- **What are the earliest defects that can be detected in the pathogenesis of type 2 diabetes, and are they the same in most individuals? Which of these defects are genetically programmed and which are acquired?**

## Future Directions

- **Identify transcriptional targets of key protein kinases involved in metabolic regulation.**

Evidence indicates that numerous protein kinases, including S6K, Akt (and other serum and glucocorticoid-inducible kinase (SGK) family members), IKKs, mTOR, glycogen synthase kinase-3 (GSK-3), and MAP kinases, are key integrators of signaling to transcription factors. A variety of post-translational modifications to proteins, including phosphorylation, acetylation, and ubiquitination, directly regulate transcriptional activity, cellular location, and protein interactions. Efforts are

needed to more fully understand the transcriptional mechanisms of pathway integration and identify key nodal points for effective intervention. Development of additional probes for protein components of these systems is essential for use in cellular and *in vivo* imaging.

- **Develop the ideal “molecular signature” of nuclear receptors and transcription factors.**

Combinatorial diversity in the components of transcriptional and other signaling complexes leads to subtle differences in gene expression patterns, particularly concerning nuclear receptors, which are established drug targets. Research to solve the structures of these complexes using x-ray crystallography and cryo-electron microscopy will help scientists identify the components of these signaling complexes and the most beneficial molecular conformations of co-activator/co-repressor complexes that generate a positive impact on *in vivo* energy balance and metabolism.

- **Ascertain pathways of lipid and lipoprotein synthesis and breakdown in the liver.**

Research is needed to define molecular pathways that activate the transcription factor sterol regulatory element binding protein (SREBP), and regulate cholesterol, fatty acid, and triglyceride metabolism. In particular, the role of the SREBP pathway in the pathophysiology of hepatic steatosis (fatty liver) remains poorly understood. Research to understand the relationship between ER stress pathway activation and hepatic lipogenesis—the conversion of glucose to fatty acids in the liver—is of key importance. Such studies may be able to leverage efforts in other fields, such as research on the impact of alcohol or toxins on these factors and pathways in the liver.

► **Elucidate molecular events involved in insulin action and insulin resistance.**

Insulin resistance is central to type 2 diabetes and the metabolic syndrome. Despite great progress in understanding insulin signaling, much remains to be learned about the normal function of this network in regulation of multiple pathways of cellular metabolism. In addition, defining the specific tissues and organs involved in different states of insulin resistance, such as obesity, type 2 diabetes, polycystic ovary disease, and others, offers the possibility of targeting specific pathways in different disorders.

► **Elucidate molecular events involved in insulin-stimulated glucose transport.**

Progress has been made in identifying early signaling pathways from the insulin receptor, but how these pathways regulate the trafficking of the main insulin-sensitive glucose transporter protein GLUT4 remains uncertain. Efforts are required to identify the G protein target(s) of AS160 (a substrate of the Akt serine/threonine kinase that regulates insulin-stimulated GLUT4 trafficking), the role of other kinase substrates, and the role of the exocyst and soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor, or SNARE, protein complexes. Also needed are cellular models of hormone action in muscle, especially human muscle, where some of the earliest defects in type 2 diabetes have been identified.

► **Elucidate mechanisms underlying regulation of circadian rhythms vis a vis metabolic control.**

Night-shift working and other forms of circadian misalignment lead to major metabolic abnormalities, including leptin and insulin resistance. These factors play an important role in some populations at high risk for diabetes. These control mechanisms may also play an important role in control of normal metabolism. Therefore, efforts are required to understand the mechanisms underlying integration of clock genes with metabolic processes.

► **Identify novel “tissuekines” and elucidate their role in regulation of energy balance and interplay with known hormones.**

Newly identified muscle-, bone-, and adipose-derived factors have a profound impact on metabolic pathways in other tissues. Efforts are needed to fully catalog these “tissuekines,” identify their receptors and signaling pathways, and begin to understand their physiological roles. Also, more information is needed on insulin action and cross-talk between non-traditional target tissues of insulin (brain, kidney, vasculature, gastrointestinal tract, and immune cells) and traditional target tissues (muscle, fat, and liver).

## **Inflammation and Endoplasmic Reticulum Stress—Impact on Insulin Signaling and Glucose Metabolism**

Consensus is emerging regarding some of the mechanisms resulting in insulin resistance, beta cell failure, metabolic dysregulation, and diabetic complications. Two important components are inflammation and ER stress. Inflammation in obesity, type 2 diabetes, and atherosclerosis is not the adaptive immunity that occurs in response to a broad range of extrinsic injuries. Rather, it is activation of the innate

immune system, which is characterized by abnormal cytokine production, increased acute phase reactants, and activation of a network of inflammatory and stress signaling pathways. A perhaps related phenomenon is the disruption of the integrity of cellular organelles, particularly ER. Under stress conditions triggered by misfolded proteins or metabolic signals, the ER activates the UPR, resulting in activation of the enzymes JNK and IKK and generation of reactive oxygen species, which, in turn, can modify metabolism and damage tissues.

### Key Questions

- **What biological networks and molecular mechanisms initiate and govern “chronic” inflammation? Which immune cell subtypes are critical in metabolic regulation? Can the cell subtypes be manipulated to alter metabolic outcomes?**
- **What mechanisms activate inflammatory networks within non-immune cells, such as adipocytes, hepatocytes, myocytes, pancreatic beta cells, and neurons?**
- **What are the metabolic triggers and mechanisms for ER dysfunction in obesity, diabetes, fatty liver, and cardiovascular disease? Is there a link between ER and mitochondrial dysfunction? Are there biomarkers that faithfully reflect organelle failure, ER stress, or tissue inflammation?**
- **Could the inflammatory response and ER failure link metabolic homeostasis to other clustering diseases, such as asthma, neurodegeneration, cancer, and others, which are also frequently associated with obesity and/or insulin resistance?**

- **Are there chemicals that modify the function of ER or other organelles, or influence chronic inflammation? Which molecules that demonstrate pre-clinical efficacy could be tested for proof-of-principle in humans most expeditiously and effectively?**

### Future Directions

- **Elucidate the triggers and responding cell types that initiate and maintain chronic inflammation in diabetes.**

The mechanisms leading to establishment of chronic low-grade inflammation in diabetes, including the involvement of immune and other cell types, the relationship between acute inflammatory responses and the establishment of chronic inflammation, and the identification of molecular signatures defining chronic inflammation, are important areas for research.

- **Investigate molecular mechanisms linking metabolism and chronic inflammation.**

Inflammation in diabetes occurs in the context of significant metabolic dysregulation. Studies are needed to define how signals emanating from metabolic pathways may exacerbate or modulate chronic inflammation, and how inflammation may exert an adverse impact on metabolism to accelerate disease progression. The role of inflammation in vascular endothelial cells and smooth muscles cells should also be investigated, as this forms an important link between diabetes, obesity, atherosclerosis, and cardiovascular disease.

- **Identify and develop novel targets for intervention.**

Emerging technologies are raising the possibility of identifying a wide range of new potential therapeutic targets. A thorough examination of the relationship between epigenetic change and chronic inflammation in both immune cells and the cellular targets of inflammatory damage is now feasible. Similarly, advanced chemical biology platforms and screening techniques are identifying novel small molecules that may have therapeutic promise. In all cases, the development, validation, and use of appropriate animal models, as well as early clinical research, remains key to accelerating bench to bedside translation.

► **Characterize the molecular mechanisms leading to ER dysfunction in diabetes.**

Efforts are needed to understand the different branches of the UPR and how these pathways interact to regulate target organ metabolism. The development of reagents to monitor ER function in cells and tissues from animals and humans, as well as reagents/methods to experimentally generate physiologically relevant forms of ER stress in cultured cell systems, would accelerate research in this area. Research is needed to characterize the ER, its resident proteins, lipids, structural and morphological properties, and folding environment, as well as the links between different inflammatory responses, mitochondrial function, and ER stress. This line of research should incorporate chemical biology platforms for small molecule discovery, genome-wide functional screens, and development of new experimental models to monitor cellular responses and live animals during the course of ER stress/metabolic disease. Finally, clinical proof-of-principle studies of promising pharmacological interventions are needed.

## Mitochondrial Metabolism

Mitochondrial dysfunction has emerged as a potential explanation for the tight relationship of obesity

and overnutrition with the development of insulin resistance. One hypothesis postulates that impaired fatty acid storage by a limited adipose tissue expansion capacity leads to excess circulating fatty acids. These cause insulin resistance, either as the consequence of incomplete oxidation leading to reactive oxygen species (ROS) production, or through bioactive lipid derivatives, like diacylglycerols or ceramides. Fatty acids can exert deleterious effects directly in muscle and/or indirectly through macrophages by eliciting chronic low-grade inflammation. Because the primary disposal of free fatty acids in muscle and oxidative tissues is through mitochondrial beta-oxidation, mitochondria may play a crucial role in determining individual susceptibilities to insulin resistance and diabetes. Several lines of experimentation, including noninvasive NMR and gene profiling, have discovered deficits in mitochondrial function or in the expression of mitochondrial genes in human muscle from individuals with diabetes or a family history of diabetes. Moreover, the capacity of adipose tissue to sequester free fatty acids is correlated with its mitochondrial levels and oxidative capacity. Thus, the study of mitochondrial function and its role in type 2 diabetes is an important new research avenue.

## Key Questions

- **Are the changes in mitochondrial function cause or consequence of insulin resistance or an independent contributor to metabolic derangement?**
- **What mechanisms control mitochondrial levels and functional outputs in human tissues and how do these relate to the genetics of the disease?**
- **What is the relationship between mitochondrial energy metabolism and insulin signaling?**

- **Does mitochondrial dysfunction link aging to type 2 diabetes?**
- **What are the most promising approaches to treat mitochondrial dysfunction in metabolic disease?**

## Future Directions

- **Develop animal models of mitochondrial deficiencies that more precisely mimic human physiology, and ascertain their effect on the development of insulin resistance and diabetes.**

Current animal models that are designed to evaluate the impact of mitochondrial oxidative capacity on the development of insulin resistance are largely limited to mouse whole body or muscle-specific knockdowns of co-activators or co-repressors of mitochondrial biogenesis. The pathology associated with these manipulations tends to be extreme. More subtle, inducible genetic alterations in fatty acid beta oxidation, ATP production, or ROS generation that affect specific cells, tissues, or organs may produce models that more faithfully mimic human physiology. These and similar models would be important tools for testing the hypothesis that specific defects in mitochondrial function underlie the development or progression of insulin resistance and type 2 diabetes.

- **Systematically assess the interactions between mitochondrial energy metabolism and insulin signaling in model systems.**

Tractable genetic systems such as *Caenorhabditis elegans* (a species of roundworm) and *Drosophila melanogaster* (a species of fruit fly) have been successfully used to delineate the basic elements of insulin signaling. However, a systematic approach

to studying the interactions between mitochondrial function and insulin signaling in mammals has not been taken. The development of metrics and tools to assess mitochondrial fatty acid oxidation, ATP production, ROS production, and other mitochondrial-specific outputs in these model systems, as well as their effects on specific elements of the insulin signaling pathway, is necessary.

- **Discover the broader consequences of cellular mitochondrial energy metabolism on tissue function.**

Adipose and muscle tissue functions are dependent not only on the activities of the differentiated cell composing the tissue (i.e., adipocyte, myocyte), but on the factors that nourish and maintain communication between the tissue and the whole body, such as its vascular network. The interactivity between mitochondrial energy metabolism and the generation of signals necessary for the proper development of muscle and adipose tissue microvasculature is likely to be a key factor in energy homeostasis and needs to be studied.

## Nutrient Role in Glucose Homeostasis—Mechanisms of Overnutrition-Driven Tissue Dysfunction

The wide availability of energy-rich fast foods in U.S. society and changes in dietary habits over the past several decades have led to chronic overconsumption of all the major macronutrients—carbohydrate, fat, and protein—and to obesity. Obese humans and animals are often insulin resistant and exhibit increases in circulating lipids and amino acids even before the appearance of elevated glucose levels and type 2 diabetes, suggesting that imbalance in these nutrients may contribute to the ultimate development of hyperglycemia. Lipid abnormalities of obesity include



elevated levels of multiple fatty acids and triglyceride in the plasma, increased LDL (“bad”) cholesterol and reduced HDL (“good”) cholesterol, and accumulation of lipids in liver and muscle (ectopic fat). High fat diets, acute (6 to 12 hour) infusion of lipids, or growth of isolated muscle cells in the laboratory in the presence of high levels of fatty acids are all sufficient to cause insulin resistance. Chronic culture of islet beta cells with high levels of fatty acids or glucose impairs glucose-stimulated insulin secretion and eventually leads to activation of cell death pathways, a demonstration of the harmful effects of high concentrations of certain nutrients. On the other hand, nutrient-derived signals are important in relaying the body’s energy status and partitioning nutrients between storage and use as fuel, in inter-organ communication, and in regulating glucose homeostasis. In order to break the link between obesity and diabetes, it is important to understand why insulin resistance, tissue dysfunction, and eventually diabetes can be the body’s response to “too much of a good thing.”

### Key Questions

- **What are the key intracellular and extracellular nutrient-derived and nutrient-independent signals that trigger insulin resistance, and do humans use the same signaling pathways as animal models? In addition to macronutrient composition, which individual micronutrients play important roles?**
- **How do these nutrient-derived signals interact with genetic variability to protect or predispose people to diabetes?**
- **What are the mechanisms by which overnutrition and the overabundance of nutrient concentrations lead to impaired beta cell mass and function?**

- **What are the similarities and differences among nutrition-derived signals that mediate dysfunction in key organs and tissues involved in fuel homeostasis, including muscle, liver, vasculature, and adipose tissue?**

### Future Directions

- **Understand the factors that regulate fat storage in the adipocyte and in non-adipose tissues.**

Fat storage in adipocytes appears to protect other cell types in the body from excess lipid storage, where it is accompanied by insulin resistance, inflammation, and mitochondrial dysfunction. Research is needed to understand how adipose fat storage is governed, and how this process fails in diabetes and obesity. Further, research on how fat accumulation in beta cells, liver, muscle, and potentially endothelial cells contributes to insulin resistance and organ dysfunction could clarify the importance of ectopic fat in diabetes pathogenesis. Such studies could reveal whether this lipotoxicity plays a role, along with hyperglycemia and hypertension, in the classic diabetic complications, such as nephropathy, retinopathy, cardiopathy, and neuropathy.

- **Understand the normal signaling roles of circulating lipid and other nutrient-derived molecules.**

Lipids constitute a very large family of molecules—the “lipidome”—that vary by carbon chain length, number, and positions of double bonds and attached headgroups. Many lipids appear to play signaling and regulatory roles within and between tissues. Some amino acids act as nutrient signals that regulate protein synthesis and insulin sensitivity. It is becoming clear that nutrients

and their metabolites interact with some nuclear proteins to regulate gene transcription. Therefore, the exchange of nutrients among organs and tissues seems to constitute tissue crosstalk that carries important regulatory information, and these molecules appear to be playing a much larger endocrine and paracrine role than has been previously appreciated. More knowledge of these roles may answer such questions as how the beta cell detects insulin resistance in the liver and muscle. Systems biology approaches will be useful to elucidate the complex nature of nutrient-derived signaling in fuel homeostasis and diabetes pathogenesis.

► **Understand the mechanisms whereby excess nutrient load leads to organ dysfunction.**

Just as chronic fat deposition in the liver and beta cell appears to interfere with tissue function, chronically elevated glucose leads to diabetic complications in most tissues, including kidney, eye, bladder, nerves, and the cardiovascular system. Acutely elevated blood nutrient concentrations also appear to have harmful effects, including insulin resistance and other functional abnormalities. Both chronic and acute effects depend on the concentrations of specific signals, on the mass effect of too much energy-dense fuel, and on the chemical properties of these nutrient molecules. These observations indicate that overnutrition can affect organ function and disease state by a variety of mechanisms, and it remains to be determined exactly what those mechanisms are, and which are most important for human health.

► **Develop noninvasive or minimally invasive approaches to measure nutrients and other metabolites in specific locations.**

Nutrients are found in different concentrations in different places in the body and likely have different

impacts, but measurements are often confined to peripheral venous blood. The liver and brain both respond to the concentrations of insulin, glucose, and fatty acids, which vary considerably between the portal vein and brain blood vessels. Novel detection methods need to be developed, such as imaging contrast agents that are sensitive to nutrient concentration, or indwelling, miniaturized, telemetric sensors that can be used in research animals.

## **New Players in Control of Metabolism: Role of the Brain and the Gastrointestinal Tract**

The elucidation of new roles for brain, gut, fat, and other tissues in regulating glucose metabolism constitutes one of the most exciting areas of type 2 diabetes and obesity research. This line of research has led to widespread enthusiasm for the idea that energy homeostasis is a whole-body phenomenon, and for the systems biology approach to research. In addition to governing eating behavior, the brain responds to hormone, molecular, and nutrient signals to coordinate liver glucose output, energy production and storage, and insulin secretion. The exact neuronal networks and molecular mechanisms remain to be fully described. The startling observation that type 2 diabetes can often be almost immediately resolved, even prior to significant weight loss, by bariatric surgery in obese patients has led to a search to understand the influence of gut microorganisms and for additional gut-derived signals beyond the classical incretins, such as gastric inhibitory polypeptide (GIP) and GLP-1, that are known to stimulate insulin secretion in response to a meal. Such discoveries yield important, novel insights into the pathophysiology of the disease, and open the door to novel therapeutic approaches. Newly identified functions for nutrient receptors in the gut and other places and

how they may affect obesity and diabetes also need to be explored. Recently developed technologies are expected to yield numerous key advances in diabetes research over the next decade, particularly those used to manipulate and monitor neuronal pathways, combined with high-throughput “omics” approaches and functional neuroimaging.

## Key Questions

- **What are the primary neurons in control of peripheral metabolism, and how are they integrated into a functional neurocircuit? To what extent are these pathways plastic and what factors can control their development and function?**
- **What are the relevant neuropeptides, transmitters, and intracellular signaling pathways in control of peripheral metabolism?**
- **Can functional neuroimaging reveal novel neural networks and pathways, and can it be a tool for personalized therapeutic approaches to treat metabolic disease?**
- **What is the full complement of gut-derived signals that participate in metabolic regulation, and what are their target tissues and modes of action?**
- **What specific physical alterations and humeral factors account for metabolic improvement following bariatric surgery?**
- **What can systems biology approaches reveal about gastric surgery in metabolic disorders or about the role of gut microorganisms in metabolic disease?**
- **Do intestinal microbiota play a role in diabetes and energy homeostasis? Is this role affected by diet and body weight?**

## Future Directions

- **Characterize the functional neurocircuitry, including its adaptation and integrated regulation by hormones and nutrient components.**

Early studies in this area have identified primary neurons responsible for mediating the effect of individual peripheral mediators, such as insulin and leptin, as well as nutrients, such as glucose, fatty acids, and amino acids. However, developments in genetically encoded neuron tracing and remote control of defined neurons will lay the groundwork to define the functional neurocircuitry in control of peripheral metabolism. Moreover, defining the integrated control of numerous factors regulating the activity of key convergence nodes in this functional circuitry will lead to efficient modification of this regulatory system. Besides the analysis of acute regulatory mechanisms of this circuitry, understanding the genetic and epigenetic mechanisms of its development could help define novel interventions for impaired perinatal programming of this system, as there is growing evidence for plasticity in these metabolically important neurocircuits.

- **Apply a systems biology approach to understand metabolic improvements resulting from bariatric surgery.**

The integrated modeling of different sets of complex molecular data, including transcript profiling, proteomics, metabolomics, and multiplex assessments of simultaneous changes in circulating humoral factors, provides a promising approach to discover metabolic alterations and their control mechanisms. This is particularly true when a single intervention, such as bariatric surgery, evokes complex interacting changes in all of these systems. Large-scale data acquisition

of these parameters and subsequent mathematical modeling may define the key pathways responsible for metabolic improvement following bariatric surgery, and may define key regulatory nodes as potential targets for pharmacological intervention.

► **Use systems biology approaches to understand the effects of the gut microbiome on nutrient homeostasis and energy metabolism.**

Recent data suggest that the intestinal microflora can profoundly alter the efficiency of nutrient uptake from food, that the relative populations of bacteria are modulated by the obese state, and that bacteria from obese mice can result in increased fat storage when transplanted into a lean mouse. An interesting open question is whether these organisms play other roles in whole-body energy balance or the pathogenesis of diabetes—do they exert an impact on the relative concentrations of nutrients and the ability of the human body to store and burn them? Do gut-derived hormones and other signals from the gut or the bacteria themselves produce these effects, and how does this depend on an individual's complement of bacteria? Do they affect the immune system in such a way that protects from or encourages insulin resistance and diabetes? This rich and relatively understudied area deserves increased attention.

## Defining the Subtypes of Type 2 Diabetes by Molecular Phenotyping

Given the accumulated evidence that type 2 diabetes can arise from any number of genetic, molecular, and environmental events, it stands to reason that different forms of the disease should respond best to therapies targeted to specific affected biological systems. Toward this end, a detailed description of

the genetic and metabolic staging of the disease in humans at the molecular and physiological level using high-throughput genetic, genomic, proteomic, and metabolomic technologies may allow researchers to define an individual's specific subtype of diabetes and stage of disease. The same technologies combined with appropriate bioinformatics and modeling will also significantly improve understanding of basic biology and disease mechanisms at a whole-body, systems biology level. Thus, it should be possible to integrate successfully these genetic, genomic, proteomic, and metabolomic data with information on functional outcomes and diseases in individuals.

### Key Questions

- **What are the molecular phenotypes of different stages in diabetes pathogenesis? Can different diabetes subtypes be identified?**
- **Can easily measurable biomarkers for insulin resistance be defined in humans and rodents, and can models to predict development of the disease and its response to treatment be developed?**
- **Can molecular phenotyping strategies be successfully used to evaluate existing and novel therapies in clinical populations?**

### Future Directions

- **Develop biomarkers for insulin resistance.**

Insulin resistance precedes and predicts the development of type 2 diabetes. Insulin resistance is also central to the metabolic syndrome and its various components—obesity, fatty liver disease, increased risk for atherosclerosis, reproductive dysfunction (especially polycystic ovarian disease), hypertension, Alzheimer's

disease, and even some forms of cancer. Nonetheless, at present, insulin resistance cannot be accurately measured at the clinical level other than by complex techniques such as the euglycemic, hyperinsulinemic clamp. A systems biology approach, with the various “omic” technologies, could be taken to identify new and more easily assessed biomarkers of insulin resistance. Such markers would serve as important research tools into disease pathogenesis, provide a biomarker for the pre-diabetic state, and be useful as tools to measure effects of therapy designed to improve insulin sensitivity in research studies and clinical practice.

- **Establish interdisciplinary research teams to study gene-environment interactions.**

To address important questions related to gene-environment interactions, basic experimental, clinical, genetic, and epidemiological studies will be required with interaction among multiple disciplines (e.g., endocrinology, nutrition, genetics, and genomics). Establishment of transdisciplinary educational and training opportunities in endocrinology, physiology, genetics, bioinformatics, computational and cell biology, and clinical research are needed to realize maximal benefit and impact from application of new technologies to diabetes research and treatment.

- **Develop a large, well-characterized clinical cohort of individuals ranging from normal metabolism to active type 2 diabetes.**

Establishing a diverse cohort large enough to include individuals with normal metabolism, individuals with various degrees of dysregulated metabolism (impairment of lipid and/or glucose homeostasis), and individuals with overt diabetes would allow researchers to apply the full complement of physiological and biochemical testing, imaging, and the various “omic”

technologies to create a platform for metabolic staging of type 2 diabetes and its disease progression. Progress toward this goal may be facilitated by pooling data from existing cohorts.

- **Develop tissue and serum banks at all stages of type 2 diabetes.**

Ready access to preassembled collections of tissue and plasma from well-characterized study participants will greatly accelerate the development of disease-specific metabolic fingerprints and allow researchers to compare results across technology platforms.

- **Employ molecular phenotyping for personalized medicine in diabetes.**

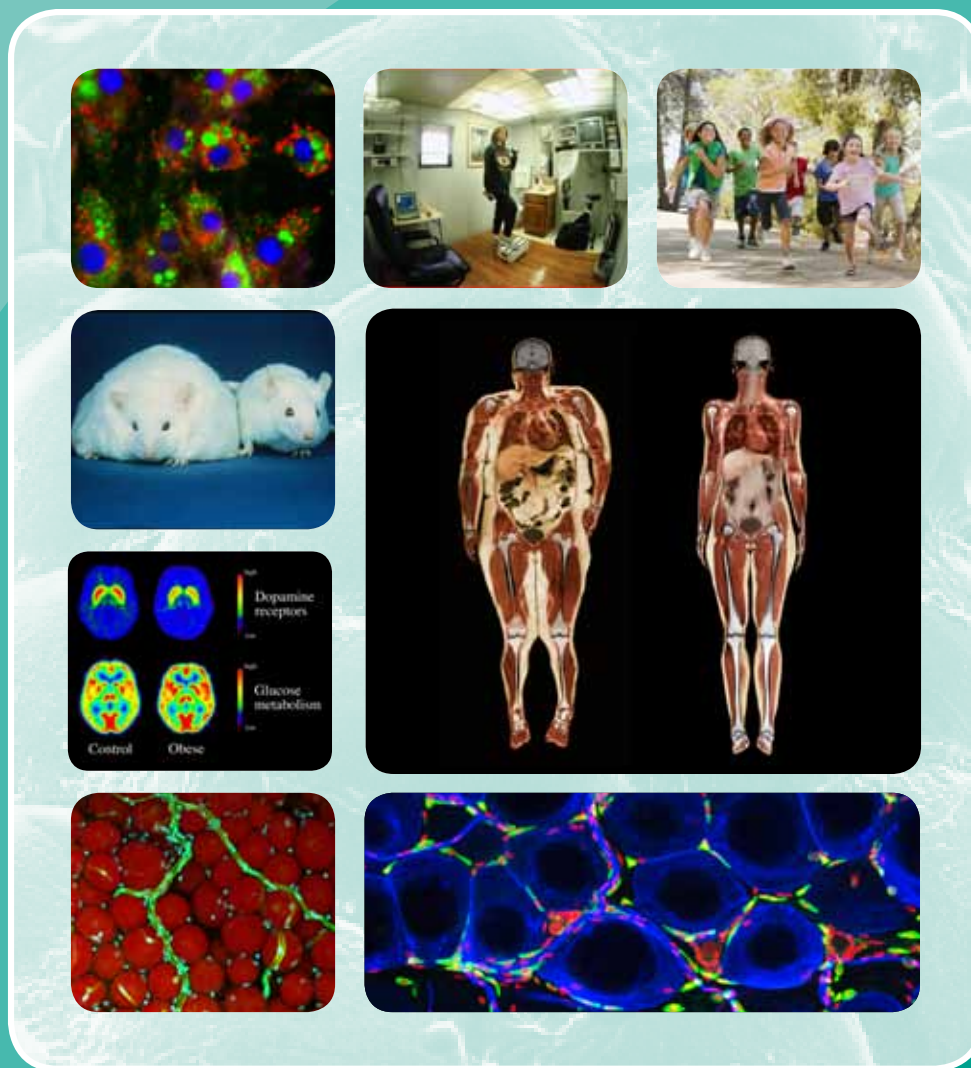
Molecular profiling technologies used along with computational and bioinformatics tools could result in new methods to stage and diagnose specific forms of diabetes. Such research could ultimately lead to the development of predictive algorithms and models for defining diabetes subtypes and directing therapy.

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

The onset and progression of type 2 diabetes affects multiple biological systems in the body, and varies from person to person—creating complex challenges for researchers and clinicians seeking to better understand, diagnose, prevent, and treat the disease. Now, new tools and technologies make it possible to assess the effect of type 2 diabetes on these systems, and vice versa. By gathering rich data sets in various aspects of diabetes biology, including gene-environment interactions, metabolism, inflammation, cell biology, the brain and

digestive tract, and nutrient signaling, scientists will have a wealth of information with which to answer important questions specific to those areas and to understand the connections between them—thereby creating a more fully realized portrait of type 2 diabetes, its diversity, its harbingers, and its consequences. People with diabetes should benefit from this approach by seeing more rapid attainment of new therapies and of tailored approaches to prevention and treatment as this research moves forward.





Research on obesity and its relationship to diabetes spans fundamental research on fat cells and the brain to clinical research strategies to prevent or treat this condition (*Image credits and information: Top row, left: Microscope image of brown fat (e-BAT, or engineered Brown Adipose Tissue) created by adding a key control switch to skin cells of mice. Presence of green-stained objects (droplets of oil stored in the cell) confirms the skin cells have been converted to brown fat-producing cells. Blue objects are cell nuclei. Image courtesy of Dr. Shingo Kajimura, Dana-Farber Cancer Institute. Top row, middle: Image courtesy of Dr. Kong Chen, NIDDK. Top row, right: Jupiter images/creatas (RF)/Jupiter images. Middle row, top left: Normal and obese mouse. Jackson Laboratories. Middle row, bottom left: Measuring dopamine receptor (top) and glucose metabolism (bottom) in brains of obese and non-obese humans. Image courtesy of Dr. Gene-Jack Wang, Brookhaven National Laboratory. Reprinted from The Lancet, 357, Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS, Brain Dopamine and Obesity, 354-7, Copyright (2001), with permission from Elsevier. Middle row, right: Images created by Wei Shen and Steven Heymsfield, New York Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University, New York. Bottom row, left: Fat cells (stained red) that make up adipose tissue can't grow without blood vessels (stained green) to nourish them. (red stain=adipocytes, green stain=vasculature, blue=DAPI). Image courtesy of Dr. David Burk, Pennington Biomedical Research Center. Bottom row, right: The swarm of inflammatory cells in obese adipose tissue: Microscopic image of abdominal adipose tissue from an obese mouse. Fat cells (blue) are surrounded by a large number of macrophages (green). These inflammatory cells infiltrate fat and form clusters around areas of dead fat cells. These macrophage generate inflammatory factors that disrupt the normal function of fat cells and enter the circulation to generate low grade chronic inflammation in other organs. A large number of other cells are also found in obese fat (nuclei are stained red) that interact with macrophages and fat cells to produce a pro-inflammatory environment in adipose tissue. Image courtesy of Dr. Carey Lumeng, University of Michigan.)*



# OBESITY

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

## INTRODUCTION

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. Obesity is commonly assessed using the body mass index, or “BMI,” which is a calculated ratio based on an individual’s weight and height. By this measure, over one-third of U.S. adults are considered obese (11). Obesity disproportionately affects some racial and ethnic minority populations—for example, 43 percent of Hispanic American women and over 49 percent of African American women meet the criteria for obesity (11). Moreover, the levels of childhood overweight and obesity have escalated in the past several decades, such that obesity now affects approximately 12 percent of children 2 to 5 years old and 17 percent of children and teens ages 6 through 19 (12)—alarming statistics matched only by the increase in type 2 diabetes in youth. Efforts to combat type 2 diabetes are inextricably linked to research to understand, prevent, and effectively treat obesity.

In understanding the role of obesity in diabetes, the broad spectrum of problems associated with obesity must also be realized. For example, 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. Central abdominal obesity (“apple shape” body type) is associated with a much greater health risk than peripheral obesity (“pear shape” body type). However, at molecular, genetic, and cellular levels, these important differences have yet to be fully explained. Physical activity and fitness are related to the risk of obesity, but 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 health hazard of obesity, even in the absence of full-blown diabetes.

Obesity results from an imbalance between energy intake and energy expenditure. A sustained “positive” energy balance will lead to storage of extra calories as fat, potentially leading to overweight and obesity. The delicate coordination of energy intake and expenditure occurs through a variety of external factors (social and environmental) and internal functions (endocrine and neural signals that emanate from adipose tissue, various regions of the brain, the endocrine system, and gastrointestinal tract). There has been tremendous progress in defining 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. Progress is being made to understand the factors that disturb these pathways and how they can resist being reset to “normal.” Research is also revealing molecular and behavioral links between metabolism, appetite, and the circadian rhythm, as well as how social and physical environments influence the regulation of energy balance.

Underlying the issues of energy balance is the fat tissue, or adipose tissue, itself. There are two major types of body fat, “white adipose tissue,” which stores energy and comprises most body fat, and brown adipose tissue (BAT), which actually burns calories to help

maintain body heat. Scientific views on adipose tissue have undergone a fundamental change over the past 15 years. Rather than a mere storage compartment for triglycerides (fats), white adipose tissue is now recognized as an endocrine organ. The crosstalk between multiple different cell types, including adipocytes, endothelial, and immune cells, gives rise to a very active tissue that releases a large number of protein and lipid factors that profoundly influence systemic energy metabolism. As such, adipose tissue assumes center stage in the underlying etiology of type 2 diabetes. Moreover, there is accumulating evidence that BAT likely plays a role in adult metabolism, and hence may influence obesity and type 2 diabetes.

It has also become clear that obesity is associated with chronic inflammation that, when present, increases the risk of metabolic syndrome, diabetes, and atherosclerosis. Although the mechanisms linking obesity, inflammation, and metabolic dysfunction are incompletely understood, it is evident that cellular inflammation is a key mediator of insulin resistance. This effect is mediated in part by cellular inflammatory responses that block insulin signaling in tissues throughout the body. A key mediator of obesity-associated tissue inflammation involves the infiltration and activation of immune system cells called macrophages. Understanding this newly recognized relationship between obesity, inflammation, and insulin resistance may lead to new approaches to halt progression to type 2 diabetes.

Finally, research has also clearly implicated behavior, environment, policy, and social relationships and context in influencing patterns of eating, nutrition, and activity. For example, obesity has been inversely associated with socioeconomic status, and changes to the built and food environment have been shown to influence energy intake and activity. These in turn affect—and are affected by—a person's nutrition, which is essential for good health. Basic social and behavioral research findings are also yielding new and important insights about factors that influence diet and activity. For example, research regarding early childhood feeding, social networks, behavioral economics, sensory input, and sleep patterns as they relate to weight offer the possibility for some novel intervention targets for the prevention and treatment of overweight and obesity.

The increased prevalence of obesity—and hence, of type 2 diabetes—is influenced by a complex set of factors that include biology, behavior, social, and environmental influences. Often these influences involve complex interactions such as biology influencing behavior or behavior and environment influencing biology. This complexity makes research in this area both interesting and challenging. Cross-disciplinary research across a range of research modalities, from fundamental studies to clinical trials and epidemiological research, seems best poised to yield important findings in the future.

## RECENT RESEARCH ADVANCES

In just the past decade, researchers have made great strides in understanding the molecular, genetic, brain, behavioral, and environmental factors underlying obesity and its role in promoting insulin resistance and diabetes, as well as in approaches to prevent and treat obesity. The following are some major examples of this research.

### **The Link Between Obesity and Inflammation:**

Research suggests that inflammatory mediators produced by activated macrophages are important factors underlying the synergistic relationship between obesity, insulin resistance, and metabolic dysfunction. First documented in adipose tissue, obesity-associated inflammation and macrophage accumulation have now been demonstrated in diverse tissues, including liver, skeletal muscle, vasculature, and brain. The macrophage represents a significant new target in developing therapies to break the link between obesity and diabetes.

### **Discovery of Hormones and Neural Circuits**

**That Contribute to Energy Balance:** While the existence of homeostatic systems that maintain body weight and adiposity at near-constant levels has long been appreciated, the mechanisms that underlie energy homeostasis have begun to be elucidated only recently. There is now a better understanding of the role of hormones, such as insulin, leptin, agouti-related peptide (AGRP), neuropeptide Y (NPY), melanocyte stimulating hormone (MSH), and melanin-concentrating hormone (MCH), that convey information related to energy storage in adipose

tissue to homeostatic brain circuits. New evidence is emerging that these brain regulatory centers also modulate glucose production by the liver as part of an integrated response to energy availability. An appetite-stimulating hormone, ghrelin, and other peripheral signals of feeding and energy status have been identified. Within the brain, particularly in the hypothalamus, a number of neural circuits and neurotransmitters that respond to and mediate the effects of leptin and other metabolic signals have been identified. Collectively, these findings reveal that alterations in body weight provoke changes in these neural systems to produce a homeostatic response to defend body weight. In addition to providing new therapeutic targets, these discoveries are opening a new window to understanding human motivation to eat.

### **Mechanisms That Underlie the Dysregulation in Energy Homeostatic Systems To Promote and Maintain Obesity:**

While the key pathogenic change(s) are not yet known, a number of processes that may alter the function of the neural circuits that modulate energy balance have been identified. These include: molecular/signaling mediators and inflammatory mechanisms that may interfere directly with signaling by appetite-suppressing hormones and/or circuits; altered early development/wiring or later remodeling of the energy homeostatic circuitry in response to dearth or excess of nutrition (and their hormonal surrogates); and alterations in access of nutritional or hormonal cues to these circuits. Armed with this knowledge, scientists can now study how these mechanisms go awry and

potentially contribute to inappropriate weight gain and/or retention. Identifying key sites of susceptibility to environmental insult and the critical periods when these changes are likely to occur will have a significant impact on design of successful interventions to prevent obesity.

### **Implication of Mutations in *MC4R* as One Cause of Severe Obesity in Humans:**

Genetic studies in animal models led to the discovery of a novel hypothalamic pathway impaired in obese mice, and implicated members of the melanocortin receptor (MCR) family in the regulation of body weight. Dominantly inherited mutations in the *MC4R* gene (*MC4R*) were quickly recognized in some humans who are obese. At least 80 obesity-related mutations of *MC4R* have been reported, and a common genetic variation near *MC4R* has been associated with increased BMI. The major effects of mutations in the *MC4R* gene on obesity are conveyed by effects on food intake, in some cases resulting in extreme hyperphagia. These effects may be greater in children than in adults. Many of these mutations affect intracellular transport of the *MC4R* encoded receptor protein, suggesting that the development of suitable molecular chaperones could provide therapeutic benefit in obesity.

### **Bardet-Biedl Syndrome (BBS) Convergent Phenotypes Due to Mutations in Components of the Ciliary Body:**

A new avenue in obesity research has been opened through study of a rare genetic syndrome whose symptoms include not only obesity, but also preaxial polydactyly (thumb duplication), retinal degeneration, anosmia (inability to perceive odors), generalized decrease in peripheral sensation, and renal/hepatic cysts. Of 14 known causative BBS genes, eight encode known components of the primary cilium, a complex sensory organelle that may require up to 1000 proteins for function, is

present in most mammalian cells, and plays a role in development, cellular maintenance, and key signaling and trafficking pathways (Wnt and Hedgehog). BBS proteins are required for leptin receptor signaling in the hypothalamus, and thus mutations in BBS genes could result in impaired regulation of energy balance through structural and/or signaling abnormalities in this key brain region. It is likely that all BBS results from complex combinations of partly functional genes (hypomorphic alleles) contributing to formation and activity of this complex cellular component. Unraveling the molecular genetics of this rare syndrome could provide the proof-of-principle that combinations of hypomorphic alleles of the components of a cellular structure, and presumably pathway, can result in obesity.

### **Genome-wide Scans for Genes Associated with Obesity:**

Genome-wide association (GWA) studies have enabled the detection of common genetic variants that are associated with specific common phenotypes. A sequence variant in the first intron of the fat mass and obesity associated gene (*FTO*) was originally identified as associated with type 2 diabetes in a study of over 30,000 well-phenotyped individuals and controls. However, controlling the original association for BMI eliminated the association of the genetic locus with type 2 diabetes, indicating that *FTO* was actually an obesity rather than a type 2 diabetes locus—a finding that has now been replicated in multiple independent cohorts. It is of note that a second gene, *FTM*, located close to the first exon of *FTO*, encodes a component of the ciliary body, and thus could account for the obesity-related phenotypes associated with this interval. Subsequent GWA studies for obesity have identified additional loci/genes (see Table 3 in the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter). As with most GWA

studies to date, the novel loci/genes are of relatively modest relative risk. However, these studies should lead to further discoveries of how genes interact with the environment and uncover heretofore unappreciated biological pathways that may provide novel insights into obesity and its treatment. (Advances in the field of genetics are more fully outlined in the “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” chapter.)

### **Limits in the Ability of Adipose Tissue To Expand in the Face of Excess Calories May Drive the Accumulation of Fat in Other Tissues, Leading to the Morbidities Associated with Obesity:**

Many of the adverse effects of obesity can be traced to accumulation of fat in organs such as liver, muscle, pancreas, and blood vessels. Research has shown that mice capable of expanding adipose tissue through adipocyte proliferation without concomitant inflammation become obese, but do not redirect fat deposition to organs other than adipose tissue. These mice appear metabolically healthy, with normal insulin sensitivity and blood lipids. Similarly, clinical data have highlighted the potentially protective nature of some fat pads, and epidemiological studies have revealed correlations between plasma levels of adipokines and systemic insulin sensitivity, diabetes, cardiovascular risk, and many additional disease states. Data from pre-clinical models further corroborates these correlations, and in many instances directly implicate the dysregulated adipokine in the development of insulin resistance. These findings provide new clues that may allow disruption of the link between obesity and type 2 diabetes and may explain the “fit-fat” conundrum by clarifying how fat accumulation in some depots is more deleterious than when it is stored in others.

**Environmental and Policy Approaches Show Effectiveness in Increasing Physical Activity and Improving Eating Behaviors:** Healthy eating and physical activity are important for preventing excess weight gain and producing weight loss across the lifespan. Research supports environmental and policy approaches to increasing physical activity and improving eating behaviors in both adults and children that could lead to significant public health benefit. Establishing local policies and practices for creation of, or improved access to, places for physical activity and healthful foods, and reducing exposure to social and environmental triggers to eat and remain sedentary can be effective in facilitating increased levels of physical activity and improved eating behaviors. Environmental and policy approaches have also shown promise as cost effective means for population-based weight management. Improved understanding of social, environmental and policy influences on physical activity and eating will guide future clinical and population-based health interventions.

### **Bioimaging Provides New Insights into Fat Tissue:**

Rapid technical developments in medical imaging, particularly in nuclear magnetic resonance imaging (MRI), have spurred new advances in obesity research. These techniques have enabled researchers not only to further explore anatomy and morphology of different tissues and organs, but also to examine their dynamic functions with increasing accuracy and reduced invasiveness in humans as well as animals. As a result of these developments, researchers can now use MRI to quantify visceral and subcutaneous adipose subdepots, and use MR spectroscopy to investigate the role of ectopic fat in muscles and liver in the pathogenesis of

insulin resistance. Functional MRI also has enabled researchers to study brain responses to food stimuli noninvasively, and also extend studies to elucidate the role of peripheral hormones, such as insulin, in the brain. PET/CT scanning has revealed the presence of significant depots of brown adipose tissue in adult humans and suggests that it could play a role in response to metabolic challenges such as cold exposure (see next Advance). These studies provide a bridge between mechanistic, but invasive, studies in animal models, and an understanding of behavior and metabolism in humans.

### **Brown Adipose Tissue and Energy Metabolism:**

The potential importance of BAT in human energy metabolism has resurfaced. The conventional wisdom that the importance of BAT in energy metabolism is limited to small mammals and human neonates has been challenged by recent evidence: Scientists have found that BAT is detectable in a substantial subset of adult humans (although not primarily in the interscapular area typical of rodents and newborn humans), that BAT can be rapidly activated by cold exposure and other stimuli in many individuals, and that this response shows gender difference, is attenuated in individuals who are obese, and may be blocked by drugs such as beta-blockers. Furthermore, obesity-resistant strains of mice have been shown to have more BAT in unusual locations, such as embedded in leg muscle. These insights set the stage for studies to determine whether reduced BAT thermogenesis (heat production) contributes to obesity pathogenesis, and whether pharmacological or other strategies to

activate BAT might be therapeutically useful. It has been shown that some BAT depots appear to be derived from precursors that are shared with skeletal muscle, whereas others may be more closely related to the lineage that gives rise to white adipose tissue. The discovery of key genes and growth factors that control BAT differentiation provides new opportunities for fundamental research in this area. Further clinical investigation will be necessary to define the potential role of BAT in pathogenesis, prevention, and treatment of obesity.

### **Impact of Bariatric Surgery on Body Weight and Glucose Metabolism:**

Bariatric surgery is the most effective available treatment for extreme obesity. One frequently performed operation, Roux-en-Y gastric bypass (RYGB), causes profound weight loss that, unlike other modalities, seems not to activate compensatory responses to weight loss that lead to weight regain, at least in some individuals. This procedure can also induce a complete normalization of euglycemia via mechanisms that appear, at least in part, to be independent of weight reduction. Potential mechanisms underlying this effect include increased secretion of intestinal hormones (e.g., glucagon-like peptide-1), neuroendocrine changes induced by excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, altered intestinal nutrient sensing, or other as-yet unidentified processes. These findings have opened a new research avenue that may lead to new diabetes treatments (see also the “Type 2 Diabetes As a Multi-Dimensional Disease” chapter and the “Clinical Research and Clinical Trials” chapter).

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the importance of obesity in diabetes and as a critical problem in its own right, emphasizing the need for enhanced basic, clinical, and behavioral research in this area. In the intervening years, the surge in prevalence of both obesity and diabetes in the United States has made research to combat these twin health problems increasingly urgent. Indeed, the NIH established an Obesity Research Task Force in 2003 to bring greater focus to the wide array of research needs in obesity. The research challenges posed by obesity cut across many fields and disciplines. Described below are research questions and opportunities to pursue in the next several years to reach the goal of understanding, preventing, and effectively treating obesity with special emphasis on mitigating it as a risk factor for type 2 diabetes.

### Obesity, Inflammation, Insulin Resistance, and Macrophage Function

Understanding the role of obesity in development of diabetes will require further study to understand the relationship between fat and inflammation. Many questions remain regarding the role macrophages play both in peripheral tissues and in the central nervous system (CNS) in mediating disordered energy intake and storage, especially in response to consumption of a high fat diet. Conversely, more needs to be done to understand macrophages and inflammation as an outcome of obesity leading to insulin resistance and other complications, such as atherosclerosis. Clarifying both the mechanisms underlying, and consequences of,

tissue-specific inflammation induced by obesity is a key priority for future research.

#### Key Questions

- **At the cellular level, what mechanisms link exposure to excess nutrients to activation of inflammatory signaling, and how do these responses cause insulin resistance?**
- **Does hyperinsulinemia exacerbate this problem by forcing the uptake of nutrients into insulin-resistant cells?**
- **What role does macrophage activation play in the deleterious metabolic and cardiovascular responses to obesity? What signaling molecules are involved?**
- **How does hypothalamic inflammation affect energy homeostasis? How do inflammatory mediators influence the relationship between microglia (the macrophages of the brain) and neural systems governing energy balance and peripheral metabolism?**
- **How does body fat distribution affect inflammatory responses observed in obesity?**

#### Future Directions

- **Determine whether inflammatory pathways can be targeted effectively in the prevention and treatment of obesity and its metabolic sequelae, and if so, which specific molecules are best suited as therapeutic targets.**



At the cellular level, inflammation induced by nutrient excess and obesity can involve multiple organelles (e.g., mitochondria, endoplasmic reticulum) and signal transduction pathways (e.g., IKKbeta-NFkappaB, JNK) depending on the cell type. Optimal strategies for limiting this type of inflammation may therefore vary across tissues, and further studies are warranted in this area.

- ▶ **Establish whether the beneficial impact of exercise on metabolism involves an attenuation of cellular inflammation induced by nutrient excess.**

To meet the demands of physical exercise, increased rates of substrate oxidation are required. At the cellular level, this process can favor the mobilization of nutrients that might otherwise accumulate and promote inflammatory responses. Thus, the effect of exercise to mobilize stored nutrients may contribute to its ability to improve metabolic function, and efforts to quantify this effect and its therapeutic potential are warranted.

- ▶ **Determine whether specific nutrients (e.g., saturated fatty acids, fructose) exert pro-inflammatory effects in obesity that are independent of energy balance per se.**

Although chronic consumption of nutrients in amounts that exceed bodily requirements induces deleterious effects on tissues throughout the body, the extent to which these effects are driven by an overall excess of calorie ingestion versus increased exposure to specific nutrients is an open question. Saturated free fatty acids are implicated as having pro-inflammatory effects, and diets high in saturated fat content seem to promote systemic inflammation more effectively than diets rich in mono- or polyunsaturated fats; indeed, foods rich in omega-3 fatty acids may have anti-inflammatory effects.

Identifying the molecular mechanisms responsible for these differences and disarticulating energy excess from responses to specific dietary components is a key research goal.

- ▶ **Investigate mechanisms whereby hypothalamic inflammation is induced by systemic inflammatory stimuli and assess their consequences for energy homeostasis.**

Like many other tissues, the hypothalamus is susceptible to inflammation induced by nutrient excess. Unlike other tissues, however, this hypothalamic response has the potential to favor weight gain, in addition to simply being its consequence. This hypothesis is based on evidence that leptin and insulin are “adiposity negative feedback” signals that convey afferent input used by the hypothalamus to control energy balance, and that neuronal inflammation causes resistance to both hormones. This effect, in turn, is hypothesized to predispose to weight gain until circulating insulin and leptin levels increase sufficiently to overcome the neuronal resistance. Thus, it is proposed that a vicious cycle can exist in which nutrient excess itself favors excess weight gain in genetically susceptible individuals. Accordingly, drugs that disrupt this vicious cycle may be effective in obesity treatment and prevention.

- ▶ **Determine the impact of macrophage activation phenotype on insulin sensitivity and assess its potential as a therapeutic target.**

As obesity-induced tissue inflammation progresses, immune cells are recruited, further exacerbating the inflammatory response. Adipose tissue macrophages are clearly increased in both number and pro-inflammatory activation in individuals who are obese,

and data from both genetic and pharmacological intervention studies implicate these macrophages in obesity-induced insulin resistance. A key event in this pathological cascade is the induction of a pro-inflammatory phenotype of macrophages in insulin-sensitive tissues (so-called “classical activation” or M1 phenotype). Yet, macrophages can also be induced to exhibit anti-inflammatory properties (“alternative activation” or M2 phenotype), and available evidence suggests that induction of this macrophage phenotype switch ameliorates obesity-associated inflammation and insulin resistance. Thus, therapeutic interventions that favor the M2 over the M1 macrophage phenotype warrant study as novel strategies for the treatment of obesity-associated metabolic disease.

- **Determine the mechanisms whereby macrophages are recruited into different tissues during obesity, and whether body fat distribution affects this process.**

The mechanism(s) underlying obesity-associated accumulation and subsequent activation of macrophages in insulin-sensitive tissues is an area of intense scientific focus. Some argue that this effect is mediated by the release of chemokines that promote recruitment of circulating monocytes into tissues, while others invoke obesity-associated cellular necrosis as a key signal driving this process. Clarifying the underlying mechanisms may lead to new approaches to ameliorating obesity-associated metabolic dysfunction.

## **Mechanisms Underlying Energy Homeostasis: Impact on Obesity Pathogenesis and Treatment**

Defining the mechanisms that contribute to the onset and maintenance of obesity will require a thorough understanding of the hormonal and neural controllers of energy balance. Each constituent of the energy

balance system and each mechanism that may act on the energy balance system to promote positive energy balance in obesity represents a potential target for therapeutic intervention. Energy homeostatic circuits exist within a complex and intertwined network, and a myriad of processes regulate each circuit in distinct ways. Adding further complexity, neurons and their networks are capable of adapting organizationally and functionally in the face of changing conditions, engaging in so-called “neuronal plasticity.” Scientists have only just begun to unravel the complex neural networks that modulate energy balance and their roles in responding to environmental perturbations, let alone their potential dysregulation in obesity. Even less is known about the impact of genetic, intrauterine, and acquired factors on these neurocircuits and how they may predispose to childhood obesity. Crosstalk from the gut that could affect these circuits is also under study, due to rapid metabolic improvements seen in some bariatric surgery patients prior to significant weight loss (see chapters on “Type 2 Diabetes As a Multi-Dimensional Disease” and “Clinical Research and Clinical Trials”). To identify targets for the generation of potential therapies, the nature of these systems and the mechanisms governing their function and dysfunction will need to be more precisely defined. Also, the potential of drug combinations needs to be explored more thoroughly to determine if targeting multiple components of this regulatory system can yield additive or even synergistic effects on body weight.

### **Key Questions**

- **What are the neural systems that respond to and control energy balance?**
- **What are the mechanisms by which the energy homeostasis machinery responds to altered energy balance?**

- **What are the mechanisms that alter these systems to promote or maintain obesity?**
- **How do cognitive inputs, such as learning and social cues, interact with these pathways?**
- **Are there inherent differences in brain connectivity and chemistry that increase susceptibility to obesity?**
- **Do nutrients, adiposity hormones, or gut peptides induce neuronal plasticity?**
- **What are the critical developmental periods (prenatal and postnatal) for the biological predicates of obesity? By what mechanism(s) are such effects conveyed?**
- **Does nutrient signaling in the brain play a major role in the pathogenesis of obesity and related metabolic disorders?**

### **Future Directions**

- **Develop a more complete understanding of the neural systems, along with the molecular mediators in these systems, that regulate energy balance by sensing and responding to signals of energy status.**

While the recognition of hypothalamic arcuate neurons and their roles in sensing and responding to perturbations in nutritional and energy status has provided important insight into mechanisms regulating energy balance, a number of lines of evidence suggest that other important systems contribute. It will be crucial to identify and study these other important energy homeostatic circuits. Obstacles to this goal include the lack of pharmacologic, molecular, or genetic tools to study many of these neural circuits. Some hypothesis-generating studies will be required to identify such tools and to thereby permit the analysis

of these poorly-understood but important circuits. The taste and smell of food can also influence the energy balance equation; additional information is needed to clarify cellular and molecular mechanisms whereby this afferent information is processed and communicated to brain areas involved in food intake regulation.

- **Understand the mechanisms by which the neural circuits responsible for maintaining energy balance mediate adaptive responses to environmental challenges.**

While some aspects of the adaptive response to decreased energy stores, such as changes in gene expression of arcuate nucleus neuropeptides, have been well-studied, scientists' understanding of many other mechanisms that may contribute is less robust. For example, the control of neuronal cell membrane potential and the mechanisms that govern the establishment and plasticity of afferent and efferent neural circuit contacts remain poorly understood and should be studied. Similarly, a number of molecular and cellular systems (including signaling pathways and metabolic processes) in the brain that modulate or mediate energy balance have been identified, but the cells and/or circuits in which many of these exert their effects remain unclear. The complexity of the heterogeneous and intertwined neural systems presents many challenges. It is also likely that the same intracellular mechanisms have different, or even opposing, effects in distinct sets of neurons. Thus, it will be important to examine these parameters in a cell-type-specific manner, an approach that may require the generation of new technologies. Finally, in addition to determining the response to hormonal and nutritional challenges, it will be important to define the response to exercise. Beyond determining how distinct mechanisms operate during the adaptive response to altered energy balance, it will

also be crucial to examine the relative contribution of each mechanism to the overall adaptive response.

- **Understand how the systems that control energy balance may be altered to promote and maintain positive and/or negative energy balance in obesity.**

In addition to understanding the mechanisms by which the systems that control energy balance mediate physiologic adaptive responses, a greater appreciation is needed of how these processes are altered or become maladaptive to promote or maintain states of obesity and how they may be reversed to promote weight loss. It will be necessary to understand changes that occur with obesity, and how events occurring early in development (e.g., *in utero* or early postnatal) may program neural circuits to affect later metabolic fate. Determining whether the neural circuitry can be reprogrammed later in life, and whether exercise, modifying dietary intake, or other activities can induce or influence this reprogramming, will also be crucial. For each of the diverse set of circuits that regulate energy balance, the role of transcriptional, molecular, inflammatory, neurophysiological, synaptic, and other fundamental processes will need to be elucidated. In addition to the challenges presented by the complexity and diversity of these neural systems, generalizing the results obtained in experimental animals to humans will require the development of new technology. Another key area of study will be to determine whether the re-setting of the defended level of body weight involves fixed changes in wiring of energy homeostasis circuits due to neuronal plasticity or other mechanisms.

- **Determine the role of nutrient signaling in the brain in obesity.**

Nutrients affect the activities of AMPK, glucokinase, mTOR, and enzymes involved in lipid metabolism in ways that affect feeding, as well as peripheral glucose and lipid metabolism. However, questions remain about how nutrients enter the brain to engage neuronal circuits, how nutrients specifically regulate neurotransmission in the hypothalamus and elsewhere, and whether experimental results based on central injection of nutrients are physiologically relevant.

- **Investigate CNS mechanisms potentially underlying pathogenesis of childhood obesity.**

Numerous environmental perturbations (such as exposure to environmental toxins, nutritional surfeit or deficiency, and altered endogenous metabolite or hormone levels) during fetal development and early childhood affect the predisposition to obesity later in childhood and beyond. Mechanisms by which early environmental perturbations may lead to obesity include programming of the brain systems that modulate energy balance. The CNS exhibits enhanced plasticity during fetal and early childhood development; this plasticity subsequently diminishes, so that the conditions experienced during early development ultimately provoke fixed changes to program later CNS function. Such programming may be mediated by epigenetic modifications of the genome, by the modulation of neurogenesis and/or apoptosis (programmed cell death), or by altered developmental “wiring” of the neural systems that contribute to the regulation of energy balance. Indeed, environmental influences modulate each of these processes during CNS development. Important future research goals in this area include defining the permanent changes produced by environmental factors during development and directly examining the causal links between such alterations in

CNS function and subsequent metabolic outcomes, such as obesity.

- ▶ **Identify CNS mechanisms that underlie weight loss in inflammatory, infectious, and neoplastic disorders.**

Pathological anorexia with disproportionately elevated energy expenditure leads to severe loss of both lean mass (cachexia) and fat mass in common wasting diseases, and involves incompletely understood alterations of the same neuroendocrine control systems that govern body weight in normal-weight individuals and people who are obese. Thus, clarifying the underlying mechanisms may ultimately identify novel targets for weight loss therapy, as well as for the treatment of wasting illnesses.

## Central Nervous System Control of Thermogenesis

In addition to the control of food intake, integrative neurocircuitry in the brain also regulates energy expenditure in the service of energy homeostasis. Although progress in understanding the biological pathways and networks involved in regulation of thermogenesis has been substantial, the connection among the hypothalamus and endocrine and autonomic pathways that control diverse functions associated with energy expenditure, including basal metabolic rate, the thermic effect of food, nutrient partitioning, and control of physical activity, remains undiscovered. While studies in many model organisms are revealing new biological targets and pathways, challenges researchers face include the limitations of rodent models to fully reflect the complex control of energy expenditure in humans and how it contributes to weight maintenance and obesity. New technologies are needed to explore these pathways and to look for their correlates in humans.

## Key Questions

- **Does impaired thermogenesis contribute to “common” obesity?**
- **How are neural, behavioral, and endocrine determinants of thermogenesis coordinated?**
- **Do brown adipocytes play a significant role in energy homeostasis in humans?**

## Future Directions

- ▶ **Determine if reduced energy expenditure contributes to “common” obesity.**

Individuals who are obese have high circulating leptin levels and reduced leptin sensitivity. In rodents, leptin resistance can affect the control of thermogenesis as well as energy intake. Quantitative, long-term energy balance studies are needed in both animal models and humans to identify the relative contributions of increased intake and reduced energy expenditure to obesity pathogenesis. Also, because energy expenditure varies as a function of body size, metabolic rate must be adjusted for this effect when comparing lean to obese animals. Optimal strategies for this normalization step are highly debated and need to be established.

- ▶ **Understand bioenergetics in the etiopathogenesis of obesity.**

The relative contributions of energy intake and expenditure to obesity in any individual may vary, and current technologies cannot accurately assess these parameters over significant periods of time. To be informative, research in this area should be conducted in individuals prior to the development of obesity and/or in response to weight perturbations, because, at stable weight and body composition, obese individuals

are in energy balance and do not differ from non-obese individuals in their energy expenditure or intake normalized to metabolic mass.

- **Long-term measurements of energy intake:** The doubly-labeled water technique can quantitate energy expenditure over several weeks, but equivalent measures of energy intake are not available. Highly accurate measurements of body composition could be combined with measures of energy expenditure to calculate intake by difference.
- **Responses to weight perturbation:** Individuals who were formerly obese and those who have never been obese display comparable responses in energy expenditure to imposed weight gain and loss. The response to weight loss includes reduction in energy expenditure beyond that explicable by reduced metabolic mass, as well as diminished satiety in meal-testing paradigms. These combined phenotypes are sufficient to account for the very high recidivism to obesity. Understanding the molecular mechanisms that mediate these changes could lead to effective strategies for the maintenance of reduced body weight that might be quite different from those used to induce weight loss per se.
- **Role of brown adipose tissue in mediating inter-individual differences in energy expenditure and responses to weight perturbation:** The ability to assess the mass and activity of brown adipose tissue in humans using PET/CT scanning can be used to explore the role of this tissue in the development of obesity and the response to weight reduction. It is possible that a portion of the reduction in energy expenditure accompanying weight loss is due to diminished activity of brown adipose cells.

- **Relating differences in energy homeostasis to genetic variation:** The strong evidence for genetic contribution to susceptibility to obesity and increasing numbers of implicated genes have not yet provided clear insights regarding the mechanisms by which these genes predispose to obesity (see the chapter on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications”). Such insights will be gained by prospective application of the techniques described above to individuals before and after the development of obesity.

## Discovering Genetic and Intrauterine Determinants of Obesity Susceptibility That Predispose to Developing Diabetes

Genes unquestionably play a major role in susceptibility to obesity and diabetes and may influence treatment response. The genes conveying susceptibility to obesity appear, in general, to be distinct from those mediating susceptibility to diabetes. However, obesity of any etiology constitutes a stress on beta cell function and can unmask individual genetic differences in beta cell mass and function, leading to the development of overt diabetes. Heritability estimates from studies of identical and non-identical twins indicate a strong genetic contribution to both metabolic problems. Other studies, such as recent GWA scans in large numbers of people, suggest that there are a large number of genes with relatively small effects for obesity and type 2 diabetes; whether there are rare alleles (population frequencies of less than about 5 percent) with high functional/physiological impact remains to be seen. Discovery of genes relevant to obesity will continue to direct researchers to molecular pathways that may be helpful both in understanding the pathophysiology of this condition and in identifying molecular targets for the development of drug therapies. If the genetics of

obesity and/or type 2 diabetes are ultimately shown to be dependent on the aggregate impact of many genes of small effect, the clinical utility of these genes in predicting individual susceptibility may not be great, but they could be helpful in selection of specific therapies for people who have these conditions or for those at risk. Virtually any of the genes identified in such searches will be strongly influenced by other genes as well as by developmental, behavioral, and environmental factors. The ability to account for the contribution of specific genes will ultimately enable better understanding of the mechanisms by which environment, development, and other genes mediate disposition to obesity. Growing evidence also suggests that, during pregnancy, maternal metabolic dysfunction can lead to developmental and/or epigenetic changes that can predispose offspring to obesity, insulin resistance, and type 2 diabetes in adulthood. Mechanisms linking changes in the intrauterine environment to such outcomes are poorly understood, as is their relationship to genetic and environmental factors that influence these outcomes. (See also the chapters on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” and “Special Needs for Special Populations.”)

### Key Questions

- **Are there rare, high impact alleles of known or unknown genes that increase or reduce susceptibility to obesity or type 2 diabetes or their sequelae?**
- **How many genes will be required to account for substantial ordinary risk variance for these phenotypes?**
- **What (if any) are the genetic substrates for the apparent impact of intrauterine and neonatal exposures to nutritional “stress”**

**on subsequent risk of obesity and type 2 diabetes?**

- **Are there genes that moderate the effectiveness of various environmental, social, behavioral, and physiological/ pharmacological interventions to prevent and control obesity and type 2 diabetes and that define population subgroups that will respond more or less to those interventions?**

### Future Directions

- **Conduct prospective analyses of genetic contributions to obesity-related phenotypes and intervention responsiveness.**

Once obesity and/or derangements of insulin and glucose homeostasis occur, it is difficult to disarticulate cause from effect in terms of underlying molecular physiology. The identification of genes and gene-gene interactions relevant to obesity and type 2 diabetes has made it possible to examine individuals at high risk for these health problems by virtue of genotype at ages and periods of development prior to the occurrence of any major medical phenotype. Careful prospective metabolic/behavioral study of such individuals and/or those exposed to different interventions should greatly enhance understanding of the basic biology underlying obesity and type 2 diabetes in humans. For example, brain imaging techniques (fMRI, PET) could be used to characterize responses to food and other stimuli in individuals identified as having one or more alleles of susceptibility genes prior to any increase in body fat. These prospective studies can also address the issue of so-called “critical periods” in the development of obesity and the contributions of genetic differences to such

periods. Characteristics that mark genetic risk of illness (even in the absence of illness), or endophenotypes, could be useful, and the use of tissue-related gene expression array data may be of great interest in this regard. Prospective analysis of such phenotypes in individuals at risk of obesity—insulin resistance, for example—could provide mechanistic insights not necessarily apparent once the systemic phenotype is established. Similarly, the potential role of genes in moderating the effects of different interventions could help identify the population subgroups to be targeted by specific interventions. For example, a particular allele may identify particular subgroups of participants who respond to a greater or lesser extent to a specific intervention. Such genetic analysis might also enable prediction of weight gain responses to specific antipsychotic drugs (see also the “Special Needs for Special Populations” chapter). In addition to conducting such studies *de novo*, an effort should be made to identify longitudinal data sets that might lend themselves to relevant *post hoc* analyses, especially those that allow examination of “naturally-occurring” or planned interventions. A very important challenge in this context is the lack of accurate measurements of energy intake in free-living humans. More satisfactory measures of energy expenditure and body composition are now available; these could be combined to calculate energy intake over extended periods of time.

- **Investigate copy number variation (CNV) as a source of inherited or sporadic phenotypes related to obesity and diabetes.**

In addition to the widely recognized effects of sporadic duplications/deletions of whole chromosomes in causing human disease, it is clear that subtler, transmissible alterations in copy number of contiguous genes can have effects on complex phenotypes. Such copy number

variants (CNVs) are not necessarily associated with “syndromic” phenotypes, hence their potential contribution(s) to a complex phenotype cannot be reliably ascertained clinically. The degree to which such variants contribute to phenotypes related to obesity and diabetes cannot be adequately assessed without high resolution maps of their locations and access to suitable quantitative assays. In addition to contiguous gene deletions/duplications, the extent to which intragenic deletions/duplications generate mutations in genes causing monogenic forms of obesity or type 2 diabetes has not been systematically addressed. The newer genotyping arrays provide the data on common CNVs and exome sequencing can be used to identify rare events.

- **Identify additional genetic variations and understand their role in pathways that contribute to obesity.**

Although 17 SNPs have been shown by GWA studies to be associated with obesity, most of the genetic effect on adiposity has yet to be accounted for. This may be because the SNPs identified so far are not the functional variants, because there are rare variants with much greater phenotypic impact that have yet to be discovered, or because of complex interactions between genes within pathways or between genes, behavior, and the environment. Better tools are needed to investigate the effects of environment on the impact of predisposing genetic variants.

- **Investigate developmental “imprinting” *in utero*.**

Poor metabolic control in women who have gestational diabetes leads to increased fetal mass/adiposity, apparently increasing subsequent risk of obesity.



Obesity per se in pregnant women who do not have diabetes appears also to predispose their offspring to obesity. Such effects—sometimes referred to as “metabolic imprinting”—are conveyed by unknown mechanisms. It is likely that placental biology and the intrauterine environment are affected by metabolic consequences of maternal obesity, and that such changes could influence aspects of brain, adipose tissue, and pancreatic islet development in a fetus in ways that would predispose to obesity and type 2 diabetes. Studies are needed to determine whether the genetic status of the fetus interacts with such environmental effects, in a manner similar to what is likely to occur in the extrauterine environment. Pursuit of these studies will require very sophisticated experimental models and clinical/epidemiological analysis.

Allele-specific differential methylation of DNA during gametogenesis, or “genomic imprinting,” can affect the levels of expression of specific alleles in offspring; histone acetylation may influence this process and/or have independent effects on the expression of specific alleles. Environmental effects, such as maternal metabolic state and diet, may play a role in this process. The extent to which such phenomena modulate otherwise classical genetic and environmental influences on susceptibility to obesity in humans is unknown. Systematic comparisons of gene methylation (and CNV) status in identical twins discordant for obesity could provide important insights.

## Adipose Tissue Biology

More than just innocent bystanders, adipocytes are present in close physical proximity to all major organ systems and as such can influence neighboring cells. Understanding how to properly manipulate these cells and enhance their metabolic flexibility is key for a successful therapeutic approach for diabetes. Brown fat represents an unappreciated and potentially significant

metabolically active tissue that may contribute to overall energy balance. In addition, the variability in brown fat mass or function may underlie some aspects of susceptibility to excess caloric intake. Important areas for future research include study of the mechanisms that determine adipocyte number and size and those that determine the relative size and function of different white fat depots, and developing improved tools for measuring these end points; investigation into the link between the anatomy of body fat deposition and metabolic sequelae; epidemiological analysis of the effect of fat distribution on metabolic risk; and study of the mechanisms governing adipose tissue development *in vivo*.

### Key Questions

- **What mechanisms determine adipocyte number and size? Can improved tools be developed for measuring these end points?**
- **What mechanisms link variation in body fat deposition to metabolic sequelae?**
- **What mechanisms govern adipose tissue development and distribution *in vivo*?**

### Future Directions

- **Discover factors that control the adipogenic and mature adipose gene expression profiles in different fat pads, and determine how these factors are affected by metabolic cues.**

Differential gene expression is achieved through regulation of distinct “modules” in which groups of genes are coordinately regulated. These programs are regulated differentially between males and females, are characterized by unique combinations of these modules in different fat pads, and are regulated by adipocyte cell size, the local microenvironment, and systemic signals.

A better understanding of the cellular machinery regulating gene expression in these programs—nuclear receptors, their co-activators, and co-repressors—will be essential for this process.

➤ **Identify the molecular events that maintain functionality of expanding adipose tissue.**

Biological responses underlying adipose tissue expansion include the process of angiogenesis, as well as recruitment and local proliferation of pre-adipocytes, and studies are needed to identify “local triggers” that promote adipocyte expansion versus differentiation.

➤ **Characterize additional key lipid and protein factors released by adipocytes.**

Hepatocytes (liver cells) and adipocytes share in common numerous secreted factors, such as acute phase reactants. Additionally, adipocytes are likely to release many important lipids, but the identity of these mediators awaits further study. Lipidomics and proteomics can be employed to identify adipocyte contributions to systemic levels of these factors under different conditions. Adipocytes may well signal to other tissues, such as muscle and other fat depots, and may receive information from liver, muscle, brain, gut, and other tissues through as yet undiscovered signaling moieties that underlie connections between obesity and diabetes through their contribution to the coordinated response to changes in energy availability among tissues.

➤ **Investigate heterogeneity of white adipose tissue in different fat depots.**

It has been recognized for over 20 years that central obesity produces a high risk of diabetes and metabolic syndrome, whereas peripheral obesity is not associated with such a risk and may even be protective against

metabolic disease. Both BMI and adipose distribution, as measured clinically by waist-hip ratio, are strongly genetically determined, but what specific genes are involved has been unknown. Studies have begun to identify the genes involved in fat distribution and indicate that these genes exhibit large difference in expression even in cells in the preadipocyte stage—i.e., before differentiation to fat. These findings raise the possibility that white fat is more heterogeneous than previously thought. Defining the factors that program this heterogeneity may provide new insights into the link between obesity and metabolic disease.

➤ **Investigate mechanisms underlying the causes and impact of sexual dimorphism on specific adipose depots.**

Women differ from men both in regional patterns of fat distribution and in extent of adiposity. Individuals of either gender also show marked differences in pattern of white fat distribution, and this pattern can further change during periods of weight gain or loss and with aging. Delineating the mechanisms involved, as well as the critical periods in which patterns diverge, is essential for a better understanding of how different adipose depots affect metabolic function and diabetes risk.

➤ **Explore the potential for therapeutic manipulation of specific fat depots to reduce morbidity associated with certain depots.**

As a better understanding of depot-specific characteristics of adipose tissue emerges, tissue specific gene expression, cell ablation, or other methods can be utilized to modify those characteristics predisposing to metabolic dysfunction. Modest expansion of certain fat depots could be explored as an intervention that

ameliorates organ dysfunction by reducing fat deposition in muscle, liver, and other non-adipose tissues.

► **Investigate mechanisms for maintaining fully functional mitochondria in adipocytes.**

Accumulation of damaged mitochondria over time, especially in an oxidative environment, may contribute to pathological consequences of adiposity. Methods to stimulate mitochondrial biogenesis and repair may contribute to improved metabolic outcomes.

► **Accelerate technology development, including the use of noninvasive tools, such as magnetic resonance spectroscopy and labeled substrates, to investigate adipose tissue biology *in vivo*.**

These tools are essential both to translate discoveries made in animals into a better understanding of human biology and to monitor efficacy of novel therapeutics.

## Obesity Prevention and Treatment

Behaviorally based lifestyle interventions in adults show efficacy for modest weight loss, and large scale trial data—such as results of the landmark Diabetes Prevention Program—clearly show that this modest weight loss reduces the incidence of type 2 diabetes in high-risk individuals. In overweight children and adolescents, lifestyle interventions with a focus on diet, physical activity, sedentary behavior or behavior change can produce clinically meaningful reductions in weight. Although the strongest weight control efficacy data for children is for family-based interventions, these interventions have not been translated into widespread practice. Theory-driven prevention programs in schools and other community settings have demonstrated some efficacy for preventing weight gain in population-based samples of children and adolescents. However, there

is considerable room to improve both prevention of unhealthy weight gain and achievement of sustained weight loss across the lifespan, especially in populations disproportionately affected by obesity and type 2 diabetes. The impact of dietary composition and choices needs to be better understood to allow for evidence-based recommendations related to serving size and content in relation to the cost and availability of food. Research on the determinants of energy expenditure should include identifying factors that promote or deter physical activity, as well as understanding the link between fitness (aerobic and anaerobic) and metabolic disease independent of obesity. Research uncovering the behavioral mechanisms of obesity, and how they are driven by, or interact with, both biological and social and physical environmental factors, could point to novel approaches to treatment and prevention at the individual and population levels. Research on the safety and efficacy of non-surgical methods (e.g., structured meal plans, pharmacotherapy, and lifestyle) for weight control and diabetes improvement for those with extreme obesity (BMI of 40 or greater) is also needed, given that only a small fraction of eligible people seek or can obtain bariatric surgery. Preventing weight gain, maintaining weight loss in weight-reduced individuals, and promoting weight loss may each require strategies that are at least somewhat distinct, and research can help identify what works best for each of these types of weight management.

In addition to beneficial changes that can be implemented at the individual level (e.g., lifestyle management, therapeutics, bariatric surgery), strategies for inducing energy balance changes at the community/population level (e.g., education, environmental, economic, or policy interventions) are required. Translation and implementation are key challenges for research on how best to apply existing, effective

approaches in real-world settings. Finally, integrated research is needed to uncover biological (e.g., genetics, sensory or neural processing), cognitive, and behavioral factors for obesity as they interact with family/cultural and other social and physical environmental influences across the lifespan.

## Key Questions

- **What strategies, methods, and approaches most effectively prevent inappropriate weight gain across the lifespan?**
- **How do prevention and treatment interventions work most effectively, individually and/or in concert, at multiple levels of influence (e.g., individual, social, policy, and environment)?**
- **What are the most “potent” modifiable behavioral, social, economic, physical environment, and policy influences on obesity, eating, and physical activity?**
- **How do patterns of eating, physical activity, and sedentary behavior develop and contribute to obesity and prevention of obesity in children and adolescents?**
- **How do developmental factors interact with biological, social, and physical environmental factors to contribute to obesity and prevention of obesity in children and adolescents?**
- **How are the processes of achieving weight loss versus maintaining weight loss versus preventing excess weight gain biologically and behaviorally distinct?**
- **How can technology and other innovations be used to translate findings from efficacy studies of obesity prevention and/or**

**treatment to larger populations in real-world settings?**

- **What are novel targets (e.g., drug, behavior, and social and physical environments) for obesity management that can improve weight loss outcomes and reduce risk of developing type 2 diabetes?**

## Future Directions

- **Develop multi-level obesity prevention interventions across the lifespan, especially those at the organizational level (health systems, schools, government, worksites, industry, and media).**

Intervention studies are needed to test novel approaches for preventing excess weight gain during high-risk periods for obesity development with the goal of reducing overall obesity prevalence, as well as disparities across racial, ethnic, and socioeconomic groups. Examples of approaches to investigate include interventions that modify the food, physical activity, sedentary behavior, or other environmental factors for children from infancy through young adulthood; systematic primary care or community-based interventions with pregnant women; social marketing of healthful foods and physical activity; behavioral economics strategies to promote more healthful eating and activity patterns; and increased opportunities for physical activity in schools and worksites. Approaches that simultaneously target multiple levels of intervention are promising, including modification of individual behaviors, family context (e.g., household availability, feeding practices), neighborhood environments (e.g., density of fast food restaurants or physical activity outlets), and societal-level factors (e.g., social networks, food advertising). Research on effective multi-level and systematic approaches to eliminating

disparities in obesity among minority and socially disadvantaged populations are needed. Studies to determine effective policy approaches to promote healthy weight in children and adults could inform population-wide approaches to prevention. Future dissemination of evidence-based obesity prevention programs would be enhanced by study design and measures that support evaluation of intervention implementation, generalizability, and costs.

► **Identify non-biological determinants of obesity and obesity prevention and build further evidence of key interacting influences on eating, sedentary behavior, physical activity, and obesity.**

More research is needed to understand how biological, cognitive, behavioral, social, and physical environmental factors interact to influence obesity-related behaviors and development of obesity. Differences and high-risk periods across the lifespan and across vulnerable populations also need to be explored. Measurement of the full range of potential determinants in both observational and experimental studies would enhance research in this area. For example, developmental neurobiological aspects and eating behaviors related to excess energy intake might be studied in conjunction with interactions among food preferences, dietary composition, household food environment, parental feeding, and food marketing influences. At the social and physical environmental levels, studies to identify neighborhood factors, media exposure, and social networks and their interactions with individual behaviors, cognitions, and motivations could reveal additional influences on obesity development and prevention.

► **Examine methods to improve long-term weight loss maintenance.**

Methods for long-term weight loss maintenance should be guided by a better understanding of the behavioral and biological context after weight loss in children and adults. Basic information is required about the reduced-obese state, such as assessments of physiological, nutritional, cognitive, affective, behavioral, and socio-cultural and physical environmental factors that affect an individual's predisposition to regain weight or maintain weight loss. Studies comparing before and after weight loss and/or successful versus non-successful weight loss maintainers could be informative. These may allow for identification of protective individual, social, or environmental factors that reduce risk for weight gain and inactivity in an otherwise obesogenic environment. Intervention studies are needed to examine the efficacy of various weight maintenance approaches (e.g., behavioral, pharmacological, environmental, combination) after a minimum of a 7 to 10 percent weight loss.

► **Evaluate novel technologies and tailored methods of weight control interventions.**

Research is needed to examine the stand-alone or added efficacy of using technologies (e.g., ecological momentary assessment, smart phones, texting, social networking applications, devices to track physical activity and dietary intake) and other innovative strategies to facilitate diffusion and use of empirically validated strategies (e.g., self-monitoring) with less face-to-face contact. These technical approaches could support individualized and tailored delivery of interventions outside of the clinical setting. Research should also evaluate technology-based and/or tailored interventions delivered in locations where people already convene for other purposes (e.g., worksites, places of worship). Studies could assess the relative efficacy of various technologies (alone or in combination) or tailored

messages and/or the minimal dose of face-to-face contact required for clinically beneficial weight loss.

## Improving Clinical Investigative Tools

Technological advances in instrumentation are allowing scientists to characterize body composition and mechanisms of body weight regulation, such as energy intake and expenditure in humans, and begin to establish links between obesity, diabetes, and metabolic syndrome. In clinical research centers, investigators can modify energy and nutrient intake in well-controlled environments and quantify changes in energy expenditure, body composition, and related physiological parameters. Because some of these changes can be very small, measurement is only possible with the improved precision and dynamic range of newer generation whole-room calorimeters, dual-energy x-ray absorptiometry scanners, MRI, and other specialized instruments. This increased measurement capacity and precision allows clinical studies in well-controlled environments to quantify small but significant between-individual differences or within-individual changes in energy balance that may be important to body weight regulation. These measurement techniques also allow researchers to examine differences under varying conditions (e.g., over or underfeeding, exercise, sedentary states, and pharmaceutical interventions). Further development of clinical tools and measures is needed to continue to facilitate and simplify these studies.

Objective, unobtrusive, relatively simple, and cost-efficient measures, monitors, and sensors are particularly needed for use in free-living and population-based research. Portable sensors and monitors are increasingly useful for continuous monitoring of an individual's physical status, including heart rate, blood glucose level, hydration, body and ambient temperatures, physical activity, posture,

geo-location, sleep, pain, environmental lighting, and many other factors. Developments in this area are fueled by advances in sensors, processors, memory storage, wireless communication, and Web-based data transport, processing, and sharing. For example, in the area of dietary assessments, emerging technologies are exploring the use of cell-phone cameras and Web-based imaging recognition software for energy intake determinations. Further research and refinement are needed to improve the accuracy, reliability, acceptability, and efficiency of these tools. Likewise, validation and testing are needed to develop brief assessment tools that capture relevant and immediately useful information on risks for obesity and weight-related behaviors across the lifespan in medical settings, particularly primary care. A particular need is for measurement approaches that can be used in children.

## Key Questions

- **What are the best ways to measure individual variability and improve classification of various obesity phenotypes (e.g., cognitive, behavioral, metabolic, and body composition)?**
- **How can existing and emerging technologies be used to improve the accuracy and efficiency of assessment in intensively controlled laboratory or clinical research?**
- **What technologies can be harnessed or developed to bring accurate, acceptable, and low-cost assessments of energy intake, energy expenditure, physiological responses, and body composition into real-world settings with free-living humans, such as medical clinics, schools, and communities?**

- **What new tools, methods, and technologies are needed to assess nutrient intake, specifically the amounts and types of foods and beverages consumed over discrete periods in free-living humans?**

## Future Directions

- **Improve measurement accuracy, sensitivity, and feasibility of clinical obesity research tools for phenotyping.**

Improved tools for both short- and long-term monitoring of body composition, energy intake, energy and substrate utilization, physical activity and fitness, diet composition, and behavioral assessment in human studies are needed. These tools are needed across the lifespan, from infancy throughout adulthood. Body composition measurement for use in both research and practice settings is a particular area of research opportunity. While BMI is a good general estimate of overweight and obesity in a population, it is not ideal for understanding individual body composition status or changes and is not necessarily equivalent across all sex, age, or race/ethnic groups. Improvements in the capacity to measure body composition accurately in all age groups in clinical settings would allow research studies of the relationship between body composition and clinical features, and would facilitate translation to medical management in real-world situations. Additional priorities include brain imaging by functional MRI and PET scanning, measures of adipocyte, muscle, bone, macronutrients (lipids, carbohydrates, and protein) and their metabolite turnovers and depositions, and heat generation and dissipation in tissues and organs. Clinical research centers (such as those supported by Clinical and Translational Science Awards) are an example of a good venue for supporting both mechanistic (bench-to-bedside) studies and the creation of reference

standards for free-living clinical and population research.

- **Establish and reduce cross-center (laboratory) variability in the same measurements.**

Despite using the same techniques and instruments (even from the same manufacturer), assay results often differ across different research sites. Standard operating procedures and references need to be established that include strategies to correct for instrument variability and thus improve the accuracy and/or consistency/agreement in data collected across multiple sites.

- **Improve free-living assessments.**

Development is urgently needed for measurements in free-living humans of diet (energy intake, macro and micronutrients, body water content, appetite, satiety, and eating patterns), physical activity and inactivity (frequency, intensity, type, duration, and social context), living and working environments (including sleep), and stress (physical and emotional), as well as population-level assessment tools of social networking and the built environment. This area of research will require the development of new data collection and analytic tools designed to enhance information derived from clinical and population-based studies.

- **Develop assessment tools for clinical settings.**

It is important that inappropriate weight gain trajectories or weight fluctuations be identified earlier in primary care settings. Many clinicians in primary practice frequently do not record or plot BMI values or address weight gain trajectories, even in people who are overweight by BMI criteria. Development of brief, cost effective and predictive obesity risk

assessment tools for assessing and monitoring weight and weight-related behavior that are validated for use in clinical settings and trials would represent a crucial step toward rectifying these practices. In addition to validity and reliability, the needs of health care providers, their patients, and participants in clinical studies are important to consider in developing these tools. Assessment tools are needed across the lifespan that address quantitative nutrient, caloric, and energy expenditure information, as well as qualitative dietary and activity habits, such as frequency of eating at restaurants or fast food establishments, excessive consumption of sweetened beverages, consumption of excessive portion sizes, and bouts of sedentary (e.g., screen time) and non-sedentary behavior.

► **Overcome limitations in current brain and metabolic tissue imaging techniques.**

MRI and single photon emission computed tomography (SPECT) reflect changes in blood flow to the brain as a surrogate for direct assessment of neuronal activity. PET technology permits direct assessment, but the repertoire of suitable reagents is limited, and radiation exposure reduces applicability. Access to the anatomy of connections among neuronal groups can be provided by diffusion tensor imaging. Research is needed on complementary *in vivo* electrophysiology (e.g., EEG) and techniques for integrating all such measures with sophisticated quantitative and qualitative assessments of ingestive behaviors. New, relatively noninvasive technology is also needed to enhance the ability to monitor the incidence of BAT in the human population, and to measure BAT mass, metabolic activity, and its contributions to overall energy balance.



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

Obesity is the major driver of the increased rates of type 2 diabetes worldwide and a serious sequela of intensive insulin therapy in type 1 diabetes. Thus, reversing the trends toward weight gain both in the general population over time and in individuals over their lifetimes is key to conquering diabetes. The past decade has seen huge gains in understanding of the exquisite and intricate regulation of energy balance and of the mechanisms by which excess nutrient intake and inadequate physical activity exert their deadly effects. This information, as well as knowledge yet to be developed, creates opportunities to intervene. One such prospect involves breaking the links between obesity, inflammation, and altered metabolism. Another entails restoring optimal energy balance through re-setting of signaling networks that regulate appetite or inducing increased peripheral energy expenditure. Alternatively, the ability to modulate the development of fat or direct

deposition of nutrients to specific locations could turn out to be potentially protective against obesity-associated health problems. This potential strategy will entail understanding how to enhance adipogenesis in a way that reduces inflammation, which could have a positive impact on all tissues. A better understanding of genetic contributors to obesity and type 2 diabetes may identify new therapeutic targets and help tailor therapeutic strategies for people at risk. Likewise, developing and testing multiple approaches to help diverse populations avoid inappropriate weight gain across the lifespan will boost efforts to prevent type 2 diabetes and its health complications in the United States. New technologies and tools could help health care providers detect weight issues sooner and help clinical investigators tackle the challenges of how biological, behavioral, and environmental factors affect weight loss and gain in real world settings.



Closing the loop. The development of an artificial pancreas that automatically links devices to measure blood glucose levels (left) and deliver insulin (right) via advanced computer programs should help to reduce the burden of diabetes management on people with this disease.  
*(Image credit: Fang-Mei Liu, The Scientific Consulting Group, Inc.)*

# BIOENGINEERING APPROACHES FOR THE DEVELOPMENT OF AN ARTIFICIAL PANCREAS TO IMPROVE MANAGEMENT OF GLYCEMIA

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

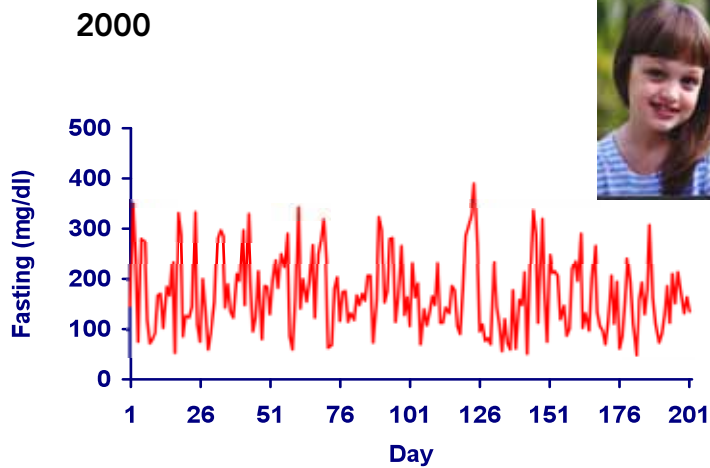
## INTRODUCTION

Large prospective clinical trials have established the long-term benefits of intensive blood glucose control in people with type 1 or type 2 diabetes. The research has shown that good blood glucose control is a key factor in lowering risk of many of the devastating long-term complications of diabetes, including blindness, kidney failure, and cardiovascular disease. For children and adults with type 1 diabetes, this has led to the widespread use of intensified insulin therapy to prevent or minimize the onset and progression of diabetes-related complications. However, the global application of this approach has been limited by a lack of technologies that would enable people with diabetes to easily and appropriately adjust delivery of insulin in response to minute-to-minute changes in circulating glucose. Currently, most people receiving insulin treatment for diabetes need to check their blood glucose levels several times a day with finger sticks and hand-held glucose meters, so that they can adjust their insulin doses to avoid extreme high and low glucose levels. For most insulin-treated people, this is very difficult. Not only is it uncomfortable, but more importantly, this approach cannot replicate the exquisitely precise and dynamic regulation of insulin levels achieved by the insulin-producing beta cells within the pancreatic islets. Instead, individuals only see brief snapshots of the pattern of glucose changes over a 24 hour period. Thus, despite a person's best efforts, glucose levels can rise excessively (hyperglycemia)—particularly after meals—and at other times fall dangerously low (hypoglycemia), causing unconsciousness, seizures, and even death. Moreover, as the frequency of hypoglycemia increases, individuals lose the ability to perceive its warning symptoms, preventing them from taking corrective

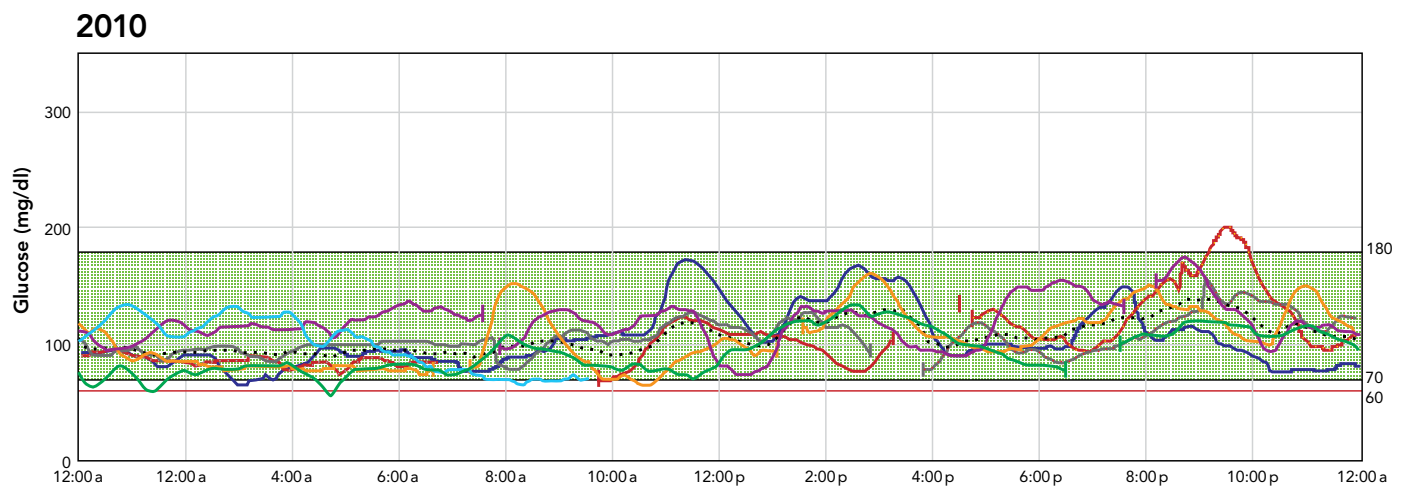
action by eating, a phenomenon called hypoglycemia unawareness. As a result, most people who need to treat their diabetes with insulin do not meet optimal targets for glucose levels, because their immediate fear of hypoglycemia outweighs their fear of future, long-term complications (see sidebar, “Hypoglycemia: An Achilles Heel in Therapy To Prevent Diabetes Complications”).

To improve insulin treatment and the care for people with diabetes, new methods of insulin delivery need to be developed and tested that more effectively simulate the functions of beta cells. There is a need for: 1) more accurate and rapid detection in real time of glucose levels throughout the day; 2) improved methods for rapidly translating real-time glucose measurements into adjustments in insulin delivery; 3) infusion devices that can deliver insulin more effectively, conveniently, and physiologically; and 4) improved insulin preparations that can more rapidly respond to changes in blood glucose.

Encouragingly, scientists, engineers, and patients have already taken the first steps toward the development of a mechanical “artificial pancreas.” Mechanical continuous glucose monitors (CGMs) are now being used clinically to give people with diabetes and parents of young children with the disease the ability to view real-time glucose levels, review trends and fluctuations in recent blood glucose levels, and receive alerts when blood glucose levels become too high or too low. These CGMs combine a continuous glucose sensor with a unit displaying glucose levels. The sensors are inserted



Advances in diabetes technology are bringing hope for improved glycemic control. The top part of the figure shows wide swings in glucose levels over the course of 200 days in the life of an 8-year-old girl with type 1 diabetes a decade ago. The bottom part of the figure shows glucose levels from multiple days (differently colored lines) in a newly diagnosed youth with type 1 diabetes using a CGM, demonstrating comparatively reduced swings in glucose and infrequent dips into hypoglycemia (below the green shaded target range). (Top image courtesy of Drs. Jay Skyler and Norma Kenyon, University of Miami School of Medicine; bottom image courtesy of Dr. Bruce Buckingham, Stanford University School of Medicine.)



under the skin for up to 3 to 7 days and transmit readings of glucose levels in tissue fluid (called interstitial fluid)—an approximation of blood glucose levels—every 1 to 5 minutes to a receiver carried by the individual. Although currently approved glucose sensors remain less accurate than traditional blood glucose meters, they offer people with diabetes who use these new devices an opportunity to spend more time in the close to normal glucose range, without increasing the risk of brain injury from severe hypoglycemia. NIH-sponsored research is helping to accelerate validation of these devices—for example, the NIH-sponsored Diabetes Research in Children Network (DirecNet) is

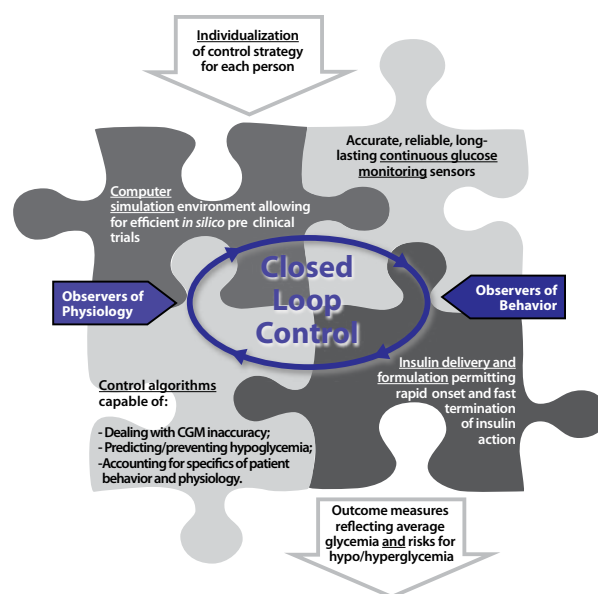
studying use of these sensors and their ability to improve management of type 1 diabetes in children. Thus, the availability of real-time continuous blood glucose monitoring represents a critical first step toward the development of a mechanical artificial pancreas.

Before a mechanical artificial pancreas can be fully realized, however, other important biological and engineering issues will need to be addressed. To more closely approximate the blood glucose lowering effect of pancreatic beta cells, a series of incremental steps will need to be introduced. These steps include the development of more accurate and robust glucose-sensing devices, improved methods of insulin delivery,

and the development of improved computer algorithms that appropriately translate glucose measurements into changes in the delivery of insulin, including its interruption—i.e., methods that can “close the loop” between glucose sensing and insulin delivery. Specifically, there is a need to produce smaller insulin infusion devices, optimize the site of insulin delivery in the body, develop more effective and rapidly-acting insulin preparations, and determine the benefit of combining insulin delivery with delivery of its counterbalancing hormone, glucagon, to reduce hypoglycemia. Amylin, a hormone co-secreted with insulin by beta cells, is also under study. Amylin has potent inhibitory effects on gastric emptying, appetite, and food intake in humans, and could be administered as part of an integrated closed-loop system for better control of post-prandial (meal-related) glucose excursions. Studies will also need to be done to assess the capacity of the artificial mechanical pancreas to improve overall metabolism, increase patient well-being, restore hypoglycemia awareness, and preserve existing pancreatic beta cell function. For example, DirecNet and another NIH-sponsored network, Type 1 Diabetes TrialNet, are collaborating to study use of a closed-loop system to initiate intensive metabolic control in people with new-onset type 1 diabetes.

Moreover, adoption and use of a new technology for diabetes treatment, such as an artificial pancreas, in real-life settings require behavior change and modification. Key factors, such as the extent to which people with diabetes accept a technology, use it appropriately, consider it as beneficial and convenient versus burdensome or intrusive, and identify its clinical benefits, are all equally important for success. The user interface requirements will also be different across the lifespan. For example, the way a technology is used may require different behavioral approaches when

it is employed in different age groups, such as young children, adolescents, and adults. For a new technology to be successful and widely accepted, it should help individuals overcome problems related to diabetes self-management and reduce the burden of living with diabetes. The high prevalence of diabetes-related physical, cognitive, and psychological limitations and disabilities also necessitates that a technology address accessibility and universal design features. For example, a device should be easy to operate for people with visual impairments and require only basic levels of math



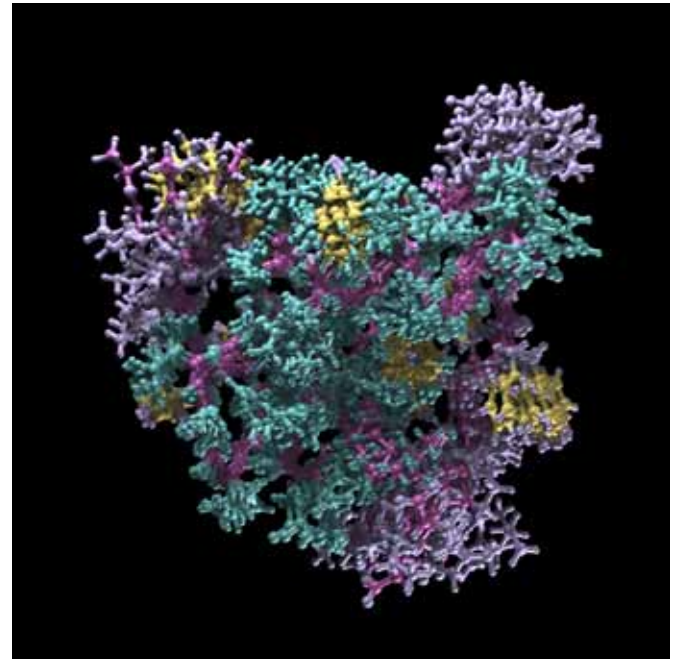
A closed-loop control system will rely on several key elements, including glucose sensors, insulin delivery devices, and a control algorithm reading sensor data and computing optimal insulin delivery. The control algorithm will be initialized by a screening procedure that will tailor the algorithm to each person’s specific parameters, and will be informed in real time by system observers – subroutines that estimate the state of a person’s glucose and insulin requirements, as well as behavioral specifics such as rest or physical activity. The system development and testing will be greatly facilitated by comprehensive *in silico* environment, which will permit efficient and cost-effective pre-clinical trials. The outcome of closed-loop control will be judged not only by metrics of average glycemia, such as HbA1c, but also by risk measures accounting for the expected reduction in hypoglycemia and hyperglycemia. (Image courtesy of Dr. Boris Kovatchev, University of Virginia.)

and reading skills. The successful adoption of devices may also facilitate their integration into telemedicine approaches to diabetes management, an important new area of study.

While scientists are vigorously pursuing this very encouraging therapeutic approach for diabetes treatment, there are likely to be certain limitations to a mechanical artificial pancreas. For example, there are many other factors besides glucose that modulate islet function that would not be recognized by a glucose-driven mechanical pancreas. Thus, a complementary strategy to pursue is to use bioengineering to develop cellular or molecular methods for replacing or regenerating pancreatic islets. Currently, islet transplantation is limited by the sparse supply of donor islets, as well as by the destructive immune response generated by transplanted beta cell antigens (autoimmunity) and foreign tissue (rejection). These barriers to islet transplantation may be overcome by: 1) genetic alteration of beta cells and/or optimization of immunobarrier-encapsulation technologies so that the transplanted beta cells are not recognized by a person's immune system; 2) the generation of beta cells from stem cells or gene therapy; and 3) technologies that may facilitate the *ex vivo* expansion of generated cells and their long-term preservation. These approaches offer great promise in the future, although it will likely be many years before they can be applied clinically, particularly in children. A potential intermediate step could be a bioartificial pancreas involving combinations of biological and engineering approaches. For example, islet transplantation might be combined with a

mechanical artificial pancreas to supplement insulin delivery and reduce hyperglycemic stress on marginally functioning islet transplants. The topic of islet replacement is covered in greater depth in “The Beta Cell” chapter.

Bioengineering has improved diabetes care today and offers considerable potential for the creation of an artificial mechanical pancreas for the treatment of diabetes in the future. This chapter describes research advances and opportunities that could make the achievement of this goal a reality in the next decade.



Three-dimensional model of the insulin molecule. Different formulations of insulin are being developed to improve strategies for insulin delivery from insulin pumps and, ultimately, in an artificial pancreas. (Photo credit: ©iStockphoto.com/theasis)

## RECENT RESEARCH ADVANCES

### **Introduction of Short-Term Continuous Glucose Monitoring into the Clinic:**

A major advance has been the development by industry of CGMs for use by people with diabetes. These needle-like percutaneous glucose sensors use an enzyme (glucose oxidase) coupled to electrochemical detectors to measure glucose levels. They are inserted under the skin by the user, operated for several days to one week, and then replaced. The combined number of users is estimated to have reached several hundred thousand and is still growing. In addition to facilitating self-monitoring of glucose levels by individuals, the most important lesson learned from the use of this glucose sensor technology is that blood glucose actually varies to a much greater extent during the course of the day than was previously thought, even in presumed well-controlled individuals. The sensors have also made possible research on, and initial clinical applications of, controllers, algorithms, and automated insulin delivery systems. Studies conducted by the NIH-supported DirecNet have investigated the capacity of current glucose monitoring technology to improve the management of type 1 diabetes in children. While there are still a number of caveats and limitations to current devices, such as the requirement to calibrate devices using finger sticks and the need to do so frequently, developments to date in continuous glucose monitoring technology have laid the groundwork for a new era of advances in therapies for diabetes.

### **Continuous Glucose Monitoring Enhances**

**Intensive Insulin Treatment:** Clinical studies have shown significant benefits of CGM use by people with diabetes. Recent clinical trials have focused

on CGM use among adults and children already on intensive insulin therapy, and whether it can improve hemoglobin A1c (HbA1c) values and reduce time spent outside of normal blood glucose levels. These trials have shown that CGMs, when used near-daily, not only help people with type 1 diabetes get into control—which can have a significant positive impact on lowering the risk of complications—but also enable them to stay in control without increasing the near-term risk of hypoglycemia. Study results have also highlighted particular challenges that will need to be addressed in future research, including identifying barriers to CGM use in children and adolescents so that they may reap the full benefits of this technology.

### **Development of New Algorithms To Help “Close the Loop”:**

A key aspect of closing the loop between glucose sensing and insulin delivery in a mechanical artificial pancreas is the development of algorithms, special instruction sets for computers. In the case of the artificial pancreas, these sophisticated computer programs are needed to interpret continuous glucose sensor data and instruct the insulin pump to dose the proper amount of insulin, and also potentially direct glucagon delivery to help prevent hypoglycemia. Two primary algorithm approaches are under investigation: the classic proportional-integral-derivative (PID) algorithm, and model predictive control (MPC). These algorithms are already being tested in clinical trials of closed-loop blood glucose control in carefully controlled hospital settings, with encouraging results. The further development of these algorithms is essential for the rapid implementation of closed-loop glucose control.



### Development of *In Silico* Models as a Resource for Pre-Clinical Testing:

In 2008, the FDA accepted the use of an *in silico*, or computer-based, model of diabetes as a pre-clinical testing tool for closed-loop research. This and other optimized simulators will facilitate the development of new control algorithms by enabling researchers to test and refine artificial pancreas algorithms quickly. It will also allow for computer-based algorithm comparisons. Finally, *in silico* models may eliminate or minimize the need

for testing in animal models, allowing investigators to focus instead on in-hospital human clinical trials, potentially saving time and money. This approach may also lead to a more expedited and better defined process of receiving regulatory approval for human trials of closed-loop systems. As the simulator is equipped with a wide array of tools for precise fine-tuning, it should help to bring promising algorithms closer to perfection in a shorter time frame.

## HYPOGLYCEMIA: AN ACHILLES HEEL IN THERAPY TO PREVENT DIABETES COMPLICATIONS

Keeping blood glucose levels under control has important, proven health benefits for people with diabetes. Dramatic reductions in risk for eye, kidney, nerve, and cardiovascular complications are all possible with good control. Yet, current strategies to achieve this goal come with a serious risk: abnormally low blood glucose, or hypoglycemia. While usually mild and easily treatable, severe hypoglycemia can lead to seizures, coma, and even death. Therefore, researchers are focused on finding ways to prevent or reduce hypoglycemia in people with diabetes.

Intensive insulin therapy is the biggest culprit in hypoglycemia. Recommended for most people with type 1 diabetes and some with type 2 diabetes, this aggressive treatment strategy requires individuals to monitor blood glucose levels frequently throughout the day, and to balance food intake and exercise with frequent

doses of insulin to maintain blood glucose levels in a healthy target range. If the amount of insulin administered exceeds the body's needs, however, blood glucose levels can fall precipitously. Acute episodes of hypoglycemia are a major complication for people with type 1 diabetes. Events occur on average 2 to 4 times a week; a severe bout causing loss of consciousness is rarer, but, on average, can occur annually. It is estimated that 2 to 4 percent of people with type 1 diabetes die as a result of brain injury or arrhythmia due to a hypoglycemia event (13). Children are very vulnerable to hypoglycemia, especially at night. Although hypoglycemia is less frequent in people with type 2 diabetes, even among those treated with insulin, the risk of severe events progressively increases with disease duration. As a result, many people with diabetes who are treated with insulin have difficulty meeting target goals for blood

glucose control, because their immediate fear of hypoglycemia overshadows their fear of future long-term complications.

The urgency of addressing hypoglycemia as a complication of intensive insulin therapy first became clear in the NIH-led Diabetes Control and Complications Trial (DCCT). This trial in people with type 1 diabetes showed for the first time that rigorous glycemic control, achieved through intensive insulin therapy, dramatically reduces the risk of developing long-term serious eye, kidney, and nerve complications of diabetes. Together with similar results observed for people with type 2 diabetes in the United Kingdom Prospective Diabetes Study, the DCCT findings led to current recommendations for blood glucose control in people with diabetes. However, the DCCT also reported a 3-fold higher rate of severe hypoglycemia in participants who were in the intensive insulin therapy arm of the trial, compared to those in the then-standard-treatment arm—revealing hypoglycemia as the “Achilles heel” of intensive insulin therapy. This vulnerability was reinforced recently by results from the NIH-led Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial. The ACCORD trial found that attempts to lower blood glucose levels to near normal levels (lower than current recommendations) in older people with longstanding type 2 diabetes using a variety of methods, including intensive use of insulin, resulted in a 3-fold higher rate of hypoglycemia in the intensively treated group than in the group receiving standard treatment.

Because of the tremendous long-term health benefits of good glucose control demonstrated

by the DCCT, its follow-up study, and related studies, researchers are working vigorously to find ways to engineer blood glucose monitoring and insulin therapy so that people automatically get the right insulin dose at the right time—thus avoiding episodes of hypoglycemia. This highly anticipated artificial pancreas technology is discussed in the main chapter text. As this research moves forward, it is also important to study hypoglycemia and find ways to minimize it so that people with diabetes can reap the full benefits of good control now. For example, a key factor in severe hypoglycemia events is “hypoglycemia unawareness.” Individuals with this condition lose the ability to recognize impending hypoglycemia and take protective action, such as eating. Compounding this problem, repeated episodes of hypoglycemia attenuate the body’s ability to counteract falling blood glucose levels, leaving people more vulnerable to severe hypoglycemia. Elucidating how the body senses and defends itself against falling glucose levels—and how hypoglycemic episodes alter these behavioral and biological defenses—is thus critical not only for developing strategies that can limit acute hypoglycemia episodes, but also for reducing long-term risk of severe hypoglycemia. Scientists are making progress in this area. For example, a complex network of “glucose sensors” has been described in both the brain and tissues outside the brain, with those in the brain most likely playing the dominant role. Recent studies suggest that previous hypoglycemic episodes induce adaptations in brain glucose sensing via changes in neurotransmitters, cellular receptors, and the metabolic efficiency of glucose-sensing cells—thus revealing a number of potential therapeutic

targets for drugs to minimize hypoglycemia and potentially prevent development of hypoglycemia unawareness and defects in glucose counter-regulation.

Another problematic aspect of hypoglycemia is its effect on brain function and the potential for injury. In general, tasks that primarily involve higher cognitive processes, such as following directions for medication, are more sensitive to acute hypoglycemia than simple motor tasks, such as picking up a piece of paper. In more severe episodes, the insult to the brain can result in seizures, coma, and even death. New strategies to protect the brain from acute hypoglycemia-induced injury are essential for optimizing the benefits of insulin therapy. One prospect is “alternative fuels.” While glucose is its primary fuel source, the brain can utilize alternative fuels—such as the molecule acetate—to maintain its energy requirements. Exposure to prolonged fasting and/or repetitive episodes of hypoglycemia appears to enhance the brain’s ability to utilize alternative fuel sources. For example, researchers have found that brain uptake of acetate is increased in people with type 1 diabetes receiving intensive insulin therapy—suggesting that these individuals, by virtue of their increased exposure to hypoglycemia, develop an enhanced ability to use alternate fuels in the brain, increasing the appeal of this potential therapeutic approach. Moreover, alternate fuels might help by protecting the brain during acute hypoglycemia while at the same time not causing deleterious hyperglycemia.

In their ongoing battle to overcome hypoglycemia, scientists can draw on many recent advances. For example, studies have shown that islet transplantation—an experimental therapy currently being used to treat “brittle” type 1 diabetes—is highly effective in reducing severe hypoglycemia events, even in cases in which transplant recipients have subsequently lost their insulin independence. This beneficial effect of islet transplantation has also been shown for hypoglycemia awareness, which is restored after transplantation and sustained even if the transplant fails—observations that researchers can exploit in developing new therapies (see the chapters on “Type 1 Diabetes and Autoimmunity” and “The Beta Cell” for more information on islet transplantation and cell replacement therapies). Tools such as newly improved animal models, gene therapy, and selective gene “knockdowns” in brain cells provide an opportunity to answer questions about glucose sensing that could lead to ways to restore the body’s normal ability to counteract hypoglycemia. Studies of alternate brain fuels that could lead to new strategies to protect the brain from hypoglycemia will benefit from recent advances in brain imaging methods (fMRI, MR spectroscopy, PET). Combined with work on artificial pancreas technologies, these opportunities provide hope that people with diabetes will soon be able to treat their disease without the fear of hypoglycemia.

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, anticipated current efforts to develop biomechanical approaches to insulin replacement and, ultimately, an artificial pancreas. To help speed progress, these efforts have been fostered through strategic planning processes for the *Special Statutory Funding Program for Type 1 Diabetes Research* and through the 2006 “*Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan.*” As opportunities to advance and refine glucose sensing, insulin delivery, algorithm development, and other key aspects of an effective closed-loop system for patients continue to evolve at a rapid pace, new directions for research have been identified to help guide these efforts.

### Glucose Sensors

The unique advantage of the continuous glucose sensor is its potential value for directing insulin dosing and for hypoglycemia warning. In contrast to the intermittent information provided by finger stick glucose monitoring, continuous sensors can provide minute-by-minute glucose trend data. A reliable and accurate glucose sensor is key to the implementation of new therapies based on insulin delivery devices, automated control systems, and faster-acting insulins, and is absolutely essential to the safety of these therapies. For widespread acceptance, the sensor must be unobtrusive and user-friendly, require only occasional recalibration, and otherwise be generally suitable to a broad group of people with diabetes.

### Key Questions

- **Can accuracy and reliability of glucose sensors be improved?**
- **Can new glucose-sensing technologies be developed?**
- **Will the incorporation of nanotechnology strategies and the use of smart biomaterials be able to improve reliability and durability of sensors?**
- **Will it be possible to develop a reliable and durable implantable sensor?**
- **Will it be possible to develop new technologies/strategies for a noninvasive, reliable, low cost, continuous glucose sensor?**
- **Will universal design strategies for sensor development be applied to facilitate use by people with diabetes?**

### Future Directions

- **Develop improved glucose sensors.**

There is a need for a new generation of sensors that have sufficient overall reliability and safety to support more aggressive therapies and can be expected to be widely acceptable by people with diabetes. The sensors should be small, fully implantable for periods of months to years, require only occasional (weekly to monthly) recalibration, be accurate enough for insulin dosing and warning of hypoglycemia without the requirement for

confirmation by finger stick, be easily implanted and replaced, and be unobtrusive to the user. Research in the field of nanotechnology, and application of smart biomaterials to improve sensing sensitivity and accuracy and promote biocompatibility, may contribute to the development of more effective glucose sensors. It is important to facilitate the introduction and development of new glucose detection principles, such as optical, ultrasound, and magnetic-impedance-based detection. The development of non- or minimally-invasive glucose sensors that are specific, continuous, and reliable is a critical step in reaching the goal of an artificial mechanical pancreas.

► **Validate glucose-sensing technologies.**

Glucose sensors need to be tested extensively and remain accurate under a variety of conditions such as during exercise, sleep, hyperglycemia, and especially hypoglycemia. There is a need to develop an acceptable implantation approach, including establishing an appropriate implantation site, development of methods for implantation and replacement, and documentation of device biocompatibility. It is also important that the sensor responds more rapidly to changes in glucose, so that the time lag compared to blood measurements is sufficiently short. In parallel with glucose measurements, it may also be advantageous to continuously monitor certain physiologic variables such as heart rate, temperature, perfusion in the vicinity of the sensor, physical activity, gastric emptying, lactate, and insulin. Implanted telemetry devices that send sensor data to external receivers must be small, long-lived, and hermetic. New strategies for data management will be needed to distribute and use the continuous stream of information most effectively. Development and introduction of this type of glucose sensor system is critical because of its central importance to clinical implementation of new

insulin replacement technologies and its potential for widespread acceptance by users.

► **Translation.**

The effective transfer of technology from the research stage through industrial development and on to clinical introduction requires special attention. It is also crucial that information from clinicians and users is rapidly fed back for incorporation in technology evolution. New and more thoughtful approaches to technology transfer may be needed. For example, application of universal design principles would stress making glucose-sensing devices usable by all patients, to the greatest extent possible, without the need for adaptation or specialized design at the user end. The issue of interoperability of the devices and the potential application of universal design strategies must be taken into consideration for better usability of the devices at the point of care, and for collection and transmission of data to health care providers—leading to more effective feedback and greater quality of care (see the “Telemedicine” topic in this chapter). Translation will also require diabetes health care providers to learn ways to use the output from these devices in a way that improves outcomes and enhances adherence to diabetes self-management issues.

## Algorithm Development—*In Silico* Simulation Models

People with diabetes face a life-long optimization problem: to maintain strict glycemic control without increasing their risk for hypoglycemia. The engineering challenge related to this problem is to design algorithms that use automated insulin delivery to exert optimal closed-loop control of glucose fluctuations. Fortunately, the mathematical modeling of glucose-insulin interaction is already one of the most advanced applications of quantitative science to medicine. Beginning with

the now classic Minimal Model of Glucose Kinetics (MMGK), a number of elaborate models have been developed. These models can be classified in three broad classes: (1) **models to measure** parameters that are not accessible by direct lab tests, such as MMGK assessing insulin sensitivity; (2) **models to simulate**, which enable *in silico* pre-clinical trials; and (3) **models to control**, which are used to empower algorithms such as MPC. Because computer simulation is a mainstream engineering tool, the recently developed first computer simulator capable of substituting for animal trials in certain pre-clinical experiments holds great promise to accelerate the development of closed-loop control systems and to optimize clinical trial design. Due to the complexity of glucose regulation, a person's response to insulin can vary even under identical conditions. Thus, an additional requirement for a successful closed-loop control strategy is that it will have to be adaptive and to account for both changes in physiology and perturbations caused by a person's behavior. The key to adaptation is system observation. An approach to closed-loop control of emerging importance is thus modular design, including not only control algorithms, but also automated observers, which estimate in real time the physiological, and possibly behavioral, states of the person. With this modular design in mind, several key questions emerge.

### Key Questions

- **What outcome measures are suitable for judging the effectiveness of closed-loop control in relatively short-duration clinical trials? What would be the “standard” performance criteria? What degree of control error is acceptable?**
- **What are the requirements for designing control modules?**

- **Can *in silico* models of human metabolism be improved by making them more powerful in terms of generating “virtual participants” for *in silico* trials? Can a rich tracer database on type 1 diabetes (adult and children) be developed? Can counter-regulation and exercise be incorporated? Can a type 2 diabetes simulator be developed?**
- **What safety features can be incorporated into controllers?**

### Future Directions

- **Using system biology approaches, develop a comprehensive computer simulation environment allowing for efficient and cost effective *in silico* experiments with diabetes treatments.**

This should be a large-scale collaborative effort, with several centers contributing data and engineering expertise. Archival databases need to be scanned for useful information. However, for this effort to be successful, additional data collection is required to reconstruct critical elements of the human metabolic network, most notably hypoglycemic counter-regulation and the metabolic effects of physical activity.

- **Develop effective closed-loop algorithms for clinical and outpatient use.**

One size may not fit all in terms of algorithms for an artificial pancreas. Patient-to-patient variability and individual differences could render this difficult—thus, creating a generic, off-the-shelf algorithm might not be feasible. It might be necessary to develop a unique control for each individual, which would be time-consuming and costly. Current sensors are not

sufficiently accurate, and insulin delivery systems now in use do not deliver insulin rapidly enough or to the optimal site (the portal vein). Robustness of control is also yet to be achieved for everyday activities (e.g., exercise, stress, and meals). An approach to overcome this challenge could be to develop a standardized set of observation and control modules that can be assembled into individually-tailored algorithms, including, but not limited to, modules that direct:

- Detection of glucose sensor errors caused from lags in glucose transport between blood and interstitial fluid;
- Mitigation of time lags inherent with glucose sensor analyses and subcutaneous insulin delivery;
- Hypoglycemia prediction, alarms, and prevention via automated insulin pump control, including through automated, sensor-controlled interruption of insulin delivery.
- Overnight closed-loop control;
- Automated, sensor-controlled administration of small doses of glucagon during impending hypoglycemia;
- Bio-behavioral control combining steady-state closed-loop control with behavioral, user-initiated “open-loop control” of meals and physical activity. During open-loop control, the bioengineering system would assume an advisory role, providing information to the user;
- Control-to-range, which aims to prevent extreme glucose excursions, but not necessarily the maintenance of blood glucose level at a certain preset target.

A high degree of collaboration and coordination between multiple centers is necessary to develop such modules and requires a combination of modeling, *in silico*, and

clinical studies. While it is envisioned that *in silico* trials may accelerate the development process, *in silico* experiments cannot serve as the definitive answer to the questions asked—rather, they may indicate which treatment scenarios are ineffective, and help with the selection of an algorithm for subsequent clinical studies. Clinical trials are required to provide definitive validation of all methods.

## Insulin—Improving Delivery and Formulation

Since the discovery and preparation of insulin nearly a century ago, the attempt to mimic insulin’s real-life physiologic properties has been and remains a challenge. Exogenous insulin replacement therapy via injection or pump can be affected by modulating the insulin formulation per se, by changing the delivery route, and by adjusting the dosing scheme. Alternative insulin delivery technologies offer the potential to improve glycemic control without the cost, safety, and resource-availability limitations of cell- and gene-based therapies. A number of approaches aim to provide commercially available insulin more rapidly or less invasively than is achieved with current methods; this could be achieved through novel technologies for continuous infusion under the skin or into the abdominal cavity, as well as through pulmonary, oral, and transdermal routes to decrease the number of required daily injections. Several alternative delivery approaches require a novel device combined with uniquely formulated insulin. Each approach, whether applied externally or implanted, includes electromechanical devices with glucose sensors and delivery systems and/or glucose-responsive materials based on competitive glucose binding or enzyme-controlled mechanisms. Some approaches have even attempted to build the glucose-sensitivity directly into the insulin molecule to eliminate the need for devices altogether. Technical challenges in this field include

optimizing device material biocompatibility, improving the accuracy and increasing the rapidity of glucose-responsive action, eliminating the potential for unwanted delivery of excess insulin, and reducing the immunogenicity associated with alternative sites of administration and/or modification of the insulin molecule.

## Key Questions

- **Which insulin delivery approaches result in clinically relevant improvements and are acceptable to the user?**
- **How do market-specific cost constraints influence the optimization of novel delivery methods, devices, and insulins?**
- **What changes in insulin chemistry and/or physical properties would most likely improve its use in alternative delivery routes, devices, and/or materials?**
- **How can the potential risk of alternative delivery sites and insulin chemistries to produce unwanted metabolic, toxic, or immunogenic effects be quantified and reduced?**
- **How may the automated delivery of insulin counter-regulatory hormones such as glucagon be integrated into current or future closed-loop systems? What changes in glucagon chemistry and/or physical properties are needed to have more effective and stable glucagon formulations for delivery by pumps?**

## Future Directions

- **Establish standardized pre-clinical models for safety and efficacy testing of alternative insulin delivery methods, materials, and**

## **devices that dependably predict their potential clinical utility.**

There is a need to develop, validate, and then capitalize on a broad array of experimental animal models for testing of treatment modalities. For example, in addition to rodent models of diabetes, spontaneous diabetes is known to occur in dogs and cats. Researchers interested in developing and testing new therapies would benefit from access to a spectrum of validated animal models that would allow testing of new approaches in a broad array of physiologic systems and disease states. The ability to test new treatments in a battery of models may increase the likelihood that pre-clinical findings would ultimately be translatable to people with diabetes in the clinical setting.

- **Develop integrated insulin delivery systems that improve the quality of life.**

Daily diabetes management should not be overwhelming or hugely time consuming to the individual. Devices should be user-friendly and any functions (checks, dosing adjustments, refills, recharging) handled quickly, accurately, and discreetly. The “patch pump” concept is emerging; however, cost margins currently limit widespread adoption. Integration of pumps with glucose-sensing devices will reduce the need to carry or insert multiple devices. Development of fully implantable devices will further minimize inconvenience and visibility as long as maintenance procedures are also kept to a minimum. In addition, fully implantable systems potentially offer alternative insulin delivery routes, such as the vasculature or the abdominal cavity.

- **Develop failsafe devices or biomaterials that respond based on low glucose levels to release**



### **glucagon or other insulin-counteractive therapeutics to prevent hypoglycemia.**

The major immediate clinical risk of state-of-the-art methods of insulin delivery is severe hypoglycemia due to the dangerous “dumping” of insulin from highly insulin-loaded materials and devices. Therefore, it is essential to develop approaches that link delivery of insulin and glucagon with devices that monitor glucose levels to reduce the excessive or inappropriate administration of insulin and to correct impeding hypoglycemia.

- ▶ **Reduce immune responses to facilitate alternative site and/or long-acting polymeric insulin delivery systems.**

One of the factors that can diminish the ability of insulin or insulin delivery devices or glucose sensors to act/operate effectively is the induction of immune responses. Thus, the development of new insulins or delivery and monitoring systems will require the development of materials that reduce the risk of immune reactions that could impair function over time.

- ▶ **Develop new insulins with increased stability at high concentrations and minimal, reproducible subcutaneous absorption delay time.**

Insulin preparations for subcutaneous administration typically contain six-molecule aggregates (hexamers) that cannot pass directly into the bloodstream. Observed delays in subcutaneous insulin absorption are attributed to the time it takes for insulin hexamers to dissolve, followed by diffusion-driven absorption. The rapid absorption with minimal delay times that is needed for optimal insulin delivery requires administration of highly concentrated insulin in monomeric form. Unfortunately, current commercial

insulin preparations tend to multimerize and irreversibly aggregate at such high concentrations. New insulin formulations are needed.

- ▶ **Develop a family of non-toxic, non-antigenic, low molecular weight molecules that effectively and specifically bind glucose in the presence of serum components and across the physiological range of glucose concentrations, from hypoglycemic to hyperglycemic levels.**

Many novel glucose-responsive biomaterials and insulins function by competitively binding glucose molecules in the body, similarly to naturally occurring sugar-binding proteins called lectins. Early attempts at implementing safe lectin-like molecules for use in these systems have involved synthetic and chemically-engineered lectins, molecularly imprinted polymers, recombinant human proteins, and polynucleotide/peptide-based aptamers. Optimal materials need to be minimally cross-reactive with non-glucose molecules, responsive in the physiological range, and capable of being manufactured cost effectively in large quantities.

## **Telemedicine**

The widespread adoption in everyday life of information and communication technology—e.g., the Internet, mobile phones, and personal digital assistants (PDAs)—is providing an excellent opportunity to improve the delivery of diabetes care and lower treatment costs by improving communication between patients, health care providers, and health care systems. This effort has been aimed at supporting the management of diabetes, mainly via electronic patient records, decision support systems, and telemedicine. Telemedicine is defined as the use of telecommunications to support health care. It includes timely transmission and remote interpretation of patient data for follow-up and preventive interventions

over the Internet. Data are uploaded and instructions are downloaded by way of wireless or hardwired communication tools. Telemedicine has been demonstrated to be: 1) sound, in terms of accurately transmitting and processing data; 2) possibly effective, in terms of improved HbA1c levels; and 3) somewhat practical, in terms of being designated as legal, being considered as standard of care (rather than malpractice), and being reimbursed in fee-for-service but not capitated practice settings. Challenges to the practicality of telemedicine include concerns about the privacy and security of data that is housed on a Web site and linked to an electronic medical record with many portals where potentially illicit downloading can occur. Currently, little research is available as to the economic impact and longer-term benefit of telemedicine practices. Many outcome studies of telemedicine to date have significant limitations, including small sample size, lack of controls, or a lack of demonstration of long-term benefit. Carefully designed, robust studies of telemedicine are needed, as well as long-term studies to see whether potential benefits persist over time. Future research in information and communication technology for diabetes should concentrate on providing new sophisticated technological tools and instruments to increase the quality of telemedicine solutions, and, at the same time, properly modify the health care delivery process to more effectively exploit the opportunities provided by novel telecommunication systems.

### Key Questions

- **What are the best technological solutions (both hardware and decision-support software) to best enable telemedicine to be easily and effectively applied in clinical practice?**
- **What types of behavioral modification tools or incentives can be developed to facilitate communication and adherence to telemedicine-generated instructions?**
- **Can high blood glucose or low blood glucose alerts be sent automatically from a glucose meter to a health care provider by way of a Web server to elicit an immediate assistance response that could reduce emergency room visits?**
- **Can PDA applications (“apps”) for diabetes management, which track blood glucose, food intake, insulin, and exercise, improve outcomes?**
- **How can telemedicine platforms be integrated into an automated closed-loop system?**

### Future Directions

- **Develop telemedicine approaches that can be incorporated as components and/or adjuvants of an artificial pancreas.**

To accomplish this goal, a software developer should be designated specifically to work hand-in-hand with investigators. Telemedicine components could potentially provide two-way communication by the phone or Internet, algorithms to provide advice on diabetes management decisions, accelerometers to track physical activity that could be used in diabetes management decisions, and global positioning system (GPS) technology so that a person could be located if he or she needed assistance. These platforms could form the basis for a more effective and user-friendly artificial pancreas. If standards were established for meter, sensor, and

pump communications, it would allow consumers to choose the combination of sensor, meter, and pump that best fits their needs.

- **Determine whether online peer-to-peer management can improve diabetes outcomes.**

The value of online group “chat rooms,” mandatory interactions, and text messaging by patient leaders who have been successful in their diabetes management should be tested and evaluated as part of a telemedicine instrument to improve the management of diabetes. A “chat” with a mental health specialist could also be included at regular intervals; the benefits of such an addition should be evaluated as well. Adolescents, who are often the hardest age group in which to achieve good glucose results, are heavy users of social networking and text-paging. As peer support is important to adolescents, the use of these services may be extremely beneficial in this age group.

## Tissue Engineering for Replacement of Pancreatic Islets

The prospect of replacing the beta cell deficit of both type 1 and type 2 diabetes with islet transplantation or beta cell regeneration has been a research focus for several decades. An important proof-of-principle has been established in humans receiving both pancreas and islet transplants. Normal control of blood glucose levels has been restored, but at the expense of the requirement for immunosuppressive therapy. Moreover, glucose control with islet transplants is usually lost within a few years due to loss of beta cells from immune injury and inadequate vascular perfusion. Tissue engineering approaches may help to overcome some of these challenges.

## Key Questions

- **Will the development of novel biomaterials contribute to more effective immunobarrier/encapsulation methods to establish and maintain a functional bioartificial pancreas using transplanted islets from different sources?**
- **What methods can be developed for effective vascularization of islets after implantation?**

## Future Directions

- **Improve perfusion of islet cells within a graft site.**

Because beta cells are metabolically very active, one of the key factors affecting long-term maintenance of insulin production from transplanted islets will likely be the establishment of an adequate blood vessel network to assure sufficient oxygenation and supply of nutrients to the cells. It would be ideal to find ways to restore vascularization in grafts to the same rich pattern of vessels found in islets within the pancreas. Work with tissue engineering and bioscaffolds holds promise in this area.

- **Develop new biomaterials and immunobarrier protection for transplanted islets.**

The concept of protecting transplanted islets from immune destruction with a barrier is more than 30 years old, but has proven challenging in practice. Biomaterials that have been used for these barriers include: alginate, agarose, polyethylene glycol (PEG), polytetrafluoroethene (PTFE), chitosan, and others.

Configurations have included planar devices, hollow tubes, conformal coatings of islets, micro-gel beads, macrobeads, and gel slabs. While results obtained in rodents have been impressive, success has been limited in large animals and humans. Thus, work needs to be done to develop better biomaterials for this purpose. Some development and implantation options include islets in microcapsules (or more complex devices) placed in the abdominal cavity, and microcapsules or planar devices inserted in a subcutaneous site. For planar devices, challenges include the packing density of the islet cells, which must be optimized so that the surface area of the device is small enough for surgical implantation. Finding ways to optimize oxygen delivery to islets will also be important. Moreover, it is not clear how much selective permeability will be required to limit immune responses. Materials for sustained localized delivery of immunosuppressants to minimize risk of systemic effects while maximizing the potential to eliminate rejection should be developed. Another avenue is to optimize distribution and function of islet cell clusters by using matrices and other three-dimensional approaches made possible with bioengineering advances.

➤ **Pursue approaches to scale up and commercialize production.**

The success of these approaches will ultimately depend on a close interaction between the applied sciences and industry. Once technical obstacles have been adequately addressed, commercialization of this type of therapy will likely be more difficult than previous therapies. New and more thoughtful approaches to technology translation may be needed.

## Impact of Closed-Loop Control on the Pathophysiology of Diabetes

Building on evidence that continuous glucose monitoring devices can be used successfully in the outpatient setting, research can now advance further toward the development of a mechanical artificial pancreas that can close the loop between glucose sensing/monitoring and insulin delivery. As this closed-loop research moves forward, studies need to be pursued not only on the efficacy of individual device technologies to control glucose levels, but also on how these technologies affect the overall pathophysiology of diabetes. For example, investigators have long pondered the importance of delivering insulin directly to the liver (a major target organ for insulin action) via the portal vein, instead of systemically, when considering open-loop and closed-loop control protocols. This more physiological route of delivery may help people with diabetes achieve blood glucose control without chronic systemic elevation of insulin levels (hyperinsulinemia) and its side effects, but there is currently insufficient long-term evidence demonstrating this potential benefit. It is anticipated that the institution of closed-loop control in type 1 diabetes would reverse hypoglycemia unawareness and prevent brain injury in young children, but there is currently insufficient long-term evidence demonstrating this as well. Another major challenge for closed-loop control is how to predict the insulin infusion rates necessary to normalize glycemia as rapidly as possible without producing hypoglycemia; new approaches are needed. Moreover, there is speculation that use of a closed-loop artificial pancreas would more effectively

preserve beta cell function in people with new-onset type 1 diabetes, thereby reducing daily insulin dose requirements and potentially restoring glucagon responses to hypoglycemia—a win/win combination. Studies testing this hypothesis could lead to changes in type 1 diabetes care at disease onset.

## Key Questions

- **Can an artificial mechanical pancreas or islet replacement restore glucose counter-regulation and hypoglycemia awareness and preserve brain function in people with type 1 diabetes, especially young children?**
- **Can early intensive insulin therapy increase beta cell survival and prevent the loss of the glucagon response to hypoglycemia in people with new-onset of type 1 diabetes?**
- **What are the short- and long-term consequences of the route of delivery of insulin on glycemic outcome, vascular complications, and body weight?**
- **Is glucose the only target that should be used in developing closed-loop systems? Should additional compounds be measured online, e.g., insulin, glucagon, other metabolites?**
- **Are the differences between systemic and portal administration significant enough to favor technologies (mechanical or cellular) that deliver insulin to the liver—its primary site of action?**
- **Can incorporation of automated glucagon delivery increase defenses against hypoglycemia without excessively raising blood glucose?**

## Future Directions

- **Determine the impact of an artificial mechanical pancreas on brain function, fuel metabolism, and structure, especially in children.**

The development of improved imaging methods to examine brain structure, function, connectivity, and fuel metabolism has opened the door to studies that can elucidate the effect(s) of treatment with an artificial mechanical and/or islet replacement therapy on brain function in people with diabetes. This is particularly important in young children who are more vulnerable to brain injury and cognitive deficits caused by severe hypoglycemia.

- **Determine if a closed-loop system artificial mechanical pancreas is sufficient to restore normal glucose counter-regulation and reverse hypoglycemia unawareness.**

Individuals currently receiving intensive insulin therapy and/or with long-standing type 1 diabetes lose their ability to activate hormonal defenses against hypoglycemia and to develop symptoms that tell them to take corrective action, namely, to eat. It is believed that a major clinical indication for closed-loop glucose control would be for treatment of these patients; however, studies are needed to see if closed-loop glucose control is sufficient or might be further enhanced by drugs shown to improve hypoglycemia defense mechanisms in animal models of diabetes.

- **Determine whether an artificial mechanical pancreas (or implanted engineered islets) can preserve beta cells and maintain alpha cell**

**responses to hypoglycemia in type 1 diabetes if given early, when some insulin secretion is still present.**

Multi-center clinical trials should be pursued to determine if closed-loop glucose control is able to preserve beta cell insulin secretion, insulin sensitivity, and glucagon release by alpha cells in people with recent onset of type 1 diabetes. However, this key outcome is likely to require additional medical therapy. Thus, drug interventions should be pursued in diabetic animal models aimed at promoting beta cell regeneration and the restoration of the glucagon response to hypoglycemia. One challenge that limits such studies is the current lack of methods to accurately assess beta cell mass in humans.

- **Determine whether insulin delivery via the portal vein will be more effective in achieving normoglycemia by reducing insulin resistance and enhancing portal sensing of glucose and gut peptides.**

There is increasing evidence that the portal circulation is a sensory locus in which portal glucose, and potentially portal GLP-1 and other gut peptides, may be detected. Thus, portal administration could in principle be advantageous in achieving long-term metabolic control, but there is currently insufficient evidence to show this. Long-term studies in large animals are needed in which insulin is delivered either intraportally or systemically using closed-loop control, which will mismatch systemic insulin levels. The impact of higher blood insulin levels produced by peripheral versus portal insulin delivery on insulin sensitivity, free fatty acid levels, gut hormones, and on body weight regulation will provide important information on the preferred route of insulin administration. This will be best accomplished in large experimental animal models of diabetes. Such

data are important in the cost/benefit analysis regarding mechanical insulin infusion systems which allow for peripheral delivery versus cellular-based systems which will allow for portal delivery.

- **Develop methods to measure insulin levels in real time, to provide input to closed-loop feedback algorithms.**

Many private sector companies have developed micro methods for the measurements of metabolites and proteins (i.e., metabolomics and proteomics). These approaches have allowed for the measurement of many compounds in very small amounts of sample. It will be valuable to exploit these methods, which in many cases have been automated, to develop an online approach, which can provide additional information (e.g., plasma insulin) to the feedback algorithm so that it can then make more intelligent decisions regarding exogenous insulin infusion, and moment-to-moment estimations of *in vivo* insulin sensitivity. Collaborations should be developed between groups designing closed-loop artificial pancreas devices and experts in measuring proteins and metabolites from small samples in real time.

## Behavioral Aspects

The public health benefits of bioengineering advances in health care are realized not only through development of accurate and clinically effective therapeutic technologies, but ultimately through the use of these devices by people with diabetes and their health care providers to improve health outcomes and quality of life. The full benefits of self-monitoring of blood glucose, and continuous glucose monitoring, in particular, have not been realized due to a need for improved individual, family, and provider awareness and skill in effective utilization of the information and data yielded. It is

essential for new technologies not only to incorporate a broad array of patient behavior dynamics and cognitive and psychological limitations in their design, but also to account for the impact of new technologies on an individual's personal and social relationships, which, in turn, could affect his or her diabetes management. People with diabetes and their families are more likely to adopt innovations if they reduce disease burden, lead to better health outcomes, and improve quality of life.

### Key Questions

- **What are the challenges and benefits of new diabetes technologies for individuals with the disease, including physical (e.g., complexity of use, ease of availability), behavioral (e.g., cognitive load, adherence, time requirements), psychological (e.g., quality of life, fear of hypoglycemia), and social (vocational and family functioning) impacts?**
- **What factors contraindicate the use of specific diabetes technologies for individuals with diabetes (e.g., age, knowledge, psychological status, cognitive development, functional status, treatment regimen, type and stage of diabetes, and home environment and disease management support)? How can accessibility and usability be increased across populations?**
- **How can these technologies be more accessible to people from different backgrounds and those with educational, sensory, motor, and cognitive limitations? Has the human/technology interface been designed to be easy to use for people with limited literacy and numeracy skills?**

- **What are the most effective ways for health care providers to incorporate new technologies and the data they produce into practice?**

### Future Directions

- **Quantify the broad-ranging impact of new diabetes technologies on people with diabetes.**

Research needs to be pursued to account for impact of new technologies across multiple indices, such as behavioral, psychological, and social. For example, studies should be performed to assess how technologies affect the ability to carry out daily life activities including work, leisure, and self-care as normally as possible (functional outcomes). Investigators also need to determine how technologies can reduce the extent to which diabetes treatment and management interfere with a person's life tasks, and whether technologies can positively affect a person's mood and emotions. Data need to be obtained on how convenient it is for people with diabetes to fit a technology into daily life, and to enhance the range of options to fit individual needs and preferences. The impact of technologies on family and social outcomes (e.g., can use of diabetes technologies help relationships within a family and with friends, reduce family conflict, improve communication, and help build positive social support) should also be evaluated without the need for adaptation or specialized design at the user end.

- **Increase accessibility and usability of technologies by people with diabetes-related (and non-diabetes-related) functional impairments and disabilities.**

Research to address this issue should take into account visual impairment/blindness, fine motor skill

impairment, mild cognitive impairment, and other motor/mobility deficits.

➤ **Increase adoption and effective use of technologies across the lifespan.**

Strategies are needed for bringing technologies that improve diabetes care into wider use. This can be enhanced by industry application of universal design principles to technology development. Studies will be needed to optimize patient, parent/caregiver, provider, and community-based education and training, including implementation of multi-modal training, use of educational guidelines in development of instructions and other educational materials for therapeutic devices, and testing of instruction for literacy and numeracy demands. An important aspect of future studies will be increasing the emphasis on understanding the benefits and limitations of the different technologies/therapeutic advances as applied to biological, psychological (cognitive and emotional), and interpersonal outcomes. Data will also be needed on how to best provide training for use of information gained from technologies in order to take action for self-management (e.g., problem-solving training for what to do with self-monitoring data). Finally, research should be pursued on tailoring of technologies for diabetes care across the lifespan.

➤ **Increase employment of generic new technologies to promote positive health behavior change in people with diabetes.**

Studies should be conducted on ways to capitalize on existing and general use technologies, such as smart phones and the Internet, in delivering primary psycho-behavioral interventions that can be used to initiate, prompt, track, and summarize behavior, and evaluate behavior change efforts in a larger population than

previously accessible (see the “Telemedicine” topic in this chapter).

➤ **Develop more effective information and educational and training methods for health care providers in use of diabetes technological advancements.**

Studies should test best practices to increase caregiver awareness, correct execution, and consistent employment of different diabetes technologies that can improve health outcomes.

## Design of Clinical Trials and Clinical Outcomes

Planning for the design of clinical trials and framing of appropriate clinical outcomes needs to take into account currently available technologies (CGMs) and also anticipate the development of artificial mechanical pancreas technologies. Building on recent developments, scientists are poised to answer important clinical questions about the added value of CGMs in managing people who have type 2 diabetes, in whom much less is known, as well as important questions about the impact of glycemic variability—both low and high glucose—and not simply average glucose levels on the development or progression of diabetes complications. In the case of artificial pancreas technologies, once available, such devices will initially target a population with the greatest need and the potential for maximum benefit (e.g., people with brittle type 1 diabetes, those experiencing frequent hypoglycemic episodes or diabetic ketoacidosis, or those with hypoglycemia unawareness), and then lead to expanded testing in other populations, based upon the initial experiences. Other important aspects to take into consideration for clinical study design include enrollment criteria (such as degree of



metabolic instability, age, presence of complications), study settings (highly controlled clinical environments or the less-controlled home setting), how to define hypoglycemia (severe clinical events, or time spent with blood glucose concentrations at less than 70 or less than 60 mg/dl on CGM) and glycemic variability, the relevant clinical end points (e.g., control of glucose levels, reduction in hypoglycemic episodes), and approaches to evaluating outcomes with different devices and systems.

## Key Questions

- **What are appropriate outcome measures (e.g., HbA1c, reduction in hypoglycemia, reduction in glycemic variability) for clinical trials of artificial mechanical pancreas technologies in people with type 1 or type 2 diabetes?**
- **Can CGM or an artificial mechanical pancreas be used successfully in insulin-requiring patients with type 2 diabetes to maintain HbA1c targets with less hypoglycemia?**
- **Can reduction of glycemic variability in people with type 2 diabetes who are insulin-dependent lead to improved outcomes, such as reduced diabetic nephropathy, reduction in cardiac arrhythmias in people at high risk for cardiac mortality, and/or reduction of systemic inflammation and oxidative stress?**
- **What is the value of CGM and/or closed-loop insulin delivery devices in the intensive care unit?**
- **Can an artificial mechanical pancreas prevent hypoglycemia and/or diabetic micro- and macrovascular complications?**
- **Should the measurement of vital signs such**

**as heart rate, temperature, and breathing rate be monitored together with glucose monitoring in clinical studies to prevent hypoglycemia and excessive glycemic postprandial excursions?**

## Future Directions

- **Study the impact of closed-loop glucose control on exercise and nocturnal hypoglycemia.**

Initial closed-loop studies should be aimed at preventing hypoglycemia during sleep by using the system to temporarily stop insulin delivery when hypoglycemia is projected. In addition, clinical trials are needed to test algorithms for closed-loop glucose control during exercise and to prevent hypoglycemia, which may occur many hours after a bout of exercise. Improved algorithms are also needed to optimize food intake and insulin delivery during and after exercise based on sensor and perhaps accelerometer or heart rate data. This would be a safe initial use of closed-loop technology.

- **Determine the efficacy of CGMs and eventually of closed-loop glucose control to improve disordered fuel metabolism and reduce hypoglycemia and diabetic complications in people with type 2 diabetes who require insulin treatment.**

There has been very little experience in the use of CGMs and no experience using closed-loop technology in people with type 2 diabetes. Continuous glucose monitoring will provide, for the first time, the opportunity to measure glycemic variability and undetected hypoglycemic events during insulin treatment in people with type 2 diabetes, and the potential impact of these factors on cardiac arrhythmias that could potentially be fatal. Studies of the potential clinical value of closed-

loop glucose control in type 2 diabetes will need to take into account its impact on surrogate markers of cardiovascular disease, such as lipid metabolism and blood pressure, as well as cognitive function in this older population.

- **Determine whether closed-loop glucose control can preserve beta cell function in people with new-onset type 1 diabetes or with type 2 diabetes.**

At the time of onset of type 1 diabetes, the destruction of beta cells is incomplete, while in type 2 diabetes, progression of disease is largely influenced by the loss of beta cell function and mass over time. Controlled trials using closed-loop glucose control offer the potential to see if near normalization of glucose levels can protect islets from injury caused by high glucose levels and slow disease progression.

- **Conduct long-term studies of closed-loop glucose control in children and adolescents.**

Young children with type 1 diabetes are particularly susceptible to permanent neurologic damage as a result of severe hypoglycemic events. To minimize this possibility, glucose targets are set higher for children than adults. Unfortunately, elevations of glucose levels also appear to damage brain white and grey matter, which can impair memory and learning as well. The potential of closed-loop systems to reduce brain injury in young children with type 1 diabetes will need to be tested in long-term clinical trials.

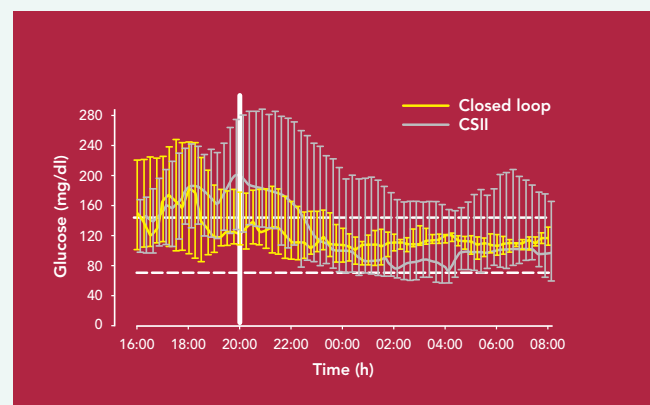
- **Study use of continuous glucose monitoring and closed-loop insulin delivery systems in people with gastroparesis.**

People with diabetes who experience slow emptying of food from the stomach caused by nerve damage from

diabetic hyperglycemia have great difficulty controlling glucose levels because meal absorption is very variable. Continuous glucose monitoring, and particularly closed-loop glucose control, may be extremely beneficial in the management of individuals with gastroparesis, and could be used to modify insulin delivery to prevent early hypoglycemia following a meal and delayed hyperglycemia.

- **Study use of closed-loop technologies in the intensive care unit (ICU).**

The ICU is perhaps well-suited for initial closed-loop studies, as there is constant supervision. The development of accurate intravascular glucose sensors with rapid response times would be ideal for closed-loop management in the ICU because insulin is given intravenously, so there is little delay in the onset of insulin action, which is ideal for closed-loop control.



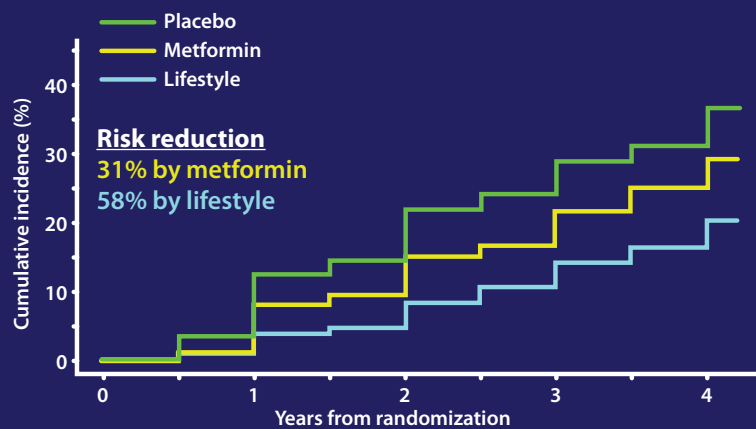
Plasma glucose concentration during closed-loop insulin delivery and conventional pump therapy (continuous subcutaneous insulin infusion, CSII) in children and adolescents with type 1 diabetes (closed-loop starts at 20:00 on the x-axis). The plot figure shows that closed loop may increase time spent in target glucose levels range (between dashed lines), reducing extreme hypoglycemia/hyperglycemia fluctuations and time spent in hypoglycemia. (Reprinted from *The Lancet*, 375, Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, Kollman C, Hovorka T, Larsen AM, Nodale M, De PA, Wilinska ME, Acerini CL, and Dunger DB, *Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial*, 743-751, Copyright (2010), with permission from Elsevier.)

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

During the past three decades, a variety of technological advances have been introduced that have significantly improved the ability of people with diabetes and their physicians to treat diabetes with insulin, including home glucose monitoring devices that allow periodic measurements of blood levels; improved insulin formulations; portable insulin pumps that provide continuous insulin delivery in a more controlled manner; and, most recently, early-phase CGMs that rely on inserting glucose sensors under the skin. These advances, however, have only partially diminished wide swings in glucose levels that can harm the health of people with diabetes, from the severe falls in blood glucose that may cause unconsciousness and brain injury, to the high glucose levels that may lead to chronic complications such as kidney failure, blindness, nerve damage, amputations, and cardiovascular disease.

Moreover, the burden of care on people with diabetes and their families has been increased in many cases. The research directions outlined in this chapter will help guide the development of new technologies and studies in animals and humans with diabetes that can drive us toward the next step: an automated insulin delivery system using more rapidly acting insulin preparations, and driven by computer algorithms derived from continuous glucose measurements obtained with the use of more rapidly responsive and accurate glucose sensors. A system like this may also be remotely assessed/monitored and even adjusted through a telemedicine platform. Artificial pancreas technology is at a very early stage of development and will require a step-wise approach and new interdisciplinary scientific partnerships between bioengineers and basic and clinical scientists for its future success.

## Incidence of Diabetes



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

# CLINICAL RESEARCH AND CLINICAL TRIALS

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## INTRODUCTION

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

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

by treatments that modulate the immune system and reduce inflammation.

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

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

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

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

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

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

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

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



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

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

## RECENT RESEARCH ADVANCES

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

### **Type 2 Diabetes Can Be Prevented or Delayed:**

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

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



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

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

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

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

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

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

development of non-surgical treatments that achieve similar results.

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

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

### **Intensive Blood Glucose Control and Cardiovascular Complications of Diabetes:**

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



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

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

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

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

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

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



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

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

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

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

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

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

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

### Preventing Type 2 Diabetes

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

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

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

### Key Questions

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

### Future Directions

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

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

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

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

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

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

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

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

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

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

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

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

## Treatment

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

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

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

## Key Questions

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

## Future Directions

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

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

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

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



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

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

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

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

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

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

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

► **Identify biomarkers.**

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

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

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

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

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

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

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

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

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

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

## **Etiology of Diabetes and Its Complications**

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

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

## Key Questions

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

## Future Directions

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

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

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

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

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

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

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

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

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

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

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

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

## Complications

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

### Key Questions

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

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

### Future Directions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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







Diabetes affects women, men, and children of all ages, races, and ethnic groups. For some, susceptibility to diabetes may have begun in the womb, while others may develop diabetes as a result of another disease or condition. Prevention and treatment strategies need to take into account the diverse needs of people with or at risk for diabetes. *(Photo credits: Top row, left image: ©iStockphoto.com/Yuri\_Arcurs. Top row, middle image: Ian Hooton / Photo Researchers, Inc. Bottom row, left image: ©iStockphoto.com/monkeybusinessimages. Bottom row, middle image: ©Suprijono Suharjoto | Dreamstime.com)*

# SPECIAL NEEDS FOR SPECIAL POPULATIONS

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## INTRODUCTION

There is no age, ethnic, or racial group free from diabetes and its serious health complications. However, the impact of diabetes on minority groups in the United States and on children and older adults, pregnant women, and people already battling other serious diseases and conditions presents special challenges that need to be addressed by research.

Of the approximately 24 million Americans with type 2 diabetes, a disproportionate number come from racial and ethnic minorities in the U.S. population. For example, after adjusting for population age differences, 2007 to 2009 national survey data for people ages 20 years or older indicate that 7.1 percent of non-Hispanic whites, 8.4 percent of Asian Americans, 11.8 percent of Hispanics, and 12.6 percent of non-Hispanic blacks had diagnosed diabetes (primarily type 2 diabetes) (1). About 16.1 percent of the adult population served by the Indian Health Service has diagnosed diabetes (1). Prevalence is also higher in Native Hawaiians and other Pacific Islanders. This profile is also reflected in the over 79 million Americans at risk for the disease: A disproportionate number of people with pre-diabetes are from racial and ethnic minority groups—including the increasing number of children at risk for type 2 diabetes. Gestational diabetes—a form of glucose intolerance that is detected during pregnancy—places women at greatly increased risk of progressing to diabetes in the 10 to 20 years after pregnancy; this condition occurs more frequently among African American, Hispanic/Latino American, and American Indian women (1). Disparities also exist in the health complications of diabetes, with, for example, greater renal failure, cardiovascular disease, and retinopathy rates in minority populations.

Distinct issues are also associated with diabetes at different times throughout the lifespan, from the intrauterine environment, through childhood, pregnancy, and older age. For example, maternal metabolic health and its effect on the developing fetus have been drawn into sharp focus by the epidemic levels of diabetes and obesity in the United States. Not only are at least 7 percent and possibly as many as 18 percent of pregnancies in the United States affected by gestational diabetes (1,6), but an increasing number of women may already have diabetes before they become pregnant. In addition to the immediate risks to the mother's health, diabetes during pregnancy places offspring at increased risk to be large for gestational age and to have birth defects. The last decade has also been marked by a new appreciation of how maternal diabetes and obesity during pregnancy exert long-term effects on the risk of these conditions and other metabolic problems in offspring. Breaking this cycle will be important to reduce the future burden of diabetes.

Diabetes also poses special challenges for children and their families. Current therapy to prevent complications of diabetes requires keeping glucose levels as near the normal range as possible while avoiding unacceptable episodes of hypoglycemia. Diabetes management requires meticulous attention to balancing food intake, medication administration and dosing, and physical activity, while monitoring glycemia. For young children, diabetes management must be done by adults—parents, other family members, and child care and school personnel—who are trained and motivated to optimize their diabetes care. As children with diabetes grow older, they need to acquire the

knowledge, skills, and attitude towards self-care that will help them successfully transition to adulthood with the best possible short- and long-term health outcomes. Children with type 1 diabetes, some with type 2, and those with certain forms of secondary diabetes (see below) are at risk to develop diabetic ketoacidosis (DKA), a life-threatening condition. A complication of DKA unique during childhood, cerebral edema, can lead to devastating complications resulting in morbidity and death, and can incur high costs to the medical system. DKA is especially frightening for families because it can develop rapidly and be the presenting sign of diabetes. The rates of DKA at the time of diagnosis and during the course of the disease remain unacceptably high in the United States.



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Research is needed to help improve diabetes self-care strategies in youth and in the transition to adulthood. (Photo credit: © iStockphoto.com/MarkHatfield)

Older Americans face a different set of challenges with diabetes and its effective management. The risk of developing type 2 diabetes increases significantly with age; moreover, advances in biomedical research have enabled more people diagnosed with type 1 diabetes in youth to live longer and reach older age. Now, among people 65 years and older, the prevalence of diabetes is 26.9 percent—nearly twice the prevalence of diabetes in middle age (1). Diabetes also disproportionately

affects older adults from minority groups. With increasing age, people with diabetes are more likely to have cardiovascular disease in addition to other health problems and are likely to be taking multiple medications (polypharmacy), increasing their chances for adverse drug reactions. Many complications of diabetes lead to physical inactivity and are associated with a higher prevalence of geriatric syndromes and functional decline. Geriatric syndromes such as injurious falls, frailty, depression, cognitive impairment, urinary incontinence, and polypharmacy are all more common among older adults with diabetes, increasing the burden of care for these individuals.

Diabetes also poses special challenges for people with major mental disorders. It has been estimated that depressed individuals are 60 percent more likely than non-depressed individuals to develop type 2 diabetes (14), and those with schizophrenia and bipolar disorder have similar or even higher risk. Increased risk is most likely mediated primarily by increased rates of obesity, smoking, and inactivity in these populations, as well as limitations in quality and access to general medical care. Certain drugs used to treat mental illnesses also appear to increase type 2 diabetes risk, in part by causing weight gain. Conversely, among individuals who already have type 2 diabetes—especially those suffering from diabetes complications—rates of depression are higher than they are in the general population (14,15). Depression and even subclinical depressive symptoms are associated with less participation in diabetes self-care, and higher blood glucose levels, complication rates, and mortality rates.

Finally, an ever-increasing number of people have secondary diabetes—diabetes that develops as a result of another disease or disease treatment. Diabetes is the most common comorbidity in people with cystic fibrosis

(CF), with CF-related diabetes present in 2 percent of children, 19 percent of adolescents, and 40 to 50 percent of adults with CF (16). Both the fibrotic destruction of the pancreatic islets and, possibly, insulin resistance induced by repeated inflammation and infection play a role in the development of abnormal glucose tolerance and diabetes in people with CF. The additional diagnosis of diabetes or pre-diabetes in people with CF is associated with lung function decline, underweight, and significantly greater mortality. In other people, drugs used to treat an illness can trigger diabetes. People who are HIV-infected, for example, are at increased

risk of developing diabetes when taking antiretroviral drugs. This increase has been associated with increased cardiovascular disease rates. HIV disease remains a major issue in the United States, where over 1 million people are infected, as well as in the underdeveloped world, with total estimates of about 33 million living with HIV/AIDS worldwide (17). Organ transplantation also raises risk for the development of diabetes in organ recipients, with perhaps as many as half of transplant recipients developing impaired glucose tolerance or diabetes as a side effect of the treatments used to prevent organ rejection—which, in turn, significantly increases the risk of transplanted organ failure and death. In all these cases, developing diabetes secondary to an already challenging disease or condition creates a new burden of care, complicates treatment, and may increase mortality.



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One question about treatment of diabetes in older adults relates to optimizing care when diabetes is one of many medical conditions. (Photo credit: © iStockphoto.com/dscz)

## RECENT RESEARCH ADVANCES

In just the past decade, researchers have made great strides in understanding the complex nature of diabetes and its effects on specific populations, including racial and ethnic minorities, women, children, older adults, people affected by psychological problems, and those with diabetes secondary to another condition. The following are some major examples of this research.

### **Type 2 Diabetes Can Be Effectively Delayed or Prevented in Diverse Populations and Across the Age Spectrum in Adults:**

Once established, type 2 diabetes currently has no cure, which makes primary prevention a compelling priority. The Diabetes Prevention Program (DPP), a randomized, controlled clinical trial, examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk for this disease. The DPP compared intensive lifestyle modification, treatment with the medication metformin, and standard medical advice (control). Of the over 3,200 participants, 45 percent were from minority groups—African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, or Pacific Islander—at increased risk of developing diabetes, and 20 percent were over the age of 60 years. Lifestyle intervention, leading to moderate weight loss through diet changes and increased physical activity levels, reduced diabetes incidence by 58 percent and treatment with metformin decreased the incidence by 31 percent, compared with placebo. The effects were similar for men and women—including women with a history of gestational diabetes—and for all ethnic and racial groups. Lifestyle changes worked particularly well for participants aged 60 and older, reducing their risk by 71 percent. Equally remarkable was the

associated finding that the same lifestyle modification was associated with reversion from pre-diabetes to normal glucose tolerance in about 36 percent of participants. Other studies have shown that type 2 diabetes can also be prevented or postponed by treatment with the medications acarbose, rosiglitazone, and pioglitazone.



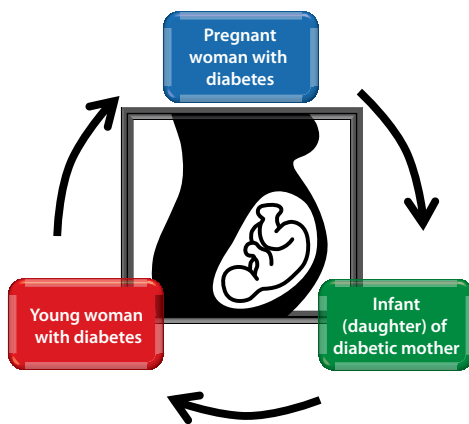
Racial and ethnic minority populations in the United States are disproportionately affected by diabetes and its complications. Research that can address these disparities is important to improving people's health and reducing the national burden of diabetes. *(Photo credit: Indian Health Service, Division of Diabetes Treatment and Prevention.)*

### **Diagnosis and Management of Gestational**

**Diabetes:** The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study confirmed a linear relationship between maternal glucose levels during pregnancy and risk of perinatal morbidities, such as neonatal hyperinsulinemia and high birth weight, even at glucose levels significantly lower than those considered to be consistent with diabetes. As a result, the diagnostic criteria for gestational diabetes may be changed to include more women with glucose-associated perinatal risk (1,6). Separately, two oral antidiabetic agents, glyburide and metformin, have been shown to achieve acceptable glycemic control and perinatal outcomes

when used to treat gestational diabetes. The long-term effects of these drugs—which cross the placenta in varying degrees and do appear in the breast milk—remain unknown. Together, these advances provide the potential to revolutionize the diagnosis and management of gestational diabetes.

**Long-Term Impact of Maternal Diabetes and Obesity on Offspring:** Recent research has extended the finding, observed earlier among the Pima Indians in the Southwest, that a mother’s diabetes and obesity can have long-lasting effects on her offspring’s risk for these conditions. The SEARCH for Diabetes in Youth (SEARCH) Case-Control study found that, in a multi-ethnic cohort of youth, youth with type 2 diabetes were much more likely to have been exposed to diabetes or obesity while *in utero* than non-diabetic youth. These results indicate a universal effect of intrauterine exposure that operates, in addition to factors such as genetics and race/ethnicity, to increase lifetime risk for developing type 2 diabetes. As there are an increasing number of people developing diabetes and obesity at younger ages, it will be important to try and break this vicious cycle by preventing or mitigating the effects of diabetes and obesity during child-bearing years and pregnancy.



Diabetes in pregnancy can lead to a cycle of diabetes affecting future generations.

**Diabetes Burden in Children and Youth:** The first population-based study to assess the burden of diabetes in youth of all major racial and ethnic groups in the United States, the SEARCH study, has found that about 1 out of every 523 persons under 20 years of age has diabetes. Annually, approximately 15,000 children and adolescents are diagnosed with type 1 diabetes, and about 3,700 are diagnosed with type 2 diabetes. Type 2 diabetes is still rare in children under 10 years, but the diagnosis increases with age, especially in minority youth. In older adolescents (15 to 19 years), type 2 diabetes occurs more frequently than type 1 diabetes in Hispanic, African American, Asian/Pacific Islander, and American Indian youth. SEARCH found a higher estimate of type 1 diabetes incidence than previous reports, suggesting that type 1 diabetes may be on the rise. Information on the rates of diabetes in children and youth is crucial to design and implement prevention strategies and to find ways to reduce risk of diabetes complications in this population.

**Intensive Diabetes Treatment for Older Adults:** In three recent large clinical trials, stringent glycemic control did not demonstrate cardiovascular benefit for middle-aged and older adults with well-established type 2 diabetes who were at high risk for cardiovascular complications and who were also receiving good control of lipids and blood pressure. One of the studies suggested that intensive glucose therapy to near-normal levels is associated with higher mortality. This important finding from the ACCORD study highlights the need to identify the optimal glycemic targets in the context of prioritizing control of other critically important risk factors, such as blood pressure and cholesterol levels, among older adults. This group will soon constitute the majority of persons with type 2 diabetes. Also, the intensive lifestyle modification proven highly effective at preventing or delaying the



onset of type 2 diabetes among older adults has also been shown to reduce cardiovascular risk factors among older adults with type 2 diabetes. These important findings indicate that, to stem the epidemic of type 2 diabetes and associated cardiovascular disease, it will be critical to develop, evaluate, and disseminate the most cost effective strategies to support lifestyle modification in this special population.

### **Increased Rates of Type 2 Diabetes and Modifiable Cardiovascular Risk Factors in People With Mental Disorders:**

Recent studies have found increased rates of diabetes and significant reductions in life expectancy, primarily due to premature coronary heart disease, in large population-based samples of persons diagnosed with major mental disorders. Recent evidence indicates high prevalence of all key modifiable risk factors in the mentally ill population, including obesity, hyperglycemia, dyslipidemia, hypertension, and smoking, along with low levels of screening and treatment interventions. These findings are important for understanding the burden of diabetes in this population.

### **Psychotropic Medication As a Risk Factor for Type 2 Diabetes:**

Some psychiatric medications, especially antipsychotic agents associated with substantial weight gain risk, can significantly increase risk for obesity, diabetes, and dyslipidemia, with a growing literature quantifying these effects for individual medications. Treatment strategies to avoid these effects are a topic of active study. In addition, individuals with pre-diabetes in the control and intensive lifestyle arms of the DPP who were taking antidepressant medication were 2 to 3 times more likely than those not taking antidepressants to develop diabetes during the study. Recent analyses from the United Kingdom General Practice Research

Database similarly suggested that some, but not all, antidepressant medications, when taken at moderate to higher doses for prolonged periods, can increase risk for incident diabetes.

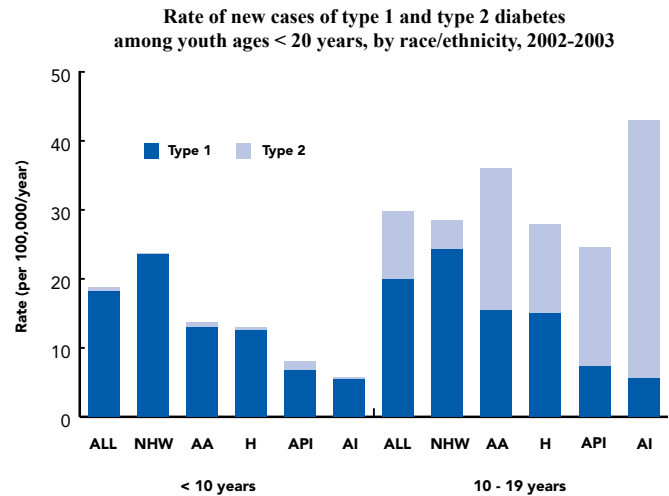
### **Effects of Glucose Dysregulation in People with Cystic Fibrosis:**

In people with CF, impaired glucose tolerance and diabetes are associated with increased protein catabolism and nutritional failure, more rapid decline in lung function, and earlier death from pulmonary disease. Recent statistics suggest that this mortality gap has narrowed as early diagnosis and treatment of diabetes have helped improve survival in people with CF-related diabetes (CFRD). Recently, a multi-center, randomized, controlled study (CFRDT Trial) showed that chronic weight loss can be reversed with institution of insulin therapy (but not the oral medication repaglinide) early in the course of CF-related diabetes before fasting hyperglycemia develops. These findings emphasize the importance of screening for hyperglycemia in people with CF and treating insulin deficiency early, as it might extend and promote improved quality of life for these individuals.

### **Diabetes Risk Is Increased and Associated with Increased Cardiovascular Risk in HIV Disease:**

Insulin resistance was initially recognized as common among people with HIV infection, and recent research has found diabetes among 14 percent of HIV-infected individuals receiving antiretroviral therapy. When adjusted for body mass index (BMI) and age, this means there is more than a 3-fold increase in the rate of diabetes in people infected with HIV compared to people without HIV. Diabetes has been associated with a 2.4-fold increase in coronary heart disease among HIV-infected persons. The increased prevalence of secondary diabetes in the HIV-infected population is likely due to specific effects of antiretroviral therapy (e.g., protease

inhibitors affecting GLUT-4, and nucleoside reverse transcriptase inhibitors affecting mitochondrial function), as well as changes in fat distribution among HIV-infected persons—including loss of protective subcutaneous fat and accumulation of excess fat in the liver, muscle, and viscera. Insulin sensitizers have been shown to improve diabetes and CVD risk in the HIV-infected population; whether lifestyle intervention can help prevent development of type 2 diabetes in this population is not yet known.



Source: SEARCH for Diabetes in Youth Study.  
 NHW=Non-Hispanic Whites; AA=African Americans;  
 H=Hispanics; API=Asians/Pacific Islanders;  
 AI=American Indians

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, recognized the disproportionate burden, unique impact, and special needs diabetes confers on certain populations in the United States, particularly women, children, older adults, and racial and ethnic minority groups. In the intervening years, the additional issues of diabetes risk in individuals with major mental disorders, such as major depressive disorder, schizophrenia, and bipolar disorder, and of diabetes secondary to other diseases, have simultaneously become better recognized and increasingly urgent. The research challenges posed by these special diabetes problems cut across many fields and disciplines. Described below are research questions and opportunities to pursue in the next several years to reach the goal of meeting clinical challenges in these important, cross-cutting areas.

### Ethnic and Racial Disparities

Because certain ethnic and racial populations have significantly higher risks of developing type 2 diabetes and subsequent end-organ complications, a broad-based research effort to understand potential genetic and biologic factors that contribute to disease development is required. In addition, further study of environmental factors, including the intrauterine environment, psychosocial triggers, beliefs, self-management skills, community support for lifestyle modification, economics, access to health care, and gene/environment interactions among different ethnic and racial populations, is urgently needed.

### Key Questions

- **What are non-traditional biologic risk factors that contribute to underlying race/ethnic disparities in the development of diabetes and its complications?**
- **What are the “non-biologic” (i.e., environmental, social, cultural, and economic) factors across the lifespan that affect diabetes prevalence and progression to complications in different ethnic and racial groups?**
- **What are the most important genes associated with type 2 diabetes in different ethnic/racial groups?**
- **What novel interventions can be developed that address the racial/ethnic disparities in diabetes incidence, complication rates, and mortality, and that take into account pharmacogenomics, environmental, social, cultural, and economic factors?**

### Future Directions

- **Determine what behavioral strategies work well to promote and sustain effective lifestyle change in minority individuals at high risk for developing diabetes.**

The DPP demonstrated that lifestyle change is an effective strategy for preventing type 2 diabetes in high-risk minority individuals. More research is

needed to understand the behavioral and psychosocial factors that lead to poor nutrition and a sedentary lifestyle and the barriers to change. Community- or work-based programs need to be tested that can target and reach large numbers of high-risk individuals. The cost effectiveness of such programs will also need to be considered. The role of social marketing and new information technologies should be explored.

- ▶ **Determine what behavioral strategies are effective in promoting and sustaining adherence to diabetes treatment regimens in individuals belonging to racial and ethnic minority groups, to improve health outcomes.**

Studies demonstrate that access to care alone does not explain racial and ethnic disparities in the outcomes of individuals with diabetes. Research is needed to better understand the attitudes and values at the individual, family, and community levels that affect adherence to treatment regimens. The roles of different behavioral techniques, such as motivational interviewing and peer support, should be studied. For example, CMS is currently working with organizations on diabetes self-management training, with a focus on minority populations, as a part of its overall focus on health disparities in the Medicare population.

- ▶ **Identify biological mechanisms underlying ethnic and racial differences in susceptibility to diabetic complications.**

Although many risk factors for diabetes and its complications have been identified for the general population, important racial and ethnic differences remain unexplained. For example, African Americans, especially those with diabetes, appear to have higher susceptibility to cardiovascular disease even at blood lipid levels that confer relative cardioprotection in other

racial and ethnic groups. Moreover, higher rates of kidney complications persist in African Americans and American Indians with diabetes even when glycemia is normalized. To understand these disparities in cardiovascular and kidney risks, research is needed to develop novel biomarkers and methodologies for analyzing the contributions to risk of established factors, such as lipoproteins, and of other, novel risk factors.

- ▶ **Identify racial and ethnic differences in the interactions among antenatal care, diet, gestational glycemic burden, and other aspects of the intrauterine environment, and the risk of diabetes and obesity in childhood, adolescence, and adulthood.**

There is an emerging understanding that the intrauterine fetal environment exerts profound effects on future health outcomes in adulthood. Excess risk is associated with both maternal undernutrition and overnutrition. Maternal undernutrition and intrauterine growth retardation (evidenced by low birth weight) expose the fetus to increased risks of obesity, diabetes, hypertension, metabolic syndrome, and cardiovascular disease in later adult life. On the other hand, maternal diabetes also predisposes the fetus to increased risk of obesity and for developing diabetes in later life. Several conditions associated with low birth weight, including poor antenatal care, undernutrition, and pre-eclampsia, are more prevalent in ethnic minority populations, as are gestational and type 2 diabetes. Moreover, gestational diabetes exacerbates rates of pre-eclampsia. Thus, ample opportunity exists for a “vicious cycle” of interactions among several obstetrical risk factors that may contribute to the current epidemic of obesity and diabetes in minority racial and ethnic populations.

- **Identify genes for type 2 diabetes and their mechanisms of action in different racial and ethnic groups to facilitate disease prevention and treatment strategies.**

Recent advances in genetics research and technology, such as genome-wide association (GWA) studies, have accelerated the identification of genes that influence the susceptibility to type 2 diabetes. To date much of this work has been done among populations of European descent. Extending this research effort to find diabetes-related genes in non-European groups is necessary to determine how type 2 diabetes differs among ethnic and racial groups. Other studies can be pursued to determine whether diabetes susceptibility genes already identified in European populations extend to other ethnic and racial groups. Studies of gene mechanisms that include intermediate phenotypes, as well as research on gene-environment interactions in specific racial and ethnic populations, should also be pursued. Once causative genes have been identified, further pharmacogenetic studies should be pursued as they may help tailor therapy for prevention and treatment of diabetes in high-risk racial and ethnic groups.

## **Pregnancy and the Intrauterine Environment**

Understanding of the immediate and long-term health consequences of diabetes and obesity during pregnancy, for both mother and child, has expanded greatly over the past decade. Recently, researchers have found that maternal blood glucose levels lower than previously regarded as abnormal can adversely affect the newborn and have long-lasting effects on the offspring. Coupled with better means of monitoring maternal glucose and fetal growth, this observation has opened up new areas of research. Several small studies have suggested that oral hypoglycemic agents, previously thought to be

potentially detrimental to the fetus, may be safe in the treatment of gestational diabetes. However, further studies are needed to vigorously evaluate the safety and efficacy of these therapies, particularly over the long-term. Finally, gestational diabetes in the mother and exposure of the fetus to diabetes can be used to identify individuals at high risk for developing diabetes. Research into optimal strategies for monitoring such individuals to determine if they are moving toward diabetes and for intervening to delay or prevent diabetes, even before glucose levels become impaired, are important future directions for research.

### **Key Questions**

- **What are the immediate- and long-term health outcomes for offspring of women treated for diabetes or placed on weight maintenance or weight loss regimens during pregnancy?**
- **What noninvasive fetal measurements can be used to quantify diabetic “fetopathy” *in utero*? How can such measurement(s) be applied clinically to identify pregnancies in need of intensified maternal glucose control?**
- **Which anti-diabetic treatments work to mitigate perinatal and/or long-term complications in such pregnancies?**
- **By what mechanisms does the intrauterine environment increase the risk of the offspring developing obesity and diabetes?**
- **What biomarkers can be used to monitor women who have had gestational diabetes to determine if their glucose homeostasis is deteriorating, even before glucose levels become impaired? What interventions can actually stop progression to diabetes?**

## Future Directions

- **Identify the safest and most effective approaches to achieve optimal glycemic control during pregnancy.**

Studies are needed to determine the most effective approaches for achieving optimal glycemic control during pregnancy in different populations of women. More research is needed to determine the optimal time to intervene, what agents should be used, the contribution of lifestyle, and recommendations for monitoring.

- **Determine the effects that different interventions for diabetes and/or obesity in mothers have on the long-term health outcomes for offspring.**

Epidemiologic data have shown that diabetes or obesity during pregnancy predisposes offspring to obesity, type 2 diabetes, and other metabolic abnormalities. It is not known whether glucose control per se in the mother is sufficient to decrease risk, or whether different types of treatment will be more efficacious in decreasing metabolic abnormalities in the offspring. For example, the long-term effects of oral diabetes drugs administered during fetal development remain unknown. Before being recommended as an alternative to insulin for routine use, their long-term effects should be determined. Long-term follow-up of offspring (20 years or more) will be required, because the metabolic abnormalities are not always evident until the second decade of life or later. Suitable cohorts need to be identified, in which mothers on either insulin or oral anti-diabetic agents have detailed obstetric histories, including the timing, dosage, and duration of drug use. Weight maintenance and weight loss interventions are approaches to managing diabetes and obesity during pregnancy whose long-term impact on offspring should

also be explored. A significant barrier to this line of research is that weight loss or maintenance is always difficult to achieve, particularly during pregnancy. Also, taboos still exist against having “inadequate” weight gain during pregnancy, and exercise during pregnancy is not universally accepted as safe. The Institute of Medicine’s recently-updated guidelines for healthy weight gain during pregnancy, which include targets for underweight, normal weight, overweight, and obese women, should help in this regard. Prenatal and neonatal metabolic information kept as part of individual medical records would be a useful research resource for these studies; health information technology should be applied to establish safe strategies to obtain this information while protecting personal information.

- **Develop new approaches to antepartum monitoring and management of gestational diabetes.**

To find new ways of managing gestational diabetes, researchers need to look beyond glucose as the only important parameter to monitor in women with this condition. The development of noninvasive methods (e.g., ultrasound, magnetic resonance imaging) to detect and quantify disease or abnormalities *in utero*, such as excessive fetal fat, will accelerate research in this field. Clinical trials could then utilize such fetal monitoring technologies to determine optimal maternal treatments and correlate fetal conditions with perinatal and longer-term outcomes.

- **Develop effective clinical approaches to prevent birth defects in diabetic pregnancies.**

Preconception glycemic control is known to dramatically reduce birth defects, but many women with known diabetes become pregnant without first instituting such control. In addition, substantial numbers of women may

have undiagnosed type 2 diabetes that is only recognized during the course of prenatal care. New approaches are needed to effectively translate research showing that it is possible to prevent birth defects in the offspring of diabetic mothers. One approach would be to test health care delivery strategies that combine diabetes testing and preconception diabetes self-management training with more common aspects of women's health, such as family planning or gynecologic care. Other studies are needed to identify strategies to improve information and outcomes for women at high risk of diabetes during pregnancy who may not have access to prenatal health care.

- ▶ **Investigate the progression to type 2 diabetes and its mitigation in women with prior gestational diabetes.**

Diabetes is a relatively late outcome of a long-term loss of beta cell function. Ideally, clinicians should be able to determine if a person's beta cell function is declining long before diabetes, or even impaired glucose tolerance, develops, so they can intervene to arrest the decline and prevent diabetes. A major research focus should be on identification of biomarkers for declining beta cell function. Such markers could then be used to test interventions for their ability to preserve beta cell function, starting relatively early in the natural history of development of diabetes. This approach could be particularly useful for monitoring and intervening in women with previous gestational diabetes at risk for type 2 diabetes, as well as to other forms of progressive loss of beta cell function, including glucose intolerance associated with HIV and CF.

## Diabetes in Children and Youth

The alarming new statistics on diabetes prevalence in youth uncovered by SEARCH and other efforts makes it

even more urgent to understand the factors contributing to this disease and its morbidity in young people. Type 1 diabetes is an autoimmune disease that usually strikes early in life; major efforts to prevent and treat disease are described elsewhere in this research plan (see the chapter on "Type 1 Diabetes and Autoimmunity").

Type 2 diabetes in youth is almost universally associated with overweight or obesity, particularly in minority children. Interestingly, SEARCH found that children with type 1 diabetes also have a higher rate of overweight than youth without diabetes, as well as very high rates of obesity, especially in Hispanic and African American youth. While some children with type 1 diabetes may gain weight as a result of insulin treatment, increasing numbers of youth with type 1 diabetes are overweight/obese at diagnosis. While this may simply mirror the obesity epidemic in the general population, the high rates of overweight/obesity in youth with type 1 may reflect an added inflammatory burden on the pancreas in individuals genetically at risk for the disease. Some children seem to have a form of "hybrid diabetes," with features of both type 1 diabetes (auto-antibodies) and type 2 diabetes (insulin resistance). The role of obesity in the etiology of each of these forms of diabetes is not clear. Understanding the connection is crucial to improving approaches to prevent and treat diabetes in youth.

While there is an appreciation of the importance of diabetes management in children, many gaps remain. Research is needed on the interplay between developing autonomy and patient self-management behaviors, as well as on factors that influence the transition of patient care in early adulthood. Improving diabetes care across the age spectrum is imperative as data exist that microvascular and macrovascular risk factors and complications may develop in childhood. The long-term course of these early complications, and strategies to

reduce risk, including lifestyle and pharmacotherapy, need to be studied. The effects of race/ethnicity; genetics; culture; socioeconomic status/parental education; puberty and growth; access to care; family dynamics and family health; and qualities of the school, child care center, and community play key roles in determining if diabetes management is successful across the age spectrum. In addition, the problem of DKA in young children needs to be addressed. DKA has virtually been eliminated in certain areas of Italy as the result of provider and public education efforts. Strategies to reduce DKA in the United States must be developed.

### Key Questions

- **What is the role of overweight and obesity in the development of diabetes—including hybrid diabetes—in children and youth? Are there racial and ethnic differences?**
- **How does the development of overweight/obesity in children or youth affect diabetes management and outcomes, and contribute to patterns of disordered eating?**
- **Do children with hybrid diabetes have the same genetic, environmental, and cultural risk factors as those with type 1 diabetes?**
- **How can children and youth be more successfully transitioned to adult management of diabetes? What are the most effective and affordable ways for parents, caregivers, and individuals with diabetes to become motivated and competent to manage diabetes?**
- **How can children and youth with diabetes obtain optimal support for their diabetes care from environments outside the home (e.g., day care, schools, colleges, community organizations)?**

- **What complications and risk factors for complications are present in youth with diabetes?**
- **Can DKA rates be significantly reduced in the United States, at presentation and over the course of childhood diabetes?**
- **How can the interactions between the four main modifiable parameters influencing glucose control (insulin administration, diet, physical activity, and stress) be better understood? What types of interventions would be successful and cost effective at achieving optimal glycemic control and improving quality of life?**
- **Can pre-diabetes be identified (by a cost effective strategy) and the development of type 2 diabetes in children and adolescents be delayed or prevented?**

### Future Directions

- **Determine whether the increase in type 1 diabetes in younger children is due to increases in obesity/overweight.**

Studies in both the United States and Europe (Eurodiab) have shown an increase in type 1 diabetes in the pediatric population, particularly in very young children. It has been suggested that the shift downward in age is due to higher weights and rates of weight gain in babies and infants, referred to as the accelerator hypothesis. Overall, how obesity and overweight interact with race/ethnicity, genetics, and environmental factors to contribute to the islet autoimmune process of type 1 diabetes needs to be investigated.

- **Characterize the role of obesity in contributing to inflammation and insulin resistance in all forms of childhood diabetes.**



Multiple small studies have shown that obesity contributes to inflammation, insulin resistance, impaired glucose tolerance, and progression to type 2 diabetes in youth. In addition, puberty appears to be a major risk factor for the metabolic complications of obesity. Mechanistic studies should be conducted to understand how overweight/obesity affects islet autoimmunity, insulin resistance, beta cell function, inflammation, and other diabetes triggers. Further investigation is also required to determine how to best assess adiposity and fat compartmentalization in youth; how to characterize patterns for the trajectory of weight throughout childhood; and how environmental, social, cultural, and genetic factors interplay to cause obesity-related metabolic disturbances.

- **Develop effective weight loss strategies, in the context of the growing and developing child, for children with all forms of diabetes who are overweight.**

Data from the SEARCH study revealed that children and youth with diabetes—including type 1 diabetes—are more overweight/obese than children without diabetes. Because all children with type 1 diabetes and many with type 2 diabetes are treated with insulin, the role of insulin administration in inducing weight gain should be evaluated. Studies to address weight loss that might include behavioral, pharmacological, and surgical interventions in children with diabetes should be conducted to help reduce the risk for disease progression and complications early in life. These studies will need to take into account that girls with type 1 diabetes are at especially increased risk for disordered eating patterns, including withholding insulin, which accelerates diabetes complications.

- **Develop cost effective methods for assessing and tracking diabetes complications and risk factors for complications in children and youth with diabetes.**

Studies should be pursued to determine if the early course of diabetes; environmental, social, and behavioral factors; or biological/genetic characteristics explain differences in glycemic control and the risk for diabetes complications.

- **Study behavioral methods to improve treatment adherence in the context of a chronic disease, including a better understanding of the way treatment approaches need to evolve with the maturation of the child.**

For diabetes management to be successful, children must have the support of their family, other caregivers, and school/child care personnel. It needs to be determined how diabetes education is best delivered to those caring for these children, how the child with diabetes should receive ongoing diabetes education that is developmentally staged, and how information is transferred amongst caregivers and health care professionals. As youth transition to adulthood and become increasingly autonomous, there is the need to determine what systems of care facilitate the transfer of individuals with diabetes from pediatric to adult providers while optimizing adherence, access, and outcomes overall. Better methods to assess adherence to treatment regimens and healthy lifestyle need to be developed.

- **Determine risk factors for the development of DKA and establish approaches to reduce rates of DKA in the United States.**

The development of DKA remains the major source of morbidity and mortality in childhood diabetes. Because diabetes incidence is increasing in young children, efforts should be directed toward increasing public and professional awareness about diabetes symptoms, particularly in infants and toddlers. Methodologies should be investigated to reduce DKA rates at diagnosis taking into account a public health approach, as well as evaluating strategies that cut across the varied systems of medical care for children.

## Diabetes in Older Adults

The care of the large number of older adults with or at risk for diabetes is associated with very high personal and societal costs. In particular, macrovascular complications are highly associated with disability and death for persons with diabetes. Moreover, as both type 2 diabetes and Alzheimer's disease increase in the older population, and having diabetes significantly increases the risk of developing Alzheimer's disease, there is the need to determine how a variety of potential mechanisms might interplay and account for the association of these two processes (see the "Diabetes Complications" chapter for further discussion of this association). The public health and health economic implications of identifying the best prevention and treatment strategies for older adults with diabetes are enormous, and should be considered especially as the Federal government works to simultaneously contain costs in the Medicare program and maximize the quality of care delivered to persons with prevalent and morbid chronic conditions such as diabetes.

## Key Questions

- **What are the optimal strategies for motivating older people to improve and sustain lifestyle changes that can help prevent or control diabetes?**
- **What are the appropriate (optimal) glycemic, blood pressure, and cholesterol targets across the spectrum of health for older adults to help prevent diabetes complications (and maintain quality of life)?**
- **If it is not feasible to reach targets for all three risk factors (glycemia, blood pressure, and cholesterol) due to therapeutic complexity, polypharmacy, costs, and/or competing medical conditions, how should risk factor control be prioritized to limit morbidity and mortality in older adults?**
- **How does diabetes and its treatment affect other health issues faced during aging, such as falling, osteoporosis, incontinence, polypharmacy, and declines in functional status?**
- **For the frail, older adult with diabetes and limited life expectancy, what are the most important treatment priorities if the goal is to maintain quality of life and decrease the risk of the geriatric syndromes?**

## Future Directions

- **Determine how to activate older adults with or at risk for diabetes to improve and sustain lifestyle modification.**

The lifestyle arm of the DPP was highly effective among older participants. However, many older adults are sedentary. Studies are needed to understand the best behavioral approaches for helping older individuals initiate and/or sustain a regular program of physical activity and to safely implement weight loss if their BMI is placing them at increased risk for complications.

- **Determine the optimal strategy to manage hyperglycemia and minimize cardiovascular risk in older adults with diabetes.**

Studies are needed to identify the optimal glycemic targets among older adults, especially in those with multiple comorbidities. In addition, many of the approaches for caring for older adults with diabetes are based on extrapolations from clinical trial results collected among younger persons. It is not known whether controlling specific risk factors leads to better outcomes in older individuals with or without multiple comorbidities. Studies are needed to determine the relative benefit of glycemic control, and treatment of high blood pressure and abnormal lipids, in older individuals who may have difficulty affording or complying with complex treatment regimens. In addition, these studies need to evaluate the prioritization of treatment goals in the context of maintaining functional status and quality of life, while limiting the risk of geriatric syndromes (e.g., falls, cognitive impairment).

- **Study differential drug clearance in older adults, as well as across the lifespan and across different races and ethnicities.**

A variety of drugs are available or under development for treatment of diabetes and its complications. However, research suggests that people may vary widely in how quickly they clear (metabolize and excrete) drugs from their bodies, depending upon factors such as

age, ethnicity, pregnancy, or developmental stage (e.g., puberty)—which, in turn, could have critical ramifications for dosing and lead to potentially deleterious drug interactions. Puberty and pregnancy could have an effect not only on drug clearance, but also drug distribution. Studies should be pursued to address these questions both in older adults, who are more likely to be taking multiple medications for diabetes and other conditions, and in ethnically and racially diverse populations across the lifespan.

## Diabetes and Psychiatric Disorders

A greater understanding of the association between diabetes and psychiatric disorders and treatments has been achieved in the past several years as researchers have looked at this problem in different populations. New challenges include uncovering the mechanisms responsible for this association and identifying strategies to reduce the impact of diabetes in individuals with mental disorders. Study of this problem will be helped by application of a variety of approaches, from basic mechanistic studies to clinical trials and population-based studies.

### Key Questions

- **How do depression and certain antidepressant medications increase the risk of developing type 2 diabetes?**
- **Does drug naïve schizophrenia or bipolar disorder increase the risk of developing type 2 diabetes, and if so, how?**
- **How do certain antipsychotic medications and certain “mood stabilizers” for bipolar disorder increase the risk of developing type 2 diabetes?**

- **Are there depression treatments that can reduce diabetes risk or improve outcomes in people who already have diabetes?**
- **Are there genetic risk factors that explain the increased prevalence of diabetes in the mentally ill, or is increased prevalence simply a function of increased rates of established risk factors such as obesity, dyslipidemia, smoking, sedentary lifestyle, and poor medical care? Do risks vary across the lifespan?**
- **What are optimal strategies to increase rates of screening, risk reduction, and treatment for pre-diabetes and diabetes in the systems of care responsible for mentally ill populations?**

### **Future Directions**

- **Identify the mechanisms by which depression, schizophrenia, and bipolar disorder, and the medications used to treat them, increase diabetes risk. Identify the individuals who are susceptible to those risks.**

Research studies should be conducted to determine whether the association between antidepressant use and diabetes risk represents a direct effect of the medication, or if instead antidepressant use is a marker for more severe or chronic depression (itself a risk factor for diabetes). Similarly, research studies should be conducted in drug naïve patient groups with a range of known diabetes risk factors (e.g., a range of baseline adiposity and insulin resistance) to determine whether the association between mental disorders (such as schizophrenia and bipolar disorder) and risk of diabetes represents an effect of the mental disorder, an effect of the high prevalence of unaddressed risk factors in people with these disorders, or a direct effect of medications.

Such studies should also assess the effect of individual medications on known diabetes risk factors such as adiposity, insulin sensitivity and secretion, and lipid metabolism.

- **Evaluate the effect of depression treatment on diabetes risk or improved outcomes in people with diabetes.**

Depression treatment has been associated with some positive metabolic outcomes, including improved glucose control in individuals with high hemoglobin A1c (HbA1c) levels before depression treatment. Larger studies are needed in individuals at risk for and with diabetes to compare the effects of depression counseling with one or more widely used antidepressant agents on outcomes. Comparing depression treatments (medication versus counseling) will be challenging for many reasons: medications might not carry similar diabetes risk, the effects of antidepressants on diabetes risk might take years to be seen, and the ideal study should involve individuals who are not taking antidepressants or receiving depression counseling on entry.

- **Develop strategies to improve diabetes screening and treatment rates in the mentally ill.**

A major barrier to this line of research is the fragmented system of care for mentally ill persons who are at risk for diabetes. Improvements in cross-talk between system administrators and researchers would facilitate research, as would dissemination of results from successful programs. A variety of approaches should be tested to better integrate diabetes screening and treatment into psychiatric care.

## Secondary Diabetes

The double burden of disease and accompanying complexity in management and treatment in people who develop diabetes secondary to a chronic condition raises critical challenges. For persons with CF, new knowledge about treatment for the most severely affected (e.g., people with CF who also have diabetes are best treated with insulin to help preserve nutritional status and lung function) has led to new questions about when treatment should begin. In HIV, some specific mechanisms contributing to secondary diabetes among the HIV-infected population have been uncovered, but critical questions remain as to optimal treatment strategies and methods to prevent the development of diabetes in this patient population. People who have undergone organ transplantation develop diabetes at high rates, particularly in association with certain immunosuppressive regimens. However, the risk profile for diabetes is unknown, and questions remain as to how diabetes should be best treated in this situation, and how diabetes adversely affects transplantation and survival.

### Key Questions

- **Should people with CF who also have pre-diabetes receive diabetes therapy, and what is the best method of treatment? What is the mechanism behind the relationship between glucose tolerance abnormalities and excessive pulmonary morbidity and mortality in persons with CF?**
- **What are the mechanisms of diabetes development in HIV-infected persons? What is the cardiovascular risk associated with the development of diabetes in this population?**

- **What are the effects of insulin sensitizers and lifestyle modification on hard cardiovascular end points in people with HIV infection?**
- **What is the risk profile for diabetes in people undergoing organ transplantation, how should diabetes be best treated, and how does diabetes adversely affect organ and patient survival?**

### Future Directions

- **Identify the best approach to treating early glucose tolerance abnormalities in CF to prevent excess mortality.**

The CFRDT Trial successfully used pre-meal rapid acting insulin to reverse chronic weight loss in participants with CFRD, but small pilot studies suggest that a single daily dose of insulin glargine (a long-acting form of insulin) may improve weight and/or pulmonary function. It is not known whether diabetes therapy affects morbidity and mortality in people with CF who have pre-diabetes. Randomized clinical trials are needed to determine the best treatment strategies. A major challenge to conducting randomized, controlled multi-center trials in CF is the recruitment of a sufficient number of participants.

- **Identify the etiology of diabetes-related morbidity and mortality in CF.**

While insulin deficiency and protein catabolism have been implicated in CF-related diabetes morbidity and mortality, the impact of intermittent hyperglycemia on inflammation and infection needs to be explored. A small pilot study demonstrated that airway fluid

glucose concentrations acutely rise in CF in response to blood glucose elevation, and that this promotes bacterial growth. Studies exploring whether increased inflammation and oxidative stress are associated with diabetes and its impact on CF lung disease are needed and should likely take place both in the laboratory and the clinical setting.

➤ **Characterize the role played by specific antiviral drugs on the pathogenesis of diabetes in people with HIV.**

Insulin resistance was one of the first metabolic abnormalities observed among HIV-infected individuals, and researchers have shown that antiretroviral drugs used to treat infection can result directly in insulin resistance. Preliminary studies suggest an important mechanism by which protease inhibitors may reduce insulin sensitivity, via GLUT-4. Nucleoside reverse transcriptase inhibitors, another major class of antiretroviral drugs, have been shown to perturb mitochondrial function *in vitro* and contribute to insulin resistance *in vivo* via a different pathway from protease inhibitors. Studies are critically needed to determine additional cellular mechanisms by which antiretroviral drugs may contribute directly and indirectly to the development of insulin resistance and diabetes mellitus. Data derived from these studies may shed light on the pathogenesis of diabetes in general, as the drugs used to treat HIV infection affect critical cellular pathways in the development of insulin resistance.

➤ **Determine the effects of lifestyle modification and insulin sensitizing strategies to prevent diabetes and reduce CVD risk in the HIV-infected population.**

Preliminary studies suggest that metformin improves insulin resistance and CVD risk markers among HIV-infected persons. Similarly, small studies have shown improvement in some CVD risk factors and HbA1c in response to lifestyle modification among HIV-infected people. However, studies to date have not assessed whether these strategies will prevent the development of diabetes and reduce hard CVD end points. Moreover, differences in racial demographics, age, and fat distribution may contribute to unique responses in the HIV-infected population. Large, multi-center, randomized, controlled studies to assess the optimal strategies to prevent the development of diabetes and reduce hard CVD end points in the HIV-infected population are critically needed.

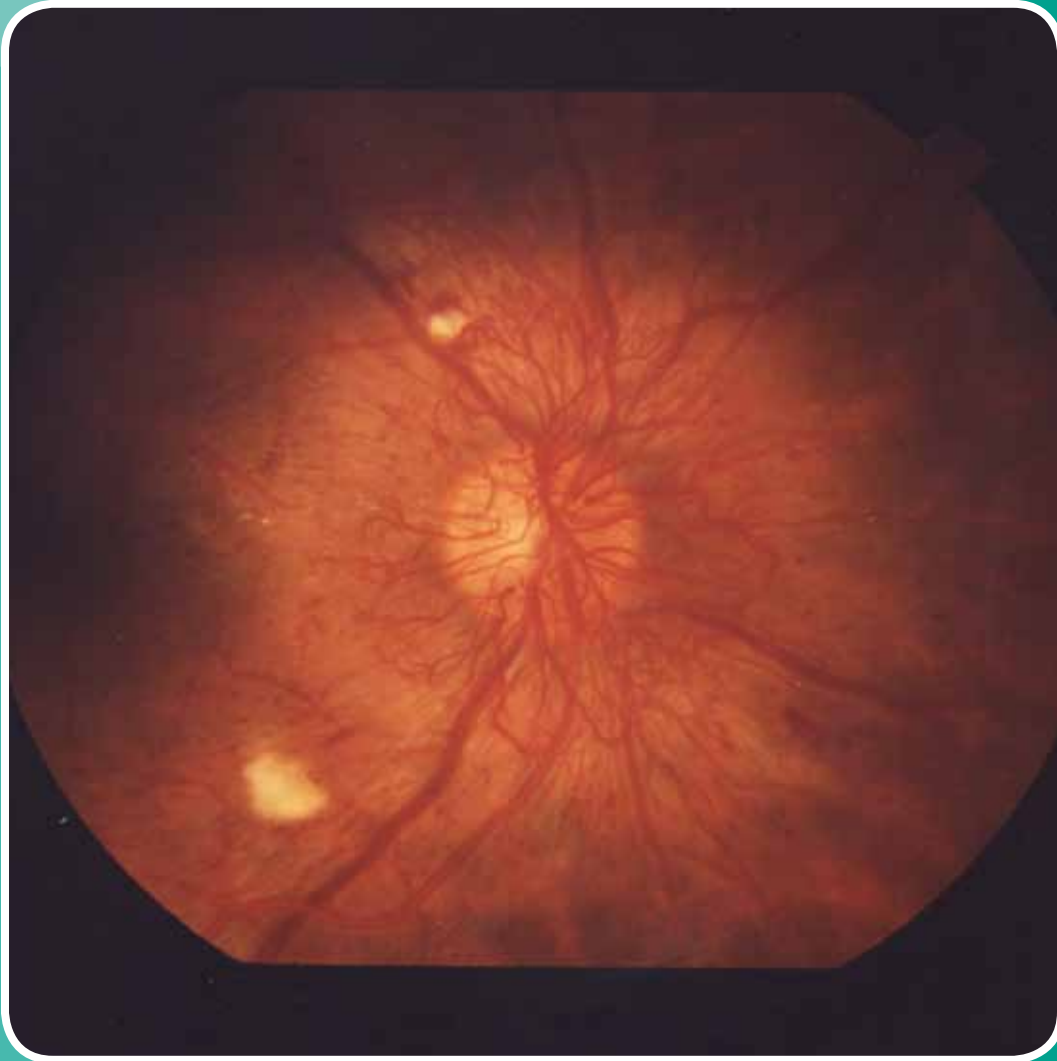
➤ **Investigate strategies to reduce the development of diabetes and improve survival when diabetes occurs in organ transplantation.**

Data from multiple sources have shown high conversion rates to diabetes after organ transplantation and generally poorer outcomes once diabetes develops. To improve graft and patient survival, studies are needed to develop risk profiles of patient characteristics including adiposity, race/ethnicity, genetics, and environmental triggers; understand the role of aggressive monitoring of glucose during the procedure and post-transplant course, and the benefit of early initiation of treatment for dysglycemia; and develop strategies to assess how to individualize anti-rejection regimens to improve glucose metabolism.

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

Further research on many of the unique challenges posed by diabetes will be key to tailoring diabetes prevention, treatment, and management strategies to the diverse needs of the U.S. population at risk for or living with this disease. As demographics change, a better understanding of the influence of genetic and environmental factors on diabetes in many different racial and ethnic groups becomes critically important. Through research on diabetes during pregnancy and its consequences, there is hope that the cycle of diabetes in mothers and their offspring can be broken, helping to preserve the health of current and future generations. To decrease the burden of diabetes in children, research should focus on decreasing DKA, type 2 diabetes in youth, and childhood overweight/obesity, in addition to vigorously pursuing ways to prevent, slow, or reverse type 1 diabetes and improve its management (as described in the “Type 1 Diabetes and Autoimmunity” and “Bioengineering Approaches for the Development of an Artificial Pancreas To Improve Management of Glycemia” chapters). Strategies that improve glycemia

in all age groups need to be evaluated in the context of multiple factors, such as environment, culture, race/ethnicity, and family context/structure, to identify those approaches that are most effective. Older Americans should benefit from research to develop improved diabetes prevention and control strategies that take into account critical biological and health changes accompanying aging, while efforts to understand specific risk factors, complications, and the transition to adult life with diabetes hold promise to help children and youth now and in the future. A better understanding of the relationships between psychiatric disorders, their treatment, and diabetes can yield new strategies to cope with and potentially prevent diabetes in affected individuals. Finally, research on ways to reduce the impact of diabetes on people already affected by diseases such as CF and HIV infection, or by conditions requiring organ transplantation, should help to sustain and improve the health of these particularly vulnerable populations.



Diabetic retinopathy, damage to the tissue that lines the back of the inside of the eyeball, is the most common form of diabetic eye disease and is a serious complication of diabetes. In retinopathy, the small blood vessels that supply the retina with oxygen and nutrients proliferate and are weak and easily damaged. As a consequence, sight is impaired. This photograph shows a retina exhibiting retinopathy. Research on blood vessel proliferation has led to a promising new treatment to reduce its effects in the eye. *(Photo credit: National Eye Institute, NIH.)*



# DIABETES COMPLICATIONS

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

## INTRODUCTION

Diabetes kills with neither speed nor precision, but with stealth and the slow accumulation of insults. It can rob a person of the ability to see, feel, think, walk, and have sex. The cost of diabetes to an individual cannot be calculated, but for the United States an estimated \$58 billion was spent in 2007 on care for chronic diabetes-related complications (1). Damage to the large blood vessels (macrovasculature) causes accelerated atherosclerosis and puts people with diabetes at a 2- to 4-fold higher risk of dying from heart attack or stroke than individuals of the same age without diabetes (1). Damage to smaller blood vessels (microvasculature) results in end-organ diseases that significantly erode quality and length of life. For example, diabetic eye disease, or retinopathy, is the most common cause of vision loss in working age Americans (1). Similarly, diabetic kidney disease, or nephropathy, is the most common cause of kidney failure, which can only be treated with dialysis or kidney transplantation and is associated with a dramatic increase in mortality post renal failure, especially from cardiovascular disease. Diabetes not only accelerates coronary artery disease but also damages the small blood vessels within the heart, as well as heart muscle cells (cardiomyocytes), leading to diabetic cardiomyopathy, which markedly increases the risk of heart failure. Diabetes-induced nerve damage, or neuropathy, can cause pain, loss of sensation, incontinence, impaired gastric motility, and sexual dysfunction. A combination of blood vessel and nerve damage contributes to poorly healing foot ulcers that result in over 65,000 lower limb amputations per year (1). People with diabetes are also at increased risk for periodontal disease, pregnancy-related complications, bone fractures, depression, Alzheimer's disease,

and other conditions, including higher rates of cancer and infections.

A person's risk for complications is influenced by the duration and management of diabetes, genetics, and the presence of other risk factors and health conditions. Thus, multiple medical strategies are needed to prevent complications or slow their progression. Landmark clinical trials, such as the NIH-supported Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have demonstrated that intensive daily management to control blood glucose levels early in the course of diabetes can reduce the risk of developing macrovascular and microvascular complications for people with either type 1 or type 2 diabetes. Multiple, rigorous clinical trials have proven that treatment to lower blood pressure and cholesterol levels reduces cardiovascular disease risk and that direct interventions, such as revascularization, can improve cardiac outcomes. Blood pressure control also reduces the risk of retinopathy and nephropathy. Regular eye exams and timely laser therapy to treat diabetic retinopathy reduce the development of severe vision loss. All these evidence-based strategies reduce the occurrence of complications and improve the quality of life for people with diabetes. However, while representing important progress in diabetes care, they also have important limitations. Most significantly, current therapies reduce but do not eliminate the risk of complications and do not directly prevent the cellular damage induced by diabetes—i.e., they do not address the root cause of the damage. In addition, optimal diabetes care is difficult to achieve and sustain over long periods of time even for highly

motivated individuals. For example, intensive insulin therapy to control blood glucose levels requires extensive efforts by affected persons and also carries its own risks, with an estimated 2 to 4 percent of people with type 1 diabetes dying from the acute consequences of very low glucose levels (severe hypoglycemia) (13). As a result, many people cannot achieve target glycemic goals because their immediate risk of hypoglycemia must be balanced against future long-term complications.



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Artery occluded by lipid buildup. Cardiovascular disease (CVD) accounts for two-thirds of deaths in diabetes (1); moreover, CVD rates are as much as 10-fold higher in people with type 1 diabetes than in the general population. (Image courtesy of National Heart, Lung, and Blood Institute, NIH.)

Progress is being made through NIH-funded research at identifying cellular pathways that are affected by diabetes and understanding the interactions among the pathways and their tissue-specific features. This knowledge is critical for developing new treatment strategies and drugs to prevent or treat diabetes complications. Diabetes not only directly damages cells and tissues, but also modifies their repair and regeneration. An appreciation is emerging that a “memory” of past glycemic levels is retained in cells and tissues that affects the course of complications. New tools will allow better study of diabetes complications in humans through large-scale genetic studies, bio-specimen analysis, and imaging techniques. The complexity of complications challenges the research community to form collaborations and apply technological advances to discover therapies that will lighten the burden of diabetes for people living with this disease. This chapter describes both major research advances and new and emerging opportunities for research in a broad array of fields that will make achieving this goal a reality.

## RECENT RESEARCH ADVANCES

Scientists working in many disciplines have learned a great deal in the last decade about the molecular underpinnings of diabetes complications, and about clinical approaches to delay onset or progression of these serious health conditions. The following are some major examples of research that has advanced understanding and treatment of diabetes complications.

**Multiple Biochemical Pathways Converge To Cause Diabetes Complications:** Research has led to the formulation of a new, unifying hypothesis for the major biochemical pathways that contribute to glucose-induced damage of vascular cells: elevated flux through the polyol and hexosamine pathways, accumulation of advanced glycation end products (AGE) and activation of protein kinase C. The hypothesis posits that all of these pathways share the common feature of overproduction of reactive oxygen species (ROS) in the mitochondria (cellular organelles that utilize oxygen to generate ATP, the cell's energy currency), which in turn leads to oxidative stress and cellular damage. Researchers can now use this hypothesis to explore common therapeutic targets for vascular complications of diabetes.

### **Mitochondrial Dysfunction from Hyperglycemia Correlates with Diabetic Complications:**

Mitochondria generate energy from glucose and lipids. Researchers have found that mitochondrial function is disrupted by long-term exposure to high glucose levels in ways that are linked to diabetic complications. For example, high glucose levels cause mitochondria to produce more ROS. Inhibition of this mitochondrial oxidative stress in diabetic animal models prevents



Scanning electron micrograph of a mitochondrion. Human cells contain many mitochondria, which are the “powerhouses” of the cell. Overproduction of reactive oxygen species by mitochondria is suspected to play a role in diabetes complications and is a potential target for therapeutic intervention. (Image credit: Professors Pietro M. Motta and Tomonori Naguro / copyright ©Photo Researchers, Inc.)

complications. In people with diabetes, decreased cardiac efficiency is associated with mitochondrial oxidative stress, suggesting that this pathway would be an important target for drug development.

### **Inflammation Fuels the Destructive Synergy Between Metabolic and Cardiovascular Disease:**

Inflammation is now recognized as both a significant contributor to the development of diabetes and a consequence of the diabetic state. Inflammatory molecules, including adipokines, toll-like receptors,

adhesion molecules, chemokines, and cytokines, are increased in both diabetes and the metabolic syndrome and are a driving force in atherosclerosis and other complications of diabetes. A major advance in the field is the identification of the receptor for advanced glycation end products (RAGE), a molecule that bridges the innate and adaptive immune system and that was originally identified as a receptor for proteins modified by AGE. RAGE expression is increased by diabetes, and the binding of RAGE to AGE and a number of endogenous ligands activates pro-inflammatory signaling pathways. Pharmacological blockade of RAGE or genetic deletion of RAGE in animal models is protective against the development of macro- and microvascular complications. In people with type 2 diabetes, blocking RAGE activity is being tested in Phase II clinical trials. Thus, these new findings about molecules important in inflammation could lead to new therapeutic approaches to reduce development of diabetes complications.

**The Repair and Regeneration Process Is Impaired in Diabetes:** Maladaptive diabetic vasculature causes significant morbidity, as typified by the chronic, non-healing foot ulcer and the poor recovery from impaired blood supply to the heart, brain, and/or limbs. Repair of tissue and revascularization after ischemia occurs in stages that involve cells and molecules in the circulation and wound site. Circulating endothelial progenitor cells (EPC) that contribute to new blood vessel formation were first described in 1997. Several recent studies report impairments in EPC number and function, as well as dysfunction of other stem cell populations, in diabetes. Trials are under way to test the ability of local injection of a person's own EPCs to promote vascularization.

Recent studies on wound healing in response to ischemia show that hypoxia-inducible factor (HIF)-1alpha is the critical transcription factor that regulates new blood vessel formation. Metabolic by-products of glucose affect both HIF-1alpha stability and activation, resulting in suppression of HIF-1 alpha target genes. The HIF-1alpha regulated cascade and other molecules involved in the repair process, such as vascular endothelial growth factor (VEGF), Akt1, nitric oxide, and netrin-1, might serve as targets for therapeutic intervention to restore tissue responses to injury.

**Long-Term Clinical Trials Revealed the Phenomenon of “Metabolic Memory” in People with Diabetes:** In follow-up studies of two large clinical trials on glycemic control in type 1 and 2 diabetes, participants who intensively managed their blood glucose during the trial have maintained a lower risk of complications for more than 15 years, even though after the trial ended, their glucose control gradually became indistinguishable from that of the participants who had received standard glycemic control measures. This apparent long-term benefit of a relatively short period of intensive glucose control has been termed metabolic memory. These results underscore the importance of intensive glucose management from the earliest stages of diabetes and point to the need for research in epigenetics and other potential mechanisms contributing to metabolic memory (see sidebar, “Sustained Effect of Blood Glucose Control on Susceptibility to Complications—“Metabolic Memory,”” for more details).

## SUSTAINED EFFECT OF BLOOD GLUCOSE CONTROL ON SUSCEPTIBILITY TO COMPLICATIONS—“METABOLIC MEMORY”

In 1993, the results of the landmark Diabetes Control and Complications Trial (DCCT) showed that, in people with short-duration type 1 diabetes, intensive blood glucose control dramatically reduced the occurrence and severity of diabetic microvascular complications—eye, kidney, and nerve disease. After the announcement of the DCCT results, many participants who had been in the standard therapy group adopted more intensive therapeutic regimens, and their level of blood glucose control improved, as measured by the HbA1c test. At the same time, the mean level of HbA1c worsened for participants who had been in the intensive therapy group. The post-DCCT HbA1c values for both groups have become nearly identical during the approximate 15 years of follow-up in the ongoing Epidemiology of Diabetes Interventions and Complications Study (EDIC).

Surprisingly and provocatively, however, the effects of a 6.5-year difference in HbA1c during the DCCT on the incidence of diabetic eye and kidney disease have persisted, and have even become greater over the subsequent years of follow-up. People who had been in the standard therapy group continued to have a higher incidence of complications, even with an improvement in blood glucose control during the EDIC. In contrast, people who had been in the intensive therapy group continued to have a lower incidence of complications, even with a worsening of blood glucose control during EDIC. In addition, early intensive therapy was recently shown to markedly reduce later development of atherosclerotic

changes, heart attacks, and strokes. This effect does not appear to be limited to people with type 1 diabetes who have used intensive insulin therapy. The UKPDS and its follow-up study came to the same conclusion for people with type 2 diabetes who used diabetes drugs or insulin to control blood glucose levels: intensive control of blood glucose lowers the risk of complications, and the benefits of intensive glucose control persist over time even if an individual's average glucose levels eventually worsen.

The phenomenon that the level of blood glucose control could have long-lasting effects, called “metabolic memory,” elicits a number of questions. How can a finite period of good—or bad—blood glucose control have such long-lasting effects? Is there a point in the development of complications in which the progression becomes relatively independent of blood glucose control? The discovery of the molecular and cellular basis of metabolic memory could suggest therapeutic solutions that mimic or induce the protective “memory” of good blood glucose control and inhibit or reverse the sensitizing “memory” of poor blood glucose control.

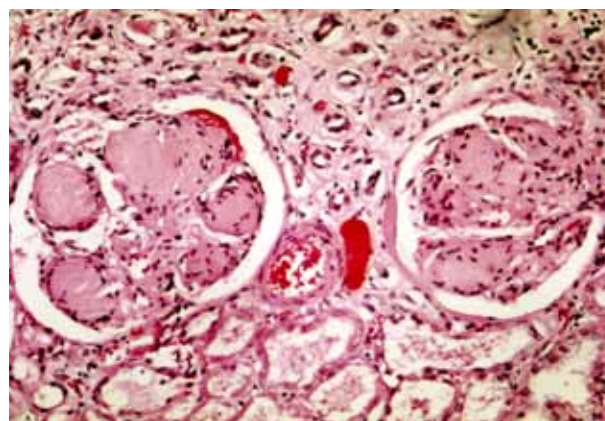
Encouragingly, recent studies in cell culture and animal models have shown a phenomenon of metabolic memory similar to the observations in people—thus providing an avenue to explore the basic mechanisms underlying metabolic memory. For example, studies in diabetic dogs and rats have demonstrated that, even after reversing

hyperglycemia, there is a sustained continuation of key microvascular complications and oxidative stress. Other experiments have looked directly at the effect of high glucose on the cells that line the inside of blood vessels, and found that growing these cells in the laboratory for even short periods in high glucose, followed by restoration of normal glucose, causes persistent increases in expression of genes involved in inflammation and signs of

oxidative stress. Similar alterations have been seen in samples of vascular cells obtained from diabetic mice, when compared with those from non-diabetic control mice. Key molecular mechanisms and genetic modifications (epigenetic changes) have been implicated in some of these animal and cellular models of metabolic memory, supporting the need for more studies in this area.

### Dysfunction of Podocytes and Endothelial Cells

**Contributes to Diabetic Nephropathy:** Diabetic nephropathy is characterized by changes in the glomeruli, structures in the kidney that filter waste products out of the blood for excretion in the urine. Two glomerular cell types—podocytes and glomerular endothelial cells—are implicated in diabetic kidney disease. A reduction in the number and density of podocytes is a strong predictor for progression of diabetic renal disease. A podocyte-specific protein, nephrin, which helps to prevent proteins from leaking into the urine, is decreased in individuals with diabetic nephropathy. In glomerular endothelial cells, a genetic difference that reduces activity of an enzyme, endothelial nitric oxide synthase (eNOS), is associated with accelerated progression of diabetic nephropathy in humans. Diabetes reduces eNOS activity, and diabetic mice lacking eNOS exhibit accelerated and dramatically more severe diabetic nephropathy than wild-type mice. In the future, identifying the cells that are damaged in diabetic nephropathy will help researchers design more sensitive measures of disease progression and find ways of reversing the specific metabolic abnormalities.



Glomeruli, the filtering units of the kidney, are damaged in diabetic nephropathy, impairing normal kidney function. (Image provided by the Centers for Disease Control and Prevention / Dr. Edwin P. Ewing, Jr.)

**Polyuria Causes Bladder Remodeling:** Many people with diabetes develop problems with urination, such as incontinence and incomplete emptying of the bladder. Now, the mechanisms underlying this health issue are starting to emerge. Poorly controlled diabetes leads to increased urine output due to the excretion of the excess glucose. Consequently, the bladder confronts not only the damaging effects of hyperglycemia on the blood vessels and nerves, but also exceptionally high urine volume (polyuria). In experimental models, increased

urine output leads to rapid and substantial bladder hypertrophy and dysfunction that are similar to changes observed in diabetic rats. Those similarities suggest that increased urine production may be a significant factor in the early storage dysfunction of diabetic bladder disease.

### **Diabetes Increases the Risk of Cognitive Impairment, Alzheimer's Disease, and Depression:**

**Depression:** The impact of diabetes on the nervous system has been studied largely in the context of understanding peripheral neuropathy. Over the last decade, the earlier onset of type 2 diabetes and refined behavioral, psychological, and neuroimaging techniques has led to an appreciation of central nervous system (CNS) injury that can be separated from other aspects of aging and vascular disease. Diabetes appears to contribute to cognitive impairment during early childhood, when the brain undergoes structural changes and development. Longitudinal studies report lower intelligence quotient (IQ), decreased mental efficiency, and worse school performance in children with type 1 diabetes compared to children without diabetes. Research has also demonstrated that diabetes contributes to cognitive dysfunction during late adulthood, when the brain undergoes neurodegenerative changes due to aging. Older adults with type 2 diabetes show a 1.5- to 2.0-fold increased risk of cognitive decline compared to adults without diabetes. Cognitive deficits in type 2 diabetes are associated with structural brain abnormalities that include cerebral atrophy and lacunar infarcts (a type of stroke). In addition, research studies indicate that individuals with type 2 diabetes have a greater than 2-fold increased risk of developing Alzheimer's disease (AD) compared to individuals without type 2 diabetes. The reduced insulin production in type 1 diabetes and insulin resistance in type 2

diabetes both can generate AD-like pathology in the CNS.

Depression is also associated with both type 1 and type 2 diabetes and this association is bi-directional, with each influencing the presentation of the other. Studies have shown that the comorbidities of diabetes and depression are linked to poor glycemic control, elevated inflammatory markers, microvascular complications, and cardiovascular disease. Therapeutic approaches to CNS diseases will be more successful with a better understanding of the biological mechanisms that link them to diabetes.

### **Major Clinical Trials Guide Therapy To Reduce Diabetes Complications:**

In previous decades, large clinical trials proved that substantial reductions in complication rates are possible when HbA1c, blood pressure, and LDL cholesterol are controlled, but important questions remained about the optimal therapeutic targets for these risk factors. Glucose control can reduce the development of microvascular complications in people with either type 1 or type 2 diabetes, but its direct effect on macrovascular complications is less clear, at least in people with long-standing type 2 diabetes. Moreover, hyperglycemia, as measured by HbA1c, accounts for only part of an individual's risk of complications. Hypertension and dyslipidemia are major contributors to diabetes complications, and optimal levels of control of glucose, blood pressure, and lipids remain to be established. Now, a major clinical trial has compared standard versus more aggressive treatment goals for these risk factors in people with long-standing type 2 diabetes and found that current guidelines yielded lower mortality than more aggressive glycemic control aimed at near normal glucose levels. The more aggressive goal of near



normal blood pressure levels yielded no improvement in the primary macrovascular disease outcome. In addition, no benefit in macrovascular outcomes was seen when a fibrate was added to standard statin therapy. These studies of more aggressive therapy exceeding current standards of care do not negate the previously proven benefits of control of glucose, blood pressure, and LDL cholesterol in reducing diabetes complications, but do provide new information helpful in balancing the risks and benefits of therapies and optimizing levels of risk factor control.

**Beyond Hyperglycemia—Other Risk Factors for Diabetes Complications:** New data are emerging on risk factors for microvascular complications. For example, the development of diabetic neuropathy is associated with abnormal levels of serum lipids, blood pressure, and urinary albumin, and with obesity. Moreover, emerging clinical and experimental data highlight roles for insulin resistance, increased peripheral insulin levels, and the loss of growth factors (C-peptide, neurotrophic factors, cytokines, etc) in the pathogenesis of diabetic complications. Taken together, these considerations highlight the fundamental requirement for understanding the synergistic pathways that contribute to diabetic complications and then developing combined therapeutic approach strategies tailored to individuals.

**Closing in on New Methods for Assessment of Diabetes Complications:** Diabetes complications develop over decades. Useful biomarkers, such as HbA1c for glycemic control, are snapshots of the disease process that can predict the future clinical outcomes and reflect the underlying mechanisms. Research in a variety of areas has led to exploration of promising

new tools and techniques for assessing complications. Skin autofluorescence shows promise as a noninvasive surrogate marker for AGE formation in the pathogenesis of diabetic complications. Skin intrinsic fluorescence levels can predict cardiovascular morbidity and mortality and kidney disease in people with diabetes. Diabetic peripheral neuropathy has two new tests under development that eventually may enhance the potential for identifying therapies. These tests, skin biopsies and corneal confocal microscopy, assess the structure of distal terminals of sensory neurons and quantify small fiber nerve damage in minimally invasive or noninvasive assays. Biochemical risk factors, vascular imaging, and stress testing can help to define CVD risk in persons with diabetes. Continued efforts to test and develop biomarkers, tests, and other tools to detect diabetes complications will be important for prevention and treatment of these conditions.

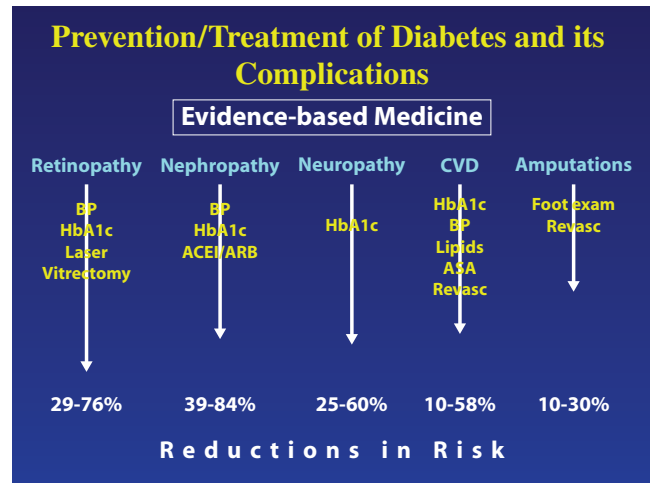


Comprehensive foot exam. Peripheral nerve and vascular damage in diabetes interferes with sensation and healing from tissue injury, heightening risk for amputations. Research is moving forward on treatments to control infections and promote or restore healing. (Photo credit: © iStockphoto.com/jorgeantonio)

## New Therapeutic Approaches for Microvascular Complications:

Over the past decade, new therapies have been developed to prevent or treat complications in people with diabetes. For example, a new treatment targeting angiogenesis has shown success in treating diabetic macular edema, an advanced complication of the disease. Results from a randomized, clinical trial conducted by the NIH-supported, multi-center, Diabetic Retinopathy Clinical Research Network have demonstrated that eye injections with an anti-VEGF drug, often in combination with laser treatment, result in better vision for more patients than laser treatment alone—nearly half of the patients receiving the drug showed a substantial improvement in vision, compared to 30 percent receiving only laser treatments. Research has also expanded on the previous findings that inhibitors of angiotensin-converting enzyme (ACE) significantly reduce the progression of diabetic nephropathy, with early results suggesting that ACE inhibitors may also benefit patients with diabetic retinopathy and diabetic neuropathy. A recent clinical trial has shown that fibrates, a medication to

lower blood lipids, can also reduce the development of diabetic eye disease. The development of new therapeutic options for microvascular complications, in addition to glucose control, can prevent or postpone disability and greatly improve the quality of life for people with diabetes.



Examples of the extent to which therapies have been proven to reduce eye, kidney, nerve, and heart disease, and amputations. BP, blood pressure control; ASA, aspirin; Revasc, revascularization. (Image courtesy of Dr. David Nathan, Harvard University/Massachusetts General Hospital.)

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The 1999 report of the congressionally-established Diabetes Research Working Group (DRWG), *Conquering Diabetes: A Strategic Plan for the 21st Century*, highlighted the importance of battling micro- and macrovascular complications induced by diabetes and of expanding work to understand and overcome diabetic neuropathy, a perspective that has been reinforced in recent plans for research on type 1 diabetes. Since the publication of the DRWG plan for diabetes research, multiple recommendations—such as to expand clinical research and clinical trials for diabetes complications, and to foster multidisciplinary research in these areas—have led to new discoveries and therapeutic improvements. The problems are far from solved, however, and additional research on understanding and preventing complications must not be allowed to lag because diabetes is still a major cause of blindness, renal failure, excess CVD, and several other complications. Moreover, the public health problem is increasing as the incidence of diabetes in the United States has also continued to rise during that time, most alarmingly in children and youth—greatly increasing the population at risk for developing and living with diabetes complications long-term. Described below are research questions and promising opportunities that may be pursued in the next decade to reach the goal of meeting the many challenges posed by the health complications of diabetes.

### Metabolic, Biochemical, and Signaling Pathways

Essential cellular pathways are disrupted in diabetes, setting the stage for development of complications. An excess of glucose, lipids, and other molecules causes

derangements in metabolic pathways and induces buildup of intermediates with toxic effects in and out of the cell. Mitochondria are implicated in many of these pathways because of their role in converting metabolic products to energy. Also, impaired insulin signaling can change the fuel source from glucose to lipids in cardiomyocytes (heart muscle cells) and eventually lead to an excess of intracellular lipid with harmful consequences for the cells. Metabolic pathways relevant to diabetes also control apoptosis and autophagy, forms of cellular “self-killing” and “self-digestion,” respectively. The abundance of molecular pathways affected by diabetes presents the challenge of understanding complex interactions among the pathways, but also the opportunity of providing multiple and potentially complementary targets for drug development.

### Key Questions

- **How do the identified molecular pathways associated with diabetes interact within the cell and does this vary for different cell types?**
- **Are there undiscovered molecular pathways that contribute to diabetes complications?**
- **What protective pathways are present and how do they interact with other pathways? Do complications arise from an imbalance of maladaptive to adaptive responses?**
- **What are the relative contributions of hyperglycemia versus impaired insulin and other growth factor signaling in the development of diabetes complications?**

- **What is the effect of large dynamic changes in the levels of glucose and other metabolites in comparison to sustained elevations?**
- **Why do cells exposed to the same systemic factors have different pathologies? Why does the apparently global pathogenic mechanism of increased mitochondrial activity have variable consequences in different cell types?**
- **What is the clinical significance of the identified biochemical changes in the cell induced by diabetes?**

### Future Directions

- **Develop better tools to assess mitochondrial function, transport, number, fission/fusion states, transcription factors, and DNA.**

Genetic mutations in mitochondrial fusion and fission proteins increase ROS production and cause neuropathies similar to diabetic peripheral neuropathy. Characterization of the mitochondrial fusion/fission states can be accomplished with recently developed fluorescence probes, transgenic mice over- and underexpressing fusion/fission proteins, and novel approaches to quantitate and locate mitochondria using confocal microscopy.

- **Improve mitochondrial function in tissues in which mitochondrial dysfunction contributes to complications.**

A decline in the oxidative phosphorylation capacity of mitochondria and an uncoupling of energy production are characteristics of diabetic cardiomyopathy. A better understanding of the regulation of these changes

in diabetes, including mitochondrial biogenesis and turnover via autophagy (mitophagy), will direct development of drugs that target the mitochondrial abnormalities.

- **Develop a better understanding of the immunologic pathways common to type 1 and type 2 diabetes and diabetes complications.**

Recruitment of the innate and adaptive immune responses is increasingly linked to the development of both type 1 and type 2 diabetes. Inflammation, triggered by the actions of immune cells such as T and B lymphocytes, monocytes/macrophages, and dendritic cells, along with the interaction of these immune cells with vascular cells, contributes to the development of diabetes. These various cell types have also been implicated as causative factors for the complications of diabetes. Identifying shared pathways that may reflect, in part, a mechanistic continuum from cause to complication is an important research goal.

- **Develop better tools to study glycation and lipoxidation of proteins.**

Hyperglycemia causes extensive glycation of extracellular matrix (ECM) proteins that leads to their cross-linking, accumulation, and altered binding properties for growth factors and circulating stem cells. This sclerotic process contributes to the pathogenesis of complications and the slow reversal of pathology with euglycemia. Methods that prevent these modifications are needed to understand their role in impaired tissue turnover rate and accumulation of glycated proteins. Novel animal models are also needed that duplicate, in the absence of hyperglycemia, the diabetic changes in ECM.

► **Determine if modulators of autophagy affect diabetes complications.**

Autophagy may contribute to the progression of complications and the increased risk and poorer prognosis of several forms of cancer associated with diabetes. Autophagy was discovered in yeast as a stress response, but is now linked to human malignancies and known to be regulated by nutrients and pathways relevant to diabetes. The human homologues of yeast autophagy genes and drugs known to affect autophagy are available to test the role of autophagy in diabetes. A better understanding of the regulation of autophagy may elucidate targets to control this process that may be involved in an excess of cell death in certain complications and a deficiency of cell death in malignancies.

► **Develop tools and approaches that produce a more global understanding of the cellular effects of diabetes and a more specific understanding of the effects of diabetes on individuals.**

The field of diabetes complications has benefited from the explosion of new genetic, biochemical, and cell biologic techniques. Appropriate systems biology tools are needed to facilitate integration of genotyping information, mRNA expression, microRNA expression, promoter analysis, proteome expression, and metabolome profiles in order to identify key biological processes and their interactions (see also the chapter on “Type 2 Diabetes As a Multi-Dimensional Disease”). In addition to better computational tools, a deeper understanding is needed of the control mechanisms of mRNA and protein expression levels in the diabetic state, such as ubiquitination, sumoylation, DNA methylation, histone modifications, and non-coding RNAs. Ultimately, this knowledge needs to be applied to

clinical diabetes through better access and techniques for understanding pathobiology in individuals with diabetes.

## Genetics and Epigenetics

Metabolic control alone does not predict an individual's risk for diabetic complications. Family studies suggest that genetic factors play an important role in the predisposition for a specific type of complication and its progression. The chapter on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” highlights research on finding genes that increase the susceptibility to diabetes complications. In addition to more classic genetics, research in this area has expanded to epigenetics and non-coding RNA. Epigenetic marks include modifications to the DNA or chromatin that do not change the underlying DNA sequence and may contribute to metabolic memory, the observation that the level of prior glucose control has persistent effects on the risk of complications (see sidebar, “Sustained Effect of Blood Glucose Control on Susceptibility to Complications – ‘Metabolic Memory’”). The elucidation of epigenetic mechanisms has the potential to identify novel therapeutic targets. Small regulatory RNAs, such as microRNAs (miRNAs), are accepted regulators of mammalian cell phenotype, and have been implicated in the regulation of biological functions associated with diabetes pathogenesis, such as metabolism, insulin secretion, and the immune response. Patterns of miRNA in various cells and tissues may provide useful disease biomarkers, while *in vivo* manipulation of specific subsets of small regulatory RNAs might be used for novel therapeutic strategies.

### Key Questions

- **What are the genes that predispose or protect people from developing end-stage**

**renal disease, diabetic retinopathy, neuropathy, and other diabetes-associated complications?**

- **How do candidate genes identified by genome-wide studies contribute to the pathogenesis of diabetic complications?**
- **How do epigenetic mechanisms fit within the context of other known cellular mechanisms for diabetes complications?**
- **Are epigenetic changes in chromatin responsible for metabolic memory? How do they interact with other persistent effects of glucose control, such as glycation and oxidation of long-lived macromolecules?**
- **Is epigenetics the mechanism by which birth weight determines adult susceptibility to diabetes and coronary heart disease?**
- **What is the role of small regulatory RNA, in particular microRNA, in the development of diabetes complications?**

### **Future Directions**

- **Identify the key genetic factors predisposing to or protecting from diabetic complications and define the population genetic architecture underlying this risk.**

Genetic predisposition clearly plays an important role in the development of diabetic nephropathy and severe diabetic retinopathy. Genome-wide association (GWA) studies using single nucleotide polymorphisms provide a means for elucidating which genes are associated with the pathogenesis or protective mechanisms for these complications. Large numbers of individuals are required to provide adequate statistical power to identify significant associations in GWA studies (typically

3,000-10,000 people). Genetic studies are particularly valuable when combined with careful phenotyping of people with diabetes to discern if specific complications (nephropathy, retinopathy, or neuropathy) are present and to characterize genetic and environmental interactions. Given the greater risk of kidney disease in African Americans and other minority groups, GWA studies need to be performed in specific at-risk populations (for more information, see the chapters on “Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications” and “Special Needs for Special Populations”).

- **Test the role of genes identified from GWA studies.**

GWA studies to identify risk or protective genes implicated in diabetes complications are ongoing. Improved cross-talk between investigators identifying genes and those studying cellular and animal models is essential to determine if genes associated with complications actually are implicated in the pathogenesis of complications. Studies in small and large animal models may be required to address these key questions.

- **Incorporate new genomic and epigenomic technologies to evaluate diabetic complications.**

Tremendous advances in epigenome, mRNA, microRNA and whole genome profiling have occurred through highly sophisticated technologies such as ChIP-on-chip, ChIP-Seq, and deep sequencing. In addition, specific patterns of chromatin histone marks and DNA methylation have been identified and shown to be associated with gene expression or repression. The challenges to utilizing these advances for diabetes complications include determining how best to apply

them to a disease model and the need for appropriate bioinformatic approaches to decipher the large amount of data. Cross-disciplinary collaborations and specialized centers would be particularly useful in overcoming these barriers.

- ▶ **Characterize epigenetic changes or patterns of changes that can be used in population studies to probe the questions of metabolic memory.**

Metabolic memory could be a significant challenge to the prevention of diabetes complications, if poor glycemic control early in the course of diabetes seals an individual's fate for complications. Epigenetic changes in chromatin histone methylation and DNA methylation may be not only the fingerprint of past glucose control, but also the finger that touches various cellular processes. Characterization of epigenetic change may provide targets for intervention when the opportunity for metabolic control early in the course of diabetes has passed. This work will be enhanced by good cellular models and by appropriate human material (e.g., clinical data and biological samples) from longitudinal studies to test for epigenetic changes.

- ▶ **Investigate the changes in microRNA profiles associated with diabetes complications and the downstream effects of identified microRNA.**

MicroRNAs are short ribonucleotides that bind to messenger RNA to modify protein translation or promote RNA degradation. Knowledge of the function and regulation of microRNA is rapidly expanding. They appear to be sensitive to the extracellular environment and could be important regulators of a cell's response to diabetes. Knowledge of microRNA signatures could be translated to therapies based on novel antagomirs,

synthetic analogues of microRNA, to interfere with their involvement in diabetes complications.

## Tissue and Organ System Injury

Tissue injury in diabetes results from cell damage and death, impaired communication among cells, dysfunction of nerves and blood vessels, and detrimental responses to systemic signals, such as inflammation. The development of the clinical manifestations depends on tissue-specific responses to injury and impairments in repair and regenerative processes. The knowledge base of the pathologic process in different tissues varies considerably, but in all organ systems a better understanding of the mechanisms is needed.

### Key Questions

- **How does systemic inflammation from dysregulation of the innate and adaptive immune systems affect specific tissues, such as the periodontium, bone, and endothelium?**
- **What are the mechanisms of injury in specialized cells, such as podocytes, pericytes, Müller cells, and interstitial cells of Cajal?**
- **What distinguishes cardiovascular, kidney, and urologic disease associated with diabetes from non-diabetes related forms of these diseases? Does diabetes accelerate the same pathologic processes or have unique components?**
- **What mechanisms are responsible for the increased mortality in people with diabetes and end-stage renal failure?**
- **Is there a point in the progression of diabetes complications when the pathologic**

**process becomes relatively independent of the diabetes-related factors that initiate it? Is there a point when the progression becomes irreversible?**

- **What are the pathological and molecular correlates of autonomic neuropathy? What are the biologic mechanisms involved in the bi-directional associations of depression and diabetes and Alzheimer's disease and diabetes?**
- **To what extent does the pain associated with diabetes reflect peripheral tissue injury versus altered CNS processing and perception of pain?**

### **Future Directions**

- **Develop *in vitro* models to study vascular complications.**

Vascular dysfunction in diabetes results from hemodynamic, metabolic, and ECM abnormalities. The interactions among these can be explored through *in vitro* models that resemble the *in vivo* situation. For example, a microfluidic bioreactor could be constructed with ECM proteins and channels seeded with vasculogenic cells in which release of growth factors and flow conditions could be tightly controlled and monitored through online imaging. Such a bioreactor might not only foster exploration of dynamic interaction among factors implicated in pathogenesis of complications, but also allow for a systematic evaluation of potential therapeutics, including small molecules and growth factors.

- **Establish bio-repositories of human cells and tissues.**

The study of diabetes complications would benefit from the establishment of a bio-repository of well-characterized human samples. However, the desire to study the effect of diabetes on human tissue is tempered with the complexity of individual variation, inaccessibility of many tissues, and uncontrolled and unknowable variables in patient history and sample processing. Some of these factors can be lessened by technological advances in testing and analyzing large numbers of samples. Patterns that could not be seen with small numbers of individuals and end points may emerge with broad platform testing. Coordination of a major effort to obtain clinical samples of tumor and normal tissue from carefully characterized individuals under standardized processing procedures has started in the National Cancer Institute, and a similar effort could be initiated for diabetes complications. Currently, a large amount of material (including DNA, urine, serum, and immortalized cells) is in storage from multiple clinical trials and large-scale genetic studies of people with diabetic complications. These samples and new collections could be analyzed by mechanistic, genomic, epigenomic, and proteomic studies, with similar samples evaluated by multiple platforms simultaneously to facilitate comparisons. (See also the chapter on “Resource and Infrastructure Needs for Diabetes Research.”)

- **Determine the mediators of dyslipidemia-induced renal and neuronal injury.**

Dyslipidemia is strongly correlated with complications such as nephropathy and neuropathy. Understanding the pathways that mediate the lipid-associated damage to cells could lead to novel treatments for diabetic complications. Study of these complications in a variety



of dyslipidemic animal models will yield important new understanding.

- ▶ **Pursue cross-disciplinary research to understand the basic science for neurovascular disease related to diabetes.**

The understanding of diabetic neuropathy, neuro-retinal abnormalities, and cerebral dysfunction has lagged behind that of vascular complications. The vascular and nervous systems are intimately connected and must be studied as a unit to understand the complexity of the interactions at a basic science level. Cross-disciplinary research is essential for progress in these diseases.

- ▶ **Understand the mechanisms by which diabetes affects the enteric nervous system and related elements in the gastrointestinal system.**

The impact of diabetes on the gastrointestinal system is multi-factorial and poorly understood. Diabetic gastroenteropathy results from dysfunction of the autonomic nervous system, enteric neurons, smooth muscle cells, and interstitial cells of Cajal, and the communication between these cell types. An inadequate understanding of the enteric nervous system in health, the lack of a critical number of investigators, and limitations in the methodology and in animal models are challenges to be addressed. An existing NIH-funded gastroparesis consortium that includes bio-repositories of DNA and serum and the emergence of a noninvasive method of obtaining human samples of enteric nervous system samples will support exploration of early defects and yield progress in this understudied area.

- ▶ **Explore the “temporal theory” of urinary incontinence and diabetic uropathy.**

Complications related to the lower urinary tract affect more than 80 percent of individuals with diabetes and significantly worsen their quality of life. Recent studies in animal models indicate a temporal effect on the development of diabetic bladder disease. The early phase of diabetes leads to urine storage problems from massive bladder remodeling and compensated bladder function. The late phase causes urine voiding problems manifested by decompensated bladder function from myogenic and neurogenic mechanisms. The “temporal theory” provides a scientific framework for understanding the role of polyuria, urine osmolarity, oxidative stress, autonomic neuropathy, and decompensation of the bladder contractile apparatus in the manifestations of diabetic bladder dysfunction. Identification of mechanistic pathways could lead to the development of effective preventive and therapeutic interventions.

- ▶ **Incorporate measures of depression, cognitive impairment, brain vascular lesions, and Alzheimer’s disease in longitudinal studies of diabetes complications.**

Progress in diabetes complications has come from the bi-directional flow of results between the laboratory and clinic. Findings from epidemiology studies and longitudinal clinical trials can inform and direct laboratory research on biological mechanisms associated with diabetes and both depression and cognitive impairment. A key mechanistic issue in the development

of cognitive impairment in the elderly is distinguishing the role of vascular disease versus the pathology of Alzheimer's disease. Identification of these mechanisms will allow development of preventive therapies that can then be tested in the clinic. The inclusion of currently available, validated measures for depression, sub-clinical depressive symptoms, cognitive impairments, and central vascular lesions in studies of people with diabetes are critical for progress in understanding the CNS complications of diabetes. Such studies will also be enhanced by including measures of potential biological mediators of these associations.

## Tissue Repair and Regeneration

Diabetes leads to tissue injury through damage to the blood vessels, ECM, and parenchymal cells. Normally, metabolic and ischemic insults stimulate repair and regeneration. In diabetes, however, these processes are impaired. Examples include non-healing ulcers in the foot, decreased neovascularization in response to inadequate blood flow (ischemia) in the heart, and the proliferation of bleeding-prone vessels in response to regional hypoxia in the retina. Circulating progenitor cells contribute to normal new vessel growth, but their number and function is altered by diabetes. Restoring the health of these cells or infusing *ex vivo*-modified progenitor cells are new therapeutic approaches. Recent advances in cell reprogramming hold great promise for future cell replacement therapies.

### Key Questions

- **Can the complications of diabetes be reversed by stimulating formation of normal new vessels and re-growth of nerves? Is this possible despite continued hyperglycemia?**
- **How do the various pathways leading to abnormal vascular proliferation, loss, and permeability contribute to complications in different tissues?**
- **Can restoration of the regulation and oxygen sensing of HIF-1alpha rescue the diabetic impairments in neovasacularization?**
- **How do dysfunctional repair mechanisms contribute to poor recovery from maternal injuries of childbirth and the resultant increased risk of stress incontinence and female pelvic floor disorders?**
- **How are specific populations of stem/progenitor cells affected by diabetes? Are these abnormalities reversible through optimal diabetes treatment or therapies targeted to stem/progenitor cells?**
- **Will new cell reprogramming techniques, such as induced pluripotent stem (iPS) cells, lead to individualized cell therapy?**

### Future Directions

- **Elucidate the mechanisms underlying the poor revascularization response to ischemia in diabetes.**

In a person without diabetes, inadequate blood flow in the heart, brain, and lower leg initiates a complex response that leads to the recovery of vascular function. Impairment of several pathways and factors such as HIF-1alpha, VEGF, netrin, and nitric oxide are implicated in the poor vascular response seen in diabetes. The relative importance of different pathways may differ among tissues, particularly in the brain. Developing drugs that normalize these pathways in various target tissues is an important therapeutic goal.

► **Characterize the impairments in stem and progenitor cell populations.**

Stem and progenitor cells are crucial for repair and regeneration after ischemia and trauma. Diabetes, possibly through metabolic memory, can lead to decreased function and quantity of progenitor cells, and these impairments are likely to play a role in diabetes complications. A barrier to understanding the impairments includes the known heterogeneity within stem cell compartments, specifically mesenchymal stem cells. Protocols are needed for the culture of progenitor cells and their thorough analysis, including genetic, epigenetic, and transcription factor analysis of individual cells and stem cell populations. Stem and progenitor cell dysfunction could become a biomarker if clear metrics are developed that correlate with diabetic complication rates specific to neovascularization and cardiovascular repair and regeneration. *Ex vivo* therapies could be developed that reverse stem cell dysfunctions, so that people could receive their own treated stem cells to improve diabetic wound healing.

► **Develop cell-based therapies.**

An intriguing prospect is the treatment of cardiovascular complications by the formation of new vessels *in vitro*. The development of a hierarchical vascular tree formed by instructing the stem/progenitor cells using extracellular materials and physical signals could overcome the poor revascularization seen in diabetes. Cell-based therapies may also come from reprogramming of cells from people with diabetes. Though iPS cells created with current protocols are unlikely to be transferred to people for treatment, these protocols offer the opportunity to take skin cells from individuals, direct their differentiation into relevant tissues, such as blood vessels, nerves, and glomeruli, and then study the sequelae of diabetes on those tissues.

## **Biomarkers, Imaging, and Bioinformatics**

Translation of the knowledge of the molecular consequences of diabetes to effective therapies requires better measures of disease progression, faithful models of the pathology, and application of cutting-edge technologies. Validated biomarkers and surrogate end points will allow rapid screening of clinical interventions prior to larger clinical trials, and can assess risk factors and treatment adequacy for patients. Surrogate end points, if adequately validated as predictors, could enable shorter randomized clinical trials and require smaller sample sizes, factors that would accelerate acquisition of clinical information. The challenge is finding biomarkers that reliably characterize risk or the disease state among numerous biomarker candidates. Animal models exist or can be developed for specific aspects of diabetes complications, but cannot completely replicate the human clinical disease. Ready access to human samples and noninvasive imaging would allow testing hypotheses within the complexity of real people with diabetes. Without question, future advances in diabetes complications will come from emerging technologies and those not yet imagined. Currently, the field is poised to benefit from new imaging methods, systems biology approaches, and bioinformatics tools.

### **Key Questions**

- **Can early diabetes-induced changes in tissues and organs be detected by noninvasive imaging?**
- **Will computational models that incorporate several biomarkers and imaging results create a composite analysis that is a better measure of disease progression than the individual components?**

- **What are the indicators that predict an irreversible step in the progression of diabetes complications, such as the identification of a vulnerable atherosclerotic plaque that is likely to rupture?**
- **Why do agents that prevent the onset of diabetes complications in rodent models not prevent complications progression in humans? Are intermediate models, such as swine or nonhuman primates, key steps in paths to translation?**
- **How can the large amount of data generated by genomic, epigenomic, and high-throughput screening experiments be synthesized into new, testable hypotheses on diabetes complications?**

## Future Directions

- **Develop biomarkers for diabetes complications.**

Biomarkers are urgently needed for the early pre-clinical stages through the late end-organ failure stages of diabetes complications and for the short- (1 to 3 months) and medium-term (12 to 24 months) responses to therapies. These biomarkers should aim to be specific for the tissue and the nature of the metabolic and cellular response, and have predictive value for the risk of a given complication developing and/or progressing. Examples of biomarkers that can be pursued include:

- **Nerve fiber density in skin biopsies and visualization of corneal sensory nerves** as measures of peripheral sensory neuropathy.
- **Collagen-linked fluorescence in the skin** as an independent predictor of complications.

- **Urine exosomes and adiponectin levels** for diabetic nephropathy.

- **Leverage technological advances in noninvasive imaging.**

Exciting new techniques for noninvasive imaging can detect and measure changes occurring early in the development of complications before established diagnostic methods or clinical signs. A variety of imaging methods are being developed or validated for diabetes complications. Examples include:

- **Positron emission tomography (PET) imaging** to quantify regional and global myocardial blood flow and substrate metabolism, measure myocardial oxygen consumption, and detect and quantify regional sympathetic denervation of the heart.
- **Positron emission tomography (PET) with F-18 FDG** to identify inflammatory atherosclerotic plaques in the aorta and carotids.
- **Molecular imaging** using radionuclides, magnetic resonance, and optical platforms with probes targeting proteins, enzymes, or receptors involved in diabetic complications, such as RAGE and integrins (angiogenesis).
- **Tissue Doppler imaging** for diastolic dysfunction as part of cardiomyopathy.
- **Magnetic resonance imaging (MRI)** for retinal vessel damage and cardiomyopathy.
- **Voxel-based morphometry using MRI** for CNS gray and white matter measurements and peripheral nerve injury.
- **Functional MRI (fMRI)** for CNS function.
- **Dynamic contrast-enhanced MRI** for blood-retinal barrier damage and retinal oxygenation.

- **<sup>1</sup>H-magnetic resonance spectroscopy** for metabolic imaging of fatty acid content in the heart and anti-oxidant content in the CNS.
- **Near-infrared spectroscopy** for muscle oxygenation.

➤ **Improve animal and cell models.**

Considerable progress is ongoing in understanding diabetes complications through the use of rodent models. The NIH-funded Animal Models of Diabetic Complications Consortium and the Mouse Metabolic Phenotyping Centers have supported research critical in determining the fundamental causes of diabetic complications. As the molecular basis of human genetic risk factors underlying diabetic nephropathy, retinopathy, and neuropathy is elucidated, transgenic and inducible knockout mouse models can be created to evaluate the role of these genes and test drugs for newly identified pathways. A barrier to understanding diabetes-specific factors in cardiovascular disease is the lack of a good rodent model, though a well-coordinated effort in this area may lead to success. Nonetheless, rodent models have their limitations because they inadequately recapitulate the human condition and have not proven to be useful pre-clinical guides for drug development. Outbred mouse models may better represent human genetics compared to the highly inbred rodent models commonly used. Also, models that incorporate multiple aspects of the diabetic condition, rather than reductionist approaches, may produce more accurate models and could be particularly useful for understanding complications with multiple pathogenic mechanisms, such as diabetic neuropathy. Large animal models for diabetes exist and should be further developed, particularly for testing of agents in late stage pre-clinical assessments. Other models, such as *Drosophila* and zebrafish, are being developed to assess

the effect of diabetes on specific aspects of complications, such as oxidant stress and angiogenesis. Improvements in cell and tissue culture techniques can also be employed for the study of diabetes complications. In particular, conditional immortalization of human cells may more closely mimic normal cell metabolism than animal models.

➤ **Transform high-throughput screening to elucidate the complexity of diabetes complications.**

Diabetes complications arise at the molecular, cell, and tissue level, so novel high-throughput assays are needed to encompass these interactions. Macromolecules that are produced or depleted by molecular pathways need to be characterized, identified, and quantified. Functional readouts and non-destructive assays are being developed for direct insight into the dynamics of cell-cell and cell-matrix interactions. High-throughput screening of cell differentiation factors can be performed on ECM microarray platforms for the culture of patterned cells atop combinatorial matrix mixtures.

➤ **Apply systems biology and bioinformatics tools to the analysis of data generated on human samples and experimental models.**

Systems biology approaches will likely show dynamic interactions and network-linked elements in different cells and conditions. Bioinformatics tools use computation, rather than intuition, to discern patterns and identify dysregulated pathways from large amounts of data. An informatics approach using pathway analyses, regulatory modules, and clustering algorithms has proven useful in the analysis of gene expression in healthy and diseased renal biopsy tissue by placing the genes in the context of regulatory elements of cellular pathways. Complexity is the hallmark of diabetes

complications. Recent advances in systems biology and bioinformatics tools may provide a new opportunity to grasp this complexity (see also the chapter, “Type 2 Diabetes As a Multi-Dimensional Disease”).

## Therapeutic and Preventive Strategies

Therapies are desperately needed for the prevention and the treatment of diabetes complications. A worthy goal has been and continues to be a therapy that prevents the damaging effects of hyperglycemia for multiple complications in the broad diabetes population. Another direction is stabilizing or reversing tissue-specific manifestations, such as retinal neovascularization, glomerular sclerosis, and unstable atheromatous plaques. Both of these endeavors will benefit from the study of the diversity of the individual human response to diabetes through the use of technological breakthroughs in biologic measurements. In the search for treatments for diabetes complications, success may come through the individual rather than the universal and the specific rather than the global. Individually-tailored therapy for specific complications is a goal with enormous public health and patient benefit.

### Key Questions

- **Do treatments that prevent the development of complications also prevent the progression of complications?**
- **What is the impact of diabetes duration and pre-existing tissue damage on the ability to respond to therapies?**
- **What behavioral interventions improve diabetes self-management and prevent complications?**
- **Will combination therapies be more effective than single therapies? Can mechanisms for testing combination therapies be developed?**
- **What are approaches that will lead to individualizing therapies? For example, which diabetic individuals will benefit from a therapy that uncouples oxidant and carbonyl stress from hyperglycemia?**
- **How can therapies be targeted to specific tissues?**

### Future Directions

#### ➤ **Personalize drug development and treatment.**

One explanation for the discordant response of agents that treat complications in rodents versus humans is that deleterious pathways that are responsive to a certain drug may be widely expressed in inbred animal models, but expressed in only a small number of individuals. Pharmacogenomic, pharmacometabolomic, and pharmacoproteomic approaches could be used to identify markers for people who would be responsive to specific agents, such as the case for haptoglobin genotypes and responses to vitamin E therapy. In addition, genotyping of individuals participating in clinical trials through networks such as the DRCCR.net can provide information on the relationship between a genetic profile and the likely response to a particular therapy. A better understanding of an individual's response to diabetes and his or her risk for complications could lead to tailoring specific therapies.

#### ➤ **Improve behavioral approaches to treating comorbid depression and diabetes.**

Behavioral interventions can reduce depressive symptoms in people with depression and diabetes, but their effectiveness to improve metabolic control is inconsistent. Development of interventions that integrate depression treatment and diabetes self-management training for individuals with comorbid diabetes and depression is important because these people have poor adherence to their diabetes regimen and are at a greater risk for vascular complications. Research will need to address the appropriate sequence of administration of a combined depression intervention, the timing of initial and follow-up interventions, and the behavioral and biological mechanisms through which the interventions work. Effective interventions will then need to be translated into existing health plan structures and clinical care settings.

➤ **Identify novel therapeutic targets and develop more effective approaches for the prevention and treatment of diabetic complications.**

- **Cardiac steatosis.** Cardiac dysfunction in diabetes is associated with myocardial lipid accumulation. Increasing export of lipids from cardiomyocytes through activation of target proteins involved in fatty acid export may reduce the lipid accumulation and reverse the cardiac dysfunction.
- **Intracellular reactive oxygen species (ROS).** New therapies that can reduce ROS levels through decreased production or increased clearance could attack a critical early step in complications.
- **Glycation of ECM proteins.** Agents that could reverse glycation may help prevent the sclerotic process in the kidney and vascular tree and improve the ability of a tissue to respond to other therapies.

- **Anti-inflammatory agents.** Inflammation plays a key role in the development of diabetes and complications. Novel anti-inflammatory approaches that act on diabetes-related inflammation may prevent the progression of complications. A promising target for further investigation is RAGE, because blockade of this pathway in animal models shows protection from diabetes and inflammation.
- **VEGF-independent treatments for diabetic macular edema.** Anti-VEGF drugs show considerable promise for restoring vision for macular edema and proliferative retinopathy. However, successful therapy may require multiple targets that vary between individuals or over time in the same person.
- **Metabolic memory.** Therapies targeted at molecular mechanisms underlying metabolic memory could provide novel strategies to reduce the development of complications. For example, epigenetic changes might be targeted, possibly through inhibition of key histone methylases. In conjunction with inhibitors of AGEs, inflammation, and ROS, these therapies may prove effective in people who are prone to complications despite glycemic control.

➤ **Target therapies to specific compartments.**

Therapies such as VEGF that might benefit vascular regeneration in the limb could worsen retinopathy. Strategies to target drug delivery could include delayed-release preparations that can be administered locally, and the use of tissue-restricted receptors to facilitate drug uptake. Topical or transdermal therapies are needed for improving diabetic wound healing and, as for any topical application, issues of poor penetration and transient activity will need to be resolved.

- **Establish a mechanism for early evaluation of therapeutic agents parallel to the pharmaceutical industry.**

Mechanisms should be established to support research on drug and biologic development that will not be supported by industry. For example, expansion of programs such as the NIH-supported Type 1 Diabetes

Rapid Access to Intervention Development (T1D-RAID) program, and establishment of clinical trial networks, would allow potential therapies to be developed and tested in early Phase I and II trials that could lead to NIH or industry supported Phase III trials to ultimately gain FDA approval.



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

Research focused on the reduction or elimination of diabetes complications has the potential to relieve much of the health and financial burden diabetes imposes on individuals, their families, and the Nation. A better understanding of the molecular effects of diabetes on cells and tissues will identify targets that can be used to develop new drugs that will ameliorate these harmful effects of diabetes. Genetic research is a complementary approach to finding pathways that retard or accelerate the development of complications and may lead to personalized therapies. Diabetes is a systemic disease; research on the different tissues will tailor therapies to overcome their unique properties and vulnerabilities. Research on the regeneration of cells

and tissues that are damaged from diabetes has the potential for the development of a therapy that would supplement the healing process that is also impaired in diabetes. Diabetes complications are variable and have complex, often multi-factorial origins, and will benefit from research technologies that allow the interpretation of complex data on the cellular effects of diabetes and the individual responses to the disease. By harnessing research knowledge and technology in many fields, the hope is to more quickly see an array of preventive approaches and treatments that address the individual needs of the millions of people at risk for or living with diabetes complications.



Clinical research studies have led to important, evidence-based strategies for prevention and treatment of diabetes and its complications. Finding ways to disseminate this information effectively to diverse populations in the United States who are living with or at high risk for diabetes remains a critical goal for research. *(Photo credits: Top row (left to right): ©iStockphoto.com/endopack; ©Monkey Business Images | Dreamstime.com; ©iStockphoto.com/YinYang. Bottom row (left to right): ©iStockphoto.com/STEVECOLEccs; Indian Health Service, Division of Diabetes Treatment and Prevention; ©iStockphoto.com/mediaphotos; Rolf Bruderer/Blend Images/Getty Images.)*

# CLINICAL RESEARCH TO PRACTICE: TRANSLATIONAL RESEARCH

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Importance of Research Goals and Strategies: How Translating Research Outcomes May Lead to Improvements in Health

## INTRODUCTION

Two landmark clinical trials, the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, demonstrated that glycemic control and cardiovascular risk factor modification can reduce the risk of diabetes complications. The Diabetes Prevention Program (DPP) and the DPP follow-up study, the DPP Outcomes Study (DPPOS), showed that an intensive lifestyle intervention involving physical activity and a healthy diet or use of the diabetes drug metformin can prevent or delay diabetes for as long as 10 years. However, a huge gap exists between the level of risk factor control for diabetes or its complications that can be achieved through intervention in clinical trials and outcomes that result from actual medical practice. Closing the gap between the ideal and current real-world practice is the essence of “Clinical Research to Practice: Translational Research.” This chapter highlights key advances, questions, and future directions for diabetes translational research with a focus on diabetes prevention, diabetes clinical care (including cardiovascular risk factor modification), patient-centered care, health disparities, and systems of care.

Individuals with diabetes differ in age, overall health status, cognitive functioning, social support, socioeconomic circumstances, and other important factors that influence disease management and health outcomes. Thus, optimal diabetes prevention or treatment that can be implemented in clinical care will vary depending on the needs of the individual, as well as the health care setting or context in which the care is delivered. Research to understand the characteristics of people with diabetes and health care delivery systems that influence diabetes prevention, treatment,

and outcomes should help pave the way to innovative methods for optimal clinical care. Similarly, diabetes self-management and patient education are essential components of patient-centered care for diabetes, but more needs to be known on how best to extend the benefits of self-management skills and education to all people with diabetes.

Diabetes affects persons of all ages, races, ethnicities, and socioeconomic circumstances. Nonetheless, in the United States, people belonging to minority racial and ethnic groups and individuals with low socioeconomic circumstances suffer a disproportionate burden of disease. They have higher rates of type 2 diabetes and certain complications than non-Hispanic whites and tend to develop diabetes at a younger age (1). The challenges inherent in diabetes clinical care are often exacerbated in members of racial or ethnic minority groups, or those who are economically disadvantaged. Significant health disparities have been documented in terms of both processes and outcomes of diabetes care. Translational research efforts are under way to identify the causes of health disparities and to develop innovative strategies for eliminating disparities and improving the health of people with diabetes who belong to minority groups. Cultural tailoring of diabetes interventions, such as the development of culturally appropriate health promotion materials in multiple languages, is an important component of successful translation. Preliminary evidence suggests that culturally tailored interventions are more effective than generic quality improvement interventions for reducing racial and ethnic disparities in intermediate outcomes, such as hemoglobin A1c (HbA1c) values, a measure of blood glucose control. In fact, some

generic interventions and reimbursement schemes could worsen disparities if they favor well-resourced settings caring for advantaged populations.

The costs of diabetes care are increasing beyond inflation in the medical care sector due in part to the rapidly increasing prevalence of type 2 diabetes. Higher costs of care for more people with all types of diabetes may cripple the ability of the health care system to attain optimal health outcomes. The current health care system in the United States is clearly not designed to optimize management of chronic conditions and implement lifestyle and self-management behaviors in an efficient, sustainable, and affordable fashion. Attempts to improve management of diabetes through changes to the health care system over the past 10 years have focused largely on behavioral interventions targeting individuals with diabetes and providers that apply only modest or piecemeal changes in delivery system design. When offered alone, many behavioral interventions show fairly small, often temporary effects. These same interventions may have a more profound impact on care processes and outcomes if combined with substantive changes in the health care delivery system and payment incentives for achieving desired outcomes. Translational research is urgently needed to design, test, and validate

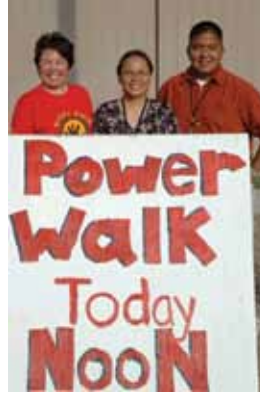
changes to the health care delivery system that can improve the processes and outcomes of diabetes care in the context of ongoing efforts to enhance provider performance, improve diabetes self-management, and implement health information tools.

This chapter on “Clinical Research to Practice: Translational Research” offers forward-looking research questions and directions that build on recent advances and chart a path for progress over the next decade. The research goals focus on the need to understand barriers to diabetes care and to develop and validate new approaches to diabetes prevention and management that benefit individuals with the disease as well as the overall health care system. Although specific policy recommendations are beyond the scope of this report, it is important to note that the results of translational research can inform the development of policies related to the health care system. For example, research to evaluate the relative effectiveness of provider incentives could have implications for efforts to reform payment policies. Thus, the research opportunities described in this chapter have the potential to address the diabetes epidemic in ways that create lasting health benefits for people with diabetes and alleviate the societal burden of this devastating disease.

## RECENT RESEARCH ADVANCES

**Paving the Way to Affordable Prevention or Delay of Type 2 Diabetes in the Community:** The NIH-sponsored DPP demonstrated that type 2 diabetes can be prevented or delayed in high-risk adults with either a lifestyle intervention or medication (metformin). The lifestyle intervention, when compared to the drug treatment, was nearly twice as effective in preventing type 2 diabetes among trial participants and it worked in all groups studied, including U.S. minority populations and the elderly. Both interventions were found to be cost effective and, subsequent to the cost effectiveness analysis, metformin became available as a less costly generic medication. In addition, with longer follow-up, researchers have recently reported that prevention or delay of type 2 diabetes with lifestyle intervention or metformin continued to be observed in DPP participants over a 10 year period. However, delivering the more effective lifestyle intervention tested in the DPP to the 57 million Americans with pre-diabetes would be both costly and challenging in primary health care settings. In recent randomized effectiveness trials, group-based intensive lifestyle interventions modeled after the DPP and delivered by trained community workers demonstrated a 5 to 7 percent weight reduction for at least 12 months. These weight loss results are similar to those that reduced onset of type 2 diabetes by 58 percent in the DPP, but the cost of delivering the intervention by community health workers was reduced more than 10-fold compared to the DPP. This model, coverage for which is already being tested by at least one health insurance group, has the potential to deliver an intervention with efficacy similar to that of the cost effective DPP, but at even lower cost.

**Narrowing Gaps in Achieving Treatment Targets for Diabetes:** Evidence-based guidelines have been developed for the management of diabetes by multiple organizations based on research documenting the benefits of controlling glucose and cardiovascular risk factors. Research indicates that multi-factorial care, including control of glucose, blood pressure, and cholesterol, along with the use of other preventive strategies, such as smoking cessation and daily aspirin therapy, where appropriate, is important for the prevention of diabetes complications and improved long-term outcomes. One study of the effect of a multi-factorial intervention found a nearly 50 percent reduction in mortality in type 2 diabetes. National data, as well as data from a variety of health care settings, including academic and community health centers in both urban and rural locales, indicate a large gap between what is known to be optimal diabetes care and the care that is delivered as part of routine clinical practice. Moreover, in past decades, about one-quarter of people with diabetes have been undiagnosed and thus have not been effectively managed. However, recent national surveillance data find that the appropriate diagnosis of diabetes is increasing, and control of glucose and cardiovascular risk factors is improving in the general population with diabetes. Further, the Translating Research Into Action for Diabetes (TRIAD) study supported by NIH and CDC demonstrated that health care system and provider changes can be systematically implemented in large health care systems to improve the delivery of important processes of care, such as glucose testing. Translational research efforts have contributed to this narrowing of the gap between



Following any successful clinical trial, such as the DPP, the next challenge becomes the search for effective ways to translate the important research findings to real-world settings and diverse communities. (Photo credits (left to right): ©iStockphoto.com/egdigital; Indian Health Service, Division of Diabetes Treatment and Prevention; ©iStockphoto.com/LeggNet)

optimal standards of care and care that is actually delivered.

### Interventions To Improve Diabetes Self-

**Management:** Diabetes requires considerable effort and attention on the part of those with the disease. Effective diabetes self-management is essential to achieving the treatment targets proven to reduce diabetes complications. Interventions to improve diabetes self-management are varied and have demonstrated improvements in diabetes outcomes, particularly in individuals with poor glucose control. Efficacy studies of self-management support have also shown improvements in patient satisfaction, healthy behaviors, self-efficacy, and, in some cases, utilization and clinical outcomes. Additionally, research demonstrates positive outcomes for a variety of diabetes self-management approaches, including programs led by patients, nurses, primary care providers, or other specialists, and delivered to individuals in groups in both health care and community settings. As a result of the body of research demonstrating the benefits of diabetes self-management training, Medicare now allows reimbursement for this service. Moreover, CMS is currently working with organizations on diabetes self-management training, with a focus on minority

populations, as a part of its overall focus on health disparities in the Medicare population.

Research also suggests that individually tailored interventions based on psychosocial or cultural factors are more effective than standardized health education materials or more generic diabetes interventions. Combined analyses of results from many controlled trials also indicate that culturally-tailored patient interventions achieve better diabetes outcomes than general patient interventions at reducing HbA1c levels among people with diabetes who belong to racial or ethnic minority groups in the U.S. population.

Family-based interventions have demonstrated improved diabetes management in children and adolescents with type 1 diabetes. For example, Behavioral Family Systems Therapy has been used successfully in families experiencing high degrees of family conflict. Future large-scale translational effectiveness trials of family-based approaches are important to validate the use of this type of intervention in the broad pediatric type 1 diabetes population.

## Health Care Delivery Changes Improve Diabetes

**Outcomes:** There is strong evidence that including non-physician health care providers in the delivery of diabetes care can improve diabetes outcomes. Involvement of case managers, including community health workers, to enhance quality of care among members of U.S. racial and ethnic minority groups has resulted in improved disease outcomes, including better diabetes control and the delayed onset of retinopathy. Case management addresses barriers to adherence by educating individuals with diabetes on nutrition, exercise, and self-management; identifying adjunct health services (e.g., home health); providing ancillary services, such as laboratory testing and vaccination; and addressing logistical issues, such as transportation. Research has also shown that nurses or clinical pharmacists using treatment algorithms and providing physician support can improve adherence to standards of care for diabetes, resulting in clinically significant improvements in risk factors for adverse outcomes, including better control of blood glucose, blood pressure, and lipids.

## Health Care System Changes that Improve

**Diabetes Outcomes:** Several studies have demonstrated that comprehensive health care systems-level changes can improve diabetes outcomes. For example, the REACH 2010 project in South Carolina demonstrated that a broad-based coalition of community and health care system partners using multi-factorial interventions could improve care and outcomes for people from U.S. racial and ethnic minority groups

who have diabetes. Sustained, large-scale, regional quality improvement efforts within health centers have also demonstrated improvement in some diabetes care processes, such as obtaining HbA1c measurements and conducting foot exams. Improved processes of care have also demonstrated improved control of HbA1c and lipids. However, improvement in HbA1c only emerged after 4 years, which highlights the importance of measuring longer-term effects of changes to the health care system even when diabetes outcomes are not improved in the short term.

The Chronic Care Model (CCM) has proven to be a useful model to conceptualize the key elements of a health care system that contribute to quality care and improved outcomes in chronic conditions such as diabetes. Elements of the CCM include the community, the health system, self-management support, delivery system design, decision support, and clinical information systems. Reviews have concluded that changes to the various features of the health care system need to be made in concert and reinforce each other to achieve maximum effects. The implementation of the CCM in primary care clinics, including a large group of Federally Qualified Health Centers, has demonstrated improvements in both quality of care and diabetes outcomes over the long term.



Health information technologies also show promise for improving diabetes care in diverse health care settings. For example, researchers have shown that decision support tools within electronic medical records can improve processes of diabetes care. Further, electronic data registries, upon which most system interventions are based, are increasingly derived from electronic medical or health records. However, decision support approaches often fail due to the lack of physician acceptance. These findings highlight the need to understand physician attitudes towards health information technologies and to examine the most effective use of electronic medical records.



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Health information technology will play an important role in diabetes prevention and management. *(Photo credit: © iStockphoto.com/YanC)*

## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

The growing diabetes epidemic in the United States places tremendous medical and financial burden on individuals with the disease as well as the entire health care system that must cope with escalating costs of treating diabetes and its multiple complications. Translational research approaches are critically important for turning the results of carefully controlled research studies into strategies for diabetes prevention and care that are effective, affordable, safe, and sustainable in diverse “real-world” contexts and populations. The research questions and directions proposed in this “Clinical Research to Practice: Translational Research” chapter are linked by a common theme: the need to understand how interventions can be designed to work in disparate populations and individuals and within discrete systems of care.

### Prevention of Type 2 Diabetes

Approximately 79 million Americans have pre-diabetes and are at high risk for developing type 2 diabetes (1). Studies have documented an increase in type 2 diabetes in children, adolescents, and adults, particularly within racial and ethnic minority populations in the United States. Importantly, researchers demonstrated in the landmark DPP that it is possible to prevent or delay the onset of type 2 diabetes in adults with pre-diabetes through intensive lifestyle intervention or medication (i.e., metformin). Successfully translating the results of the DPP and similar studies to the general population could have a profound impact on reducing or slowing the national diabetes epidemic.

### Key Questions

- **How can the outcomes of the DPP be translated in diverse settings and populations to prevent type 2 diabetes in youth and adults?**
- **What are the key behavioral and environmental factors that need to be assessed along with genetic markers to better tailor type 2 diabetes prevention approaches?**
- **How can the structures and policies of communities, worksites, and other systems influence behavioral change in individuals to prevent type 2 diabetes?**
- **How can interventions to prevent type 2 diabetes be cost effective at the societal level and financially feasible from the perspective of individual payers and health care organizations?**

### Future Directions

- **Determine methods to efficiently identify individuals in the population who are at risk of developing type 2 diabetes and would benefit most from preventive programs.**

Although the major risk factors for development of type 2 diabetes are well known, research is needed to understand how best to use this information to target at-risk individuals for prevention efforts. Risk

prediction models must take into account factors such as the optimal cut-point for a positive test and the risk-benefit ratio of treating individuals who are identified as being susceptible to the future development of diabetes. Robust prediction models are likely to depend on the demographic, socioeconomic, and clinical characteristics of a given population.

► **Develop sustainable approaches to prevent type 2 diabetes through integration of health care services and community programs.**

The DPP intervention was implemented in the rigorous, controlled setting of a clinical trial in people who met specific criteria for participation in the trial based in part on their level of risk for developing diabetes. Delivery of a group-based adaptation of this intervention in community settings is a highly promising strategy to prevent or delay type 2 diabetes in a sustainable and cost effective manner. Advancing the translation of these approaches will require improved understanding of how community programs can be linked with primary health care systems that identify persons at high risk for type 2 diabetes in order to offer access to evidence-based community programs at a cost that is affordable to them, and to provide follow-up for the possible development of type 2 diabetes and management of other cardiometabolic risk factors. Importantly, existing and new interventions targeting individuals who are at risk of developing diabetes must be evaluated in the context of any major redesign of systems of care and/or payment reform.

► **Identify components of the physical environment or place of care that influence diabetes prevention and control to inform public health efforts.**

Increased density of neighborhood fast food outlets has been associated with unhealthy lifestyles, poorer psychosocial profiles, and increased risk of obesity among older adults. Healthful food resources have been shown to be inversely related to insulin resistance—an association that is partly mediated by diet, physical activity, and body mass index. Poor housing conditions appear to be an independent contributor to the risk of diabetes among urban, middle-aged African Americans. Understanding the interaction of these and other environmental factors with biological susceptibility to diabetes is crucial for the development of tailored interventions to prevent and control diabetes in vulnerable populations.

► **Determine the best approaches for the prevention of type 2 diabetes in youth.**

Youth with or at risk of type 2 diabetes might require specialized strategies for prevention and intervention that differ from the standard approaches to care in adults. Because the DPP included only participants who were 25 and older with an average age of 51 years, it remains an open question whether the DPP interventions would be efficacious in at-risk youth. Understanding the best approaches for children and young adults has been limited by the lack of comparative, large-scale intervention studies and the difficulties in recruiting and retaining youth for long-term clinical studies. Conducting school or community-based research and multi-center trials to compare the effectiveness of prevention and treatment strategies in youth will help determine how best to delay or prevent diabetes and its complications in this vulnerable population.

## Diabetes Clinical Care

Diabetes clinical care is a multi-factorial process that goes well beyond the daily control of blood glucose levels. Clinical studies have demonstrated that individuals with diabetes have low frequency of achievement of targets for management of glycemia, blood pressure, and lipids even when they have access to medical care, increasing their risk for incidence and progression of diabetic complications. In addition, research suggests that those diabetes management targets must be tailored to take into account the needs of individuals with the disease. The NIH-supported Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) tested whether aggressive management of blood glucose levels could reduce cardiovascular disease in people with type 2 diabetes who were at high risk of having a heart attack or stroke. One arm of the trial using aggressive therapy to reduce HbA1c to below 6.0 percent (i.e., to non-diabetic levels) had to be stopped early due to a higher rate of death in participants assigned to this treatment. At first glance, this result was at odds with other clinical trials that reached the opposite conclusion: that intensive glucose management could reduce the risk of cardiovascular disease and other complications in people with type 2 diabetes. However, ACCORD participants were significantly older, had a longer duration of diabetes, and often had pre-existing cardiovascular disease, in contrast to participants in other studies. Together, these clinical trials suggest that a more personalized approach to diabetes clinical care will be needed to ensure patient benefit and safety. Future research can inform this effort by examining ways to optimize clinical care of diabetes in people with different profiles and needs (e.g., medical, behavioral, psychological, social, and cultural). Many of these issues are also addressed in the “Special Needs for Special Populations” chapter. This effort will also be advanced by developing and testing measures that predict good

health outcomes in the diverse population of individuals who are living with diabetes.

### Key Questions

- **What are the best approaches to optimize cardiometabolic risk reduction in diverse populations with pre-diabetes or type 2 diabetes?**
- **How can diabetes management and outcomes be improved in older persons with diabetes who often have serious comorbidities?**
- **How can diabetes management processes be improved to alleviate the burden of disease in younger people with diabetes?**
- **What is the most appropriate sequence, rate of intensification, and tailoring of therapeutic goals to individual patient characteristics to optimize health outcomes and safety?**

### Future Directions

- **Develop individualized care approaches to optimize outcomes.**

One-size-fits-all approaches are not appropriate for people with diabetes. Goals of care and treatment approaches should vary based upon factors such as life expectancy, comorbidities, patient preferences, and social and cultural milieu. Ultimately, improving the quality and length of life of people with diabetes are the most important goals for diabetes care. Tailored behavioral and multi-component health care system approaches are likely to be most effective in achieving these goals. The development of best care practices must take into account the many biological, behavioral, environmental, economic, and social factors that affect diabetes

progression and treatment in an individual with the disease.

► **Identify methods to improve the quality of life and outcomes of older persons with diabetes.**

Professional societies have issued detailed guidelines for the clinical care of older persons with diabetes. Optimal implementation of these guidelines has been hampered by a number of factors, including the traditional belief that one size fits all in diabetes care—in particular, the concept that intensive risk factor control is suitable in all people with diabetes. Moreover, the focus on cardiovascular risk factor modification to the exclusion of quality of life and geriatric symptoms might not be appropriate in the elderly. A lack of data from clinical trials in the elderly diabetic population has made it difficult to determine the best means to care for these individuals. Database studies, clinical trials, and studies of the incorporation of geriatric principles in diabetes care could contribute to improvements in the quality of life and better health outcomes in older persons with diabetes.

► **Identify strategies for attaining optimal health outcomes in youth with type 1 diabetes.**

Management of type 1 diabetes in children and adolescents can be challenging for them, their caregivers, and their health care providers. On a daily basis, diabetes management to avoid the acute complication of hypoglycemia while avoiding long-term complications from hyperglycemia requires careful balancing of food intake, physical activity, and insulin treatment, as well as frequent glucose monitoring. Very young children with diabetes are not capable of complex disease management and might not be able to communicate the warning signs of hypoglycemia. These

children must rely on parents and other caregivers to monitor their condition around the clock. Over time, older children and adolescents can transition to self-management as they develop the cognitive and psychosocial skills needed to assume more responsibility for their own care. Older teenagers also need support to successfully make the transition from pediatric care to adult care. Diabetes management in children and young adults must take into account the potential for long-term complications.

Several randomized trials have demonstrated that family-based strategies are effective approaches to improve diabetes outcomes in children and adolescents. However, these approaches are often time consuming and costly. An important role for future translational research is to evaluate affordable and sustainable adaptations of these efficacious interventions. Research evaluating new and age-appropriate strategies for pediatric diabetes care will also be important in advancing the quality of care for youth with type 1 diabetes. These approaches need to optimize daily glucose control to minimize the development of risk factors for future end-organ complications, while also addressing the psychosocial needs of youth with diabetes and their families.

► **Determine systems of care that optimize processes and improve outcomes for people with diabetes.**

The traditional diabetes care paradigm has relied upon the well-trained provider working with the patient to provide high-quality care and facilitate diabetes self-management. The provider-patient relationship is likely to remain the heart of quality diabetes care, but research advances have indicated the power of embedding these interactions within systems of care

that promote individualized approaches—the right care delivered to the right person at the right time. Comparing various practice and business models of care will also elucidate ways to optimize quality of care and diabetes outcomes. Research to identify the factors that define an optimal system of care for diabetes has the potential to broadly improve outcomes for large numbers of people with the disease.

► **Find ways to make clinical trials more generalizable to diverse populations in different settings.**

Traditionally, clinical trials select relatively narrowly defined populations, often without significant comorbidities, to maximize internal validity. Moreover, study participants are often selected based on demonstrated adherence, and resources that are often not available or practical in the clinical setting may be applied to further maximize adherence. Thus, the applicability of these studies may be limited for diverse populations with comorbidities who receive care in community settings outside of a research trial. Studies that specifically address how to translate important clinical trial results for the general, non-study population should be supported. As a part of this effort, novel ways to increase generalizability of research need to be explored, such as broader inclusion criteria, the use of practice-based research networks, and specific targeting of diverse populations in different settings.

## Patient-Centered Care

Diabetes is a complex, heterogeneous disease that affects men and women of all ages, races, ethnicities, and socioeconomic circumstances. People with diabetes vary considerably in terms of comorbidities, cognitive status, and ability to manage their disease. Diabetes health care must take into account the individual and

the context in which that individual is being treated. For example, the appropriate care of an otherwise healthy teenager with type 1 diabetes will differ significantly from that needed by an elderly person with type 2 diabetes and coronary heart disease. Researchers are working to define patient-specific factors that influence diabetes care, including both medical and self-management of the disease.

## Key Questions

- **What self-management approaches support clinical care and ensure better outcomes for those whose diabetes is accompanied by multiple comorbidities?**
- **Which factors unique to the individual with diabetes, intervention, health care system, and context outside of the health care setting contribute to the success of self-management approaches?**
- **How can people with diabetes become more effectively engaged in the self-management of their disease in concert with their health care provider's efforts?**
- **How can evidence-based self-management interventions, using cognitive behavioral approaches, be incorporated into clinical and community-based care?**

## Future Directions

- **Identify a concise, practical set of behavioral and psychosocial factors, including both process and outcome measures, that can be collected and used on a routine basis to inform patient-centered care.**

Translating the results of clinical research into practical changes in diabetes care is often slowed by variability

in the outcomes measures used by different trials or studies. In trials of diabetes care, routine measurements of particular factors, such as health literacy or numeracy level or other potential factors influencing treatment outcomes, would enable researchers to directly compare the results of independent trials. A common, practical, and time efficient set of participant-centered measures is needed that might include collaboratively set goals, self-management behaviors, and related psychosocial factors, such as self-efficacy and diabetes distress. Identifying a common set of measures would still leave room for investigators to incorporate unique measurements or classification strategies into their own studies. In addition, standardized measures could also be used for quality improvement of diabetes care and for research on the links between processes and outcomes.

- **Understand the long-term effects of diabetes interventions with regard to sustained behavioral change (patient and/or provider) and diabetes health outcomes.**

Clinical studies evaluating the effectiveness of diabetes intervention strategies are often limited in duration due to multiple factors, including the difficulty in retaining study participants over long periods of time. Thus, it is often difficult to identify which interventions result in temporary improvements that are not sustained after the end of the study and which lead to lasting changes in behavior and health outcomes. Long-term follow-up research to assess the sustainability of diabetes interventions and identify factors associated with enduring success is warranted.

- **Understand how to increase diabetes self-management.**

Diabetes self-management is an important tool for improving health outcomes. Yet, individuals vary in

their desire to engage in self-management, and different self-management training strategies work better in some people than others. For example, some individuals with diabetes learn self-management best in group education settings, whereas others do better by working with a case manager. Research identifying which people benefit the most from specific diabetes self-management interventions holds promise for improving the quality and efficiency of care.

Approaches to self-management education that can reach a higher percentage of people with diabetes need to be developed and validated. Strategies might include in-office education, the use of community health workers or “health coaches,” Internet-based communication (Web portals or email systems), or telephone management approaches. Research on these strategies should consider what approaches work best for which people and under what circumstances. Researchers must also consider the role of the individual’s family in self-management support, as well as changes in self-management during development and aging. Moreover, the field needs clearer definitions, typologies, and measurement tools of self-management to facilitate comparison of interventions across different studies.

## Health Disparities

While overall quality of care for diabetes across the country remains suboptimal, it is particularly worrisome for individuals with diabetes from minority groups, and those who are poor or uninsured. These troubling differences in health care delivery, processes of care, and outcomes have been demonstrated across the United States in a variety of health care settings. Several research studies have evaluated interventions to improve health outcomes among racial and ethnic minority populations in the United States. These studies suggest that improving processes of care

(e.g., frequency of lab testing or referral) do not always translate into improved diabetes outcomes. More information is needed about the causes of disparities and how to reduce the disparities in health care delivery and outcomes in the poor, the uninsured, and in ethnic and racial minority groups, including African Americans, American Indians, Asian Americans, Hispanics, and Native Hawaiians and other Pacific Islanders. Routine collection of race/ethnicity data and stratification of quality of care measures and outcomes will support efforts to identify deficiencies in care and reduce disparities.

### Key Questions

- **What health care interventions are effective at reducing disparities in diabetes outcomes?**
- **When are culturally tailored interventions necessary and more effective, as opposed to using more general interventions, in reducing health disparities in diabetes outcomes?**
- **How can health communication science be harnessed for the reduction of health disparities in the prevention and control of diabetes?**

### Future Directions

- **Identify effective interventions to reduce racial, ethnic, and socioeconomic disparities in diabetes care and outcomes.**

Reducing disparities between minority populations and non-Hispanic whites will require comparative research designs to evaluate culturally tailored interventions for improving shared decision making, self care, and outcomes. Such studies must take into account multiple

factors at the level of the individual (e.g., sociocultural barriers, limited literacy and health literacy, logistical barriers to care, trust, language barriers, and social support); provider (e.g., communication barriers, implicit bias, and information technology limitations); community (e.g., community assets and challenges, and neighborhood contextual effects); and the health system (e.g., insurance issues, resource and infrastructure inequities, and reimbursement disparities). Effective interventions must also address issues of health care financing, access to care, and the special needs of resource-poor health organizations serving vulnerable populations. The willingness of providers and health care systems to acknowledge disparities and to specifically address these differences as part of overall quality improvement programs is critical to developing and validating successful multi-target interventions.

Some minority groups, including American Indians, Alaska Natives, Native Hawaiians and other Pacific Islanders, and Asian Americans, are understudied with regard to disparities in diabetes outcomes and care. New approaches are needed to study these relatively smaller populations and to discern the underlying causes and potential remedies for health disparities in these groups.

- **Identify effective ways to improve the health of individuals on the fringe of health care systems.**

People most at risk for poor diabetes outcomes are often those who are uninsured or underinsured—i.e., on the fringe of health care systems. These individuals often disproportionately rely on urgent and emergent care facilities for routine care. Finding innovative ways of transitioning these persons to the primary care system will be important to future efforts at reducing



racial/ethnic disparities in chronic disease outcomes such as diabetes. To date, little research has been done in this area.

- ▶ **Advance the study of health communication science and technologies to test strategies for addressing health disparities in diabetes prevention and control.**

The role of culture is a critical factor in enhancing the effectiveness of health communication. Despite general agreement that interventions and materials need to be culturally appropriate for the target population, more research is needed on how best to achieve such appropriateness. An improved understanding and advancement of theoretical models of behavior change could help guide the development and testing of culturally targeted health communication designed to make information about diabetes prevention and control more relevant and effective for specific audiences. Such strategies must factor in rapidly changing information technologies, financial constraints, and the need for ongoing training of quality staff. Collaboration of diverse stakeholders, including academics, health professionals, and lay participants, will help foster research to improve organizational and public health information systems and develop audience-appropriate information for diabetes prevention and control.

## Systems of Care

Diabetes care is delivered in a variety of settings both within the traditional health care system (e.g., hospitals, health centers, physician offices) and outside of it (e.g., community centers, schools, worksites). The successful translation of research findings related to diabetes prevention and control depends on multiple factors within these settings, including payment models, the composition of health care delivery teams, the institution

of community partnerships and, increasingly, the availability and use of population management tools, such as disease registries and electronic medical records. Identifying optimal systems to support the distribution of evidence-based care and the adoption of new behaviors is a major focus of translational diabetes research.

## Key Questions

- **How can multi-level interventions, combining policy/marketing, community, organization, delivery system, provider, and patient/family components, be implemented and sustained to improve diabetes care and outcomes?**
- **What are the key principles for adapting evidence-based interventions to real-world settings in ways that make them locally relevant, preserve their effectiveness, and expand their reach to a higher proportion of people with diabetes?**
- **How do novel mechanisms for payment of health care services affect the process and outcomes of diabetes care?**
- **How can interventions to control diabetes be cost effective for society and financially feasible from the perspective of individual payers and health care organizations?**
- **What practical measures of the quality/processes of diabetes care bear the strongest relationship with better downstream outcomes? Can reporting of such measures and novel methods of payment improve these outcomes?**
- **Can decision support tools or other health information technologies be used**

## **to facilitate breakthroughs in clinical performance related to diabetes care and quality improvement?**

### **Future Directions**

- **Understand how changes in the structure of health care delivery systems can lead to improvements in diabetes care and prevention.**

Interest in the patient-centered medical home has increased rapidly over the past few years. The medical home combines the principles of continuous, comprehensive, coordinated primary care with practice innovations such as health information technology, chronic care management, and quality improvement. The patient-centered medical home changes the way care is organized, coordinated, and delivered, and thus may have an impact on diabetes outcomes. Translational research is needed to determine how to best organize care in ways that optimize outcomes. For example, does the patient-centered medical home (or other models of care) improve diabetes outcomes?

- **Develop strategies to implement and sustain organizational efforts to improve diabetes care and outcomes.**

Dissemination and implementation of interventions to improve diabetes prevention, care, and outcomes in the health care setting and community have been limited. Relatively little effort has been devoted to studying the process of implementing health care interventions. Community strategies have been limited by factors such as the time needed to develop working partnerships and the lack of incentives for community involvement. Moreover, the level of buy-in and implementation of interventions after research funding has ended

(institutionalization) depends on organizational climate and individual leadership. Innovative, mixed-method research drawing upon fields such as implementation and dissemination science, organizational readiness, and economics is needed to progress toward these goals. In addition, new paradigms for research planning, such as longer time frames to allow for the development of meaningful community partnerships, will ensure stronger foundations for sustainable programs. Translational research to evaluate programs for diabetes prevention and improved care should consider and measure factors related to adoption, cost, and sustainability.

- **Integrate multi-level interventions (combined policy/marketing, organization, provider, patient/family, community) synergistically to enhance the likelihood of success and sustainability.**

Substantive changes that link the health care delivery system to the community and incorporate multiple levels of interventions might include: co-location of primary care services and community organizational programs that support behavior change, such as primary care clinics at the YMCA; redesign of primary care clinic processes to streamline ongoing health risk assessment, tailoring of educational and counseling resources during the visit, and group meetings; planned and/or group visits that involve community program partners or peer navigators that help to link individuals with other community resources between visits; formal tracking and communication tools that help to strengthen linkages between community resources and primary health care providers; and co-location or integration of diabetes and mental health services. Studies are needed to determine which integrated programs are most effective at delivering diabetes prevention

and care services in ways that benefit individuals and the community in the long term. Such research must take into account that the optimal program for diabetes intervention might differ depending on the composition, current health status, or other contextual elements of particular communities.

► **Identify optimal settings for delivery of diabetes interventions.**

Systems theory has documented that context is critical for determining the success of interventions. These findings, along with advances in “the science of place,” have shown that settings are critically important factors that need to be addressed for translation success. For example, schools might provide an opportunity to implement diabetes prevention efforts for youth, whereas worksites or churches might be ideal venues for delivery of adult or family-based interventions.

► **Evaluate “natural experiments” that occur when policy or care changes are instituted in health care settings that affect large numbers of people with diabetes.**

Estimates that diabetes care costs will almost double in the next 25 years motivate efforts to consider a major redesign of chronic care delivery in order to expand access to and quality of health care. Structural changes in health care can be costly and challenging to evaluate. However, given considerable costs predicted for future diabetes care, it is likely that some changes in care will be implemented without the benefit of controlled trials. In these cases, research that evaluates these “natural experiments” will help clarify what changes in care work, and under what circumstances. Ideally, studies of changes in the structure of the chronic care delivery system should consider changes in the methods for financing and payment. Crucial factors such as

variation in the costs, quality, and outcomes of diabetes and related comorbidities that occur with substantive changes in the structure of the delivery system should also be evaluated. Successful evaluation of “natural experiments” may often require collaboration among multiple stakeholders, including the NIH, CDC, AHRQ, private health care providers and purchasers, and other partners.

► **Develop new approaches to study the impact of system- and policy-level interventions on diabetes control and prevention.**

Observational epidemiologic studies and randomized controlled trials (RCTs) have provided a large proportion of the current science base for interventions in clinical and public health practice, but neither traditional cohort studies nor RCTs have been adequately flexible or practical to test the continual innovation in health service approaches used in health systems and in communities. This may be because the practical and financial costs of randomization, implementation of intervention, and new data collection for interventions designed to be spread broadly across large populations often make them impractical for inclusion in traditional randomized trials. Surveillance system data have not filled this gap either, as they are often neither flexible nor specific enough to measure the impact of population-targeted interventions. These limitations, along with the increasing need for a stronger evidence base of policy-level interventions for diabetes control and prevention, point to the need for new research platforms that facilitate the study of systems- and policy-level interventions that take advantage of already occurring or imminent interventions and policy initiatives. This need may be achieved through better use of quasi-experimental or adaptive study designs, efficient time-sensitive surveillance approaches, and practical trials

of new interventions occurring as part of ongoing public health practice. These designs will require efficient assembly of diverse datasets and/or augmentation of available data systems and identification of appropriate control groups to permit inferences about causal effects of policies and interventions.

➤ **Identify promising strategies, such as pay-for-performance and public reporting of performance measures, to bridge the persistent gap in quality of diabetes care and outcomes.**

Payment coverage of diabetes services is likely to affect quality of care and outcomes. Cost sharing with high co-pay/co-insurance levels and, possibly, high deductible arrangements can have a negative impact on self-management behaviors, utilization of preventive services, risk factor control, and longer-term outcomes. Potentially beneficial changes in the delivery system design (e.g., team care, community linkages, and lay health worker and peer interventions) are not supported by fee-for-service reimbursement to physicians, but research suggests that salaried physicians do not provide better care, and individual capitation payments can result in undertreatment. Although performance incentives have been increasingly adopted by public and private insurers, their overall effectiveness at improving health care delivery and health outcomes remains uncertain, and the potential for unintended negative consequences exists. Research into the

effect of such incentives on diabetes care and diabetes outcomes is warranted. This essential question should probe beyond earlier work comparing fee-for-service, patient capitation payments, and physicians who are salaried. New ideas about blended payment systems may have clear advantages over these earlier models. Examples include condition-specific capitation and/or multi-provider, episode-of-care payments coupled with pay-for-performance. Fundamental payment reform strategies that will facilitate team-based care, provide adequate support to change the roles and responsibilities of clinical team members, reward behavior change and lifestyle intervention activities, support linkages with the community, and promote more widespread and efficient use of health information technology should also be studied.

➤ **Identify new uses of health information technology to improve diabetes care.**

The rapid development of information technology to support health care offers exciting new opportunities for improvements in diabetes care. Technologies, such as personal health records, Web portals, and other means of chronic disease management, are becoming more widely available, although the implementation and effectiveness of these tools can vary across different health care settings. Researchers are studying the best approaches to incorporate new technologies in ways that help people with diabetes become more involved in their care and improve self-management and outcomes.

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

The multidisciplinary diabetes research enterprise supported by the NIH and other public and private agencies has uncovered a wealth of information on effective means to prevent type 2 diabetes and improve long-term outcomes both for people with type 1 and people with type 2 diabetes. These findings often result from controlled, randomized clinical research trials with volunteers who have been carefully selected to meet specific criteria for participation. However, large gaps persist between knowledge generated from the most successful clinical trials and current medical practice for diabetes prevention and control. With its focus on real-world applications, translational research is essential for bridging those gaps to improve the lives and health of all individuals who are at risk of developing diabetes or who live with this disease every day.

Translational research addresses the context of diabetes prevention and care—how can the often generalized results of clinical research be adapted to suit the needs of individuals, diverse population groups, or different health care delivery settings or systems? If pursued, the translational research goals and directions described

in this chapter have the potential to make a substantial impact on the national diabetes epidemic. Effective methods for widespread prevention of type 2 diabetes in high-risk individuals and populations could significantly reduce the number of people who are affected by this devastating and costly disease. Likewise, improved diabetes care and self-management practices that are optimized for the individual can prevent or delay the onset of complications that represent a major source of morbidity and mortality and account for a large proportion of health care spending for diabetes. New, validated approaches for social and cultural tailoring can help underserved populations, including racial and ethnic minorities and the poor, receive the benefits of research to improve diabetes care and outcomes. Such efforts to reduce disparities in diabetes health care must be linked to strategies to improve the overall efficiency of the health care delivery system in managing this complex disease. Collectively, translational research efforts are key to improving the health of the American public and reducing the escalating costs of health care for diabetes in the United States.



New tools, technologies, collaborations, and human resources—from investigators to participants in clinical studies—are helping to accelerate diabetes research. *(Photo credit: Getty Images.)*

# RESOURCE AND INFRASTRUCTURE NEEDS FOR DIABETES RESEARCH

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## INTRODUCTION

Diabetes and obesity are complex medical problems with numerous causes that range from genetic susceptibility to behavioral and environmental factors. Diabetes affects organ systems throughout the body, and management of the disease to prevent or treat complications depends on multiple factors, such as an individual's age, the presence of comorbidities, and level of access to health care. Over the past decade, NIH-supported research has led to significant advances in understanding the causes of type 1 and type 2 diabetes, diabetes complications, and obesity (a strong risk factor for type 2 diabetes), as well as to new approaches and technologies for their management. Remarkable progress has been made in detecting regions in the human genome containing genes that modify risk of these diseases. For both forms of diabetes, improved glycemic control has been shown to slow the progression to complications of the disease. For type 2 diabetes,

the demonstration that the disease can be prevented or delayed with lifestyle changes and/or medical intervention has offered new hope that the rising epidemic can be contained or perhaps reversed.

Despite this substantial research progress, diabetes and obesity continue to place a large burden on the U.S. health care system and on affected individuals. Addressing the complexity of diabetes, obesity, and their care requires the collaborative efforts of the research and clinical communities, as well as the establishment of, and broad access to, shared research resources and state-of-the-art technologies. Strong NIH support for resource and infrastructure development is critical to the successful implementation of the strategic research plan for diabetes and obesity research that is laid out in the preceding chapters of this report.



## KEY QUESTIONS AND FUTURE DIRECTIONS FOR RESOURCE AND INFRASTRUCTURE DEVELOPMENT

In developing this strategic plan, the working groups identified six categories for resource and infrastructure development that, if pursued, could advance all aspects of basic, translational, and clinical research on diabetes and obesity. These categories address the need for a well-trained, diverse workforce; the benefits of creating common resources and opportunities for collaboration; the need to develop and apply advanced technologies and novel animal models for diabetes and obesity research; the importance of disseminating information about shared resources and developing policies for protecting the privacy of medical and other information about participants in research studies to facilitate access to those resources that include such information; and the synergies that are possible from public-private research partnerships.

### Research Training and Human Resource Development

The diabetes research enterprise requires a diversely-trained, multidisciplinary, and interactive workforce to fully address the complexity of disease etiology and its treatment. In addition to attracting, training, and retaining the best and brightest new researchers to the study of diabetes, it is necessary to build multidisciplinary research teams that can pursue strategies based upon an integrated view of diabetes risk, progression, and care. To stay at the leading edge of biomedical research, it is critical to encourage investigators with a wide range of expertise, as well as those in emerging or non-traditional disciplines, to apply their skills to important problems in diabetes research.

### Key Questions

- **How can training and career development in all aspects of diabetes research be enhanced?**
- **What programs can be developed to train multidisciplinary researchers capable of examining interactions among biological, psychological, behavioral, social, and environmental factors that have an impact on diabetes and obesity?**
- **How can biomedical engineers, computational biologists, mathematicians, and experts in disciplines not traditionally applied to the problems of diabetes, obesity, and complications be encouraged to pursue research on these diseases?**
- **How can training of physician-scientists be supported in critical areas such as genetics/genomics and biostatistics, population-based methods, and interventional research?**
- **How can investigators from under-represented minority groups be more effectively encouraged to pursue research careers that are focused on diabetes and obesity?**
- **What educational opportunities can be developed for clinical practitioners and for the general public to encourage participation in clinical research?**

## Future Directions

- **Incorporate transdisciplinary research opportunities into training programs related to diabetes and obesity.**

Understanding, preventing, and treating diabetes and obesity require innovative approaches that address complexity and blend the perspectives and skills of multiple disciplines. New or expanded programs that give investigators the opportunity to cross-train in more than one field would create innovative approaches and generate novel research strategies.

- **Create training programs that encourage the application of new fields of study to key problems in diabetes.**

As biomedical technologies have become increasingly sophisticated, a need has developed for recruitment of scientists with expertise in computational biology, statistical genetics, engineering, nanotechnology, imaging, medical informatics, bioinformatics, mathematics, social sciences, and other disciplines to diabetes research. Training programs that introduce such scientists to diabetes and obesity research are critical in order for this field to capitalize on the development of advanced research technologies and remain at the leading edge of biological research.

- **Enhance training opportunities for basic and clinical investigators and establish opportunities for translational research in all aspects of diabetes and obesity research.**

NIH currently supports multiple training and career development opportunities for investigators at all stages of the research career trajectory, from graduate or medical school to postdoctoral training and the establishment of an independent research

program. Efforts are needed to communicate these opportunities to trainees with an interest in diabetes or obesity research and to ensure adequate support for a pipeline of new, well-trained investigators in basic and clinical disciplines related to these diseases. Moreover, efforts are needed to enable the retention of new investigators in the diabetes research field as they make their critical, and often difficult, transition to research independence. In addition, new programs are needed to foster translational research training so that experimental results are efficiently converted into real-world solutions to improve the health of individuals living with diabetes or obesity.

- **Develop programs to educate the medical community and the general public on clinical research.**

The success of clinical research and clinical trials depends on researchers' ability to recruit and retain willing participants. Collectively, clinical research and trial protocols for diabetes and obesity require both healthy volunteers and those with diabetes or obesity, with a wide spectrum of personal characteristics (e.g., age, sex, race, ethnicity, and medical history). Education programs are needed to help the public understand the process of clinical research, as well as the risks and benefits of participation in observational and interventional protocols. Similar programs are needed to engage clinical practitioners who could refer their patients for potential enrollment in appropriate studies.

## Diabetes Research Resources

A major obstacle to research on human diabetes and obesity is the difficulty in obtaining high-quality human cells and tissues. While major efforts in type 1 and type 2 diabetes have been implemented for establishing DNA resources, individual investigators, particularly

those trained in basic science, might not have the appropriate expertise or access to patient populations in order to acquire or collect biosamples from people with or without disease. Others lack sufficient funding and space to collect, annotate, and store the hundreds or thousands of human biosamples that are needed for some studies, for example to search for biomarkers of disease progression. In the case of some conditions or tissue collections, it may be difficult for a single investigator or institution to obtain enough samples for research. The establishment of central research resources can alleviate these issues by providing broad access to well-annotated biosamples and clinical data more efficiently and at lower cost than would be required for individual investigators to develop multiple, potentially duplicative resources. Other shared resources, such as patient registries and mechanisms to encourage interactions among diabetes and obesity centers, researchers, and clinicians, would also promote the more efficient use of resources and create research synergies.

### Key Questions

- **How can access to high-quality human islets and pancreatic tissue for research be improved?**
- **What data registries or biobanks of human tissues and cell lines from people with and without diabetes would best support diabetes research?**
- **How can long-term studies of diabetes and its complications be optimized to provide research data and resources to the diabetes research community?**

- **How can transdisciplinary research and collaboration be encouraged, publicized, and supported across departments, institutions, and methodological fields?**

### Future Directions

- **Establish biobanks of annotated human tissue samples related to diabetes and obesity etiology and diabetic complications.**

Improved access to human tissues would accelerate nearly all aspects of diabetes and obesity research. For example, important differences between rodent and human islet physiology are well-documented. Scientists who are studying the role of the beta cell in human diabetes, or developing better methods for islet transplantation, rely on central procurement and processing centers for access to human cadaveric islets, and continued support for this resource is critical. A supply of human islets from individuals across the disease spectrum is necessary for efforts to understand the pathogenesis of diabetes and to provide cellular and molecular profiles that serve as a roadmap for research on embryonic stem cells and induced pluripotent stem cells. Expansion of the islet procurement processes to include islets and pancreata from individuals with type 2 diabetes and other forms of diabetes is needed. The Network for Pancreatic Organ Donors with Diabetes (nPOD) was begun as a pilot project of the NIH-supported Diabetes Centers program and was then expanded by the JDRF to collect, characterize, and distribute pancreatic and other tissues from cadaveric organ donors who had type 1 diabetes or were at high risk for developing type 1 diabetes. Further expansion

of this resource to include procurement of pancreata from individuals with type 2 diabetes and other forms of diabetes is needed. Extended support for resources such as processing centers for islets, fat, muscle, and other tissues would promote research on features of human diabetes and obesity that differ from those present in experimental models of diabetes. Support for these resources and biobanks of tissues, including fat, liver, muscle, eye, nerve, kidney, and blood vessels, is critical for translating basic science discoveries to human physiology and pathophysiology. Such biobanks would complement existing NIH-supported repositories that collect, store, and distribute human biosamples and data from clinical trials. It is critical that any material collected in this fashion be carefully annotated with regard to relevant clinical and medical/family historical information and that DNA be banked as well.



Saving samples from large clinical trials and other studies helps the diabetes research community to capitalize on these resources in new and future efforts. (Photo credit: © iStockphoto.com/choja)

► **Follow cohorts of individuals with type 1 diabetes and youth with type 2 diabetes longitudinally.**

It is critical to be able to study large numbers of individuals with diabetes longitudinally to understand the clinical course of the disease and outcomes of established and new treatments. Efforts should be made

to capitalize on existing cohorts, by extending follow-up of individual cohorts and promoting cross-cohort analyses, and to create new cohorts, where needed. Major new findings have already emerged from long-term follow-up of participants in clinical trials a decade or more after the randomized phase of the study, and similar important observations can be anticipated from follow-up of participants in current clinical studies. By studying large numbers of individuals with type 1 diabetes, researchers could develop new hypotheses for environmental triggers of type 1 diabetes onset and/or progression. As new therapies are developed to treat or prevent type 1 diabetes, longitudinal studies will be essential for tracking long-term efficacy and safety. Long-term safety studies are especially important for immunomodulatory therapies. In addition, studies are needed to better understand the time course and molecular mechanisms for development of complications in individuals with type 1 diabetes, particularly cardiovascular disease, and to understand how CVD risk factors can be effectively modulated. Long-term studies are also essential to understanding the clinical course of type 2 diabetes in children and adolescents, particularly the natural history of beta cell function and the development of complications. A better understanding of the factors that lead to deterioration of beta cell function may promote the development of strategies to maintain beta cell function, making diabetes easier to treat, or even possible to reverse. Finally, several small, clinic-based studies suggest that young people who develop type 2 diabetes may have a more virulent course, with earlier development of complications, but this has not been systematically studied.

- ▶ **Develop mechanisms to foster communication and collaboration among researchers and clinicians with an interest in diabetes and obesity.**

Mechanisms to facilitate interactions among basic scientists studying model organisms and animal models of disease, clinical researchers focused on human disease, multidisciplinary researchers with a broad view of disease, and medical practitioners who treat people with diabetes could have a transformative impact on diabetes and obesity research. Sharing of resources, such as newly developed animal models, and improved communication among these groups could accelerate the translation of important findings from transgenic mouse and other technologies into human studies. Sharing information from clinical practices, perhaps through de-identified medical records, could spur new insights or hypotheses for research. Establishing formal interactions between investigators studying genotypes and phenotypes related to diabetes and obesity could stimulate new lines of research. Promoting cross-disciplinary interactions could be incorporated into the missions of existing NIH-supported Centers for diabetes, obesity, or nutrition research.

- ▶ **Promote interactions between NIH-supported Centers for diabetes and obesity research and other research institutions to maximize access to state-of-the-art resources and training.**

The NIH supports multiple Centers that provide core resources for diabetes and obesity-related research. These Centers help to establish an interactive community of researchers within their home institution, and some Centers, such as the Clinical and Translational Science Awards, also support research training and translation of research into community

settings. With additional resources and incentives, Centers could be encouraged to extend their reach to external diabetes and obesity researchers. By providing services, training, and access to advanced technologies to a broader community, Centers would enable research that might not otherwise be possible, and build a larger, collaborative network of diabetes and obesity researchers.

## **New Technologies, Methodologies, and Measurements for Research**

Over the past decade, the development of advanced technologies and methodologies has revolutionized the biomedical research field and allowed researchers to probe human biology at a level of detail, and with an efficiency, that was previously impossible or extremely time-consuming. Now, high-throughput sequencing techniques permit unbiased, genome-wide searches for disease susceptibility genes. Advanced bioinformatics approaches make it possible to mine extremely large datasets, which can both answer specific research questions as well as generate new hypotheses through complex systems and integrative computational approaches. New methodologies and measurements for studying human behavior facilitate research to understand how the environment affects health and disease. These and other state-of-the-art technologies and methodologies have the potential to open up significant new avenues in the study of diabetes and obesity.

### **Key Questions**

- **What DNA/RNA/protein sequencing and other technologies are needed to identify and study diabetes candidate genes and to better correlate genotypes with phenotypes in humans?**

- How can mouse or cellular models be developed that are informative about the functional consequences of genetic differences associated with diabetes or obesity?
- How should evolving proteomic and metabolomic approaches be harnessed for diabetes research?
- What imaging technologies and resources are needed to advance research on diabetes, obesity, and related complications in humans?
- What bioinformatics resources and statistical approaches need to be developed or made more accessible to facilitate diabetes research?
- What tools are needed to measure energy balance in free-living humans (versus controlled research environments)?
- What new analytic methods or tools are needed to study complex, multi-level interactions within populations that affect obesity?
- Can standardized methods be developed for assessing predisposing behaviors and outcomes in human obesity trials?
- How well do self-reported and observational measurements correlate with biological markers?
- What are the best research designs to study causality in sociological systems?
- Can new instruments be developed to measure health promotion outcomes across communities and populations?
- How can more efficient communication be encouraged between people with diabetes and health care providers?

## Future Directions

- Develop and make available advanced technologies for discovering diabetes genes in humans.
- Develop analytical methods for epigenetic processes and other resources to study the relationships among genotypes and phenotypes in humans.
- Establish banks of monoclonal antibodies specific for diabetes-associated proteins.

Methodologies such as a \$1000/genome sequencer, high-throughput RNA sequencing, and deep sequencing technologies are being developed that can help to define the universe of diabetes-associated genes and to correlate genotypes with phenotypes. In addition, these and new high-throughput screening technologies will aid in the development of pharmacogenetic approaches to determine which individuals are most likely to benefit from particular therapies. New rodent, human, and mathematical models, as well as monoclonal antibodies to disease-associated gene products, are needed to definitively establish the importance of diabetes candidate genes and to facilitate their in-depth study. New methodologies for detecting and interpreting epigenetic processes would help researchers better understand how the environment influences the link between genotype and phenotype in individuals with diabetes or obesity. Evaluating the impact of epigenetic modification will require research to determine the extent to which readily accessible cells, such as those

from blood or skin, accurately reflect epigenetic patterns in diabetes-relevant tissues, like pancreas or liver, that are less accessible for routine analysis.



New technologies facilitate advances in diabetes research. (Photo credit: © iStockphoto.com/dra\_Schwartz)

Central core laboratories with access to sophisticated equipment and personnel who are well-trained in the application of state-of-the-art methodologies for sequencing, epigenetic analysis, and antibody generation and validation would be an invaluable resource. By generating high-quality reagents and data using uniform protocols, such cores could extend the application of these technologies to the broad diabetes and obesity research community and enable the direct comparison of results among laboratories.

- **Create novel cell lines and related resources for diabetes and obesity research.**
- **Encourage new approaches to diabetes research and treatment based on stem cell technology.**

Discovering ways to efficiently differentiate stem cells into insulin-producing beta cells could supply an unlimited source of beta cells to study the molecular pathogenesis of type 1 and type 2 diabetes and, ultimately, for therapeutic replacement. The development of mutation-specific hypothalamic neuronal cells lines, perhaps through the use of induced

pluripotent stem cell (iPS) technology, would provide an important tool for obesity research. Likewise, cell lines from people with diabetes could reveal novel molecular signatures reflective of disease subtypes. New cell lines for the study of vascular biology and vascularized patches would aid research on diabetic complications. Encouraging the development of these and other cell lines, whether based on stem cell technology or more conventional approaches, would promote new opportunities for diabetes and obesity research and treatment.

- **Make new technologies available as they arise, including stem cell resources.**

The development of iPS cells from individuals with diabetes could benefit many lines of research, including investigation of how specific genetic variants influence disease and the development of personalized therapies. Creating a biobank of disease-specific, well-annotated iPS lines or other experimental cell lines or reagents would make these tools available to a broader community and encourage innovative research.

- **Apply proteomic and metabolomic methodologies to research on diabetes and obesity.**

Proteomic technology enables researchers to study the entire set of proteins, including their relative abundance and the presence of post-translational modifications, in a particular cell or tissue. This technology can also be used to evaluate how those proteins and modifications differ among tissues or under varying conditions. For example, the protein complement in healthy kidney tissue can be compared to that in kidney tissue from a person with diabetic nephropathy to determine which molecular pathways are affected by the disease. Similarly, metabolomics can be used to assess the

presence of metabolites and the flux through metabolic pathways in various states of health and disease. Applying proteomic and metabolomic technologies has the potential to uncover alterations in biochemical pathways associated with obesity and diabetes, suggest new targets for therapeutic intervention, and identify biomarkers of their development or progression.

► **Develop advanced, noninvasive imaging techniques that can be used in living humans.**

A critical gap in diabetes and obesity research is the lack of reliable, affordable, noninvasive methods to image relevant cells and tissues in living humans. Innovative approaches are needed to assess pancreatic beta cell mass and function, study adipose tissue and measure adipocyte turnover, improve functional brain imaging, and monitor the development and progression of end-organ complications, among other uses. The development of enhanced imaging techniques would benefit basic research on disease pathology and accelerate clinical trials by more quickly and specifically evaluating trial participants' responses to new therapies.

► **Develop statistical and bioinformatical methods and resources for integrating and analyzing large datasets generated by state-of-the-art technologies.**

Many advanced technologies, including deep sequencing, proteomics, metabolomics, and imaging, generate massive datasets. New bioinformatics approaches are needed to analyze and mine these data sets to derive conclusions and generate new hypotheses. In addition, bioinformatics approaches are required to relate and integrate data generated by different technologies—for example, to correlate genotypic data from a deep sequencing project with phenotypic data derived from an imaging technique or a proteomic assay. Such

approaches can help researchers develop a systems-level understanding of diabetes and obesity, which have wide-ranging effects on the body.

► **Design innovative tools for studying energy balance under real-world conditions.**

Advances in diabetes and obesity research have shown promise for preventing or treating these diseases in participants enrolled in carefully controlled clinical trials. Translating these results to real-world conditions requires new tools for both short- and long-term monitoring of energy intake, energy expenditure, physical activity, and relevant behavioral assessments in humans. Such tools must be accurate and cost effective for use in real-world conditions over time.

► **Develop new methods for studying the impact of the environment on obesity.**

Research clearly demonstrates that a person's environment makes a significant contribution to their risk for obesity. New analytical methodologies are needed to study complex, multi-level interactions within populations, including the effects of social networking and the built environment, in relation to obesity.

► **Improve and standardize measurements for translational research.**

Standardizing the use of effective behavioral and environmental measures would facilitate comparison of results from translational research projects in diabetes and obesity. In particular, standardized clinical outcomes measures, both self-reported and observational, and standardization in community and population methods, including sensitivity to differences among populations, are needed.



► **Develop new methodologies for comparative effectiveness research.**

The variety of pharmaceutical, biologic, and/or behavioral therapies for diabetes and obesity can create uncertainty among clinicians and patients regarding the most effective and appropriate treatment. Comparative effectiveness research aims to directly compare two or more therapies to determine the best treatment for individuals. Such research might involve head-to-head clinical trials, evaluation of past trials, or analysis of outcomes data from clinical registries, data networks, or other electronic records.

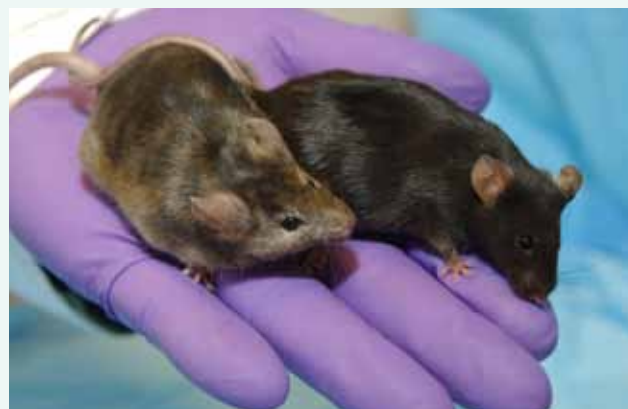
► **Develop advanced Web-based and mobile technologies for capturing clinical data, enhancing education, and facilitating data management.**

Diabetes and obesity researchers have an opportunity to capitalize on emerging Web-based and mobile technologies to enhance clinical research as well as translational research to implement research findings in the community. These technologies offer the potential for real-time collection of clinical data, more frequent communication between researchers and trial participants, and improved data management.

## **Animal Models for the Study of Diabetes and Obesity**

Biomedical research relies on the use of animal models for studies of physiology and pathophysiology that are not possible in humans. Animal models are also essential for pre-clinical testing of new therapeutic agents to assess safety and efficacy before human trials can begin. Although research on animal models has led to great insights on the causes, progression, and treatment of diabetes and obesity, no animal model perfectly mimics these diseases in humans. For example, diabetic

mouse models do not all develop the same range of end-organ complications as humans. Similarly, non-human primates, which are an important model of islet transplantation for type 1 diabetes, do not spontaneously develop autoimmune diabetes. New animal models that are more comparable to human diabetes and obesity would help researchers to better understand these diseases, develop new interventions, and predict how people will respond to potential new therapies.



Animal models are important to research efforts to understand and develop interventions for diabetes and obesity. (Image credit: National Human Genome Research Institute, NIH.)

### **Key Questions**

- **What new small and large animal models are needed to accelerate research on type 1 and type 2 diabetes?**
- **Can animal models be developed that mimic human obesity etiology and treatment outcomes?**
- **Can animal models be developed that better simulate complications of human diabetes? Can new biomarkers be defined for complications in both animal models and humans?**

- **How can functional brain imaging techniques be improved for use in animal models?**
- **What new resources are needed to improve the phenotyping of animal models for diabetes and obesity?**

## Future Directions

- **Develop new small and large animal models that better represent the pathology and treatment of human diabetes and obesity.**
- **Develop *in silico* models of disease pathogenesis in type 1 and type 2 diabetes.**

Research is needed to develop novel small and large animal models that more closely simulate human type 1 diabetes, type 2 diabetes, diabetes complications, and obesity. The development of mouse models with immune systems more closely resembling those of humans, as well as primate models of autoimmunity, is critical to understanding the immune process in human type 1 diabetes. Better models of beta cell autoimmunity could lead to new insights regarding beta cell function, failure, and regeneration that might be applicable to both major forms of diabetes. Animal models that more closely mimic human type 2 diabetes are needed. Mouse models that are genetically modified to label specific neuronal populations could be used to investigate neuroanatomy and function, as well as to understand the causes of diabetic nerve damage. Animal models of gastrointestinal bypass surgery that mimic the changes in weight and metabolism observed in humans could help scientists understand the hormonal and other short- and long-term effects of this surgery. Animal models of metabolically benign obesity are also needed. These are

only a few examples of the many types of new animal models that could be useful for diabetes and obesity research.

Researchers are now taking advantage of discoveries in computational sciences to build *in silico* models of diabetes. Such models that map complex biochemical pathways and cellular processes can be used to understand the effects of pathophysiologic perturbations, identify therapeutic targets, and predict an organism's response to drugs. *In silico* models might also reveal similarities and differences between the physiology of animals and humans that can lead to new hypotheses of disease development and progression that can then be tested *in vitro* and *in vivo*. Support for the development of improved animal and *in silico* models of diabetes and obesity will help researchers to develop an integrated view of these diseases that can then be translated for the benefit of people.

- **Standardize research protocols involving diabetes-related mouse models.**
- **Develop standard definitions of abnormalities in mouse models of diabetes and obesity.**

Experimental results in animal research are influenced by a multitude of factors, some of which may be controlled. Standardizing controllable aspects of research protocols (e.g., diets, daily care, environmental circumstances, and research protocols) that involve diabetes and obesity-related mouse models would facilitate effective collaboration and comparison of results among laboratories, particularly those located in different medical centers. Likewise, the development of standard definitions of pathophysiology would promote

better comparison and evaluation of experimental results from different laboratories.

► **Develop improved methods and technologies for phenotyping of mouse models.**

Mouse models have proven invaluable for research on many diseases due in part to the ease of genetic engineering in this species and a relatively short generation time. Because of the widespread use of numerous mouse models for diabetes, complications, and obesity research, adequate facilities are needed to make sophisticated phenotyping techniques available to the broad research community. In particular, resources are needed to develop and provide access to advanced imaging technologies for mouse models that can be related to equivalent studies in humans.

## **Distribution and Sharing of Human Data and Biosamples**

As described in the previous sections of this chapter, new diabetes research resources, emerging technologies and methodologies, and animal models would have the most impact if standardized and shared widely within the diabetes and obesity research communities. Likewise, distribution of clinical biosamples and datasets would allow independent investigators to analyze well-annotated specimens and data from multiple perspectives and gain unique insights without the need for duplicative sampling programs. Mechanisms are needed to disseminate information about the availability of biosample and data collections and to ensure the protection of study participants' privacy when materials are made available beyond the originating investigator or group.

## **Key Questions**

- **How can communication be fostered between basic scientists and clinical investigators conducting clinical studies and trials?**
- **How can awareness of and access to human biosamples and data from clinical trials be enhanced in order to facilitate biomarker discovery?**
- **How can awareness and use of new diabetes and obesity intervention programs and research tools be enhanced?**
- **What mechanisms or resources are needed to make datasets of de-identified medical records available to researchers?**
- **How can universal electronic medical records be made accessible for research while safeguarding patient and provider privacy?**

## **Future Directions**

- **Communicate the availability of datasets and biosample repositories and improve access to these resources by qualified diabetes researchers.**

Repositories store human biosamples or maintain datasets under high-quality conditions for long periods of time. Streamlined methods are needed to make the research community aware of new and existing repositories and to make the materials available to qualified investigators in an equitable and ethical

manner. Efforts should be made to standardize data storage formats to facilitate comparisons across studies.

➤ **Improve technology capabilities for dissemination of intervention programs.**

Many intervention programs are being tested for the prevention and treatment of diabetes and obesity. Harnessing new information technologies, including Internet- or PDA-based systems, for the rapid and efficient dissemination of validated intervention protocols, actionable research tools, or related materials would help researchers build on successful programs to stem the epidemic of these diseases in diverse populations across the United States.

➤ **Develop policies that facilitate research using electronic medical records while protecting individuals' right to privacy.**

The development of electronic medical records (EMR) has provided an unparalleled resource for research on both rare and common human diseases. EMRs that are linked to repositories of DNA, pathological specimens, imaging data, or other medical samples are particularly valuable. As EMRs become standardized in the context of health care reform, policies are needed that facilitate research based on these important data sources while maintaining respect for individuals' right to privacy.

## Public-Private and International Partnerships

The NIH is the primary Federal agency responsible for conducting and supporting biomedical research in the United States; however, many agencies at the Federal, state, and local levels share a common goal in the protection and improvement of public health. In addition, the United States has a strong biotechnology

and pharmaceutical industry that invests heavily in research and development for new therapies to prevent and cure disease. Private foundations and health advocacy organizations also play a significant role in planning and supporting biomedical research. Foreign governments, multilateral institutions, and international donors also support substantial research efforts and resources that complement efforts in the United States. International research is particularly relevant to the United States, which includes immigrants from around the globe. Much may be gained by understanding the genes and predilection for diseases that these groups brought from their ancestral populations abroad. Already, pooled analyses of hundreds of thousands of samples from many countries have been crucial for identification of diabetes risk genes. Moreover, other countries have health care and medical records systems that are particularly useful for clinical research. By fostering partnerships with other interested agencies and organizations, the NIH has an opportunity to enhance basic, clinical, and behavioral research, accelerate the validation and approval of new therapies, and ensure that the results of its research efforts are disseminated to individuals who have or are at high risk of diabetes and obesity.

### Key Questions

- **How can NIH collaborate with clinical care providers and payers to conduct clinical research in real-world settings and to conduct comparative effectiveness research more efficiently?**
- **How can policies for protecting the privacy of research participants be updated to foster multi-center clinical trials, associated biomarker studies, and the**

**sharing of genetic materials between the public and private research sectors and internationally?**

- **What new NIH policies are needed to facilitate international collaborations?**
- **How can regulatory and financial issues be resolved in order to support the development of glucose management technologies, new therapeutics for microvascular complications, agents for glycemic control with adequate information on cardiovascular and other risks, and combination therapies for diabetes and obesity?**
- **How can NIH support and encourage partnerships between researchers and their local communities?**

## **Future Directions**

- **Build or strengthen partnerships between NIH and other government agencies, the pharmaceutical industry, the health insurance industry, and private foundations with an interest in diabetes and obesity research.**

In addition to the NIH, agencies within the Federal government that are tasked with improving the health of the American people include the FDA, CDC, IHS, VHA, DOD, AHRQ, and HHS—all of which are members of the statutory DMICC. New and existing partnerships, collaborations, and information exchanges among these and other DMICC member agencies should continue to be encouraged, as they are critical to the success of diabetes and obesity research. For example, ongoing dialogue between the NIH and FDA is needed to validate and gain regulatory acceptance of

biomarkers that can dramatically shorten clinical trials of new therapies for diabetes complications. Continued communication is also needed to establish standards for assessing the safety of new cell-based, biological, and genetic therapies for diabetes and obesity. Partnerships between the NIH and public and private insurers could potentially reduce the cost of clinical trials if those organizations pay for usual care that is not part of the trial.

NIH partnership with non-governmental agencies or international research organizations would enhance academic research on diabetes and obesity. In addition, mutual support of research and training partnerships between U.S. and foreign academic institutions will build a cadre of diabetes researchers worldwide who may then collaborate as full and effective partners. Pharmaceutical companies are often reluctant to share genetic material, other biosamples, or data collected in the course of clinical trials due to privacy issues and other concerns. By facilitating interactions between those companies and academic investigators, the NIH could complement and expand on publicly-supported repositories as described previously in this chapter. Likewise, the NIH could act as an intermediary to promote sharing of large datasets and materials between U.S. investigators and those in other countries. Communication and collaboration with non-profit voluntary groups, including the ADA and the JDRF, benefit all parties in the research enterprise by reducing the duplication of resources and encouraging progress toward mutual goals.

- **Foster practice-based and community-based participatory research to promote the prevention and control of diabetes in vulnerable populations.**

Community-based participatory research relies on close collaborations between academic investigators and partners in a local community at all stages of the research process from design and implementation of a study to interpretation of results. It is important to actively involve a wide variety of organized community groups, such as faith-based organizations, schools and workplaces, not only to facilitate the highest quality research on the prevention and control of diabetes, but to ultimately improve the health and well-being of community members. By actively engaging the public,

community-based research has the potential to identify interventions for diabetes prevention and control that are effective and sustainable in distinct populations. Such research can give rise to innovative solutions for reducing health disparities in diabetes prevention and treatment that disproportionately affect individual communities. New approaches are needed to encourage community-based participatory research partnerships in ways that recognize and support the strengths and skills of all partners.







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# GLOSSARY

**Acarbose** – A drug that reduces hyperglycemia by altering intestinal absorption of carbohydrates.

**Adipocyte** – Fat cell.

**Adipogenic** – Inducing the formation of fat.

**Adiponectin** – A protein hormone produced in adipose tissue that affects metabolism in multiple ways.

**Afferent neurons** – Cells that carry nerve impulses from receptors or sense organs toward the central nervous system.

**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.

**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.

**Allele** – Any of two or more alternative forms of a gene that occupy a specific site on a chromosome. Synonym of genetic variant. For example, certain alleles of *HLA* are the most significant genetic risk factors for type 1 diabetes.

**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 thus has an opposite effect to that of insulin.

**Angiopathy** – A disease of the blood vessels. Macroangiopathy involves large blood vessels and microangiopathy involves small blood vessels. Diabetes damages both types of vessels.

**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.

**Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)** – Classes of drugs used to treat high blood pressure. These drugs can slow the progression of kidney disease in patients with diabetes.

**Antagonist** – 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 are recognized by the immune system.

**Antioxidants** – Drugs or natural substances, such as vitamins C and E, that prevent or reduce the process of oxidation, thereby protecting the cells or tissues from the damage of toxic oxidative end products.

**Apoptosis** – A form of programmed cell death.

**Artificial pancreas** – A medical device for use in people with diabetes, intended to act in lieu of one or more of the major functions of the pancreas: in particular, automatically responding to elevated blood glucose by releasing an appropriate amount of insulin into the bloodstream. *See also:* “Closed-loop system.”

**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 generated in a person that react against that person’s own body. For example, antibodies created by a person’s immune system against his or her own beta cells, which may lead to destruction of these insulin-producing cells, causing 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 1 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 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.

**Autophagy** – Self-digestion of cellular components.

**Bariatric surgery** – Refers to any of several surgical procedures intended to result in significant weight loss by altering the size of the stomach and/or resecting and re-routing the small intestine.

**Beta cell** – A type of cell in the pancreatic islets that makes and releases insulin.

**Bioinformatics** – The application of statistics and computer science to large, complex biological data sets, such as the human genome sequence.

**Biomarker** – A substance or characteristic that can be measured and used to assess a biological state, such as a disease or a response to therapy.

**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.

**Biguanides** – A class of drugs including metformin, which is used to help control blood glucose in people with type 2 diabetes.

**Body mass index (BMI)** – A measure of obesity, defined as body mass in kilograms divided by height in meters squared. BMI is used to help determine if a person is underweight, normal weight, overweight, or obese.

**Brittle diabetes** – A term used when a person’s blood glucose level moves often from low to high and from high to low.

**Calorimetry** – A method of measuring energy content or consumption, such as body heat (calories) used in activity. Tools used to do this are calorimeters.

**Central obesity** – An excess amount of fat stored in the abdominal area and assessed by measurement of waist to hip ratio.

**Closed-loop system** – A medical device that combines a glucose sensor and an insulin delivery system, automatically modulating blood glucose levels without patient involvement. *See also:* “Artificial pancreas.”

**Continuous glucose monitor** – A medical device that automatically tests blood glucose levels every few minutes.

**Coronary heart disease** – A chronic state of inadequate blood supply to the muscles of the heart and the tissues around it. Also known as coronary artery disease.

**C-peptide** – A portion of the insulin protein which is clipped off the rest of the hormone and secreted along with it, sometimes used as a biomarker of insulin production by the pancreas.

**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.

**Diabetic ketoacidosis (DKA)** – A major acute complication of diabetes characterized by severe elevation of blood glucose and ketone 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 when chronically elevated blood glucose causes 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 which supply oxygen and nutrients to the retina, at the back of the eye. 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.

**DNA** – An acronym for deoxyribonucleic acid, the genetic material.

**DNA methylation** – A type of chemical modification of DNA that is stable over rounds of cell division but does not involve changes in the underlying DNA sequence of the organism.



**Dual-energy x-ray absorptiometry** – A medical test for measurement of body composition, including adipose tissue (fat) and bone mineral density, which characteristically declines as part of osteoporosis.

**Dyslipidemia** – Unhealthy concentrations 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 affect a person’s risk for heart disease.

**Ectopic fat** – The deposition of triglycerides within cells of non-adipose tissue that normally contain only small amounts of fat.

**Efferent neurons** – Cell that carry nerve impulses from the central nervous system toward muscles, glands, or other effector tissues.

**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 for continued survival.

**Energy balance** – The balance between energy intake (food calories) and energy expenditure (body heat and activity).

**Endoplasmic reticulum (ER)** – A vast network of membranes within eukaryotic cells where all secretory and membrane proteins are assembled and proper folding, maturation, storage, and transport of these proteins take place.

**Endothelium** – The layer of cells that lines the heart and blood vessels.

**Epigenetics** – The study of modifications to DNA or proteins bound to DNA that do not change the DNA sequence, but which confer persistent effects on gene expression.

**Euglycemia** – Normal level of glucose in the blood. Also called normoglycemia.

**Extracellular matrix (ECM)** – Fibrous-like tissue that surrounds cells; an excess accumulation of this matrix may contribute to diabetic nephropathy.

**Fatty acids** – A component of fat. Fatty acids can be bound to glycerol to form a fat such as triglyceride. Fatty acids can circulate in blood as part of lipid particles or as “free” fatty acids attached to albumin (protein). The body (except the brain) may burn fatty acids for energy as a substitute for glucose.

**Gene** – The unit of heredity in living things. Typically, a gene is a DNA sequence that encodes a protein or RNA that has some function within the organism.

**Gene expression** – The transcription of a gene into RNA and/or translation of that RNA into protein; may also refer to the rate of that transcription or translation.

**Genetic variant** – Any of two or more alternative forms of a gene that occupy a specific site on a chromosome. Synonym of allele. For example, variants of the gene *TCF7L2* are associated with an increased risk of type 2 diabetes.

**Genome** – Complete genetic complement of an organism.

**Genome-wide association (GWA) studies** – A scientific attempt to identify genetic contributors to health and disease by correlating known genetic variants throughout the genome with specific diseases, characteristics, or health outcomes.

**Genotype/ genotypic** – The genetic constitution of an individual, particularly in reference to that individual's allele or alleles for a particular gene. A genotype may or may not have a detectable impact on that individual's characteristics or health.

**Gestational diabetes mellitus (GDM)** – A form of glucose intolerance diagnosed during pregnancy, characterized by abnormally high levels of blood glucose. The level may return to normal after delivery or can be a precursor to the development of diabetes later in life.

**Glucagon** – A hormone produced by the alpha cells of the pancreas that counteracts insulin and raises blood glucose.

**Glucokinase** – An enzyme that catalyzes the formation of glucose-6-phosphate from glucose. It contributes to the glucose-sensing activity of beta cells.

**Glucose** – A simple sugar found in the blood that is the body's main source of energy. *See also:* "Blood glucose."

**Glucose counterregulation** – The net effect of hormones, such as glucagon, that counteract the effect of insulin and restore normal levels of glucose in the body if glucose levels drop too low (hypoglycemia).

**Glucose intolerance** – Abnormally high levels of blood glucose after an oral glucose tolerance test (OGTT). *See also:* "Impaired glucose tolerance."

**Glutamic acid decarboxylase (GAD)** – 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** – Relating to carbohydrates (sugars), particularly glucose.

**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 (HbA1c, or A1C)** – A variant of the hemoglobin A protein, which is the major carrier of oxygen in the blood. HbA1c results from the addition of sugar molecules to hemoglobin A, which occurs more easily in people with chronically elevated blood glucose. Because HbA1c is very stable, it is a good biomarker for how well a person's blood glucose has been controlled over the previous 2 to 3 months.

**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.

**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 other complications of diabetes.

**Hyperinsulinemia** – A chronically 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.

**Hypoglycemia** – An abnormally low level of glucose in the blood.

**Immune system** – The body's system for protecting itself from viruses and bacteria or any "foreign" substances.

**Immune tolerance** – The process by which the immune system considers a protein or other molecule as self, and does not mount a destructive response against cells or tissues containing that protein.

**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 disease.

**Impaired glucose tolerance (IGT)** – A disorder in which blood glucose levels are intermediate between normal and diabetic. Because studies have shown that IGT increases the risk of developing type 2 diabetes and its macrovascular complications, IGT is sometimes referred to as "pre-diabetes."

**Inflammation** – Part of a complex biological response to certain stimuli, particularly infection. While inflammation is a normal and valuable immune system process, chronic inflammation may contribute to diseases including diabetes and coronary heart disease.

**Insulin** – A hormone secreted by the beta cells of the pancreas that regulates the metabolism of glucose.

**Insulin analog** – A form of insulin modified to have desirable properties for therapy. It may have more rapid onset of action or be more long-lasting.

**Insulin pump** – A mechanical device that pumps 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 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 hormone 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.

**Ischemia** – Poor blood supply to an organ, such as the heart, that is often marked by organ dysfunction and pain.

**Islet transplantation** – Transplanting pancreatic islets (as opposed to a whole pancreas or a section of a pancreas) from a donor 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 such as insulin that aid in the metabolism. (Referred to as “islets” in the Strategic Plan.)

**Ketoacidosis** – *See:* “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 often used to store energy in animal (or plant) tissues. Lipids include cholesterol and triglycerides. Elevated levels of lipids in the blood are associated with diseases such as atherosclerosis.

**Loci** – Plural of locus.

**Locus** – The position of a sequence within the genome.

**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.

**Magnetic Resonance Imaging (MRI)** – 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, causing them to spin. The spinning nuclei can be detected and pinpointed in the body to produce an image.

**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 (also called extracellular matrix).

**Maturity Onset Diabetes of the Young (MODY)** – A type of diabetes distinct from type 1 or type 2 diabetes characterized by early onset and a primary defect in insulin secretion, caused by a single genetic flaw that can be inherited from either parent.

**Mesenchymal stem cells** – A group of cells that can differentiate into a number of important cell types, including bone- and fat-producing cells (osteoblasts and adipocytes).

**Meta-analysis** – A study that combines data and results from multiple previously published studies, and applies statistical methods to answer questions that could not be addressed by the previous works, or more precisely than was possible in the previous works.

**Metabolic syndrome** – A combination of medical disorders that increase the risk of developing both cardiovascular disease and type 2 diabetes. Precise definitions vary, but the syndrome is generally marked by several of the following: central obesity (large waist circumference), high blood pressure, unhealthy levels of fats in the blood, and impaired glucose tolerance or elevated fasting blood glucose. (Also called Syndrome X.)

**Methylation** – Addition of a small chemical group (methyl group) to another molecule. Methylation of DNA and proteins bound to DNA in chromosomes affects how genes are expressed and is a form of epigenetic modification.

**Microangiopathy** – *See*: “Angiopathy.”

**Microarray** – A two-dimensional array of a large number of small samples (e.g., DNA, RNA, protein, or other chemical compounds), that can be assessed for one or more scientifically interesting properties through high-throughput screening.

**Microbiome** – The complete collection of microbes that live in a particular environment (such as a human being) and/or their collective genomic information.

**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.

**Mitochondria** – Compartments within cells that convert calories derived from food into fuel the cells can use for most biological processes.

**Monoclonal antibodies** – Antibodies of a single type that recognize a particular antigen, usually mass-produced from a cell hybrid that is formed by the fusion of a normal antibody-producing cell to a tumor cell.

**Murine** – Pertaining to rats and mice.

**Myocardial infarction** – Damage to the heart due to coronary artery disease. Also known as heart attack.

**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.”

**Non-Insulin-Dependent Diabetes Mellitus (NIDDM)** – Former term for type 2 diabetes.

**“Omics”** – systematic approaches to studying the complete collection of a particular set of biological compounds from an organism. For example, genomics is the systematic study of the whole genome, proteomics is the study of all of an organism’s proteins, and metabolomics is the study of the chemical intermediates and products of an organism’s metabolic processes.

**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 (*See also*: “Reactive oxygen species”). 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.

**Penetrance** – The proportion of individuals with a particular genetic trait who also exhibit the characteristics associated with that trait. For example, the fraction of people with a gene that can cause a disease who actually develop the disease.

**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.

**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 pancreatic islets, as part of an autoimmune process that ultimately destroys the insulin-producing beta cells.

**Phenotype/phenotypic** – Having to do with the characteristics of an individual (or group) that can be detected and that result from the interaction of genetic and environmental factors.

**Phosphorylation** – The metabolic process of adding a phosphate group to an organic molecule; important in diabetes because it is involved in the breakdown of glucose, action of insulin, cell signaling, and other processes.

**Plasticity** – Capacity to change.

**Platelets** – The smallest cells in the blood, necessary for blood clotting.

**Polymorphism** – A genetic variant.

**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 diabetes drugs act through this receptor. *See also*: “Thiazolidinedione drugs.”

**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. Inhibitors for the different types of PKC are being studied for 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 (macroalbuminuria) reflect late stages of kidney disease.

**Reactive oxygen species (ROS)** – Chemically-reactive molecules containing oxygen that are generated normally during cellular metabolism. An excess of ROS can damage cellular structures.

**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.

**Renin Angiotensin System (RAS)** – 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. Drugs acting on the pathway lower blood pressure and protect against diabetic nephropathy.

**Retinopathy** – *See*: “Diabetic retinopathy.”

**RNA** – Ribonucleic acid. Chemically similar to DNA, RNAs of different sequences and structures have numerous roles in the body.

**SNP** – Single nucleotide polymorphism; a particular position within the genome that varies from individual to individual.

**Stem cell** – A cell with the capacity to divide and form multiple cell types.

**Sulfonylureas** – A class of orally active hypoglycemic drugs commonly used to treat type 2 diabetes by promoting increased insulin secretion by the pancreas.

**Sumoylation** – Attachment of one of a family of small proteins (small ubiquitin-like modifiers, or SUMO proteins) to another protein in cells to modify its function.

**Telemedicine** – The provision of consultant services by off-site health care providers to health care professionals on the scene or directly to patients – for example, by closed-circuit television or over the Internet.

**Thiazolidinedione drugs** – A class of insulin sensitizers that improve the body’s use of insulin by acting on a protein called PPAR gamma. Examples include rosiglitazone and pioglitazone.

**Tomography** – A technique of x-ray photography by which a single plane is pictured without the outlines of the structure of other planes. *See also*: “Positron Emission Tomography (PET).”

**Transcription factors** – Proteins that can bind to or form complexes on DNA to 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 into the DNA of a different genome. For example, 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. Because insulin is needed to remove triglycerides from the blood, people with diabetes have elevated levels of triglycerides in their blood.

**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/or reduced capacity to produce insulin. About 90 to 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.

**Ubiquitination** – Addition of a small protein known as ubiquitin to another protein, usually targeting it for degradation.

**Unfolded protein response** – A self-protective response of cells against endoplasmic reticulum (ER) stress resulting from accumulation of unfolded/misfolded proteins in the ER.

**Variant** – *See*: “Genetic variant.”

**Vascular endothelial growth factor (VEGF)** – A molecule that stimulates new blood vessel growth.

**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.

**Xenobiotic** – A chemical found in an organism in which it does not naturally occur.







# APPENDICES

## APPENDIX A: STRATEGIC PLAN PARTICIPANTS

### Members of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) During Development of the Strategic Plan\*

#### Chair:

**Judith E. Fradkin, M.D.**

National Institute of Diabetes and  
Digestive and Kidney Diseases

#### Executive Secretary:

**Sanford A. Garfield, Ph.D.**

National Institute of Diabetes and  
Digestive and Kidney Diseases

**Kelly Acton, M.D., M.P.H.**

Indian Health Service

**Ann Albright, Ph.D., R.D.**

Centers for Disease Control and Prevention

**Jane C. Atkinson, D.D.S.**

National Institute of Dental and  
Craniofacial Research

**Larissa Avilés-Santa, M.D., M.P.H., F.A.C.P., F.A.C.E.**

National Heart, Lung, and Blood Institute

**Barbara A. Bartman, M.D., M.P.H.**

Agency for Healthcare Research and Quality

**Sanja Basaric**

National Human Genome Research  
Institute

**Perry Blackshear, M.D., D.Phil.**

National Institute of Environmental  
Health Sciences

**Mark Chavez, Ph.D.**

National Institute of Mental Health

**Linda C. Duffy, Ph.D.**

National Center for Complementary and Alternative  
Medicine

**Irene Dankwa-Mullan, M.D., M.P.H.**

National Institute on Minority Health and Health  
Disparities

**Chhanda Dutta, Ph.D.**

National Institute on Aging

**Eve Essery, Ph.D.**

U.S. Department of Health and Human Services

**Zhigang (Peter) Gao, M.D.**

National Institute on Alcohol Abuse and Alcoholism

**Garth Graham, M.D., M.P.H.**

HHS Office of Minority Health

**Gilman D. Grave, M.D.**

National Institute of Child Health and  
Human Development

---

\* Former DMICC members are listed with the name of the Institute, Center, or agency they represented at that time.

**Rachel Hayes, M.P.H., R.D.**

U.S. Department of Health and Human Services

**Jerrold (Jerry) Heindel, Ph.D.**

National Institute of Environmental Health Sciences

**Ann Jerkins, Ph.D.**

Center for Scientific Review

**Kathleen Jett, Ph.D., R.N., G.N.P.-B.C.**

National Institute of Nursing Research

**Jag H. Khalsa, Ph.D.**

National Institute on Drug Abuse

**Donna Krasnewich, M.D., Ph.D.**

National Institute of General Medical  
Sciences

**John P. Kugler, M.D., M.P.H.**

Department of Defense

**Rongling Li, MD, Ph.D., M.P.H.**

National Human Genome Research Institute

**Alan McLaughlin, Ph.D.**

National Institute of Biomedical Imaging  
and Bioengineering

**Laura Moen, Ph.D.**

National Center for Complementary and Alternative  
Medicine

**Tanya Pagan Raggio Ashley, M.D., M.P.H., F.A.A.P.**

Health Resources and Services Administration

**Mary Parks, M.D.**

Food and Drug Administration

**Audrey S. Penn, M.D.**

National Institute of Neurological Disorders and Stroke

**John Peyman, Ph.D.**

National Institute of Allergy and  
Infectious Diseases

**Leonard M. Pogach, M.D., M.B.A.**

Veterans Health Administration

**Robert C. Post, Ph.D., M.Ed., M.Sc.**

U.S. Department of Agriculture

**Kyu Rhee, M.D., M.P.P., F.A.A.P., F.A.C.P.**

National Institute on Minority Health and Health  
Disparities

**Sheila H. Roman, M.D., M.P.H.**

Centers for Medicare and Medicaid Services

**Daniel Rosenblum, M.D.**

National Center for Research Resources

**Grace L. Shen, Ph.D.**

National Eye Institute

**Elliot R. Siegel, Ph.D.**

National Library of Medicine

**Joan Wasserman, Dr.P.H., R.N.**

National Institute of Nursing Research

**Baldwin Wong**

National Institute on Deafness and Other  
Communication Disorders

**Samuel Wu, Pharm.D.**

Health Resources and Services Administration

## Members of the Diabetes Research Strategic Plan Leadership Group

### Chair:

#### **Judith E. Fradkin, M.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Domenico Accili, M.D.**

Columbia University

#### **Steven J. Adelman, Ph.D.**

Vascular Strategies, LLC

#### **Beena Akolkar, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Guillermo Arreaza-Rubín, M.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Mark A. Atkinson, Ph.D.**

University of Florida

#### **Olivier Blondel, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Marshall H. Chin, M.D., M.P.H.**

University of Chicago

#### **Sanford A. Garfield, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Carol R. Haft, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Larry Hausner**

American Diabetes Association

#### **Eleanor F. Hoff, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Christine Hunter, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **James Hyde, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Teresa Z. Jones, M.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **C. Ronald Kahn, M.D.**

Harvard University/ Joslin Diabetes Center

#### **Francine R. Kaufman, M.D.**

University of Southern California/Medtronic, Inc.

#### **Maren Laughlin, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

#### **Mitchell A. Lazar, M.D., Ph.D.**

University of Pennsylvania

#### **Barbara L. Linder, M.D., Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Catherine McKeon, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**David M. Nathan, M.D.**

Harvard University/ Massachusetts General Hospital

**Stephen S. Rich, Ph.D.**

University of Virginia

**Griffin P. Rodgers, M.D., M.A.C.P.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Sheryl M. Sato, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Peter J. Savage, M.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Ann Marie Schmidt, M.D.**

Columbia University

**Michael W. Schwartz, M.D.**

University of Washington

**Salvatore Sechi, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Robert Sherwin, M.D.**

Yale University

**Philip Smith, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Lisa Spain, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

## Working Groups

### Working Group 1: Genetic Basis of Type 1 Diabetes, Type 2 Diabetes, Obesity, and Their Complications

#### **CHAIRPERSON:**

**Stephen S. Rich, Ph.D.**

University of Virginia

**Beena Akolkar, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**David Altshuler, M.D., Ph.D.**

Massachusetts General Hospital/Broad Institute

**Michael Boehnke, Ph.D.**

University of Michigan

**Lisa Brooks, Ph.D.**

National Human Genome Research Institute

**Nancy Cox, Ph.D.**

University of Chicago

**Zafar Iqbal, Ph.D.**

Veterans Health Administration

**Catherine McKeon, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**John Todd, Ph.D., F.Med.Sci.**

University of Cambridge



## Working Group 2: Type 1 Diabetes and Autoimmunity

### CHAIRPERSON:

**Mark A. Atkinson, Ph.D.**

University of Florida

**Jeffrey A. Bluestone, Ph.D.**

University of California San Francisco

**George Eisenbarth, M.D., Ph.D.**

University of Colorado Health Sciences Center

**Carla Greenbaum, M.D.**

Benaroya Research Institute at Virginia Mason (BRI)

**Dale Greiner, Ph.D.**

University of Massachusetts Medical School

**Matthias von Herrath, M.D.**

La Jolla Institute for Allergy and Immunology

**Norma S. Kenyon, Ph.D.**

University of Miami School of Medicine

**David A. Kosub, Ph.D.**

National Institute of Allergy and Infectious Diseases

**Clayton E. Mathews, Ph.D.**

University of Florida

**Diane Mathis, Ph.D.**

Harvard University

**John Peyman, Ph.D.**

National Institute of Allergy and Infectious Diseases

**Pere Santamaria, Ph.D.**

University of Calgary

**David Serreze, Ph.D.**

The Jackson Laboratory

**Lisa Spain, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

## Working Group 3: The Beta Cell

### CHAIRPERSON:

**Domenico Accili, M.D.**

Columbia University

**Lydia Aguilar-Bryan, M.D., Ph.D.**

Pacific Northwest Diabetes Research Institute  
(PNDRI)

**Susan Bonner-Weir, Ph.D.**

Harvard University/ Joslin Diabetes Center

**Thomas A. Buchanan, M.D.**

University of Southern California

**Barbara Corkey, Ph.D.**

Boston University Medical Center

**Matthias Hebrok, Ph.D.**

University of California San Francisco

**Steven Kahn, M.B., Ch.B.**

University of Washington

**Douglas A. Melton, Ph.D.**

Harvard University

**Kenneth S. Polonsky, M.D.**

Washington University in St. Louis

**Alvin C. Powers, M.D.**

Vanderbilt University

**Doris A. Stoffers, M.D., Ph.D.**

University of Pennsylvania School of Medicine

**Nancy Thornberry**

Merck & Co., Inc.

**Sheryl M. Sato, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

## Working Group 4: Systems Biology of Diabetes

### CHAIRPERSON:

**C. Ronald Kahn, M.D.**

Harvard University/ Joslin Diabetes Center

**Olivier Blondel, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Jens C. Brüning, M.D.**

University of Cologne

**Silvia Corvera, M.D.**

University of Massachusetts Medical School

**Caroline Fox, M.D., M.P.H.**

National Heart, Lung, and Blood Institute

**Carol R. Haft, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Gökhan Hotamisligil, M.D., Ph.D.**

Harvard School of Public Health

**Maren Laughlin, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Marc R. Montminy, M.D., Ph.D.**

Salk Institute

**Christopher B. Newgard, Ph.D.**

Duke University Medical Center

**Jerrold M. Olefsky, M.D.**

University of California San Diego

**Alan R. Saltiel, Ph.D.**

University of Michigan

**Salvatore Sechi, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Gerald I. Shulman, M.D., Ph.D.**

Yale University School of Medicine

**Bruce M. Spiegelman, Ph.D.**

Harvard Medical School/ Dana Farber Cancer Institute

**Juleen R. Zierath, Ph.D.**

Karolinska Institute

## Working Group 5: Obesity

### CHAIRPERSON:

**Michael W. Schwartz, M.D.**

University of Washington

**Rexford S. Ahima, M.D., Ph.D.**

University of Pennsylvania

**Kong Y. Chen, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Gary Foster, Ph.D.**

Temple University

**Caroline Fox, M.D., M.P.H.**

National Heart, Lung, and Blood Institute

**Christine Hunter, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Zafar Iqbal, Ph.D.**

Veterans Health Administration

**Barbara Kahn, M.D.**

Beth Israel Deaconess Medical Center/ Harvard  
Medical School

**Jag H. Khalsa, Ph.D.**

National Institute on Drug Abuse

**Lisa Klesges, Ph.D.**

University of Memphis

**Rudolph L. Leibel, M.D.**

Columbia University

**Martin G. Myers, Jr., M.D., Ph.D.**

University of Michigan Medical School

**Thomas N. Robinson, M.D., M.P.H.**

Stanford University

**Philipp E. Scherer, Ph.D.**

University of Texas Southwestern

**Philip Smith, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

## Working Group 6: Bioengineering Approaches To Improve Management of Glycemia

### CHAIRPERSON:

**Robert Sherwin, M.D.**

Yale University

**Guillermo Arreaza-Rubín, M.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Richard N. Bergman, Ph.D.**

University of Southern California

**Bruce Buckingham, M.D.**

Stanford University

**Claudio Cobelli, Ph.D.**

University of Padova

**Daniel J. Cox, Ph.D., A.B.P.P.**

University of Virginia

**Francis J. Doyle III, Ph.D.**

University of California Santa Barbara

**David A. Gough, Ph.D.**

University of California San Diego

**William Heetderks, M.D., Ph.D.**

National Institute of Biomedical Imaging and Bioengineering

**Felicia Hill-Briggs, Ph.D., A.B.P.P.**

Johns Hopkins Medical Institutions

**Irl B. Hirsch, M.D.**

University of Washington

**David C. Klonoff, M.D., F.A.C.P.**

University of California San Francisco

**Boris Kovatchev, Ph.D.**

University of Virginia

**Aaron Kowalski, Ph.D.**

Juvenile Diabetes Research Foundation International

**Arleen Pinkos**

Food and Drug Administration

**Kerstin Rebrin, M.D., Ph.D.**

MicroCHIPS, Inc.

**W. Kenneth Ward, M.D.**

Oregon Health & Science University

**Gordon Weir, M.D.**

Harvard University/ Joslin Diabetes Center

**Michael Weiss, M.D., Ph.D.**

Case Western Reserve University

**Todd Zion, Ph.D.**

SmartCells, Inc.

## Working Group 7: Clinical Research and Clinical Trials

### CHAIRPERSON:

**David M. Nathan, M.D.**

Harvard University/ Massachusetts General Hospital

**John B. Buse, M.D., Ph.D.**

University of North Carolina School of Medicine

**Ralph DeFronzo, M.D.**

University of Texas Health Science Center

**Robert H. Eckel, M.D.**

University of Colorado Denver

**Jose C. Florez, M.D., Ph.D.**

Harvard University/ Massachusetts General Hospital

**Caroline Fox, M.D., M.P.H.**

National Heart, Lung, and Blood Institute

**Hertzel Gerstein, M.D., M.Sc., D.A.B.I.M.,  
F.R.C.P.C.**

McMaster University

**Thomas H. Hostetter, M.D.**

Albert Einstein College of Medicine

**Paul L. Kimmel, M.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Kenneth A. Jamerson, M.D.**

University of Michigan

**William Knowler, M.D., Ph.D., M.P.H.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Barbara L. Linder, M.D., Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Robert A. Rizza, M.D.**

Mayo Clinic and Foundation

**Peter J. Savage, M.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Jay Skyler, M.D.**

University of Miami

## Working Group 8: Special Needs for Special Populations

### CHAIRPERSON:

**Francine R. Kaufman, M.D.**

University of Southern California/Medtronic, Inc.

**Samuel Dagogo-Jack, M.D., M.B.B.S., M.Sc.,  
F.R.C.P.**

University of Tennessee Health Science Center

**Brian Gibbs, Ph.D.**

Johns Hopkins Medical Institutions

**Steven K. Grinspoon, M.D.**

Harvard University/ Massachusetts General Hospital

**Barbara V. Howard, Ph.D.**

MedStar Research Institute

**Jag H. Khalsa, Ph.D.**

National Institute on Drug Abuse

**Barbara L. Linder, M.D., Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Carol Mangione, M.D., M.S.P.H.**

David Geffen School of Medicine University of  
California Los Angeles

**Antoinette M. Moran, M.D.**

University of Minnesota

**John W. Newcomer, M.D.**

Washington University School of Medicine

**David Pettitt, M.D.**

Sansum Diabetes Research Institute

**Richard R. Rubin, Ph.D., C.D.E.**

Johns Hopkins University School of Medicine

**Peter J. Savage, M.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Desmond A. Schatz, M.D.**

University of Florida

**Elliot R. Siegel, Ph.D.**

National Library of Medicine

**Guest member:**

**Thomas A. Buchanan, M.D.**

University of Southern California

## Working Group 9: Diabetes Complications

### CHAIRPERSON:

**Ann Marie Schmidt, MD**

Columbia University

**Evan Dale Abel, M.D., Ph.D.**

University of Utah

**Lloyd Paul Aiello, M.D., Ph.D.**

Harvard University/ Joslin Diabetes Center

**Barbara Araneo, Ph.D.**

Juvenile Diabetes Research Foundation International

**Jane C. Atkinson, D.D.S.**

National Institute of Dental and Craniofacial Research

**Larissa Avilés-Santa, M.D., M.P.H., F.A.C.P., F.A.C.E.**

National Heart, Lung, and Blood Institute

**Matthew D. Breyer, M.D.**

Lilly Research Laboratories

**Michael Brownlee, M.D.**

Albert Einstein College of Medicine

**Nigel A. Calcutt, Ph.D.**

University of California San Diego

**Firouz Daneshgari, M.D.**

Case Western Reserve University

**Zahi A. Fayad, Ph.D.**

Mount Sinai School of Medicine

**Eva L. Feldman, M.D., Ph.D.**

University of Michigan

**Sherita H. Golden, M.D., M.H.S.**

Johns Hopkins University

**Geoffrey C. Gurtner, M.D.**

Stanford University

**Teresa Z. Jones, M.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Christian Ketchum, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**George L. King, M.D.**

Harvard University/ Joslin Diabetes Center

**Walter Koroshetz, M.D.**

National Institute of Neurological Disorders and Stroke

**Merrill Mitler, Ph.D.**

National Institute of Neurological Disorders and Stroke

**Laura Moen, Ph.D.**

National Center for Complementary and Alternative  
Medicine

**Vincent M. Monnier, M.D.**

Case Western Reserve University

**Rama Natarajan, Ph.D.**

City of Hope

**Pankaj J. Pasricha, M.B.B.S.**

Stanford University

**Clay F. Semenkovich, M.D.**

Washington University in St. Louis

**Grace L. Shen, Ph.D.**

National Eye Institute

**Gordana Vunjak-Novakovic, Ph.D.**

Columbia University



## Working Group 10: Translational Research

### CHAIRPERSON:

**Marshall H. Chin, M.D., M.P.H.**

University of Chicago

**Ronald T. Ackermann, M.D., M.P.H.**

Indiana University School of Medicine

**David Aron, M.D., M.S.**

Louis Stokes Cleveland VA Medical Center

**Sanford A. Garfield, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**Russell E. Glasgow, Ph.D.**

Kaiser Permanente of Colorado

**Edward Gregg, Ph.D.**

Centers for Disease Control and Prevention

**Margaret Grey, Ph.D., R.N.**

Yale University School of Nursing

**Debra Haire-Joshu, Ph.D.**

George Warren Brown School of Social Work  
Washington University in St. Louis School of Medicine

**William H. Herman, M.D., M.P.H.**

University of Michigan

**Christine Hunter, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

**David G. Marrero, Ph.D.**

Indiana University School of Medicine

**Tanya Pagán Raggio Ashley, M.D., M.P.H., F.A.A.P**

Health Resources and Services Administration

**Monica Peek, M.D., M.P.H.**

University of Chicago Pritzker School of Medicine

**Joe V. Selby, M.D., M.P.H.**

Kaiser Permanente of Northern California

**Thomas D. Sequist, M.D., M.P.H.**

Harvard University/ Brigham and Women's Hospital

**Roberto Trevino, M.D.**

University of Texas Health Science Center

## **Working Group 11: Resource and Infrastructure Needs for Diabetes Research**

### **CHAIRPERSON:**

**Mitchell A. Lazar, M.D., Ph.D.**

University of Pennsylvania

**Stephen S. Rich, Ph.D.**

University of Virginia

**Matthias von Herrath, M.D.**

La Jolla Institute for Allergy and Immunology

**Alvin C. Powers, M.D.**

Vanderbilt University

**Christopher B. Newgard, Ph.D.**

Duke University Medical Center

**Rudolph L. Leibel, M.D.**

Columbia University

**David C. Klonoff, M.D., F.A.C.P.**

University of California San Francisco

**David M. Nathan, M.D.**

Harvard University/ Massachusetts General Hospital

**Barbara V. Howard, Ph.D.**

MedStar Research Institute

**Ann Marie Schmidt, M.D.**

Columbia University

**Debra Haire-Joshu, Ph.D.**

Washington University George Warren Brown School  
of Social Work

Washington University School of Medicine

**James Hyde, Ph.D.**

National Institute of Diabetes and Digestive and  
Kidney Diseases

## Other Contributors

**Kristin M. Abraham, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Michael C. Appel, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Catherine C. Cowie, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Thomas L. Eggerman, M.D., Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Richard A. Farishian, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Lisa J. Gansheroff, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Mary C. Hanlon, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Teri Manolio, M.D., Ph.D.**

National Human Genome Research Institute

**Susan McCarthy, Ph.D.**

National Cancer Institute

**Jim McNamara, M.D.**

National Institute of Allergy and Infectious Diseases

**Deborah Olster, Ph.D.**

NIH Office of Behavioral and Social Sciences Research

**B. Tibor Roberts, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Corinne M. Silva, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Myrlene Staten, M.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Julie A. Wallace, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

## APPENDIX B: ACRONYMS AND ABBREVIATIONS

### Organizational Components

ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
CSR	Center for Scientific Review
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
DMICC	Diabetes Mellitus Interagency Coordinating Committee
DOD	Department of Defense
FDA	Food and Drug Administration
FIC	Fogarty International Center
HHS	U.S. Department of Health and Human Services
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
JDRF	Juvenile Diabetes Research Foundation International
NCI	National Cancer Institute
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities

NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OBSSR	NIH Office of Behavioral and Social Sciences Research
ORWH	NIH Office of Research on Women’s Health
USDA	U.S. Department of Agriculture
VHA	Veterans Health Administration

## Research Programs

ACCORD	Action to Control Cardiovascular Risk in Diabetes
AMDCC	Animal Models of Diabetic Complications Consortium
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BCBC	Beta Cell Biology Consortium
CITC	Clinical Islet Transplantation Consortium
DCCT	Diabetes Control and Complications Trial
DirecNet	Diabetes Research in Children Network
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DPT-1	Diabetes Prevention Trial-Type 1
DRCR.net	Diabetic Retinopathy Clinical Research Network
EDIC	Epidemiology of Diabetes Interventions and Complications
FIND	Family Investigation of Nephropathy and Diabetes
GoKinD	Genetics of Kidneys in Diabetes Study
ITN	Immune Tolerance Network
IIDP	Integrated Islet Distribution Program
Look AHEAD	Action for Health in Diabetes
MMPC	Mouse Metabolic Phenotyping Centers
NHPCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
SEARCH	SEARCH for Diabetes in Youth Study
T1DGC	Type 1 Diabetes Genetics Consortium
T1D-RAID	Type 1 Diabetes—Rapid Access to Intervention Development
TEDDY	The Environmental Determinants of Diabetes in the Young
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth
TRIAD	Translating Research Into Action for Diabetes
TrialNet	Type 1 Diabetes TrialNet
TRIGR	Trial to Reduce IDDM in the Genetically at Risk

## Other Acronyms and Abbreviations

ACE	angiotensin-converting enzyme
AGE	advanced glycation end products
AMPK	adenosine monophosphate-dependent protein kinase
ARB	angiotensin receptor blocker
ARE	antioxidant response element
AS160	Akt substrate of 160 kDa
ATP	adenosine-5'-triphosphate
BAT	brown adipose tissue
BMI	body mass index
CGMs	continuous glucose monitors
<sup>11</sup> C-DTBZ	<sup>11</sup> C-dihydrotetrabenazine
CNS	central nervous system
CVD	cardiovascular disease
DMK	dystrophia myotonica kinase
DPP-4	dipeptidyl peptidase 4
EMR	electronic medical record
ER	endoplasmic reticulum
ES	embryonic stem cell
fMRI	functional magnetic resonance imaging
GAD	glutamic acid decarboxylase
GIP	gastric inhibitory polypeptide
GLP	glucagon-like peptide
GSK3	glycogen synthase kinase-3
GWA	genome-wide association
HbA1c	hemoglobin A1c
HGF	human growth factor
HLA	human leukocyte antigen
HMGB1	high mobility group box 1
HTS	high-throughput screening
IDDM	insulin-dependent diabetes mellitus
IGRP	islet specific glucose-6-phosphatase catalytic subunit related protein
IKK	IkappaB kinase
IPEX	immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
iPS	induced pluripotent stem
JNK	c-Jun N-terminal kinase
LDL	low-density lipoprotein

MAP	mitogen-activated protein
MHC	major histocompatibility complex
MODY	maturity onset diabetes of the young
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
mTOR	mammalian target of rapamycin
NAD	nicotinamide adenine dinucleotide
NDM	neonatal diabetes mellitus
NIDDM	non-insulin-dependent diabetes mellitus
NKT	natural killer T cells
NMR	nuclear magnetic resonance
NOD	non-obese diabetic
PKC	protein kinase C
PET	positron emission tomography
PI 3	phosphatidylinositol 3
PTPN22	protein tyrosine phosphatase N22 gene
RAGE	receptor for advanced glycation end products
RAS	renin angiotensin system
RCT	randomized controlled trial
ROS	reactive oxygen species
SES	socioeconomic status
SILAC	stable isotope labeling with amino acids in cell culture
SNARE	soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor
SNP	single nucleotide polymorphism
SPECT	single photon emission computed tomography
SREBP	sterol regulatory element binding protein
TGF	transforming growth factor
UPR	unfolded protein response
VEGF-A	vascular endothelial growth factor A
VNTR	variable number of tandem repeats region





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## Scientific Expertise and Leadership: Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK

### **Judith E. Fradkin, M.D.**

Director

### **Beena Akolkar, Ph.D.**

Immunopathogenesis and Genetics of Type 1 Diabetes Program Director

### **Guillermo Arreaza-Rubín, M.D.**

Director, Clinical Immunology, Type 1 Diabetes Program

### **Olivier Blondel, Ph.D.**

Director, Endocrine Systems Biology Program

### **Sanford A. Garfield, Ph.D.**

Senior Advisor for Biometry and Behavioral Research Program

### **Carol R. Haft, Ph.D.**

Senior Advisor for Cell Biology

### **Christine Hunter, Ph.D.**

Director, Behavioral Research

### **James Hyde, Ph.D.**

Senior Advisor for Research Training and Career Development

### **Teresa Z. Jones, M.D.**

Diabetes Complications Program Director

### **Maren Laughlin, Ph.D.**

Metabolism and Structural Biology Program Director

### **Barbara L. Linder, M.D., Ph.D.**

Senior Advisor for Childhood Diabetes Research

### **Catherine McKeon, Ph.D.**

Senior Advisor for Genetic Research

### **Sheryl M. Sato, Ph.D.**

Director, Neurobiology of Obesity and Developmental Biology

**Peter J. Savage, M.D.**

Senior Advisor, Clinical Diabetes Research

**Salvatore Sechi, Ph.D.**

Proteomic Program Director

**Philip Smith, Ph.D.**

Deputy Director; Co-Director, Office of Obesity Research

**Lisa Spain, Ph.D.**

Director, Immunobiology of Type 1 Diabetes Program and Autoimmune Endocrine Diseases Program

**Production Management and Integration: Office of Scientific Program and Policy Analysis, NIDDK**

**Richard A. Farishian, Ph.D.**

Director

**Lisa J. Gansheroff, Ph.D.**

Deputy Director

**Michael J. Grey, Ph.D.**

Health Science Policy Analyst

**Eleanor F. Hoff, Ph.D.**

Health Science Policy Analyst

**Mary C. Hanlon, Ph.D.**

Health Science Policy Analyst

**B. Tibor Roberts, Ph.D.**

Health Science Policy Analyst

**Julie A. Wallace, Ph.D.**

Health Science Policy Analyst

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