# FDA/NIH Joint Symposium on Diabetes

## Targeting Safe and Effective Prevention and Treatment

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## DAY 1: MAJOR CHALLENGES TO DEVELOPMENT OF NEW THERAPEUTICS AND DIAGNOSTICS

***Welcome***

Dr. David G. Orloff, Director, Division of Metabolic and Endocrine Drug Products, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), U.S. Department of Health and Human Services (DHHS), opened the symposium by noting that this meeting was bringing together world leaders in the study of diabetes, from basic scientists to clinical researchers, to epidemiologists, to those directly involved in commercial therapeutics, devices, and diagnostic tools. Dr. Orloff thanked those present for their willingness to assist the FDA and the National Institutes of Health (NIH) in identifying therapeutic gaps and challenges for the safe and effective prevention and management of diabetes, both type 1 and type 2. Dr. Orloff was hopeful that together they could find the most appropriate and expeditious paths to improve public health in this area.

This symposium was sponsored by the FDA's Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, CDER, and the Office of the Commissioner and by NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. Orloff announced speaker and panel member changes in the agenda and called the participants' attention to items in their meeting packets and program booklets, including speaker biographies; copies of previously submitted PowerPoint presentations; speaker, panel member, and participant lists; and a handout from the Juvenile Diabetes Research Foundation International (JDRF). Dr. Orloff then introduced Dr. Allen M. Spiegel, Director of NIDDK.

Dr. Spiegel welcomed the attendees and thanked Dr. Orloff and Dr. Robert Meyer, Director, Division of Metabolic and Endocrine Drugs, of the FDA and Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEM) , NIDDK, and Dr. Sanford Garfield, Senior Advisor for Biometry and Behavioral Research Program, DDEM, NIDDK, and other members of FDA and NIDDK for their efforts in organizing the meeting. Dr. Spiegel stated that a number of NIH institutes and offices are working together to foster research in type 1 and type 2 diabetes. They have created consortia and clinical trial networks to further progress in prevention and intervention in diabetes. For example, for type 1 diabetes, there is a schema of natural history, partially developed by one of the day's speakers, Dr. George S. Eisenbarth, that clearly shows that type 1 diabetes is a slowly progressive, autoimmune illness beginning with a genetic susceptibility and followed by environmental triggers or other inciting events and a period of "silent β-cell loss," largely because we do not yet know how to functionally monitor β-cell mass in a non-invasive way. Dr. Spiegel stressed that being able to do so is an important goal of NIH-supported research through the Beta Cell Biology Consortium, as this would provide an

enormously important biomarker. Following this silent β-cell loss, the overt onset of diabetes occurs and, in some instances, what is termed "brittle diabetes," as a function of complete loss of β-cell reserve.

Dr. Spiegel highlighted several current trans-NIH initiatives in type 1 diabetes including the following:

- Type 1 Diabetes Genetics Consortium (T1D GC), an international consortium to identify the additional genes that are known to underlie susceptibility.
- Environmental Determinants of Diabetes in the Young (TEDDY), a consortium that will follow the prenatal and postnatal development of children to try to determine the environmental triggers that remain unknown.
- TrialNet, a network of regional cooperative clinical groups for prevention and reversal of recent onset type 1 diabetes in partnership with the Immune Tolerance Network (ITN), which looks at the mechanistic aspects of monitoring T-cell function.
- A new islet transplant consortium that will be launched in the fall of 2004.
- DirecNet (Diabetes Research in Children Network), a pediatric network to look at non-invasive glucose monitoring.

In presenting a slide depicting the natural history of type 2 diabetes, Dr. Spiegel showed that the disease follows a similar course to that of type 1. There is a genetic susceptibility, along with an environmental trigger, which, for type 2, is well known. This slide was developed by another speaker, Dr. David Nathan, and his colleagues, and was also based on years of study of the Pima Indians in Phoenix, Arizona, by NIDDK's intramural branch. Although Dr. Francis Collins of the National Human Genome Project has explained that everyone has some "misspellings" in their genome, the natural history of type 2 diabetes follows a spectrum from what is termed "normal" to a state now identified as pre-diabetes, due to the stress of obesity and factors that impinge on β cells.

Dr. Spiegel stated that based on new American Diabetes Association criteria, there may be as many as 40 million individuals in the United States with pre-diabetes, *twice the amount previously estimated*. Their overt β-cell failure can lead to overt type 2 diabetes. Many of these individuals are undiagnosed because, unlike type 1, type 2 diabetes is an insidious disease. He added that the landmark Diabetes Control and Complications Trial (DCCT) demonstrated that macrovascular complications (such as cardiovascular disease) ensue as a function of poor glycemic control and ultimately lead to disability and death.

Dr. Spiegel listed the following major NIH type 2 diabetes studies:

- BARI2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study, which is primarily supported by the National Heart, Lung and Blood Institute (NHLBI), but NIDDK is involved.
- ACCORD (Action to Control Cardiovascular Disease Risk in Diabetes) and LookAHEAD (Action for Health in Diabetes) studies, which are examining various measures of glycemic, weight, blood pressure, and lipid control, as a way of converting cardiovascular complications in established type 2 diabetes.
- Diabetes Prevention Program (DPP) and the observational cohort follow-on DPPOS (Diabetes Prevention Program Outcome Study); DPP showed that an intensive lifestyle intervention or metformin could reduce the incidence of development of overt type 2 diabetes in those with so-called pre-diabetes.
- STOPP-T2D (Studies to Treat or Prevent Pediatric Type 2 Diabetes), a pediatric effort in children and adolescents for treatment of type 2 diabetes in those in whom it is established and an interventional study to prevent the markers of pre-diabetes in middle-school children.

In summary, Dr. Spiegel stated that NIH is making major investments and taking a proactive role at every stage of the spectrum, focusing on primary prevention wherever possible, because that is cost-effective, but also working to ensure that its research investment is fully translated. He emphasized that basic science studies have to be translated for the development of new therapeutics and new devices and efficacy trials have to be translated to show effectiveness in the community. To accomplish this requires partnerships with other agencies and organizations, as demonstrated by this FDA/NIH meeting.
Dr. Spiegel then introduced Dr. Janet Woodcock, FDA's Acting Deputy Commissioner.

Dr. Woodcock welcomed the group and reminded them that the impending burden of diabetes is not just a national public health problem but also a personal one since nearly everyone has a relative or friend affected by this disorder. She explained that the focus of this conference is on state-of-the-art prevention and treatment interventions for diabetes. Dr. Woodcock agreed with Dr. Spiegel that there is a growing recognition that biomedical research needs an increased focus on translating new scientific knowledge into new therapies, as reflected in NIH's Roadmap Initiative that was launched 6 months ago. In recognition of this need, FDA is partnering more directly with NIH and is sponsoring several new initiatives to facilitate the movement of innovative science into the clinic. The Innovations in Medicine Initiative, launched about a year ago, has as a goal to write new guidance on diabetes trials and development of new anti-diabetes products. Dr. Woodcock expected this symposium to assist the FDA with that activity.

Recently, FDA produced a report called, "Innovation or Stagnation: Challenges on the Critical Path to New Medical Technologies." The central thesis of this report reflected FDA's belief that, in addition to the basic sciences, more emphasis is needed on product development science and on new evaluative tools that will move new therapies more quickly into the clinic. Dr. Woodcock noted that this thesis is very relevant to the current meeting, since new tools are needed for drug, biologic, and device development and evaluation. For example, the meeting program calls for discussion of cellular therapies, such as use of islet cells and so forth, topics that have been a dream for a long time in this field. FDA has identified a broad series of challenges about the use of cell therapies, not strictly related to islet cells, but any type of cellular therapy. Dr. Woodcock listed a few of these. For example, what tools exist to characterize these cells? When interventions are studied in the laboratory, there is a controlled environment. However, a very different set of challenges present themselves when trying to control the cells and keep them stable in a mass production environment. New genomics and proteomics tools must be developed to evaluate characterization of cells in a production environment and help developers produce stable products with predictable characteristics. Dr. Woodcock said that FDA is working to develop and introduce genomics and proteomics, now prominent in the basic science realm, as new fields in industrial production.

Dr. Woodcock stated that medical devices are going to play an increasingly important role in the therapy of diabetes as drug delivery systems, as well as probably in the treatment of complications. FDA's Center for Devices and Radiological Health (CDRH) has identified a need for new computer tools to accomplish this. The medical device industry is continuously pursuing engineering type activities to alter devices and improve their performance. Computer models are needed to evaluate the impact of incremental changes on a device's performance, rather than the present method of evaluating these changes through costly and time-consuming clinical trials. Otherwise, clinical use of these improvements falls several cycles behind the engineers' developments. This delay also creates a barrier to innovation in this area.

According to Dr. Woodcock a range of issues need to be addressed in the area of drug therapies. For example, hepatotoxicity is a major barrier to drug development. Better predictive tools to identify hepatotoxicity and remove drugs earlier from the production pipeline or to predict who would be at risk if exposed to the drug would greatly enhance drug development by saving the billions of dollars of investment in drugs that, either late in clinical evaluation or once out in the market, are found to have

serious hepatotoxicity. Another opportunity for improving drug development would be to decrease the cost of clinical trials, another large barrier, by developing improved clinical trial designs.

As part of FDA's Critical Path initiative, Dr. Woodcock said the agency is meeting with many people during the spring and summer of 2004 to identify opportunities for improving development processes, such as learning what new scientific tools are needed to assist the development pathways for various medical products. In the fall of 2004, FDA will publish a list of the outstanding opportunities and enlist support in putting scientific effort behind solving these challenges. Given the challenges the Nation's healthcare system faces, Dr. Woodcock emphasized that meetings like this symposium were essential to help generate ideas and identify the kinds of problems that have to be addressed to accelerate the pace of innovation in diabetes, as well as in other serious diseases.

The agenda for the 1-1/2 day symposium addressed major challenges to development of new therapeutics and diagnostics for diabetes and perspectives on the future of prevention and therapy. Presentations covered the following topics:

- Overview of diabetes mellitus and vascular disease outcomes.
- New molecular targets in type 2 diabetes and immunomodulation in type 1 diabetes.
- Beta cell preservation in type 1 and type 2 diabetes.
- Islet transplantation.
- Glucose monitoring devices and insulin pumps.
- Prevention of type 2 diabetes including new perspectives on the metabolic syndrome and findings of the Diabetes Prevention Program.
- Industry and advocacy perspectives.

Speakers and symposium attendees participated in discussion periods throughout the meeting, concluding with a panel and participant discussion on targeting safe and effective prevention and treatment steps as FDA and NIH move forward in bringing research findings to the primary practitioner's office. Copies of Dr. Spiegel's slides and the speakers' slides used in the following presentations are available at http://www.niddk.nih.gov/fund/other/conferences-arch.htm. The conference program book containing the agenda, speaker abstracts, and speaker and participant contact lists is also available at that URL.

## Session I: Overview/Setting the Stage

*Moderator: David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products, Center for Drug Evaluation, FDA*

### Diabetes Mellitus 2004: Biomarkers and the Development of New Therapeutics and Diagnostics

***David M. Nathan, MD**, Director, General Clinical Research Center, Diabetes Center, Massachusetts General Hospital; Professor of Medicine, Harvard Medical School, Boston*

Dr. Nathan presented information predominantly from clinical trials about the role of biomarkers or surrogates in understanding the clinical course of diabetes mellitus and in the development of new therapeutics.

Dr. Nathan defined diabetes mellitus as a chronic disease characterized by abnormal metabolism of glucose, as well as other nutrients such as protein and fat, and accompanied by the risk of long-term complications specific to diabetes that affect the eye, kidney, and nervous system. Both type 1 and type 2 diabetes begin with a pre-diabetic phase. Diabetes is usually clinically diagnosed on the basis of hyperglycemia. Glycemia is a recurring theme in discussing diabetes and is, in a sense, a biomarker.

There is a latent period, during which the disease or the condition is present but before the patient develops either early or late complications that ultimately lead to morbidity and mortality. Dr. Nathan discussed some of the surrogates or biomarkers for different stages of the disease.

A surrogate is a predictor, or early warning sign, or marker of a phenomenon present before the disease occurs. Dr. Nathan explained that one of the inevitable questions during the development of clinical trials is always, "We want to measure heart disease, but could we reliably measure something that is not quite a heart attack? Something that precedes or predicts a heart attack? Wouldn't that be more efficient and potentially increase the power of a study?" This question leads to "What would be an acceptable substitute for a specific outcome?" In such discussions, the term "biomarker" has come into common use and been used instead of surrogate as an indicator of the outcome.

Dr. Nathan presented the interesting fact that dictionaries did not list "biomarker" as a word until very recently, yet there are more than a quarter of a million citations in PubMed (more than 3,000 since the beginning of 2004). Dr. Nathan searched Medline for "biomarker" and "diabetes" in 2004 and found 10 citations, including coronary calcification, CVD (cardiovascular disease), inflammatory markers, oxidative stress, proteomics, periodontal disease and CVD risk, and urinary isoprostanes. For the purposes of the meeting, Dr. Nathan defined a biomarker as a "biological process or biochemical indicator that precedes the development of disease and is usually indicative of the future development or progression of the disease, and as such can be used to measure the effects of treatment."

**Primary Prevention—Type 1 Diabetes**. Using Dr. Eisenbarth's concept of the natural history of type 1 diabetes, Dr. Nathan listed specific analytes that accompany the different stages: first, genotyping looking at cytotoxic T-cells and autoimmune T-cell profiles; antibody generation during the developmental stages; then, later on, abnormal insulin secretion that can eventually be measured with a stress test such as an intravenous glucose tolerance test; and finally, relatively late, abnormal glycemia. For primary prevention, an important question is whether any of these would substitute as an indicator for the actual development of hyperglycemia, which is a rather late phenomenon. As an example, since the generation of antibodies, and especially multiple antibodies, is quite a good indicator of who is going to develop type 1 diabetes, would preventing antibody generation be an acceptable biomarker for prevention of type 1 diabetes?

In the Diabetes Prevention Trial–1 (DPT–1), the outcome was hyperglycemia detected by oral glucose tolerance testing. The study demonstrated a high level of accuracy in predicting the development of diabetes. Dr. Nathan asked if some of the analytes from that trial could be used as biomarkers for new prevention studies. Dr. Nathan noted that several studies have used biomarkers, such as C-peptide secretion, but most investigators have considered these not reliable enough; however, as stated in the DPT–1 report, increased "understanding of development of diabetes may refine predictive markers" and result in alternative outcomes for future intervention studies.

**Primary Prevention—Type 2 Diabetes**. Dr. Nathan presented the pathophysiology of type 2 diabetes as beginning with insulin resistance, mediated by obesity, genetics, and other endocrine disorders, which leads to progressive postprandial hyperglycemia, then to impaired glucose tolerance and to fasting hyperglycemia, and finally to type 2 diabetes. He said there may actually be two different subpopulations of type 2—those who get fasting hyperglycemia may actually be different than those who progress through the postprandial route. Downstream of all of these stages are the duration-dependent complications.

Dr. Nathan referred to the "wounded" β-cell and resultant cyclic decrease in insulin secretion as the important players in the progression of this disorder that finally leads to glucose toxicity. The various measurements used to chart the course of the disease process—from clamp, HOMA, and minimod to the

oral glucose tolerance test (OGTT) and finally fasting glucose and hemoglobin A1c (HbA1c)—could be used as biomarkers in prevention studies if investigators were convinced that changes in the results of these measurements at the various stages in disease progression would equate to a decrease in the risk of developing type 2 diabetes.

Dr. Nathan pointed out that all of the studies for prevention of type 2 diabetes—DPP, the Finnish Diabetes Study, the Da Qing Study, and the STOPP-T2D—have used development of diabetes based on fasting or glucose tolerance testing, indicating general acceptance of diabetes as a disorder of hyperglycemia. Dr. Nathan suggested that other potential biomarkers could include lesser degrees of glucose intolerance. Changes in insulin resistance and other metabolic changes such as changes in free fatty acids might also be used as markers. He added that the importance of looking at different levels of hyperglycemia or insulin resistance goes beyond the issue of diabetes. Affecting sub-diabetic levels of hyperglycemia may have a benefit in and of itself. For instance, glucose intolerance and insulin resistance are components of the metabolic syndrome, which is a risk indicator for cardiovascular disease (CVD) as well as diabetes.

To illustrate the relationship of glycemia to the metabolic syndrome and CVD risk, Dr. Nathan presented data from the Framingham Offspring Study, a population-based study of the children and spouses of the children of the original Framingham cohort. During the fourth 4-year cycle of the offspring study, the participants were given glucose tolerance tests and then divided into normal, impaired glucose tolerance (IGT), and diabetic groups. The normal glucose tolerance group was divided into quintiles. The curves showing the level of glucose tolerance in these groups relative to elements of the metabolic syndrome, such as hypertension and hyperlipidemia, and the presence of the metabolic syndrome itself (which requires a grouping of factors), showed levels increasing along with glycemia. Dr. Nathan stressed the continuous risk function based on glycemia in the sub-diabetic range for both men and women for all of the elements of the metabolic syndrome. Every one of the elements of cardiovascular disease risk goes up continuously in the sub-diabetic, and even in the sub-pre-diabetic range, which indicates that rising glucose levels, perhaps mediated by increasing insulin resistance and by other factors, play a role here. Thus, examining glycemia as a biomarker of cardiovascular disease risk may be of benefit. Other biomarkers, such as inflammatory and hemorheologic abnormalities, followed the same trend across all quintiles.

Dr. Nathan noted that the Diabetes Prevention Program also had the goal of determining whether the interventions would decrease cardiovascular disease, cardiovascular disease risk factors, or biomarkers for cardiovascular disease. He offered data currently in press that was presented at the American Diabetes Association meetings in 2003. Year one mean change in t-PA, a biochemical risk factor (or a biomarker) for CVD, was reduced in the intensive lifestyle group and in the metformin group, compared with the placebo group. Similarly, CRP (C-reactive protein) was significantly lower in the female population in both the intensive lifestyle and the metformin groups.

**Secondary Intervention**. Dr. Nathan presented possible surrogates or biomarkers used in the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). In DCCT and most studies of diabetes, HbA1c is used as an index of chronic glycemia and as the usual surrogate for chronic glycemia. Dr. Nathan presented data showing that it has been known for some time that there is an association between glycemia and complications, such as retinopathy and kidney disease. For example in DCCT, a 10-percent reduction in HbA1c through intensive glycemic control resulted in a 43-percent reduction in risk for retinopathy. Retinopathy was tested using fundus photography that assessed changes in the vasculature of the eye. Since the tight relationship of HbA1c and the biomarker for pre-retinopathy (changes in the eye associated with development of vision loss, not actual vision loss) was demonstrated strongly in DCCT and in a 4-year follow-up, Dr. Nathan suggested that pre-disease levels of retinopathy or HbA1c could be used as biomarkers in primary and secondary intervention trials

for type 1 diabetes. DCCT also showed decreases in kidney disease (predominantly microalbuminuria, another biomarker) associated with decreased HbA1c; thus decreases in HbA1c could be used as a biomarker in clinical trials of therapies and interventions to prevent nephropathy.

Since the incidence of CVD events in the DCCT was too low to determine if intensive therapy reduced cardiovascular disease, Dr. Nathan said that it was decided in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the follow-up to the DCCT, to look at biomarkers of CVD such as atherosclerosis measured by carotid ultrasonography. EDIC showed that in the DCCT cohort, intensive therapy, compared with conventional therapy, significantly decreased the rate of progression of thickening in the common carotid and in the internal carotid arteries. Other studies have demonstrated that IMT (intimal medial thickness) of the carotid artery may be a good biomarker for cardiovascular disease. Thus, biomarkers of CVD, such as measures of atherosclerosis as IMT and coronary calcification, have been shown to be sensitive to glycemic intervention. Further follow-up may demonstrate a benefit of intensive therapy on the CVD events. If further follow-up shows a correlation between the measures of atherosclerosis and CVD events, then Dr. Nathan would urge the use of these measurements in secondary prevention trials as substitutes for actual hard clinical events.

**Tertiary Intervention**. Until the past 10 years or so, this is the area (decrease in mortality or severe morbidity) that received the most attention. Dr. Nathan stated that there are a lot of interventional data available. By this late stage of disease progression, lipids and blood pressure, rather than glycemia, are probably the important targets for cardiovascular events. Dr. Nathan noted that the next speaker, Dr. Peter Wilson, would be discussing the possible biomarkers for this stage.

Dr. Nathan concluded by stressing that diabetes represents a chronic, long-term, degenerative disease for which there are numerous potential targets with regard to the biology of disease. Use of these targets can certainly increase the efficiency of future interventional trials.

### Diabetes Mellitus and Vascular Disease Outcomes

***Peter Wilson, MD**, Professor of Medicine, Section on Endocrinology, Diabetes, and Medical Genetics, and Program Director, General Clinical Research Center; Medical University of South Carolina, Charleston*

Dr. Wilson began his presentation by stressing that the United States has an epidemic in diabetes, with obesity contributing to the increasing numbers of adults with type 2 diabetes, of whom two-thirds will have a cardiovascular outcome as cause of death. Virtually every obese diabetic will have CVD before they die. Dr. Wilson also offered data showing that diabetes, along with hypertension, are the two primary causes of end-stage renal disease (ESRD), another major reason to be concerned about the diabetes and obesity epidemics. Type 1 diabetes also leads to kidney failure, coronary artery disease, and other complications of diabetes such as infections; approximately a third of type 1 diabetics eventually die from CVD. The DCCT showed that with tight glycemic control, microvascular events could be reduced but, as Dr. Nathan had said, the number of macrovascular events was too small for tight glycemic control to be predictive of these.

From NHANES III data (M. Harris, Diabetes Care, 23:754, 2000), Dr. Wilson showed that of persons with type 2 diabetes in 1994, 45 percent had a body mass index (BMI) greater than 30 (i.e., obese), 63 percent had hypertension, and 58 percent had HbAlc greater than 7 percent, all risk factors for complications. Dr. Wilson's data from the Framingham cohort indicated that for younger persons (ages 35-64), diabetes doubles their risk for CVD and stroke for men and triples it for women. In the older age group (65-94), diabetes doubles the risk for men and women, except for heart failure and stroke, where the risk is higher. Dr. Wilson stressed that older persons with diabetes and hypertension tend to slip into heart failure post-heart attack.

Dr. Wilson presented data from Dr. Steve Haffner and the Finnish East-West study that indicated a non-diabetic was at lowest risk for a second heart attack. Those at the highest risk were diabetics who had had a prior myocardial infarction (MI). At equal risk were non-diabetics with a prior MI and diabetics with no prior MI, which shows that having diabetes puts a person at equal risk of a heart attack with a person who has already had a heart attack. Dr. Wilson said this is why NHLBI and other groups recommend treating diabetics as aggressively as one treats people with known coronary events. The Nurses Health Study demonstrated that, like microvascular disease in type 1 diabetes, the longer the duration of type 2 diabetes, the greater the risk for macrovascular disease.

**Glycemia and Vascular Risk**. Observational data on hyperglycemia in middle-age adults and risk for vascular complications in type 2 diabetes from the Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) showed a higher risk for retinopathy than for cardiovascular disease. As with the lower hyperglycemia in middle age adults with type 2 diabetes in WESDR, DCCT showed that tight glucose control affected progression of small vessel disease in the eye in type 1 diabetes and also decreased microalbuminuria and macroalbuminuria.

Dr. Wilson noted that the UKPDS was largely about glucose control but also had a hypertension arm. This 10-year study included nearly 4,000 newly diagnosed non-obese type 2 diabetics whose median age was 54 at onset of the trial, of whom approximately one-third were treated with a conventional therapy and diet, receiving drugs if needed, and two-thirds received intensive treatment with oral agents or insulin. Dr. Wilson stressed that 10-year studies are no longer an option in this field because answers are needed sooner and therapies are changing very fast. For instance, today blood pressure treatment is two generations beyond what was used in the UKPDS hypertension arm. Intensive glucose control in NKPDS showed a strong decrease in microvascular endpoints. For coronary artery disease (CAD), decreases in HbA1c and systolic blood pressure and increases in HDL cholesterol decreased risk by 11 to 15 percent. A 39 mg/dl decrease in LDL cholesterol decreased risk by 57 percent. Dr. Wilson pointed out that the focus on multiple interventions probably produced better results than focusing on just one intervention does. He added that until recently, diabetics were often excluded from blood pressure trials.

**Blood Pressure and Vascular Risk**. Dr. Wilson summarized the results of the following studies that have included blood pressure and vascular risk in diabetes:

- WESDR: Some relationship of systolic pressure, but not diastolic, to progression of retinopathy in younger diabetics, but in older patients, the relationship to systolic and diastolic was about equal.

- SHEP (Systolic Hypertension in the Elderly Program): Diabetics benefited nearly twice as much as non-diabetics from blood pressure treatment with chlorthialidone.

- SYSEUR (Systolic Hypertension in Europe): Use of a calcium channel blocker was effective for stroke in both diabetics and non-diabetics, but less so for cardiac events.

- HOT (Hypertension Optimal Treatment): This Scandinavian-led study produced lower levels of diastolic pressure in diabetics through aggressive treatment and led to new guidelines from the American Diabetes Association (ADA) (a diastolic of 80 for diabetics and 75 for diabetics with kidney disease) and the National Cholesterol Education Program (NCEP).

- HOPE (Heart Outcome Prevention Evaluation): A powerful angiotensin converting enzyme (ACE) inhibitor trial using ramipril showed that CVD risk could be reduced in high-risk patients, including those with diabetes.

- UKPDS: Use of beta blockers for tight control of blood pressure indicated positive endpoint results in heart failure, stroke, diabetes death, and microvascular disease.

- RENAAL (Reduction of Endpoints in NIDDM with Angio II Antag Losartan): Using an ARB (angiotensin receptor blocker) versus placebo, Dr. Barry Brenner and colleagues had positive results for diabetics in endpoint incidence of chronic kidney disease, ESRD, and death.

Dr. Wilson stated that the number of positive results from trials of ACEs and ARBs is producing a strong message for guidelines to include the use of these sooner rather than later in treating type 2 diabetes.

**Dyslipidemia and Vascular Risk**. Dr. Wilson explained that abnormal LDLs are similar in diabetics and non-diabetics; however, in diabetics, it is common for HDLs to be low and triglycerides to be high, particularly in women, as shown by data from the Framingham Offspring Study. In four secondary prevention trials to reduce CVD risk (Scandinavian Simvastatin Survival Study (4S) and simvastatin, CARE and pravostatin, LIPID and pravostatin, and the Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT) and gemfibrozil), regardless of the agent, except for simvastatin, or whether patients were diabetic or non-diabetic, the results were similar in reducing relative risk in high-risk patients.
Dr. Wilson's main point was that these lipid interventions work as well in diabetics as they do in non-diabetics. In the ASCOT study, a joint Scandinavian and Great Britain trial using atorvastatin, there were not enough diabetics in the group to get a strong result versus non-diabetics.

**Multifactorial Issues**. Dr. Wilson presented data (Stamler, J. Diabetes Care, 1993, 16:434-44) showing that having multiple risk factors for coronary artery disease gradually increases risk of death in non-diabetics, but doubles or triples the risk in diabetics. The Steno-2 study of 160 persons with type 2 diabetes, a mean age of 55, a conventional diabetes treatment and intensive treatment group (80 in each), with an 8-year follow-up, was a multifactorial intervention trial that had as outcomes composite CVD death, nonfatal MI, nonfatal stroke, revascularization, and amputation. The intensive treatment group included total dietary fat and saturated fat restrictions of less than 30 percent and less than 10 percent, respectively; 30 minutes of exercise 3 to 5 times each week; smoking cessation for those who smoked; and treatments to reduce HbA1c, and lower blood pressure, elevated cholesterol, and elevated triglycerides. With the exception of HbA1c, the intensive group was very successful in reaching their goals. After 8 years, the outcome to prevent CVD was, in Dr. Wilson's words, "a real win," with only about 20 percent of the intensive treatment group developing CVD while nearly 60 percent of the conventional therapy group had CVD. Dr. Wilson strongly recommended that the next generation of aggressive trials build on the Steno-2 model by using multiple interventions.

In summary, Dr. Wilson said that for microvascular disease such as retinopathy and nephropathy, glycemic control is very important, blood pressure control is a little less so, and lipids are the least important in diabetes. Macrovascular disease in diabetes is more complicated. Abnormal lipids double the risk in men and triple it in women, especially for women in middle age. Unfortunately, after a cardiovascular event, diabetics have a higher risk and a very poor prognosis for outcomes. He highly recommended multifactorial interventions to prevent macrovascular disease in diabetics, including blood pressure therapy, treatment for abnormal lipids, diet and exercise, and glycemic control for its mild effects on macrovascular disease.

## Discussion

Dr. Orloff led off the discussion by saying that in adding details to our understanding of the step-wise progression to overt type 1 and type 2 diabetes, we have arbitrarily defined and redefined diabetes. He added that we have increasingly accepted as valid certain biomarkers of the pathogenic course of the disease that relate to chronic exposure to glucose and metabolic abnormalities and the risks that accrue from these, which have provided us with targets for prevention at a much earlier stage of the disease. He asked if it should be conceded that our definitions of diabetes have always been somewhat arbitrary, and, more specifically, should FDA and NIH be thinking about standards of evidence for safety of new interventions as we start to intervene earlier and earlier in the course of the disease.

Dr. Nathan responded that since diabetes is a continuum of pathophysiologic processes, we must be aware of the clinical trial participants' or patients' stage in the continuum when testing or recommending interventions. For example, more risk is taken in doing stenting or angioplasty on a patient who has had or is close to having an MI in order to prevent a heart attack than the risk in prescribing a drug or lifestyle change for someone with high blood pressure. One is usually willing to take a greater risk when the downstream outcome is very near, whereas with a chronic, degenerative disorder, there is less willingness to risk. An example would be questioning the use of cyclosporin to prevent type 1 diabetes in pre-diabetic children. It is a case-by-case decision on how close the patient is to a life-affecting disease process as opposed to how early in the disease process the patient is. Another example Dr. Nathan gave was the decision in DPP to stop using troglitazone as the study group accumulated evidence that it might be dangerous and DPP was working with high-risk, possibly pre-diabetes, but non-diabetic patients. Later the drug was removed from the market. The challenge with cardiovascular disease and atherosclerosis is that this is a process that takes place over decades and so one must decide when in the process it is most effective clinically and economically to intervene and with which drugs. With today's statins and blood pressure medicines, this is mostly a cost-effectiveness issue. Still the questions are "Do we start treating young men in their 20's to prevent an MI at age 50 or 60? And which young men should be treated then?" This is more a health economics issue than a safety issue. Dr. Nathan said that as we identify effective, reliable preventive measures to apply early in the continuum, there will have to be case-by-case decisions made.

Dr. Orloff remarked that the speakers' talks clearly showed that there is a large amount of basic science data and clinical trial data available and that thus we need to be careful in moving forward to not address questions to which we already have the answers. On the issue of treating asymptomatic disease or pre-clinical disease, this raises the issue of whether we ought to, in some instances, be thinking not about ultimate proof of effectiveness trials, but about safety trials. He asked Drs. Nathan and Wilson what they saw as the highest priority questions for clinical trials in prevention and management of type 1 and type 2 diabetes to prevent sequelae.

Dr. Wilson recommended trials similar to that of Steno-2, which, since it was a European trial, has not received much attention from the average physician in North America. It was published in the *New England Journal of Medicine* (Gaede. NEJM 348:383-393, 2003), so scientists in diabetes and heart disease probably know about it, but again the problem is translation to the average physician. A second issue is that it takes a lot of time to care for someone with type 2 diabetes and for them to get their protocols right. Most diabetics are on four to eight medicines. Hypertension also is not a one-medication problem. British literature has been discussing a "polypill" approach for prevention of CVD in type 2 diabetes. A trial for this would not be simple because the answer is not simple. Dr. Wilson therefore suggested trying to design larger trials based on something simpler with still important outcomes.

Dr. Nathan felt that trials are large enough now and are designed with safety considerations. For example, for the Diabetes Prevention Trial-Type 1 (DPT-1), it was carefully considered whether giving insulin

parenterally would be dangerous; it turned out not to be and a much larger study is not needed to pick up the half-a-percent or so who had very low level complications. Dr. Nathan agreed with Dr. Orloff that we have an enormous reservoir of information as to what we could be doing in prevention but not enough studies like Steno-2 that show what might happen with CVD if we applied what we know, even using old-fashioned medications or diuretics. He suggested that what we need is translational research on how to apply what we know, how to make the therapies more accessible in order to stem the diabetes epidemic.

Dr. Simeon Taylor, Bristol-Myers Squibb Company, commented that just as HbA1c was identified and accepted through epidemiological studies as a valid biomarker for first one mechanism and then a number of mechanisms, there are other biomarkers such as HDL that have been identified through epidemiology. He asked how the scientific community and the regulatory agencies go from a hypothesis or even validation for a single mechanism to the next step where it is assumed that this represents a universal truth for all mechanisms. Does the biomarker have to be validated for each novel mechanism?

Dr. Nathan replied that although HbA1c was demonstrated in numerous studies to be a concrete marker for glycemia and also a surrogate for the glycemia component of microvascular and neurological complications, the DCCT/EDIC also did a sub-study that showed that glycated dermal collagen was even more directly related to a complication. Dr. Nathan's point was that although a biomarker may be an excellent surrogate across many mechanisms, there probably exist more direct measures downstream in the pathogenesis of complications. He suggested the most direct way of proving this is to ensure that there is enough stored tissue specimens in the NIH repository so as new suggestions come up, associations can be looked for to identify potential new biomarkers. He noted that there is still a great deal to be explained in the pathogenesis of complications.

Dr. Wilson stated that most of the really good markers are now standardized, such as cholesterol and blood pressure. C-reactive protein is not yet standardized. Advanced glycosylated endproducts had great promise but there were problems with measurement and standardization. This is also true for some of the lipoproteins compared to standard lipids. Standardization of new markers is therefore a key issue and tends to be a tremendous problem with surrogate markers. For example, carotid analysis is a highly advanced skill unlike testing for glucose.

Dr. Judith Fradkin, NIDDK, raised the issue of when a clinical trial finding can be pronounced ready for translation to the community. For example, NIH and the Centers for Disease Control and Prevention (CDC) have developed the Small Steps initiative in the National Diabetes Education Program (NDEP) to translate the DPP findings about early intervention to protect loss of β-cell function before the β-cells are severely wounded in those at risk for pre-diabetes. The DHHS Agency for Healthcare Research and Quality, however, feels it has not been clearly demonstrated to their satisfaction that we should be identifying people with pre-diabetes or that it is cost-effective to intervene in that situation. FDA will clearly be faced with this issue as other trials are underway, looking at additional agents that might prevent progression. Dr. Fradkin asked what should be the public health message from such trials.

Dr. Nathan answered that in the past those who did clinical trials that ultimately have public health implications have shied away from the issue of the public health messages. The attitude has been "We did the science. The message is up to someone else." This is changing. Dr. David Marrero, who was a member of DPP, is very involved with NDEP and has been very active in developing the Small Steps program. Dr. Nathan added that every clinical trial today needs to be judged as to whether it is translatable. There are very few large clinical trials these days that do not have a health economics group working side-by-side with the investigators. CDC has been partnering with DCCT/EDIC and with DPP for more than a decade. Studies that use a lot of resources need to keep in mind that ultimately there is going to be a translation message.

Dr. Nathan continued that it is not surprising that there are concerns expressed by different agencies. Further follow-up may be needed to convince agencies and other groups of the wisdom of the DPP message. For example, the findings from DCCT that were accepted almost universally in 1993 have now been reinforced 10 years later by EDIC and shown to be a very inexpensive intervention to prevent complications. The DPP follow-up will hopefully do the same.

Dr. Wilson pointed out that about half of type 2 diabetes occurs after age 65, at a time when persons are beginning to lose muscle mass and brain mass and developing more adiposity and losing β-cell function, and this will continue through the ensuing aging years. From Dr. Wilson's perspective, the time to head off the diabetes problem is therefore earlier, between 35 and 65.

Dr. Nathan agreed by emphasizing that it was critical to shift the focus from treating disease to preventing disease if we are to stem the epidemic. If not, there will be so much disease around that the entire healthcare budget and all the limited resources that exist will have to be spent on late-stage, tertiary prevention of complications in a growing population of 800,000 to 1.2 million new diabetic patients per year. There will not be enough resources to take care of the kidney disease, the heart disease, and everything else that will occur.

In response to a question from Dr. Richard Pratley, University of Vermont, regarding the validity of HbA1c as a marker for microvascular disease in type 2 diabetes and cardiovascular disease, Dr. Nathan said that the UKPDS tends to substantiate this but it was not a Government-supported study and did not have the tight controls that DCCT had; therefore, some of the evidence is not firmly established. It would be a public policy issue as to how high a level of resources should be invested in such an effort. He recommended again that trials be designed so that samples exist in repositories and data is stored in a databank in order to examine new biomarkers without the large investment of a DCCT. With regard to CVD, Dr. Nathan said that clearly blood pressure and lipids have a demonstrably greater effect than HbA1c does and there is not convincing data to show that glycemic intervention itself lowers the risk of CVD. The ACCORD study is examining that.

An issue of discussion was that given that a primary care physician has approximately 7 minutes per patient to treat the illness or condition with which the patient is presenting at this appointment, there is little opportunity to diagnose type 2 diabetes or hypertension in the early stages nor are there protocols for treating the possibly pre-diabetic patient. Although glucose and the components of metabolic syndrome should not be ignored over time, there are no obvious short-term benefits for the doctor or the patient in dealing with them immediately since the patient is then asymptomatic. Dr. Wilson noted that there are important issues, pro and con, in performing early intervention with drugs. Dr. Nathan added that currently we are initially dealing with sub-clinical events as we face chronic disease management for the next millennia. In terms of immediate, short-term benefit, he agreed one may have to balance the possible benefit against the side effects of the medication. This is the difference between trying to prevent and initial MI, rather than treating an already existing condition. Whereas, with regard to the silent epidemic of all the cardiovascular disease risk factors and diabetes, there is no penalty, there is no motivation, necessarily, to address these factors right then, and unfortunately, they tend to "float on." Dr. Nathan's preference would be to aggressively treat all risk factors.

Dr. Harold Lebovitz, State University of New York, stated that he felt early diagnosis and intervention for hyperglycemia was important since hyperglycemia causes structural damage and most people, by the time they are diagnosed with diabetes, already have complications or sub-clinical complications, not just risk factors. Dr. Lebovitz asked about the issue of obesity in diabetics. Dr. Wilson stated obesity is the determinant for type 2 diabetes. Diabetologists recognize the need for the patient to lose weight; now they are concerned with the metabolic syndrome as a risk factor.

Dr. Jorge Plutzky, Harvard Medical School, emphasized that there needs to be outreach to the internist and the family practitioner to identify early on those 1.5 million Americans who die from their first cardiac event, of whom a large percentage are pre-diabetic or have the metabolic syndrome and could have had a different outcome if there had been an intervention. In patients with late-stage disease, there has to be a lot of "catch-up" for disease that is too advanced, so that even if trials show relative risk is low, persons with pre-diabetes or the metabolic syndrome would benefit from earlier treatment.

Dr. Plutzky asked what happens when an unexpected outcome from a seeming surrogate occurs, as when an ACE inhibitor decreases convergence to diabetes. He also asked what is necessary to indicate use of a drug to prevent or delay convergence to diabetes.

Dr. Nathan responded that several studies, one of which is HOPE, have suggested that ACE inhibition or a statin may play a role in diabetes prevention. Most of these studies were not designed primarily to study diabetes prevention, and bias of ascertainment may play a role in some of them. However, the HOPE study has performed detailed secondary analyses that suggest a beneficial effect of ACE-inhibition. Several ongoing clinical trials are examining whether ACE-inhibition is effective in diabetes prevention. Dr. Nathan said he doubted that the currently available data would affect labeling of ACE inhibitors, which he feels are not being used enough. Without adding diabetes to the list of indications, ACE-inhibitors are already indicated for the treatment of hypertension, and are beneficial for cardio-protection and renal protection. He thought it was important to use ACE-inhibition more frequently for its current, well-established indications. If future studies show that ACE-inhibition (or receptor blockade) helps prevent diabetes, it would be an important development. However, no convincing data currently demonstrate this.

Dr. Plutzky summarized that an internist, recognizing the importance of ACE inhibitors and seeing a metabolic syndrome patient would then say to him/herself "Blood pressure is 135 and the patient is thick around the waist so, based on the choices available to me, I am going to take advantage of an approved indication for an ACE inhibitor, not only to improve this person's blood pressure, but possibly also to influence convergence to diabetes or to delay it." Dr. Plutzky said that those looking for insulin sensitizers might ask themselves "When can I do the same thing with metformin?" based on DPP data.

Dr. Nathan applauded the emphasis on prevention issues and reminded the group that even people with recognized cardiovascular disease and its risk factors in diabetes are currently undertreated, a barrier that needs to be overcome.

## Session II: New Targets of Intervention

*Moderator: Judith Fradkin, MD, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK*

### New Molecular Targets in Type 2 Diabetes Mellitus

***Nancy A. Thornberry,*** *Senior Director, Department of Metabolic Disorders, Merck Research Laboratories, Merck and Company, Inc., Rahway, New Jersey*

To set the stage for her review of the molecular targets that have the most potential within the next 10 years, Dr. Thornberry briefly reviewed the pathogenic defects that result in hyperglycemia–hepatic glucose overproduction, insulin resistance, and insulin secretory dysfunction. She stated these defects are thus the primary targets for current and future therapies to treat elevated blood glucose. There are three major classes of oral antihyperglycemic agents (AHAs):

- Sulfonylureas that stimulate insulin secretion in the pancreas, but may increase risk of hypoglycemia, cause drug interactions, exhaust β cells, or cause weight gain.

- Metformin and PPARs that lower glucose overproduction in the liver; metformin may have gastrointestinal side effects and cause lactic acidosis; PPARs also may have drug interactions, increase weight gain, or cause edema.
- PPARs that improve insulin resistance in muscle, but have the possible side effects listed above.

Dr. Thornberry stated that future potential therapeutic classes will include these three major classes of insulin sensitizers, insulin secretagogues, and mediators of hepatic glucose output. She presented the rationales and key issues for various therapeutic agents in each of these classes.

**Insulin Sensitizers: PPARα and PPARγ Agonists**. PPARs are ligand-modulated transcription factors. Dr. Thornberry explained that the PPAR is a nuclear hormone receptor involved in differentiation and function of fat cells; ligands bind to the nuclear receptor but the downstream mechanism is not fully understood. PPARα agonists target dyslipidemia and atherosclerosis by correcting lipid abnormalities. PPARγ agonists are a target for type 2 diabetes to correct insulin resistance. The rationale for using these as dual activators is to improve and simplify treatment of diabetes patients while decreasing cardiovascular risk. There is preclinical proof in animal studies of the efficacy of using them as dual agonists. Key issues are their combined adverse effects. For PPARα, this includes myopathy and a potential for hepatotoxicity. Adverse effects for PPARγ are weight gain, edema, mild anemia, mild leucopenia, and the potential for increased risk of heart failure.

**Insulin Sensitizers: SPPARγMs**. Dr. Thornberry said that safety concerns are a key barrier in widespread use of PPARγ full agonists such as thiazolidinediones (TZDs), which has led to the selective PPARγ modulator (SPPARγM) hypothesis. SPPARγMs are potent ligands but only partial agonists. Unlike full agonists, their alternative binding motifs produce differential coactivator associations and the restricted gene expression changes profiles, so they may retain efficacy but have reduced toxicity, as was demonstrated in the db/db mouse study that compared rosiglitazone, a full agonist, and a partial "relative" of rosiglitazone that still retained full efficacy. Rodent studies also showed that the partial agonist caused only modest cardiac effects compared to the rosiglitazone. Key issues include whether or not the SPPARγMs will equal the efficacy of current TZD full agonists while avoiding the safety concerns and adverse effects of TZDs. If they are safer, then there would be an option to test higher doses.

Summarizing, Dr. Thornberry said the dual PPARα/γ agents have the potential to act on co-morbidities but may have the same safety and tolerability liabilities as individual PPARs. The SPPARγMs have a safer profile and may ultimately allow for treatment at earlier stages of diseases. She told the audience that there is a lot of effort going on in developing the next-generation insulin sensitizers with a focus on a non-PPAR mechanism, enhanced efficacy, and improved safety and tolerability.

**Insulin Secretagogues: Glucagon-like Peptide 1 (GLP-1) Analogs**. The analogs are one of two GLP-1 based therapies being studied. The other is dipeptidyl peptidase IV (DP-IV) inhibitors. Dr. Thornberry described GLP-1 as a peptide secreted from the stomach in response to food intake that has been shown in humans to have a number of beneficial effects, including stimulation of glucose-dependent insulin biosynthesis and secretion, inhibition of glucagon secretion, and slowing of gastric emptying resulting in a feeling of satiety and thus reducing appetite. In fact, modest body weight loss has been observed with GLP-1 analogs. She added that there is very intriguing data in rodents to indicate that GLP-1 may have a potential for regulating islet growth and survival.

Dr. Thornberry cited a study by Dr. Holst and colleagues (Holst et al. Lancet 359, 2002) in Copenhagen that demonstrated that as soon as 1 week after continuous infusion of GLP-1 in humans there were excellent effects on both postprandial and fasting glucose compared to saline infusion and these effects were maintained over a 6-week period. Dr. Alain Baron has reported the results of a 5-month open-label study with Exenatide (exendin-4) in 155 patients failing metformin and sulfonylureas in which the interim

analysis showed reductions in HbA1c and positive effects on body weight. There were some safety and tolerability issues such as antibody titers and nausea and vomiting that is observed with all GLP-1 analogs; however, there was decreased incidence of the stomach upset with repeated dosing, the antibody titers apparently did not impact efficacy, and there were no safety liabilities.

According to Dr. Thornberry, the vision for GLP-1 analogs is sustained efficacy, good durability, and the potential to stabilize β-cell function. GLP-1 analogs do not have any of the adverse effects associated with current agents—there is no or a low risk of hypoglycemia, no weight gain or even body weight loss, and no edema. They offer an excellent potential for use in combination with other agents for the pathology such as insulin sensitizers and mediators of hepatic glucose output. Dr. Thornberry cited rodent data showing a potential for β-cell regeneration, an attribute that, if it extends to humans, Dr. Thornberry compared to finding a "holy grail" that could lead to improvement over time in glycemic control and even reverse β-cell loss.

Key issues for GLP-1 analogs are that injections are required with the current agents in development; patients experience nausea due to delayed gastric emptying, although this may not be a issue in the long run; and the β-cell effects have not been demonstrated in humans.

**Insulin Secretagogues: DP-IV inhibitors**. Dr. Thornberry explained that DP-IV inhibitors are essentially an oral approach to GLP-1 therapy. DP-IV is the key enzyme involved in the regulation of GLP-1, which, like other peptides, is very rapidly degraded *in vivo*, with a half-life of less than 1 minute, so that inhibition of DP-IV results in raising the endogenous level of GLP-1. Proof-of-concept was provided by Dr. Holst and his colleagues in 1998. Several compounds are in clinical development. A study with a Novartis compound (Arhen et al., 2002, Diabetes Care 35) in which 93 patients were treated for 4 weeks demonstrated the compound was well tolerated and had statistically significant effects on fasting, postprandial, and 24-hour glucose.

Dr. Thornberry described the vision for DP-IV inhibitors also sustained efficacy and good durability in stabilizing β-cell function; tolerance and a good safety profile; oral therapy (versus the GLP-1 injections) and the potential for once-daily dosing; excellent potential for use in combination with other therapeutic agents; and the potential for β-cell regeneration.

The key issues are the unknown extent of the efficacy with 24-hour, chronic DP-IV inhibition; the potential that the therapy would have to be limited to mild diabetes with intact β-cell function; ability to be used in combination (likely synergistic with PPAR and metformin but may be difficult to predict efficacy with sulfonylureas and insulin); whether it will have the potential β-cell preservation and/or regeneration benefit in humans; and determination of safety and tolerability. Dr. Thornberry said that the enzyme, in addition to its role in GLP-1, has been implicated in a number of different functions, including T-cell activation and immune function, and there are a variety of substrates other than GLP-1 that are cleaved *in vitro* by this enzyme, which is true of subsurface peptidases in general. Their *in vivo* significance and whether or not they are regulated *in vivo* is very difficult to establish, which means data is needed on its long-term safety and tolerability. In addition to establishing safety and tolerability, Dr. Thornberrry said the focus for future agents should be glucose-stimulated insulin secretion, as this is the mechanism by which DP-IV inhibitors work; greater efficacy; and trying to understand what is indeed responsible for β-cell degradation so that can be targeted in a more rational way. Overall, these agents are expected to present many benefits.

**Mediators of Hepatic Glucose Output**. Dr. Thornberry highlighted these because there is some human validation for both glucokinase activators and glucagons receptor antagonists. **Glucokinase (GK)** is a key enzyme involved in the metabolism of glucose, catalyzing the phosphorylation to glucose-6 phosphate in both the liver and in the pancreas, where it is predominantly expressed. It is a member of the hexokinase

family and a rate-limiting step of glucose metabolism. Dr. Thornberry remarked that the rationale for this target is clearly the anticipation that dietary glucose would be absorbed and converted to glucose-6 phosphate, resulting in enhanced hepatic glucose uptake and decreased glucose production. Glucokinase plays a key role in the glucose sensing in the pancreas that results in insulin secretion; therefore, GK activation should result in production of insulin. In summary, the combined hepatic and pancreatic effects may translate into improved efficacy over current agents.

Dr. Thornberry stated that human validation has been provided in the way of genetic validation. Approximately 150 mutations have been identified in GK. Fifty percent of GK function has been observed in MODY (maturity onset diabetes of the young) and gestational diabetes. One hundred percent loss of GK results in neonatal diabetes, and activating mutants have been identified by Dr. Franz Matschinsky (Matschinsky, FM. Diabetes 51:S394-404, 2002) and a number of other investigators showing increases in fasting and 2-hour glucose in subjects with GK mutations as opposed to their unaffected relatives. Dr. Thornberry said that it has been demonstrated that only modest activation of GK is required to produce beneficial effects in rodents. A two-fold increase in messenger RNA in the liver of rodents lowered glucose and improved glucose tolerance. Roche published data in 2003 that demonstrated pharmacological proof-of-concept for GK activators (Grimsby et al. 2003, *Science* 301, 370).

Potential attributes and advantages listed by Dr. Thornberry included considering GK activators as a single-agent combination therapy affecting both the β-cell and the liver, so it could potentially be applied to a broad range of type 2 diabetic patients with both insulin resistance and impaired insulin secretion. It is also predicted to have a good safety and tolerability profile and the potential to be used in combination with insulin sensitizers, DP IV inhibitors, and metformin.

Key issues for this target are hypoglycemia and the potential for lipid accumulation in the liver, as with all gluconeogenesis targets.

Dr. Thornberry said those present were well familiar with the following rationale for **glucagon receptor antagonists**: glucagons have a very important role in maintaining glucose homeostasis. Being secreted by the α-cells in response to falling glucose, glucagons activate the hepatic glucagon receptor, which in turn results in glycogen breakdown and gluconeogenesis, which elevates blood glucose. Some limited proof-of-concept in humans has been provided in a study done by Bayer with a glucagon antagonist that demonstrated it blocked exogenous glucagon effect in dogs and rhesus, and in man. Dr. Thornberry gave as potential attributes and advantages that the glucagons receptor antagonist is predicted to decrease both fasting and postprandial hyperglycemia; is anticipated to have a relatively clean safety profile; is an oral agent; and has good potential for use in combination. The key issue is its potential for hypoglycemia.

In summary, Dr. Thornberry said the agents furthest along in development are the dual PPARα/γ agonists, the GLP-1 analogs, and the DP-IV inhibitors. There are a variety of other mechanisms that either are or may be in early development, including SPPARγMs, GK activators, glycogen phosphorylase inhibitors, SGLT (sodium-glucose cotransporter) inhibitors, glucagon antagonists, fructose 1,6 bis-phosphatase inhibitors. The insulin receptor phosphatase looks like an attractive target, the issue being whether or not one can truly make a phosphatase inhibitor that has suitable properties for use *in vivo*. Dr. Thornberry stated that chemical tractability is a big issue here, so there are companies that instead are pursuing an antisense approach to PTPIB (protein-tyrosine phosphatase 1B). She concluded by noting that she may have missed some others in development, but in any event, there are a number of promising therapies emerging.

## Immunomodulation in Type 1 Diabetes

***George Eisenbarth, MD, PhD**, Executive Director, Barbara Davis Center for Childhood Diabetes; Professor of Pediatrics, Medicine, and Immunology, University of Colorado, Denver*

Dr. Eisenbarth noted that we are at a somewhat unusual era in type 1 diabetes: We can predict the disease, we can prevent it in animal models, but we do not know how to intervene yet in the disease in man. The next decade will focus on taking therapies studied in the animal models and applying them to humans—a major undertaking.

Dr. Eisenbarth stated that immunomodulation of type 1 diabetes is a broad topic and referred the audience to the Barbara Davis Center's website (www.barbaradaviscenter.org) where a book on the immunology of diabetes with teaching slides provides more detail than he would cover in his presentation. He stressed the importance of weighing the benefits of prevention and treatment of a disease against potential side effects of the therapies being considered, especially some of the immunologic therapies for diseases like rheumatoid arthritis or multiple sclerosis. This perspective is also critical in type 1 diabetes.

Data from the British Diabetes Association Cohort Study (1972-93), cited by Dr. Eisenbarth, indicated almost a 3 percent excess mortality in these young individuals ages 1 through 29, compared with the general population. Primarily these are metabolic deaths, not renal or cardiovascular disease. Dr. Eisenbarth's point was that the immunologic therapies thus need to be weighed against current problems with therapy, but hopefully, other therapies such as continuous glucose monitoring, will make inroads into these metabolic problems.

Dr. Eisenbarth stated that it is crucial in developing therapies to understand that type 1 diabetes pathogenesis is basically a balance between pathogenic T-cells and regulatory T-cells as illustrated by Dr. Aldo Rossini's teeter-totter schema. Regulatory T-cells used to be called suppressor T-cells; but now it is clear that there are regulatory T-cells that are essential for immunoregulation in humans. Dr. Eisenbarth gave as an example a mutation of the FOXP-3 gene that removes a major subset of regulatory T-cells. Infants with this rare syndrome die, often in the first months of life, with overwhelming autoimmunity and can develop diabetes at age 2 to 3 days. Introduction of that FOXP-3 gene into a regular T-cell turns it into a regulatory T-cell.

Dr. Eisenbarth presented a more complex slide from Dr. Len Chess that depicted many of the players in the development of β-cell destruction, in particular, the antigen-presenting cells, with their HLA molecule that present peptides to CD4 regulatory T-cells. Cytotoxic T-cells can directly destroy β-cells or influence other portions of the innate immune system that can produce cytokines that destroy β-cells. Dr. Eisenbarth pointed out there are many therapeutic opportunities in the immunopathophysiology of diabetes, and drugs are being developed for many of the specific molecules of this immune regulatory system.

In summarizing the general paradigm for prevention and treatment of type 1 diabetes, Dr. Eisenbarth listed the major steps as:

- Identify genetic susceptibility.
- Detect initial presence of autoantibodies.
- Monitor metabolic decompensation.
- Treat overt disease prior to morbidity and mortality.
- Pursue basic and clinical research to develop prevention interventions.

**Genetic Susceptibility**. At the first stage of genetic susceptibility, the major determinant currently known is genes within the major histocompatibility (MHC) complex. Alleles of these genes make up about 50

percent of the familial risk of type 1 diabetes. Explaining the nomenclature, used in describing the complex, Dr. Eisenbarth said each different polymorphic HLA molecule is given a number that represents the amino acid sequence of that molecule. Risk can be ascribed to a given allele, like DR4, but on that same chromosome, right next to DR4, there is DQ8; these molecules present peptide antigens and one forms a high-risk haplotype. What really determines risk of type 1 diabetes in this region is a person's genotype, the chromosomes inherited, one from each parent. The highest risk genotype for type 1 diabetes in the United States is a DR3/4 heterozygous individual with DQ8/2. With a different DR4 subtype, for instance, DRB1*0403, Dr. Eisenbarth explained that about three or four amino acids would be changed, thus greatly reducing risk.

Studies based on this genetic susceptibility information include the Diabetes Autoimmunity Study in the Young (DAISY) in Denver, BabyDiab in Germany, Diabetes Prediction and Prevention (DIPP) in Finland, and now NIDDK/CDC's The Environmental Determinants of Diabetes in the Young (TEDDY). From DAISY, Dr. Eisenbarth spoke of identifying at-risk children at birth by determining HLA genotypes from umbilical cord blood. The highest risk genotype (DR3/4) is present in about 2.4 percent of children, of whom 1 of 15 will develop type 1 diabetes, approximately half of all children in Denver developing type 1 before the age of 5. The genotype also decreases the age at which the disorder manifests. In DAISY, first-degree relatives of a sibling or offspring of a parent with type 1 diabetes are also followed from birth.

**Autoantibodies**. A series of semi-automated assays for anti-autoantibodies are now available. Some are in a modified ELISA format, but most are high-sensitivity and high- specificity assays. Dr. Eisenbarth listed the three autoantibodies that are primarily measured as insulin, glutamic acid decarboxylase, and ICA512 (IA-2) autoantibodies.

Development of autobodies can be followed in the at-risk children identified at birth. Dr. Eisenbarth said insulin autoantibodies can be present at 9 months of age—or first develop at 40 years of age. He added that the practical utilization of this information is limited, because we do not have the ability currently to prevent type 1 diabetes. However, at-risk children in a close follow-up study as in DAISY do not present with classical ketoacidosis. For the children in the DAISY study versus a control population, 1 out of 30 children needed to be hospitalized at the onset of diabetes because of ketoacidosis or some other major metabolic problem versus about 40 percent of the general population.

The DPT-1, in which close to 100,000 relatives were screened and autoantibodies measured, clearly illustrated that progression to diabetes can be predicted based on the number of autoantibodies expressed. Dr. Eisenbarth emphasized that the DPT-1 data show that risk can be identified and thus we can do trials for prevention in such a cohort. He added that DPT-1 also revealed that, even given the presence of autoantibodies, there are also HLA alleles that prevent the development of diabetes. For example, DQB1*0602, DR2, even when it's combined with the highest risk alleles, like DR4, has a very low progression to diabetes amongst antibody-positive individuals.

Dr. Eisenbarth next referred to the best studied animal model in type 1 diabetes, the NOD (non-obese diabetic mouse). NOD mice, just like young children, make insulin autoantibodies, beginning somewhere between 4 and 8 weeks of age. The insulin autoantibodies actually peak and go down, and then the blood glucose rises; thus the autoantibodies are a predictor and a surrogate, although obviously not perfect as shown by an NOD mouse that never expressed insulin autoantibodies but did progress to diabetes.

Target antigens have been identified in humans and in animal models, especially at the T-cell level. Dr. Eisenbarth stated that it is reasonably clear that autoantibodies per se are not the direct cause of type 1 diabetes, since T-cells and T-cell clones can transfer the disease. Among the autoantigens in the NOD mouse, insulin is prominent. Dr. Eisenbarth gave the example of a peptide of the insulin molecule

recognized by pre-diabetic, diabetogenic T-cells in the NOD, the B:9 through 23 sequence, that can be used to prevent diabetes or to induce diabetes. He added that a difficulty with the NOD mouse is that it is perhaps too easy to prevent diabetes given more than 100 reported preventive therapies., For instance a single injection of the B:9-23 insulin peptide at 4 weeks of age prevents diabetes in 90 percent of the mice. Dr. Eisenbarth recommended that more robust models be developed such as an insulin-2 knockout, in which the insulin gene expression within the thymus is removed creating a more robust, more diabetogenic NOD mouse. In contrast to prevention of diabetes, Dr. Eisenbarth said that giving the same B:9-23 peptide to a normal BALB/c mouse induced insulin autoantibodies within weeks. The antibodies reacted with insulin and not with the inducing peptide, suggesting that, given the genetics of a normal BALB/c mouse, the mouse is ready to begin part of the process that leads to type 1 diabetes, and with genetic tricks, a mouse is produced that responds to the peptide by developing diabetes. Dr. Eisenbarth cautioned that in the area of immunologic vaccination there is much to be learned.

**What Is Missing?** Dr. Eisenbarth repeated his earlier statement that we can now predict type 1 diabetes, but we do not have therapies to prevent the disorder as illustrated by the parenteral study of DPT-1, where the prediction was accurate, but there was no effect on delaying the disease.

Dr. Eisenbarth stated the main thing missing today is an assay for pathogenic T-cells. There are several assays being developed—tetramer, ELISPOT. He cited a study from Drs. Trudeau, Tan, and Santamaria (JCI, 111:217-223 2003) indicating a T-cell assay that would help in predicting diabetes. Basically, a tetramer takes the MHC molecule, places a peptide in it, and then it binds to the T-cell receptor, so T-cells can be quantitated and the specific autoantigenic peptide can be seen. In this study, the NOD mice that went on to diabetes had T-cells reacting with the peptide of an islet-specific molecule called IGRP (islet glucose-related phosphatase), whereas the NOD mice that did not progress to diabetes did not have those circulating cells. Dr. Eisenbarth thought that, eventually, the same peptide cellular reactivity needs to be defined in the human, which is a very difficult area of research. He suggested that the T-cells will have to be found in the pancreas because it is too hard to find them in the peripheral blood due to their extremely small numbers. One possible source of these disease-causing T-cells might be from programs that screen cadaveric donors for autoantibodies to obtain a pancreas. Then the peptides the T-cells recognize must be defined and assays developed for those T-cells.

Dr. Eisenbarth presented guidelines from the Immunology of Diabetes Society for designing trials for each stage of the development of type 1 diabetes and suggested it would be helpful if trials were designed based on specific guidelines, even though arbitrary, in order to better compare data across trials and have more confidence in the results of the trials. Dr. Eisenbarth said a key factor would be the use of C-peptide as a marker of loss of β-cells, since loss of β-cells is primary in this immune-mediated disorder.

Noting that there are many in process trials of non-antigen-specific immunotherapies, Dr. Eisenbarth said the furthest advanced probably is the anti-CD3 trials of Dr. K. Herold and Dr. L. Chatenoud. The anti-CD3 antibodies are, at this point, thought to work not simply by depleting T-cells, which has the effect of clearing the insulitis, but of stimulating regulatory T-cells, in particular T-cells that are making a cytokine TGF-β. There are also trials in newborns, with dietary interventions, that are underway or about to occur. Results of these non-antigen-specific therapies are still forthcoming.

Listing some of the trials for antigen-specific therapies, Dr. Eisenbarth mentioned the parenteral insulin trial that had no effect and the DPT-1 oral insulin trial, which overall had no effect, although a subgroup analysis of those individuals with the highest levels of insulin autoantibodies suggested the possibility of an effect that the TrialNet group will follow up. There is a trial at the Joslin Diabetes Center of the insulin B chain; also altered peptide ligands in the B9 through 23 peptide; trials of hGAD from Diamyd;, and trials of heat shock protein peptides. There are a lot of potential agents to be evaluated. Dr. Eisenbarth particularly noted that to have an immunologic vaccination that prevents or delays diabetes would be a

remarkable accomplishment. Multiple sclerosis is the only disease having an FDA-approved therapy in this realm with an unusual peptide.

In summary, Dr. Eisenbarth stressed that prevention of diabetes and prevention of β-cell loss after the onset of type 1 diabetes is very important. Predicting high risk is, in quotes, "easy." Although it can be debated that not everyone who has a single autoantibody progresses to diabetes and probably not everyone with multiple autoantibodies will develop diabetes, the probability is over 90 percent. There are multiple therapies in animal models. There is an explosion of immunotherapies in man. Dr. Eisenbarth pointed out the tremendous change in comparing the PDR (*Physicians Desk Reference*) listing for therapies for immunologic disorders from 20 years ago to what is in the PDR now and what will be in the PDR within the next 10 years. He believes it is only a matter of time before there is an immunotherapy for chronic active insulitis, just as there is now a therapy for chronic active hepatitis. People with chronic active hepatitis do not have overt disease, but they are likely to develop overt disease. As outcomes, Dr. Eisenbarth listed overt diabetes and C-peptide and suggested that a short-term outcome of prevention of hypo- and severe hyperglycemia will be available within a 2-year trial because of improvement in continuous glucose monitoring. He commended the international collaboration represented by the ITN and TrialNet and the public support provided by NIH.

## Discussion

Dr. Fradkin, NIDDK, asked Dr. Thornberry and Dr. Eisenbarth to suggest how NIH could best foster bench-to-bedside translation of basic discoveries of NIH-supported scientists into development of therapeutics. Dr. Thornberry replied that continuing support for basic research in β-cell dysfunction and support of academic endeavors to identify next generation targets would be extremely helpful. Most pharmaceutical companies increasingly have collaborations with external academic investigators in order to exploit the genomic revolution and proteomics and better understand new targets for insulin sensitization and preservation of β-cell function.

Dr. Eisenbarth responded that he understood that NIH, and particularly NIDDK and the National Cancer Institute (NCI), had developed a mechanism to further pharmaceutical drug development, including animal toxicity testing, which is not easily done in an academic laboratory. He added that partnering with the pharmaceutical industry is helpful but sometimes their priorities differ with those of the academic researcher. The availability of a parallel system to facilitate development of a drug without pharmaceutical support is, therefore, very useful.

Dr. Fradkin explained that Dr. Eisenbarth was referring to a newly developed program (T1D-RAID) in which NIDDK is partnering with NCI to use a mechanism the institute had developed for cancer—rapid access to intervention development—and to make those resources available for type 1 diabetes, particularly because type 1 is a smaller market than type 2 and thus commands less industry interest and resources in developing therapeutic agents.

In response to a request from Dr. Laura Shawver, Phenomix Corporation, about other DP-IV family members, Dr. Thornberry said DP-IV, a member of an emerging protease family, is the only enzyme for which function is well understood. There is no clear evidence that any of the other enzymes play a role in glucose control. The issue of selectivity is an open one right now, and one that Merck and others are working very hard to resolve.

Dr. Nathan asked Dr. Eisenbarth to answer an either-or situation. Given that type 1 diabetes evolves over time, screening is difficult, and only a small percent of those at risk develop the disease, but the major burden for those who do lasts over a lifetime, would Dr. Eisenbarth choose to address the disease during its early development, pre-clinical stage or reverse it at a later stage?

Dr. Eisenbarth said he preferred to do both because there are therapies that work only in the pre-diabetic phase and therapies that work in the new-onset phase, which is a tremendous spectrum. Although called new-onset diabetes, studies like DAISY suggest that people have had their diabetes for 6 months to 1 year before identified. People vary greatly in the amount of C-peptide that remains. There are times to intervene even in the genetically susceptible by simply changing the diet. He agreed that screening solely for type 1 diabetes on a population level would be expensive; however, in the future it will probably fall into a category of many other immune-mediated diseases that would be screened for at the same time. For example, as a public health measure, Colorado screens newborns for more than 20 different disorders. As this public health policy and practice develops, the screening cost per disease will come down, because of the package approach.

Dr. Amy Rosenberg, FDA, asked Dr. Thornberry if the to GLP-1 analogs were neutralizing and also what the normal circulating levels of GLP-1 are and do they fluctuate. Dr. Thornberry answered that she understood they had no effect on efficacy and there were no safety concerns thus far. Secreted in response to food intake, GLP-1 circulates at very low levels. Total GLP-1 postprandially is about 20 to 25 picomolar, and a large amount is degraded peptide, so at any given time, perhaps only 20 percent is actually active. Fasting levels are closer to 5 picomolar or less. Dr. Rosenberg commented that this probably would explain the low level of immunologic tolerance.

In reply to Dr. Rosenberg's request to comment on the finding that T-regulatory cells are CD25 positive, and antibody to CD25 is actually salutary for transplant rejection, Dr. Eisenbarth said there are many different subsets of T-regulatory cells and we do not have great markers for them nor understand what some of our therapies are doing, particularly antibodies to CD25 cells. There are CD4+ and a CD25+ regulatory cell that is extremely important, but T-cells, as they become activated, also express the CD25 marker. Since there is efficacy of those markers, Dr. Eisenbarth suggested they are probably not doing anything near like what a FOXP-3 gene knockout does.

Dr. Thornberry responded to a question from Dr. David Karph, Metabolex, Inc. and Stanford University, that she had no specific data suggesting a differential role for partial PPARγ agonists in the efficacy side on lipid parameters or on inflammatory markers of cardiovascular disease. Based on pre-clinical data, she thought that, at least in rodents, one could anticipate achieving efficacy comparable to that of full agonists with respect to glucose for partial γ agonists, but she could not comment on the lipid effects.

Dr. Simeon Taylor, Bristol-Myers Squibb, commented that currently there are at least five approved mechanisms for treatment of type 2 diabetes in many compounds and from Dr. Thornberry's presentation, there could be 10 or 15 more approved over the next few years. He wondered how physicians were going to decide on the best way of treating patients. He asked if Dr. Thornberry envisioned a time when there would be either pharmacogenomics or biomarkers or some other scientific evidence-based way to select who was more or less likely to benefit or to have toxicity from a particular mechanism. She said that was one of the promises of microarrays, for example. Scientists are trying to use microarrays to categorize various subsets of diabetics and pre-clinically to look at whether or not there are markers to anticipate potential toxicities. It remains to be seen if ultimately we can predict responders and non-responders.

Dr. Fradkin offered the idea that, potentially, some of the samples being sent to repositories from clinical trials can subsequently be used to examine those kinds of questions after the potential predictors are identified. She noted this concept has been very exciting in the cancer field recently.

Dr. Louis Herlands, Chief Operating Officer, DARA Biosciences, Inc., asked Dr. Eisenbarth what the potential therapeutic implications were of a prevalent population of CD8+ T-cells in the NOD mouse—possibly amounting to as much as 40 percent of the CD8+ T-cells in the islets, possibly more—

recognizing IGRP. Dr. Eisenbarth answered that this is crucial to the antigens to which the dominant immune response is directed and raises several questions. For instance, if you knock out the IGRP gene, which is doable, and a number of groups are in the process of doing it, will that completely prevent the development of diabetes? Knocking out the insulin-1 gene reduces the development of diabetes by almost 90 percent. A major question is, "Is it multiple different antigens that are all crucial, or is it just one antigen whose recognition is crucial to the disease, whereas other reactivities mirror the disease as it is occurring?" Obviously, IGRP is a very important target to look at in the human. Thus far, there are no autoantibodies to IGRP, and T-cells are just being studied in relationship to the IGRP molecule. Dr. Eisenbarth asked, "Will we be able to develop a predictive assay with IGRP? Will creating tolerance to the IGRP molecule prevent the disease?"

Dr. Jerry Palmer, University of Washington, commented that we normally divide studies into classic type 1 and type 2 diabetes trials. He asked how often does the type 1 autoimmune attack on the β-cell participate in diabetes in general, both type 1 and type 2. This could potentially be very important therapeutically. Dr. Eisenbarth noted that actually there are good studies for latent autoimmune diabetes in adults (LADA). Between 5 and 15 percent of individuals who are called type 2 diabetics really have anti-islet autoantibodies, lose C-peptide faster, and, in his opinion, their genetics reflect this and he would call them a type 1 diabetic. On the other side, insulin resistance is likely a key determinant when someone presents with diabetes and is losing β cells. In the DPT-1 study, some children who were becoming diabetic had fasting insulins of 50 or 60; therefore, it might be possible to treat those children with an oral agent for several years, even without affecting their autoimmunity, which would be an advantage for those children. He added that as Dr. Palmer had mentioned, we have classic diseases, but there is no reason that they do not overlap.

Dr. Fred Murray, Aventis Pharmaceuticals, followed up Dr. Palmer's remarks by saying if one takes the BB rat, which is an animal model with type 1 diabetes, and breed it with the Zucker rat, which is an obese animal model, the result is the BBZ rat that in the male has type 2 diabetes and in the female has impaired glucose tolerance. Dr. Murray also presented the question: Since it is known or believed that type 2 diabetes and cardiovascular disease are both inflammatory diseases, and some agents, like the PPARs, have anti-inflammatory effects as well as insulin-sensitizing effects, are there inflammatory markers we can use to identify a pre-diabetes condition that occurs before impaired glucose tolerance? For instance, there are several ongoing trials to prevent diabetes in those with impaired glucose tolerance. Some of the problems there have to do with the hypoglycemia seen in type 1 diabetes. If there were better biomarkers, perhaps cytokines, to identify early diabetes, then trials and agents would be safer.

Dr. Eisenbarth replied that we have the techniques now to look across a broad spectrum of cytokines for inflammatory changes in both type 1 and type 2 diabetes and in the pre-diabetic group. Dr. Thornberry agreed that there is a great deal going on in the inflammation arena about which we need to be aware.

Dr. Alex Szidon, DARA Biosciences, commented that one of the issues with type 2 diabetes is the number of target tissues for interventions to regulate metabolism as a whole. For example, recently, there have been findings regarding interventions at the hypothalamus actually affecting both gluconeogenesis in the liver and food intake. He asked Dr. Thornberry where she looked to affect metabolic change and what her general sense was of intervening at targets in the hypothalamus to treat multiple facets of the disease. Dr. Thornberry agreed that this was an emerging area of interest and there is accumulating evidence that lipogenic targets may indeed control effects such as feeding and glucose metabolism via effects in the brain. AMPK, is a recent example that has been implicated in controlling metabolism via its effects in the brain. Dr. Thornberry felt that it is too early to know if there are going to be good targets there and whether or not it will be consistent to target them both in the periphery and in the brain.

Dr. Christopher Saudek, The Johns Hopkins University School of Medicine, asked what the current thought was on the so-called 1B or non-autoimmune type 1 diabetes. Dr. Eisenbarth said that, for the most part, if there is not an identified genetic mutation, then the disorder is classified either type 1A or type 1B. The trouble is, according to Dr. Eisenbarth, that he is not sure just what he would classify as a type 1B diabetic. Reports from Japan, where they have a low percentage overall of type 1 diabetes, report a significant percentage of patients with what they call fulminant diabetes. These are patients, some of them adults, who present with a normal HbA1c and an extremely elevated blood glucose, which is rarely found in the United States. Originally, it was proposed that they were an initial example of type 1B, but it turns out their HLA reflects the HLA of high risk for type 1A diabetes in Japan and they have infiltration, especially of the acinar pancreatic tissue by lymphocytes. Dr. Eisenbarth said the question is whether these individuals are a form of type 1A that is extremely fulminant and without time to make the auto-antibodies. On the other hand, there are other surprising results that have not been factored in yet, such as the detection or evidence of chronic enteral viral infection within β-cells.

In response to the question of whether there is a role for antibodies and their ability to cause epitope spreading and enhanced antigen presentation in T cells and whether there might be a ping-ponging effect, Dr. Eisenbarth said he thought both B-lymphocytes and antibodies might well participate in the disease. There is good evidence in the NOD mouse that antibodies are important to development of the disease. If there are no transplacental antibodies, the incidence of diabetes goes down by about 90 percent. Also, B-lymphocytes are potentially very important for antigen presentation.

Dr. Jose Caro, Aventis Pharmaceuticals, asked about the relative importance of different antibodies as predictors of type 1 diabetes (i.e., is anti-GAD (glutamic acid decarboxylase) more important than anti-islet). The response was that there are fine distinctions and specific antibodies do make a difference. At first cut, probably the number of auto-antibodies is very important. The IA2 auto-antibodies are the most predictive. They are usually associated with the presence of the other auto-antibodies and, in some ways, they are the easiest to measure. This might depend on assay ability. The insulin auto-antibodies are highest in the youngest children developing type 1 diabetes. There is a very peculiar log inverse linear relationship. GAD, if anything, is fairly flat and just the opposite and IA-2 is shallow. So the specific antibodies make a difference.

Dr. Caro asked Dr. Eisenbarth if in the DAISY cohort, did they look at the number of children who were antibody-negative initially and then developed positive antibodies over time and ultimately developed diabetes. Dr. Eisenbarth answered that, if you measure early enough, say at 3 months, most are antibody-negative and then develop the antibody later. As best as they could tell, children are not born with the antibodies, although there is transplacental passage for a group that is probably not pathogenic. He said that if the fundamental question was what is the best timing for measuring antibodies, at what ages, this had not absolutely been defined. Dr. Eisenbarth's guess was antibodies can be picked up in the first 9 months of life, and in very young children, an annual testing might be necessary.

In response to a question about investigation of altered antigen presentation mechanisms in high-risk genotypes, Dr. Eisenbarth said there is a debate in the field about whether or not there is less stability in the highest risk genotypes, but he felt the bulk of the data is that these HLA molecules are normal, even though they are creating diabetes susceptibility. For instance, the haplotype that prevents 98 percent of type 1 diabetes is the high risk haplotype for multiple sclerosis. It appears that these HLA molecules are determining which target antigen and thus which tissue, rather than being abnormal in overall function.

Dr. Alain Baron, Amylin Pharmaceuticals, referred to the seriousness of type 1 diabetes as evidenced by Dr. Eisenbarth's data on the high mortality rate in patients between the ages of 20 and 30. This brings up the risk benefit issue regarding novel therapies, when the only current agent is insulin. He asked where Dr. Eisenbarth would rank type 1 diabetes on a scale of 1 to 10 with cancer ranking as a 7 or 8. Dr.

Eisenbarth said therapies needed to be weighed against problems with diabetes from age 0 to 30, even before the chronic complications occur. Type 1 diabetes is a difficult disease to treat. It completely changes family members' lives. The risk of hypoglycemia is a major limitation as efforts are made to lower blood sugar. The Barbara Davis Center cares for about 3,000 children and 2,000 young adults. Over the past decade, there have been at least 20 deaths in that cohort, so this is a very serious disease for anyone. Dr. Eisenbarth stressed that if there was no hypoglycemia and there was good metabolic control, the mortality rate would change dramatically.

## Session III: Beta Cell Preservation

*Moderator: Ilan Irony, MD, Medical Officer, Division of Therapeutic Biological Internal Medicine Products, Center for Drug Evaluation and Research, FDA*

### Assessment of Beta Cell Preservation in Type 1 Diabetes

***Jerry P. Palmer, MD,*** *Professor of Medicine and Director of the Diabetes Endocrinology Research Center, University of Washington, Seattle; Director of Endocrinology, Metabolism, and Nutrition, Veterans Affairs Puget Sound Health Care System, Seattle*

Dr. Palmer began by stressing that the target of the type 1 auto-immune disease process is the pancreatic β-cell, so it makes excellent sense to try to preserve the function of that target cell. Studies of the preservation of β-cell function fall into two categories: intervention studies with persons who already have type 1 diabetes and prevention studies for those at risk.

Dr. Palmer noted that intervention studies have, with varying degrees of success, tested azathioprine and steroids; cyclosporin; anti-CD3, an antibody to T-cells; and DiaPep 277, a fragment of heat shock protein. A trial of MMF (mycophenolate mofetil) and DZB has begun in TrialNet, and a future trial of anti-CD20, a monoclonal antibody directed at β -cells, is under consideration.

Of the many studies of cyclosporin, Dr. Palmer considers the Canadian-Diabetes-France (Plus) Study to be the most important because patients were randomized, received intensive therapy, and if patients went into remission, rather than stop the cyclosporin, it was continued until they again went out of remission. The results showed that immunomodulatory therapy in type 1 diabetes can work. Almost 50 percent of patients who received cyclosporin versus placebo went into remission, defined as being insulin-free. Remissions also were longer in the patients treated with cyclosporin versus placebo. Although these results are remarkable, Dr. Palmer explained that the medical community has essentially decided that cyclosporin therapy is too toxic a way to try to alter the type 1 disease process.

As Dr. Nathan had said earlier, the DPT-1 prevention study showed that parenteral insulin was not effective, nor was the overall trial for oral insulin, although in a subset of persons with high auto-antibodies, there may have been a treatment effect and that is being followed up. A large-scale European trial of nicotinamide also was unsuccessful in preventing type 1 diabetes. The large international Trial to Reduce the Incidence of type 1 Diabetes in the Genetically at Risk (TRIGR), led by the National Institute of Child Health and Human Development (NICHD), is asking whether the first formula that an infant uses, whether cow-milk-based or not, has an effect. The primary endpoint of TRIGR is the development of antibodies and then over 10 years the development of type 1 diabetes.

TrialNet, an NIDDK-led international network of 18 regional cooperative clinical centers in the United States, Canada, Europe, and Australia, has as its goal to alter the type 1 disease process in those who already have disease, in relatives at risk of disease, and in those who have a high genetic risk. It also will further define the epidemiology, natural history, and risk factors of this disease. The network has a coordinating center and core laboratories in genetics, immunology, metabolism, biochemistry, and viral infections. Dr. Palmer heads up the β-cell function core laboratory.

TrialNet selected measurement of C-peptide as the endpoint for its intervention strategies. Dr. Palmer listed several of the advantages of C-peptide as an endpoint. In the structure of the proinsulin molecule, C-peptide connects the α- and the β- chains of insulin. There is a one-to-one molar ratio of insulin to C-peptide in terms of secretion. Insulin undergoes a variable and substantial first-pass extraction in the liver of up to 50 percent but C-peptide does not. For a number of years, there have been excellent assays that accurately measure the very low levels of C-peptide in persons with type 1 diabetes. These assays are effective even when treating the patient with insulin, and also the insulin auto-antibodies that patients develop do not interfere with the assays. TrialNet also is also planning to test omega-3 fatty acids, GLP-1, and oral insulin.

Dr. Palmer explained that the literature can be confusing because there are two major ways c-peptide is reported, either as ng/ml or nmol/l; therefore, it is important to pay attention to which of the units the reader is seeing. The detection limits of the standard assays is 0.1 ng or 0.03 nmol/l. Dr. Palmer stressed that a very important point is that the half-life for insulin and C-peptide are dramatically different, which is important in interpreting C-peptide values. For insulin, it is about 3 minutes; for C-peptide it is closer to 35 minutes.

Factors that affect residual β-cell function include age at diagnosis, duration of diabetes, metabolic control, and marked inter-individual variation. Dr. Palmer cited data from TrialNet showing that, in terms of age at diagnosis, C-peptide is lower in those who are in the 12- to 17-year-old age group than in those over 18, and it is much lower in those who were diagnosed prior to age 12.

C-peptide was an entry criteria for the DCCT with the cut-point for entry being stimulated C-peptide of 0.5 nmol/l. Mixed meal tolerance tests (MMTTs) were performed on 3,736 type 1 diabetic patients to identify the 1,441 patients who ultimately participated in that study. Dr. Palmer showed two slides that plotted the C-peptide levels in those screened, one for those diagnosed over the age of 18 and one for those diagnosed under the age of 18. He noted that a remarkably large proportion of people (48 percent) who had type 1 diabetes for up to 5 years according to their physicians' diagnoses after the age of 18, still had meaningful and biologically important C-peptide. For those diagnosed under the age of 18, the values tended to be lower, although again there were a lot of individuals with C-peptide above 0.2 nmol/l, a level that has been shown in a number of studies to be associated with better diabetes control and less complications.

In the DCCT, those individuals who had diabetes from 1 to 5 years and C-peptides between 0.2 and 0 .5 nmol/l were brought back each year for a follow-up mixed meal stimulation test. Dr. Palmer said the control in the DCCT had a dramatic effect on C-peptide levels. For the 303 individuals meeting the criteria stated above and randomized to intensive therapy versus conventional therapy, the intensive group had a 57 percent reduction in risk of C-peptide falling below 0.2. Dr. Palmer emphasized that DCCT is the largest and best study showing that intensive glycemic control is a powerful means to protect underlying β-cell function.

In the feasibility stage of the DCCT, Dr. Palmer said one of the things asked was, "How much C-peptide does it take to be important in terms of metabolism?" At the time of screening, patients were divided into those with very low C-peptides, those between 0.05 and 0.1, 0.1 to 0.2., and above 0.2. Patients above 0.2 had substantially lower fasting glucose and HbA1c levels. There was evidence for a dose-response curve, because even though glycemic control becomes significantly better at 0.2 versus 0.1 nmol/l c-peptide,, it took less insulin to achieve the same degree of control with stimulated c-peptide of 0.1 nmol/l. Similar data were observed in a later stage of the DCCT. In intensively treated patients who were defined as non-responders (i.e., with C-peptide less than 0.2) or responders, the responders had lower HbA1c. Dr. Palmer

described what he called a virtuous cycle as opposed to a vicious cycle: Better diabetes control leads to less β-cell damage, less β-cell damage preserves β-cell function, which leads to better diabetes control.

Dr. Palmer presented DCCT data regarding the 3+ step change in retinopathy progression that showed that the intensely treated responders, who achieved β-cell preservation as measured by C-peptide levels, had a dramatically greater risk reduction than the non-responders. In another analysis of DCCT data, Dr. Palmer showed that those who sustained their C-peptide levels from entry to 1 year at 0.21 to 0.5 had a 4.6 times difference in retinopathy and a 4.4 times difference in albuminuria as a measure of nephropathy. Another observation from the DCCT is that not only is there better HbA1c and less complications when C-peptide is preserved (and thus β-cell function), but the Achilles heel of intensive therapy, namely hypoglycemia, is also helped. In the responders in the intensive treatment group (those with C-peptide above 0.2), there was a 62-percent risk reduction in hypoglycemia with coma and seizures.

Dr. Palmer said there is additional data (some of the best from Dr. Christian Binder) that demonstrates that stimulated C-peptide around 0.2 is the level at which differences in ease of metabolic control and improvement in complications are clearly seen. To show the relationship between C-peptide and hypoglycemia, Dr. Palmer presented data from a Japanese study (Diabetes 37:81-88, 1988) that used what the researchers called a supersensitive assay, but was really an extraction method. The study recruited patients who were C-peptide negative in a standard assay and divided them into those who were responders and non-responders to C-peptide with their supersensitive assay and induced hypoglycemia in these individuals. They then measured glucose, glucagon, epinephrine, nor-epinephrine, and cortisol. The responders had less severe hypoglycemia but they also had better measurements for the counter-regulatory hormones.

Dr. Palmer mentioned literature covering a variety of animal and human studies with either acute or chronic administration of C-peptide showing that the possible direct effects of C-peptide include lowering of diabetes-induced increased blood flow; decreased microalbuminuria, improvement in nerve conduction velocity and autonomic function, and augmented glucose utilization. Thus, in addition to being a biomarker

Dr. Palmer's "take home" home messages about C-peptide were the following:

- Excellent assays are available.
- C-peptide levels are higher than commonly assumed many years after diagnosis of type 1 diabetes, contrary to the textbooks that say C-peptide is undetectable 5 years after onset of type 1 diabetes.
- Glycemic control preserves C-peptide.
- Preserved C-peptide results in improved glycemic control.
- Higher C-peptide results in less retinopathy and nephropathy.
- Higher C-peptide results in less hypoglycemia.
- C-peptide may have direct beneficial effects beyond being a biomarker for β-cell function.

In conclusion, Dr. Palmer listed several ongoing activities on C-peptide as the primary outcome measure for type 1 diabetes clinical trials to preserve β-cell function. The Immunology of Diabetes Society published recommendations (Diabetes 52:1059-65, 2003). The report of an American Diabetes Association-sponsored workshop on markers that could be used for type 1 intervention studies was recently published (Diabetes 53:250-264, 2004). Currently there is a Wet Workshop coordinated by the University of Missouri on the optimal assay for C-peptide and asking how it can be standardized so that results are comparable from one lab to another. There is an international program comparing the MMTT, the test usually done on this side of the Atlantic versus the glucagon-stimulated test (GST), the test done in Europe, to determine how comparable they are and whether one test is preferable to the other.

## The Case for β-Cell Preservation in Type 2 Diabetes Mellitus

***Steven Kahn, MB, ChB**, Professor of Medicine, Division of Metabolism, Endocrinology, and Nutrition and Associate Director, Diabetes Endocrinology Research Center, University of Washington, Seattle; Director of Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle*

Dr. Kahn emphasized the importance of looking for markers to identify persons early on in the development of type 2 diabetes in order to preserve β cells and β-cell function. He also stressed the concept that there are multiple factors that are responsible for the loss of β cells in type 2 diabetes, which means that scientists need to start thinking "outside the box" about how to handle the potential causes of reduction in β-cell mass that occurs in type 2 diabetes.

Dr. Kahn cited data from the UKPDS showing that people with type 2 diabetes at time of entry into the study only had 50 percent of their β-cell function remaining as measured by the HOMA method. During the 6-year follow-up, β-cell function continued to decline. Assuming that the loss of β-cell function is linear, if one performed a linear regression and extrapolated this data back, one could predict that β-cell function was last normal over a decade prior to the presentation and enrollment into the study. Mr. Kahn noted that data such as that from the UKPDS and other studies is a basic reason for the increased focus on β cells.

The acute insulin response to glucose, a measure of the ability of the β cell to release insulin in response to an intravenous injection of glucose was used to highlight the deficit in individuals with type 2 diabetes. Dr. Kahn demonstrated this with a slide showing the response of a group of healthy control subjects and a group of persons with type 2 diabetes who were given a glucose injection. In the control group, prior to the injection, plasma insulin concentration was stable; then there was a brisk increase in the plasma concentration in what is called first-phase response, and then a second-phase response of decreased concentration. In individuals with type 2 diabetes, the first phase response was essentially absent and the second-phase response was dramatically reduced compared to the healthy controls, indicating deficient insulin secretion. Dr. Kahn said that enhancing β-cell function and lowering glucose in these patients clearly would be useful, but it would be better to intervene prior to the stage of diabetes progression of these individuals to try to preserve β-cell function and insulin secretion in general.

Dr. Kahn stated that understanding what modulates the β cell is necessary to address this issue. Clearly, the β cell is modulated by the nature of the stimulus and the magnitude of the stimulus *and by other factors*. For example, the first-phase response is markedly diminished in patients with impaired glucose tolerance (IGT). On the other hand, healthy individuals have a broad range of plasma insulin responses to glucose, thus raising the question "Why?" Studies in the late 1980s and early 1990s tried to look at the impact of insulin sensitivity on acute insulin response. It was recognized that when the β cell is given a stimulus, it secretes insulin, which then acts in a variety of tissues that are sensitive to its effect, the major organ systems being the liver, the muscle, and adipose tissue. Because the insulin response seemed to be so well regulated in not only bringing the glucose levels down to normal, but also shutting off appropriately to ensure hypoglycemia does not occur after meals, it was thought that there must be a feedback loop that controls the magnitude of the stimulus, either through the bloodstream or through the brain, or potentially through both systems.

In following up the concept of a feedback loop, investigators in Seattle looked at data from healthy individuals. The investigators related the acute insulin response to glucose as a measure of insulin response of the β cell to insulin sensitivity quantified using the minimal model of glucose kinetics. Using data from the 93 healthy subjects, males and females, they were able to show mathematically that the relationship between insulin sensitivity and insulin response is not a straight line, as is commonly applied

to biological assessments, but instead, it is a curve, a hyperbolic relationship. Dr. Kahn explained that this hyperbolic relationship means that insulin sensitivity and insulin response are related in such a manner that the product of the two—insulin sensitivity times the insulin response—is a constant. An example would be that an individual who had an insulin sensitivity of 10 and fell on the line that represents the 50$^{th}$ percentile or mean relationship for the group, for that individual, the insulin response would be about 250, giving a product of 2,500 (sensitivity index of 10 times a response of 250). An individual with an insulin sensitivity of 5 also would have a product of 2,500, because the insulin response would be 500. Thus low sensitivity resulted in high responses. This study supported the concept of a feedback loop and a regulated system that was dependent on a *healthy* individual's insulin sensitivity being a determinant of the magnitude of the person's insulin response, assuming that the healthy person had normal β-cell function.

The study with the healthy subjects indicated that if there was insulin resistance at the level of the insulin-sensitive tissue, because of the feedback loop, either through the bloodstream or through the brain, the islet senses that there is a change occurring at the site where insulin is supposed to act, and it simply increases its insulin output in response to the stimulus of the glucose injection. In type 2 diabetes, Dr. Kahn said it is thought that what happens is either failure of the islet to respond to the stimulus or failure of the feedback loop to be operating normally. This failure results in a reduction in insulin secretion and development of hyperglycemia in individuals who have insulin resistance, as seen typically with obesity.

Dr. Kahn asked how this understanding could help researchers develop approaches to identify persons at high risk for type 2 diabetes who could then be the subjects of intervention trials using therapies and compounds, other than those from DPP, at early stages. He also asked how could biomarkers be identified, such as measures of secretion and sensitivity, that could be used as endpoints instead of full-blown diabetes, which would reduce the need for large-scale, expensive clinical trials.

To address the questions he had raised, Dr. Kahn referred the audience again to the data and curve from the study with the 93 healthy individuals. Researchers calculated percentiles for the relationship between insulin sensitivity and insulin secretion based on a pair of numbers for those two variables for any individual. Based on these percentile plots and data from other studies performed in Seattle and studies by others, Dr. Kahn illustrated the concept that diabetes is a disease where there is both insulin resistance and a loss of the insulin response by showing that individuals developing type 2 diabetes and those who are at high risk have reduced percentile values for the relationship between insulin sensitivity and insulin secretion..

To illustrate how this measurement model and the calculated percentiles could be used to identify those who are likely to progress to diabetes, Dr. Kahn presented data from several studies. It was previously believed that it was insulin resistance that begets type 2 diabetes and that persons with impaired glucose tolerance did not have a β-cell defect because they did produce insulin. Mr. Kahn offered data from a study at Emory University of individuals with type 2 diabetes who had an insulin sensitivity index of 1 and an insulin response of 150 picomoles/liter and thus were very insulin deficient. He compared this study with a study in Chicago with individuals with IGT who were as insulin resistant as the group from Emory but had an insulin response of 500 (producing only 20 percent of the normal product of 2,500). Based on their insulin sensitivity index and their insulin response, the IGT persons already had severe β-cell dysfunction and were headed towards developing type 2 diabetes. This was also true for a group of elderly subjects in Seattle who had an insulin sensitivity of 3, an insulin response of 250, giving a product of 750—again far below the norm of 2,500, placing them on the 2$^{nd}$ percentile in the hyperbolic relationship and thus progressing in the direction of full-blown diabetes. Other groups recognized as being at very high risk for type 2 diabetes are women with a history of gestational diabetes (GDM), who convert to diabetes at a rate of approximately 10 percent per year, and women with polycystic ovarian syndrome. Studies with these groups and with a group of relatives of individuals with type 2 diabetes

placed them at the 5th (GDMs), 17th (polycystic ovarian syndrome), and 25th (relatives) percentiles, respectively, showing that each group was at risk for developing type 2 diabetes.

Another Seattle study of 34 first-degree relatives of persons with type 2 diabetes looked at a variety of parameters. At baseline in 1994, their BMI put them in the overweight category. Over the 7 years of follow-up, they gained weight and in 2001 were classified as being obese. This weight gain appeared to be central; waist circumference increased but hip circumference did not change significantly. Their fasting glucose and fasting insulin concentrations also did not change dramatically. Their fasting glucose was well below 100. Dr. Kahn noted that fasting glucose and progression to diabetes is a late phenomenon; therefore, other biomarkers, possibly 2-hour glucoses, are needed to diagnose diabetes risk and progression earlier. Over the 7 years of the study, the 34 subjects had a 7-percent reduction in insulin sensitivity and a 16-percent decrease in acute insulin response to glucose, placing them at the 15th percentile for relationship between insulin sensitivity and insulin secretion, in keeping with the progressive loss of β-cell function over the follow-up period. Over the 7 years, there was also deterioration in glucose tolerance as measured by an oral glucose tolerance test (OGTT). In 1994, approximately 50 percent had IGT and 50 percent normal glucose tolerance. In 2002, less than 50 percent were normal and more than 20 percent had progressed to type 2 diabetes.

Further information gained from this study of first-degree relatives showed that those who initially had normal glucose tolerance measured by OGTT but did not maintain this over the 7 years also initially fell into a lower percentile (based on insulin sensitivity and insulin response) than those who maintained their normal glucose tolerance. In other words, they already had an abnormality in β-cell function even with normal glucose tolerance, a point in time when no one would have considered intervening with them or testing them in a clinical trial to prevent progression to impaired glucose tolerance and later diabetes. In the group that maintained normal glucose tolerance for 7 years, β-cell function barely changed according to their insulin sensitivity/insulin response measurements and percentiles. Dr. Kahn suggested that in finding biomarkers of β-cell function, there is a potential to identify high-risk individuals much, much earlier than is done currently with IGT and to intervene with them to try to preserve β cells and β-cell function and thus hopefully prevent type 2 diabetes.

Dr. Kahn referred to a Pima Indian study (Weyer C. et. al. J Clin Invest 104:787-794; 1999) highlighting that pathophysiology of diabetes in Native Americans is very similar to that of other U.S. population groups. Insulin sensitivity was measured by the clamp technique. Thirty-one persons maintained normal glucose tolerance over the 5 years of follow-up, and although they became more insulin resistant over time, their β cells simply increased insulin secretion to compensate, keeping them on their curves and thus maintaining normal glucose tolerance. In contrast, there were a group of individuals who progressed, over the 5 years of follow-up, from normal glucose tolerance to impaired glucose tolerance, and then on to diabetes. These individuals had a fall in insulin secretion over time resulting in a deterioration of glucose tolerance and also development of diabetes. Again, these individuals at baseline had a markedly disturbed relationship between their insulin sensitivity and their insulin secretion, which Dr. Kahn believes indicates the presence of β-cell dysfunction. He repeated that this marker of insulin sensitivity related to insulin secretion could therefore identify persons with normal glucose tolerance who actually are at high risk and who could be recruited for prevention studies investigating a variety of agents that might preserve β-cell function *before* they reached the high-risk category of the DPP cohort who had impaired glucose tolerance.

In discussing the problems with the OGTT, Dr. Kahn referred to data from an American Diabetes Association study of first degree relatives of persons with type 2 diabetes. Of these 513 people given an OGTT at baseline, 100 were unaware that they already had diabetes, 191 had IGT, and 240 had normal glucose tolerance. From the early insulin response during the OGTT, it became evident that β-cell dysfunction was a characteristic not only of type 2 diabetes but also of IGT. Based on this and similar

data, Dr. Kahn recommended using measures that are more sophisticated than the OGTT in order to show subtle defects very early on before hyperinsulinemia leads to β-cell failure.

Dr. Kahn listed glucotoxicity, lipotoxicity, and loss of β-cell mass as possible causes of β-cell dysfunction in type 2 diabetes. A study of autopsy samples of β-cell mass from non-diabetic obese individuals (based on BMI criteria) and non-diabetic lean individuals (Butler, AE et al. Diabetes 52:102-110, 2003) showed that the obese persons had substantially greater β-cell volume compared to the lean persons, possibly as a compensation mechanism by which the obese person increased insulin response to insulin resistance. On the other hand, obese persons with impaired fasting glucose had decreased β-cell volume compared to those with normal glucose tolerance. Both the obese and the lean persons with type 2 diabetes had β-cell volume lower than that of either group of non-diabetic subjects, indicating that there is an association between diabetes and β-cell mass.

Why does this reduction in β-cell mass occur? One hypothesis is that islet amyloid deposits replace β-cells in persons with diabetes. In Alzheimer's disease, deposition of amyloid in the brain is a cause of the mental changes in the disease. The amyloid is deposited at a local site where a unique peptide component for those deposits is produced. Similarly, in type 2 diabetes, in the islet amyloid deposits is the peptide islet amyloid polypeptide (IAPP), also known as amylin, which is a unique 37 amino acid peptide. This peptide has a critical amino acid sequence between amino acids 20 and 29 that gives it the amyloidogenic potential in humans. Dr. Kahn said that a problem in studying diabetes in animal models is that, in rodents, amino acid substitutions in the 20 and 29 amino acid region of the molecule result in an inability of the IAPP or amylin molecule to form deposits; therefore, unless the animal is transgenic, it never develops amyloid deposits as seen in humans with type 2 diabetes. Dr. Kahn said another important answer to be found is why the peptide forms deposits in diabetics and not in non-diabetics.

Dr. Kahn explained that his group has developed a microscope-based system to quantify islet area, β-cell area, and amyloid area and also developed measures to show how much amyloid is being deposited and how much β-cell mass might be lost. Using these measures, they can quantify for an individual the number of their islets that have amyloid deposits, the amount of amyloid deposited in each islet, and thus the severity of the amyloid deposition. Dr. Kahn said that the data generated (to be shown at the ADA meeting in June) suggest that the development of amyloid is a diffuse process that involves all islets, and as the degree of the disease is progressing, the degree of amyloid deposition also increases and β-cell mass decreases in a strong inverse relationship to the severity of the amyloid deposition. Dr. Kahn explained that what is not known is whether the decrease in β-cell mass occurs before or after the amyloid development; however, studies in the transgenic mouse strongly suggest that amyloid deposits develop long before hyperglycemia, which indicates that amyloid may play a role in the loss of islet β-cell function in type 2 diabetes.

In the transgenic mouse, as in humans, amyloid deposition occurs profusely and involves nearly all the islets before it starts to become severe and replaces β cells. Increasing dietary fat in these mice increases amyloid deposition, an interesting observation since the incidence of diabetes is increasing and is related, at least partially, to the environment, decreased exercise, and increased fat consumption. Dr. Kahn added that, unlike what has been suggested with Alzheimer's disease and mouse models of Alzheimer's disease, apoE is not a critical component required for amyloid deposition in islets in these mice.

Dr. Kahn said that studies with the transgenic mouse are very valuable because equivalent studies in humans would be very difficult. Other information derived from the studies includes that in the transgenic mice that are getting amyloid deposits, there is an increased rate of apoptosis and the magnitude of amyloid deposition is positively correlated to the rate of β-cell death, suggesting strongly that amyloid formation in islets increases apoptosis and β-cell death. The amyloid deposition also suppresses the islet's normal regenerative response to build β-cell mass in response to the apoptosis and β-cell death. Dr. Kahn

expects that these two effects of amyloid deposition—suppression of regenerative response and β-cell death—also occur in human type 2 diabetes with, ultimately, loss of β-cell mass, which contributes to the development of hyperglycemia.

Dr. Kahn reviewed information from another transgenic mouse study in which there were three groups: a control group, a growth group given rosiglitazone, and a group given metformin. The mice were fed high-fat diets for a year. In the control mice, 32 percent had amyloid compared to about 10 percent of the mice in the rosiglitazone and metformin groups, indicating that the drugs did not prevent amyloid formation in these mice but they did reduce it. Both of the drugs also had dramatic effects on the severity of amyloid measured by the number of islets containing amyloid deposits and the amount of amyloid within these islets. Dr. Kahn recommended that these studies be followed up.

Dr. Kahn pointed out that one of the difficulties of studying amyloid in models of type 2 diabetes is that such studies take a year to produce data. Clearly, one wants to be able to test compounds that work earlier in the diabetes cycle. As an example, he presented a slide from an in vitro study in which an islet from an hlAPP transgenic mouse that had been cultured in 16.7 mM glucose already showed amyloid deposition in just 1 week. Using this system, Dr. Kahn's group was able to test an agent that more or less obliterated amyloid formation. This compound, of course, is no where close to being applied to type 2 diabetes. There is still a great deal of work to be done both by the pharmaceutical industry and those in academia to understand the β cell, why its function declines, and how to preserve it. He suggested that amyloid inhibition might be one of the possible approaches down the road.

In conclusion, Dr. Kahn acknowledged the work of outstanding post-doctoral fellows and faculty members of the University of Washington with whom he has collaborated, the researchers from around the world for their contributions to the field, and those people who participate in clinical trials. He expressed his appreciation to ADA for their support and seed money for the transgenic mouse studies, without which the field could not be where it is today. He also thanked NIDDK for support for clinical studies and the amyloid studies; the VA for its career development grants, and GlaxoSmithKline, which supported the studies in rosiglitazone.

## Discussion

To begin the discussion, Dr. Irony asked Dr. Palmer which he considered the best approach to use to investigate products that would protect β-cells in patients with type 1 diabetes—C-peptide with a mixed meal tolerance test or a glucagon stimulation test. Dr. Palmer responded that part of the reason for international collaboration being authorized as part of TrialNet is to answer the crucial question of whether or not one gets differences in C-peptide response with an MMTT versus a glucagon stimulation test. The MMTT usually takes 2 hours, but can take 4 hours. The glucagon stimulation test is classically done with a baseline measurement and then one measurement 6 minutes later, after a 1mg dose of intravenous glucagon. Thus the tests are dramatically different in terms of how the β cells are stimulated. The small amount of data available suggests that in normal controls the tests will give comparable responses. What still needs to be asked is "What is the difference in people with diabetes?" and "As people progress toward diabetes, does one of the tests give you a different answer?"

Next Dr. Irony asked Dr. Kahn, "With regard to the continuum of impaired glucose tolerance and impaired fasting glucose as an individual moves toward type 2 diabetes and with the availability of potential treatments in the future for earlier conditions of β-cell defects, will diabetes again be redefined as tends to happen as treatments become available for diseases?" Dr. Kahn answered that, in fact, there has recently been a change in the criteria for impaired fasting glucose from 110 to 100, which prompted that week's announcement about how many more people are at risk for developing diabetes. During DPP, the definition of diabetes as a fasting glucose level was reduced from 140 to 126, which was clearly a

challenge for a clinical trial, but showed the potential in a clinical trial to adapt to changes occurring in the outside world. Dr. Kahn felt this would continue to happen down the road as he thinks the change in impaired fasting glucose was the first step and he believes the criteria for diagnosing type 2 diabetes in terms of fasting glucose is also going to be lowered, because there is a disconnect between the fasting response and the 2-hour response. In part, this change also will be driven by clinical trials. Dr. Kahn recommended that clinicians and investigators work with FDA to ensure that some of the treatments that are being defined for diabetes are not limited to diabetes but are moved into the general public health arena. The metformin results from DPP would be a good example as well as the lifestyle changes.

Based on Dr. Palmer's presentation of C-peptide as a good reflection of β-cell mass and Dr. Kahn's data that β-cell function is reflected by dynamic tests of insulin secretion, the question was asked if it was possible that in the DCCT, adolescents in whom C-peptide was present were actually a subgroup of patients with a different disorder, such as metabolic syndrome or type 2 diabetes presenting at a younger age. Or conversely, can people with type 2 diabetes who progress to decreased β-cell mass be reflected by studies of on Dr. Palmer's presentation of C-peptide as a good reflection of β-cell mass and Dr. Kahn's data that β function without measuring C-peptide?

Dr. Palmer replied that he would not want to leave the impression that C-peptide is a good measure of β-cell mass, but rather that there is a correlation between β-cell mass and all measures of β-cell function. β-cell function is really what is being measured by C-peptide, which is not equivalent to measuring β-cell mass. He stressed that for type 1 diabetes, and possibly also for type 2, part of the disease process is damaged β cells, not necessarily dead β cells. In animal models and increasingly in humans, with aggressive treatment, especially glycemic treatment, but also with immunologic treatment in the animal models, there is a surprising recovery of β-cell function

Dr. Kahn agreed that measuring β-cell function is difficult and that C-peptide has become the best way to do so in type 1 diabetes because those individuals are being treated with insulin. There are arguments to use C-peptide in type 2 diabetes as well, since hepatic clearance, which can be so variable, does not come into play. The problem is the expense. It is easier to measure insulin, especially with ADA's move to have the insulin assay standardized; therefore, it may be that insulin will be used in most instances. Dr. Kahn also agreed that C-peptide is not truly a measure of β-cell mass. Also, he did not wish to leave the impression that β-cell mass is all that is wrong with type 2 diabetes. He suggested there is a functional defect that might actually contribute to the amyloid formation. Amyloid formation and loss of β-cell mass appear to go hand-in-hand in contributing to the loss of insulin secretion.

Dr. Kahn continued that the issue of how best to assess this is a real problem, because clearly the intravenous tests he described in his presentation are not ones that can be done in the clinic in large-scale clinical trials, whether they are NIH-based clinical trials or pharmaceutical-based clinical trials. He did think that with the use of more precise measures of β-cell function, the number of individuals needed in some of these trials could be reduced and it may even be possible to use some of these measures, rather than glucose, as biomarkers when one is making assessments in clinical trials aimed at preventing β-cell loss. By reducing the number of subjects in clinical trials, Dr. Kahn believes more centers can do the studies, and, hopefully, in time the FDA and other groups will look on tests and approaches like this as ways to assess early disease and enable us to develop interventions. He also felt that assessing interventions early on in people with normal glucose tolerance to see if this would prevent diabetes would require many years of follow-up, which would be extremely difficult and expensive.

As an aside, Dr. Kahn noted that he and Dr. Harry Shamoon and Dr. Bill Knowler have been involved in writing up the insulin secretion and sensitivity data from the DPP and that data indicates that the lifestyle intervention, which did best in preventing or delaying diabetes, also had the most effect in improving **β-**

cell function. OGTT-derived measures were used to measure this and could certainly be used in clinical trials to look at compounds and how they might change sensitivity and β-cell function.

Dr. Alan Moses, Novo Nordisk Pharmaceuticals, commented that he agreed about the need to do better in terms of assessing both β-cell mass and function, particularly in looking to drugs to change the early natural history of type 2 diabetes. He asked if the UKPDS curve based on the HOMA method was a linear curve or was it a combination of lipotoxicity, perhaps glucotoxicity, at very mild levels of hyperglycemia, and perhaps amyloid accumulation that made it something other than a linear curve. Dr. Kahn said that it was possible that it was linear at that point in time. In more recent studies trying to measure secretory capacity by raising the glucose to the maximum level (above 450 mg/dl) and then giving a stimulus like arginine, to examine at β-cell secretory capacity, it was found that the relationship between β-cell function and hyperglycemia is a curve as well. Individuals can lose 75 percent or more of β-cell function before developing hyperglycemia.

In response to a question about how the curves of insulin sensitivity versus insulin secretion might vary for different categories of obesity in early pre-diabetes and whether they would be shifted from those observed in subjects with normal glucose tolerance, Dr. Kahn answered that their data with people of varying BMIs indicated that in older people and in those with impaired fasting glucose, the curves, and they are definitely hyperbolic curves in these other groups, are shifted down and to the left. Dr. Kahn felt these curves indicate that, in people at very high risk, simply using the product of the two measures—insulin sensitivity index and insulin secretion—as a measure of β-cell function might be a way of following these individuals down the road.

The question was asked whether the subjects in UKPDS who developed diabetes might actually never have had normal β-cell function and in relation to islet volume measurements in those people who progressed to diabetes versus those who did not, could the difference in the two groups been a defect in β-cell volume to begin with in those who got diabetes. Dr. Kahn replied that he believed that diabetes is certainly a genetic *and* an environmental disease. If these subjects could have been studied at 2 years of age, he thought that those who later developed diabetes at 65 probably already had decreased secretion at 2. In other words, there was probably a genetic component in those who developed diabetes, but that increased dietary fat and other environmental factors that contribute to obesity have a very deleterious impact on insulin secretion and thus, it was the environment, in Dr. Kahn's opinion, that was the major player in what happened to individuals who were genetically predisposed to develop β-cell dysfunction and diabetes.

With regard to islet mass, Dr. Kahn thought that islet mass might genetically also be reduced. Most of the genes that have been identified so far for diabetes appear to be transcription factors, such as PDX1, which is a major player in terms of islet development. However these people had not been studied in this regard. In animal studies using systems with nuclear staining and counting cells and looking at islet adaptation to higher fat diets and obesity, there is β-cell hyperplasia, but not hypertrophy or much neogenesis. Based on these studies, it is thought that there is replication occurring within the β cell. In mice, a very strong linear relationship has been observed between the degree of adiposity in the mice and the number of β cells. The question again is that if this is a linear relationship, would it have been monolinear up at the top in these animals? Dr. Kahn said they really do not know what is normal. His guess would be that in humans β -cell mass might be genetically determined in part and then the environment has a detrimental effect, restricting complete β-cell adaptation, along with other factors such as amyloids.

Dr Amy Rosenberg, FDA, asked Dr. Kahn if his group had dissected further the amylin protein in the transgenic mice to target the particular amino acids involved in the amyloid deposition. She also asked why he felt fat per se results in lipotoxicity. If the mice had a high-fat diet but calories were controlled, would there still be lipotoxicity and does the kind of fat make a difference?

Dr. Kahn replied that in terms of the amino acid sequence in the animals, the transgenic mouse was created because normal mice have protein substitutions in their 20 to 29 amino acid sequence that appear to be critical. Mice and rats never get amyloid. Monkeys, cats, and dogs do get amyloid, so the sequence appears to be critical. His group has not worked further with this subject. With regard to fats, *in vitro* studies have clearly shown that fatty acids are deleterious in terms of islet function and insulin secretion. This seems to vary a bit, depending on the fatty acid employed. The high-fat diets in the transgenic mice were the high-fat diets associated with obesity and what was seen was that insulin secretion appeared to be disturbed. A similar result was seen with dogs fed a high fat diet. These animals developed obesity, insulin resistance, β-cell dysfunction, and thus glucose intolerance. Dr. Kahn added that the mechanism by which the high-fat diet is producing this effect *in vivo* is unclear and this is one of the limitations of doing clinical physiology in humans or animals.

## Session IV: Islet Transplantation

*Moderators: Cynthia Rask, MD, Division Director, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research, and Richard McFarland, PhD, MD, Medical Officer, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research, FDA*

### Islet Transplants: Past, Present, and Future

***Bernard J. Hering, MD**, Director of the Islet Transplant Program, Associate Director of the Diabetes Institute for Immunology and Transplantation, and Associate Professor of Surgery, University of Minnesota; Co-Director, JDRF Islet Transplant Center, University of California/University of Minnesota*

Dr. Hering pointed out that it is important to recruit many more investigators to capitalize on the current opportunities for developing islet translation to a viable and widely available treatment option for people with type 1 and type 2 diabetes. In the past, the challenge has been to achieve and to restore insulin independence. The challenge now is how to implement what we have accomplished. For the future, innovation will be critically needed.

**The Past**. Dr. Hering listed three barriers in the past that challenged achieving insulin independence: low engrafted islet mass, high metabolic demand, and immunologic graft loss. It was felt that the islet mass transplanted was inadequate, that the engraftment of islets was impaired by hypoxia and immunity, and that the function of the engrafted islet mass was compromised by insulin resistance and by impaired insulin secretion caused by diabetogenic drugs and possibly by underlying diabetes itself. At that time, islets were subject to rejection and beta-cell toxic immunosuppressive regimens..

Dr. Hering briefly reviewed the 30-year history of islet transplantation:

- **1974:** First transplant was performed by Drs. John Najarian and David Sutherland. Basic components of the 1974 protocol have remained much the same. Islets are still recovered from deceased donors, collagenase and density gradients are used, islets are infused into the portal vein, and anti-lymphocyte globulin or other T-cell antibodies are used for recipient treatment.
- **Late 1980s**: Dr. Ricordi made a significant contribution by developing a new technique for islet isolation from the human pancreas.
- **1990**: First, well-documented case of insulin independence was reported by Drs. David Scharp and Paul Lacy using islets prepared from two donor organs. The type 1 diabetes patient achieved insulin independence 10 days after transplantation and glucose control remained fairly stable.

- **1990**: Pittsburgh group reported on nine simultaneous islet liver transplants in patients with surgical diabetes, using a prednisone-free protocol. Seven of nine patients became insulin independent, and at 1 year, five of the nine had remained insulin independent—a remarkable success rate in patients with surgical diabetes.
- **1991 and 1992**: Edmonton group used islets from one fresh pancreas together with cryopreserved islets from four additional donors (10,000 islet equivalents per kilogram) and reported the first example of insulin independence and euglycemia for more than 1 year duration after islet transplantation in Type 1 diabetes.
- **1992:** Dr. Hering and others developed the Geissen protocol that successfully prevented islet graft failure in most of their patients. Outcome was measured in basal C-peptide levels exceeding 1 nanogram per ml. Insulin independence was achieved in about one-third of patients treated with high-dose cyclosporin and prednisone after a single-donor islet transplantation.
- **1993**: Dr. Paul Gores reported on insulin independence in type 1 diabetes after a single donor transplantation using unpurified islets.
- **1998**: First type 1 diabetic islet recipient remaining insulin independent for more than 5 years, was reported by Washington University, St. Louis.
- **2000:** Dr. Shapiro reported an 85-percent success rate for insulin independence at 1 year post-transplant using a modified Edmonton protocol with a new streptomycin-based, steroid-free, immunosuppressive and islets from two to three donor organs.

Dr. Hering stated that the Edmonton protocol changed the field. He felt the high rate of insulin independence achieved was probably due to the increased islet mass engrafted, the lowering of metabolic demand, and the new protocol's prevention of graft loss due to autoimmunity and allo-immunity. More than 300 patients have received transplants following the Edmonton protocol, with a number of groups achieving success rates as high or nearly as high as at Edmonton.

**The Present**. Dr. Hering named several current concerns in making successful islet transplantation available to more persons who suffer from difficult-to-manage diabetes. These included the low efficiency of the procedure, safety issues, limited availability, and uneven integration of the procedure into the diabetes care community. Specific questions within these concerns are: What is the cost utility, what is the duration of successful islet transplants, do we need multiple donors, is the academic setting adequate to deliver against demand, how do we resolve the logistics of pancreas allocation, will third-party reimbursement bear the cost, what are the risks of the procedure, and importantly, what are the risks of long-term immunosuppression, are those risks known, and what would be the most adequate approach? Dr. Hering's priorities to address these issues were to focus on single donor islet transplants, steroid- and calcineurin inhibitor-free regimens, the FDA biologics license application, and randomized clinical trials to determine when to use islet transplantation versus insulin therapy.

***Single-Donor Islet Transplant Approaches***. Dr. Hering's rationale for single-donor islet transplantation was based on the fact that a second transplant increases cost by $75,000, which cannot be handled easily; single-donor transplants allow ultimate validation of islet potency assays, which is important to move the field forward and to improve islet processing techniques; and single-donor transplants facilitate evaluation of immunotherapeutic protocols. He added that adopting single-donor transplants will promote FDA approval and insurance coverage, promote donor pancreas allocation to islet patients, and therefore promote overall availability of islet transplantation.

A new approach and protocols have been developed by Dr. Hering and his colleague, Dr. Jeffrey Bluestone, for successful transplantation of cultured islets from two-layer, preserved pancreases with anti-CD3 antibody immunotherapy. Four of six recipients achieved and maintained insulin independence after single-donor transplantation. The basic approach uses maintenance treatment as described by the

Edmonton protocol. Dr. Hering used two additional protocols, one of which involved the addition of a soluble TNF (tumor necrosis factor) receptor blocker to mitigate early inflammatory responses to the transplant islets and rabbit antithymocyte globulin (ATG). Dr. Hering stated that immunotherapy with a new generation anti-CD3 antibody may facilitate minimization of maintenance immunosuppression (Hering et al., Am J Transplantation 4:390-401, 2004).

Patients with sustained insulin independence after single-donor islet transplantation showed acceptable metabolic control with normal HbA1c levels, normal OGT responses in 8 of 10 recipients, and acceptable acute C-peptide and insulin responses to arginine and insulin. Hypoglycemia was avoided in all recipients who suffered from recurrent episodes of severe hypoglycemia pre-transplant. There were no prolonged serious adverse events, procedural complications, or opportunistic infections. Dr. Hering explained that studies indicate that different induction protocols may produce a different engraftment index (i.e., the acute C-peptide response to arginine, divided by the transplanted islet mass per kilogram). Preliminary data suggest that the addition of soluble TNF-receptor blockers could promote engraftment of transplanted islets. Based on successful use of this protocol in a series of 20 recipients, Dr. Hering believes it possible to build on the achievement and make it available to more centers for single-donor transplants.

Dr. Hering suggested the following as other opportunities to achieve single-donor success on a more consistent basis: improvement of islet mass and potency by working on donor pre-treatment, pancreas preservation, using recombinant enzymes, process engineering, and gene transfer and protein transduction for the purpose of protecting islets during processing. For example, in islet processing what will be important is having a validated, reliable, preferably real-time assay of islet β-cell mass and potency, which is an area in which Dr. Hering and others have been working. Dr. Hering presented a slide showing there are now real-time release assays that show very good correlation with post-transplant function, the β-cell mass per kilogram, oxygen consumption rate (OCR) per DNA, and ATP (adenosine triphosphate). His example from work done by Drs. Papas, Koulmanda, Weir, Colton, Ikle, and Nelson showed that in the rat-to-mouse model, the assay had a predictive value of 89 percent, a sensitivity of 93 percent, and a specificity of 94 percent. By plotting OCR per DNA as a measure of the fraction of viability of tissue and the implanted viable islet equivalents, then, with a very low dose of islets, just 75 islet equivalents per mouse, diabetes can be reversed with a high fraction of viability. As the fraction of viability decreases, probability will decrease. The example also showed that even a very high number of islets will not reverse diabetes if the fraction of viability is below 75 nanomole per minute per milligram DNA. Dr. Hering said there is more and more information from human islet transplants and pig islet transplants suggesting that this probability of transplant success based on OCR per DNA and viable islet equivalents per kilogram is also present in pre-clinical and clinical situations.

Dr. Hering suggested an islet engraftment can be optimized by targeting immunity through developing new islet delivery techniques using biodegradable scaffolds or using pro-angiogenic, anti-apoptotic, anti-inflammatory, and immunoregulatory peptides. One islet implantation site that his center has become interested in is the small intestine subserosal space, a highly vascularized space. In a pig islet transplant model, diabetes was reversed and outcomes were comparable with an intraportal islet transplantation site. Local immunotherapy can possibly be easily performed at this site and promote engraftment and survival.

***Steroid and CNI-Free Regimens***. According to Dr. Hering, lower metabolic demand can be achieved by avoiding both corticosteroids and calcineurin inhibitors. Two protocols have recently been developed: one based on CD28 blockade using LEA29Y, a CTLA4 IG mutant, and a second one based on FTY720. Compared with the Edmonton protocol, the protocol published by the Emery group basically replaced the calcineurin inhibitor, FK506, with LEA29Y. Work done at Dr. Hering's institution, in collaboration with Miami, used FTY720 instead of FK506. This approach lacked islet, kidney, and cardiovascular toxicity. The impact on protective immunity is unknown, but Dr. Hering considers this a very promising

development. With LEA29Y, it was possible to reverse diabetes and protect transplant islets, whereas in the control group, all animals rejected the islets. With FDY720, basiliximab, and RAD (a rapamycin derivative), again it was possible to prevent rejection in a non-human primate transplant model. It was also possible to reverse diabetes with a very low islet dose of 5,000 islet equivalents per kilogram, and animals became insulin independent and remained euglycemic after discontinuation of insulin, suggesting that avoiding calcineurin inhibitors may promote engraftment and may improve insulin secretion.

***FDA Biologics Response Modifiers Advisory Committee***. In October 2003, FDA hosted a meeting focused on islet transplantation and addressing manufacturing and clinical study design issues related to clinical trials designed to support a biologics license for human islets. The Biological Response Modifiers Advisory Committee was asked to review the status of the field. Dr. Hering thought the consensus in the field was that control and consistency of islet manufacturing has progressed to the point that a license could possibly be considered. More work will be necessary in the area of islet potency assays, and it was unclear whether substantial evidence of safety and effectiveness are available. A proposed indication on labeling also was discussed. Restoring euglycemia in type 1 diabetes as a clinical endpoint was also considered.

Dr. Hering emphasized that for a small subgroup of people with type 1 diabetes who suffer from recurrent episodes of severe hypoglycemia, islet transplants can achieve remarkable improvement. He added this is important in relationship to the DCCT findings that risk can be reduced but not without increasing the rate of hypoglycemia. He presented several slides supporting his statement.

***Randomized Trials and Islet Transplantation Vs. Insulin Therapy***. Dr. Hering said the current overall question is whether the field has developed to the point where randomized clinical trials should be considered. Other questions include whether to focus on hypoglycemia-associated autonomic failure, whether costs per quality-adjusted life year can be approved, and whether to focus on chronic complications and ask if microvascular lesions in type 1 diabetic patients with, for example, microalbuminuria treated with renin angiotensin system blockers (RASB), will continue to progress if normal glycemia is not restored. There is emerging consensus in the field that randomized clinical trials are probably needed to document the benefits of islet transplantation. Dr. Hering noted that a lot of support has been provided by NIH and the field has clearly benefited from this support and by FDA's interest. He felt additional Federal agencies will need to be involved in the trials. Pancreas allocation and health insurance coverage are two very important issues. In support of initiating trials, Dr. Hering stressed that progress has been made in islet transplantation; efficiency and safety have improved. He cited integration and availability as important areas requiring further work.

**The Future**. Dr. Hering emphasized that innovation is needed, for example to develop a state of immunologic tolerance and to provide an unlimited β-cell source or possibly β-cell replication *in situ*.

***Immunologic Tolerance***. The current paradigm suggests depletion of pathogenic T-cells and establishment of a state of regulation is necessary to achieve stable and robust tolerance. This has become possible, as reported by the Alabama group, with anti-CD3 immunotoxin combined with deoxyspergualin (15-DSG), which inhibits allo-immunity, dendritic cell maturation, and antigen presentation. Dr. Terry Strom's group developed another apparently successful approach in a very difficult NOD mouse model and also in non-human primates, involving three different strategies—rapamycin, agonist interleukin 2, and antagonist interleukin 15—promoting deletion and regulation.

With support provided by the Immune Tolerance Network, Dr. Hering's group will begin testing anti-CD3 immunotherapy with rapamycin to see if it can achieve tolerance in type 1 diabetic islet recipients. It has been shown that this antibody can actually lead to a contraction of 8.5 to 0.1 percent of the anti-T-cell repertoire in the peripheral circulation. A striking increase in the percentage of regulatory T-cells after

immunotherapy with this antibody has been noted, suggesting that tolerance could possibly be accomplished. A paper published on-line suggests a 40,000-fold expansion of CD25+CD4+ T-cells *ex vivo* over a period of only 3 or 4 weeks.

***β-Cell Source***. A number of different strategies have been proposed to develop a β-cell source including maximization of decreased donor pancreas utilization, living donor islet transplants, xenogeneic islet transplants, precursor cell-derived islet beta cell transplants, and beta cell replication *in situ*. Dr. Hering believes β-cell mass and supply for transplantation can be increased. Pig islets are already being tested in animal studies.

In the area of xenotransplantation, Dr. Hering's center transplanted pig islets into immunosuppressed diabetic monkeys and demonstrated reversal of diabetes. Normal glycemia was achieved for more than 100 days. A liver biopsy showed 90 percent of islets without any evidence of infiltration. Dr. Hering stated a number of strategies are becoming available to decrease immunosuppressive risks. It was his opinion that adult stem cell-derived islets probably would not become a source. A paper by Dr. Douglas Melton (Nature 429:41-46, 2004) suggested that new β-cells are formed by self-duplication of pre-existing β-cells and are not formed by stem or progenitor cells during adult life. Dr. Hering thought the other important message from the paper is that there is a very high proliferative capacity and turnover of terminally differentiated β-cells. The question is, "Can this capacity be exploited for expansion to a clinically useful mass?" Also, with respect to islet transplantation, "Is the longevity of islet transplants determined by the proliferative potential of transplanted β-cells?" Dr. Hering continued that Dr. Peter Butler keeps reminding him that, based on mathematical modeling, transplants can only last for 5 years, unless there is replication of transplanted β-cells. Dr. Hering believes, from clinical observations, that replication happens. He gave as an example an islet auto-transplant patient with chronic pancreatitis who has been insulin independent and normal glycemic for 20 years, suggesting islets can survive long-term; this may also be evidence of intrahepatic islet replication more than neogenesis.

In conclusion, Dr. Hering said cell-based therapeutics will soon play an increasingly significant role in diabetes care, particularly if documentation of benefits of islet transplants using clinically relevant endpoints is possible. Considerable effort and new concepts will be needed to overcome translational obstacles in the implementation and integration of cell-based therapeutics into the healthcare system.

### Obstacles and Hurdles Facing the Clinical Application of Islet Transplantation

***Robert S. Sherwin, MD****, C.N.H. Long Professor of Medicine and Director, Diabetes Endocrinology Research Center and General Clinical Research Center, Yale University School of Medicine*

Dr. Sherwin explained that he became interested in the issues of islet transplantation as a diabetologist and an *ad hoc* member of the Biological Response Modifiers Advisory Committee. As Dr. Hering said, the Edmonton study was the turning point in the story of islet transplantation. Today there are remarkable improvements, but we still cannot ensure normality for people with islet transplantation, only about 50 percent of whom become insulin independent over the first year. Although considered clinically successful, normal glucose tolerance is extremely rare in these patients. About a third of the insulin-independent patients resume insulin therapy within 2 years, although they often require less insulin, have less hypoglycemia, and are more stable metabolically. In other words, clinically they are greatly improved. One can anticipate, given the numbers today, that there are quite a few patients who will resume insulin over time. However, the majority of transplant patients self- report improved quality-of-life. At present there is little data regarding microvascular and macrovascular complications in islet transplant patients.

Regarding the mechanism for the loss of β-cell function post-transplant over time, Dr. Sherwin feels there are multiple factors involved. Chronic rejection undoubtedly contributes, since it is unlikely that there is no allo-response in these patients. In many cases, there is the recurrence of autoimmunity, as demonstrated by the formation of antibodies in some patients who required insulin. The immunosuppressive drugs themselves have adverse effects on β-cells. Tacrolimus, which is the part of the Edmonton protocol, clearly reduces β-cell function, and rapamycin, another component, inhibits the mTOR signaling pathway involved in protein synthesis and probably has a role in reduced β-cell proliferation, which may be an important factor. An article in Diabetes Care (Davidson, Diabetes Care 24; 2004) reported that there is a high rate of incidence of diabetes with tacrolimus compared to cyclosporin, which also had some adverse effects. In the best of circumstances, even immediately after transplantation, there is probably only about 20 to 30 percent of β-cell mass present, thus only marginal β-cell function. One thing that little is known about is whether there is insulin resistance, a critical factor in β-cell function.

On the positive side, Dr. Sherwin reported pooled data compiled by Dr. Hering showing that progress was being made. The pooled data on cultured islet transplants from three centers where 75 patients received transplants since 2000, showed that 74 of the 75 (99%) demonstrated primary function based on C-peptide post-transplant, 72 (96%) were C-peptide positive after 1 year, and 64 (85%) remained insulin independent at 1 year.

Dr. Sherwin noted that there are complications associated with the Edmonton experience, which is critical when asking FDA to consider instituting this kind of therapy and licensing it. Safety is a key element in such deliberations. The major acute islet-related complication was bleeding, although generally it was modest (10 percent incidence) but this often requires transfusion. There was also occasional thrombosis at the injection site (4 percent incidence). Chronic islet-related complications included fatty liver. A host of side effects and drug-related complications also occur, some modest, some significant. Certainly mouth ulcers are a problem for patients as well as increased cholesterol, increased blood pressure, and diarrhea.

Dr. Sherwin reported that the major questions at the FDA meeting of the Biological Modifiers Advisory Committee in October 2003 were "What manufacturing requirements and clinical evidence should be needed for FDA approval of allogeneic islets as type 1 diabetes treatment?" In Dr. Sherwin's opinion, the outcome from the meeting was that there are still many basic and clinical questions that need to be resolved. However, some centers have made substantial progress and therefore may ultimately be able to provide sufficient data for FDA approval for islets as a licensed product.

Next Dr. Sherwin listed the following obstacles and hurdles to be overcome for FDA approval, noting there are probably others he did not list:

- Islet procurement is a major problem. Islet transplantation centers have tremendous difficulty getting islets for islet transplantation.
- Optimization of islet production and culture methods needs to be refined.
- There needs to be development of islet viability and function tests *in vitro* that relate to clinical outcomes. Although there is progress in this area, there is not a gold standard yet.
- Optimization of immunosuppressive regimens are needed.
- The preferred site for islet engraftment needs to be studied and determined.
- Methods to reduce implantation local phenomena, such as inflammation, clotting, and perfusion deficits need to be developed.
- Appropriate clinical outcome measures must be defned.
- Data is needed to assess the risk-benefit ratio for approval.

- Methods to detect early islet rejection must be devised. This is a major problem, because currently rejection is detected by hyperglycemia, which is too late.

**Pancreas Allocation**. Dr. Sherwin pointed out that the pancreas allocation process is an issue of importance and a major obstacle to islet transplantation. The vast majority, probably over 95 percent, of pancreas organs from obese and older (>50 years of age) patients are not used and yet they are not offered in a timely manner to the islet transplant community. This is important since cold ischemic time is highly critical for islet transplantation, much more critical than for pancreas transplantation. Dr. Sherwin added that, surprisingly, the United Network for Organ Sharing (UNOS) kidney-pancreas allocation committee, which is not under FDA, has no representation from either the islet transplant community or the diabetes community. Dr. Sherwin recommended that the pancreas allocation policy be amended to include (1) limiting time to less than 4 hours for offers for pancreas transplantation or provide pancreases directly for islet transplantation from donors with a BMI greater than 30 or older than 50 years of age; and (2) involve the islet transplant and diabetes communities in the pancreas allocation process.

**Clinical Outcome Measures**. The current clinical outcome measure for successful islet transplantation is insulin independence. The criterion for insulin independence is HbA1c less than 6.5 percent when off insulin. Dr. Sherwin recognized that this means many of these insulin-independent patients obviously have pre-diabetes or diabetes. He suggested that although insulin independence is obviously important to the patient, clinical outcomes would be better defined on the basis of ADA criteria of glycemic control, such as normal glucose tolerance, IGT, IFG, and non-insulin-requiring diabetes.

For partial success in islet transplantation, the current clinical outcome is C-peptide secretion and reduction in insulin dose. Dr. Sherwin said it is important to keep in mind that the studies of islet function that are used in the transplant community are largely based on arginine stimulation or mixed meal tolerance tests, rather than the gold standard used by diabetologists to assess diabetic state, namely glucose-stimulated insulin/C-peptide secretion.

Referring to the NIH Roadmap Initiative, Dr. Sherwin said that what was needed to move forward is an in-depth assessment of islet transplantation with multi-disciplinary centers such as General Clinical Research Centers (GCRCs) able to conduct state-of-the-art physiological, end organ, and behavioral outcomes studies on islet graft recipients, who, he added, are not an enormous population.

**Clinical Assessment of β-cell Function, Glycemic Control, Hypoglycemia, and Complications**. Dr. Sherwin presented two suggestions for clinical assessment of β-cell function in islet transplant patients—one for insulin-independent patients and one for insulin-requiring patients. For him, the gold standard for the insulin-independent patient is an oral glucose test, preferably OGTT, with early insulin and C-peptide sampling to better characterize secretory responses. Second, as a crude measure of β-cell mass, he recommended stepped glucose infusion, possibly with arginine added. Third, as a measure of insulin sensitivity to assess β-cell function (insulin secretion data), he suggested the euglycemic insulin clamp. Lastly, Dr. Sherwin said there needs to be more direct measures of islet cell mass, which we do not have yet. Insulin-requiring patients will obviously not have much glucose-stimulated β-cell function; therefore Dr. Sherwin's suggestion for clinical assessment of them was mixed meals, focusing on C-peptide; maybe a stepped glucose infusion with arginine; and again, the β-cell mass.

For clinical assessment of glycemic control and hypoglycemia in islet transplant patients, Dr. Sherwin would do an OGTT, with 24-hour glucose monitoring in the hospital to monitor glucose excursions and hypoglycemia, especially in the insulin-independent patients. Additionally, he would want monthly profiles of these patients (pre- and 2-hour post meal, bedtime, and 3 a.m.), including glucose meter measurements; a continuous glucose monitoring system (CGMS) for postprandial hyperglycemia and lability; and a validated hypoglycemic scoring system.

Dr. Sherwin proposed clinical assessment of complications in islet transplant patients should include fundus photos and checks for microalbumin excretion and glomerular filtration rate (GFR), essentially as done in the DCCT; sensory testing, nerve conduction, RR interval; endothelial function studies; carotid IMT and perhaps coronary perfusion studies; measurement of hypoglycemic counterregulation and awareness; and potential complications related to therapy.

**Risk-Benefit Assessment**. Dr. Sherwin stated a risk-benefit assessment also is needed. On the benefit side would be insulin independence, which is everyone's dream for patients with type 1 diabetes, or at least sufficient C-peptide secretion to make glucose control easier without hypoglycemia and to have better glucose control than is achievable with current methods. Another major benefit would be the potential decrease in diabetic complications. On the risk side, Dr. Sherwin identified the risk of acute complications of the procedure, the side-effects of the anti-rejection regimens, and the potential for neoplasia, infections, poor wound healing, pneumonitis, and so forth. Remaining questions raised by Dr. Sherwin included uncertainty about the diabetic nephropathy benefit; potential adverse effects with respect to cardiovascular disease, since other kinds of transplantation clearly accelerate cardiovascular disease and produce hypertension and hypercholesterolemia; and uncertainty about the duration of islet function with these grafts being sufficient to have a clinical long-term outcome.

One of the key questions for Dr. Sherwin was, "Will islet transplantation prevent or reverse nephropathy?" The pros are that the University of Washington, Seattle, group showed reversal of mesangial accumulation and base membrane thickening, 10 years after successful pancreas transplantation (Robinson et al. NEJM, 2004). On the other hand, in 2003 the *New England Journal of Medicine* reported development of renal failure in 3 years in 17 percent of non-kidney graft recipients (Ojo et al. NEJM, 2003). *Transplantation* (Majur et al. Transplantation, 2004) reported a 38-percent decrease in GFR in patients who had bladder drained pancreas transplants (one patient actually required a kidney transplant); granted bladder drainage produces dehydration, which probably contributed to this, but it is something to consider. Dr. Sherwin also pointed out that pancreas transplantation currently produces better and more sustained glycemic control than islet transplantation.

Dr. Sherwin also cited the report of Dr. David Harlan (JAMA, 2003), who looked retrospectively at studies. Using the UNOS database (1995 through 2000), Dr. Harlan divided patients according to procedure (pancreas alone, pancreas after kidney, or simultaneous pancreas/kidney). He then compared these patients to a control group, based on 4-year follow-up period from the database. Dr. Sherwin admitted it could be argued that those in the control group, such as people on a waiting list who did not receive a pancreas, might not have been in as desperate circumstances as those who did get pancreas grafts. Nevertheless, the data showed that those who received simultaneous pancreas/kidney transplants clearly benefited. However in the other categories, 4 years out, there was not much benefit compared to the control group who received conventional therapy. Dr. Sherwin concluded that, although retrospective studies that compare different populations can be questionable, this one does raise issues regarding the risk-benefit ratio.

**Islet Transplantation or Insulin Therapy?** Comparing intensive insulin therapy in 2004 with islet transplantation, Dr. Sherwin scored glycemic control generally better; hypoglycemia, much better; central nervous system (CNS) function in patients who have severe hypoglycemia, unknown; quality of life, most say better; retinopathy, probably better; nephropathy, unknown; neuropathy, probably better; cardiovascular disease; unknown; malignancy, probably worse; and long-term survival, unknown. Based on his "scorecard," Dr. Sherwin concluded there are only two current indications for islet transplantation: (1) patients with severe recurrent hypoglycemia and hypoglycemia unawareness, which is the major clinical problem encountered with insulin therapy in a subgroup of type 1 diabetes patients; and (2) patients who have had a kidney transplant and are already receiving steroid-free regimens that are like the

ones used for islet transplantation. Dr. Sherwin said that only rarely should poorly controlled or labile type 1 diabetes patients be considered for islet transplantation because these patients are doing reasonably well today compared to the past. Survival and quality of life have improved, largely due to DCCT/EDIC and to the newer insulins and insulin delivery systems, the statins, lipid control, improved diets, and so forth. Dr. Sherwin concluded that due to these improvements in standard of care, judging the need for islet transplantation is different today than it was 10 or 20 years ago.

Dr. Sherwin noted that severe hypoglycemia remains a problem and is far more common than appreciated. Sympathoadrenal responses and cognitive awareness are markedly reduced in these patients and 50 percent of severe events occur while people are sleeping. In most patients treated intensively, the fear of hypoglycemia exceeds their fear of complications, which is anxiety promoting and leads to decreased commitment to treatment in patients, their families, and their physicians. Dr. Sherwin stated that patients with severe recurrent hypoglycemia with unawareness, who fail to respond to modern multiple injection and insulin pump therapy delivered by a diabetes specialist for a period of time (and this is arbitrary) are very good candidates for islet transplantation. He added that severe hypoglycemia and unawareness needs to be well-defined and documented. Basically, it is considered a history of two serious events a year such as coma, hospitalization, or requiring help from another person, with documented glucose meter readings and, ideally, hypoglycemia clamp studies or some form of study to evaluate function. Dr. Sherwin said that these measurements are important because sometimes improved management can reduce iatrogenic hypoglycemia and improve responses, and although this can be difficult and may not be practical in many settings, it s worth considering prior to undergoing transplantation.

For Dr. Sherwin, an acceptable outcome in the patients with severe hypoglycemia could be both insulin-independent and insulin-requiring, C-peptide-positive patients, with insulin independence obviously more acceptable. In patients receiving islet transplants after kidney transplant, again, insulin independence and insulin requiring C-peptide positive secretion would be acceptable outcomes because better control would probably be achieved in those patients since they would be on the same regimen. Dr. Sherwin questioned there being an acceptable outcome in patients with impaired renal function, especially if they would be insulin-requiring, C-peptide positive, given his concerns about presently available regimens. He was uncertain about an acceptable outcome for patients with poor control of their diabetes.

Cautioning that clinical trials are expensive, Dr. Sherwin recommended the following kinds of clinical trials to further examine the potential benefits of islet transplantation for certain patients with type 1 diabetes:

- Patients with severe hypoglycemia: relatively short-term (1 to 2 years) observational studies.
- Patients for islet transplant after kidney transplant: matching of patients with historical controls and data with 2 or 3 years of follow-up.
- Patients with poorly controlled labile diabetes: a 5-year, DCCT-type randomized trial to assess the long-term impact of this treatment.

## Discussion

In response to a question about the regulatory pathway to approval of manufacturing of islets, Dr. McFarland said that there are nuances since one islet preparation is not the same as another islet preparation; however, the principle under which the Center for Biologics Evaluation and Research (CBER) grants licenses, at least going back to the granting of the first biologics license for monoclonal antibodies, is that processes are very important in the development of the product. Islets are regulated at the level of the cellular product, but the process to make that product is evaluated as part of the application. This is also true at the level of the investigational new drug (IND) applications for investigational products. As islet technology improves and changes occur, FDA will be informed and also will have bridging studies to show that the lot release tests are similar and that the products are similar in function.

Dr. David Marrero, Indiana University School of Medicine, Indianapolis, stated that quality of life is a key phrase in considering the potential for new treatments and targets for treatments. It is important to consider a patient's quality of life and the trade-offs that are involved with decisions to invoke certain treatment, not only for transplantation, but for virtually anything, be it a drug or device, or whatever the technology under discussion. Dr. Sherwin said that for patients and their families, severe hypoglycemia is a dominant player. Avoiding this phenomenon has an enormous impact on quality of life for that group. One of the purposes of islet transplantation is to improve quality of life and if there is anybody whose quality of life is going to be improved the most, it will be the patient with severe hypoglycemia, provided that the side effects of the drugs are minimal. Given the fact of very limited resources, Dr. Sherwin would give priority to the patient with recurrent severe hypoglycemia.

Dr. Marrero, a type 1 diabetes patient of 26 years, followed up by saying that what was of interest to him about hypoglycemia was that many of the therapies that have evolved in his lifetime have a dual-edged component, where initially there is an increased risk but over time or exposure or experience with the treatment, the results become better. He said FDA and NIH may need to plan on how to balance the risk-benefit ratio between an acceptable level of risk versus what in fact may turn into a benefit over time.

Another participant, commenting on the Edmonton protocol and the importance of non-immune factors in progressive β-cell mass loss and loss of secretion, asked Dr. Hering what is being done with human islet transplantation in terms of biopsies or such to learn what is really happening to β-cell mass from non-immune processes. He also asked how the acute and long-term or chronic effects might be dealt with in the future if only about 25 percent of the β-cell mass that has been transplanted is functional.

Dr. Hering agreed this is currently a problem of increasing importance. Most centers see their patients with initially successful islet transplants later experience failure. The reason or reasons are not really known. Biopsies will help in the short-term. A major focus of the new islet transplant consortium that is being established in 2004 will be mechanistic studies with respect to pre-transplant evaluation of islet mass potency and also post-transplant immune monitoring using the most sophisticated and developed technology that is available to monitor allo-immunity, autoimmunity, and innate immunity after transplantation. This will be very sophisticated metabolic monitoring involving studies looking at insulin sensitivity, insulin action, and so forth. Dr. Hering also expected to see progress in the field of islet bioimaging to monitor islets post-transplant using non-invasive technology. There is not just one approach to the problem of why some transplants fail. Maybe it is because a marginal mass was present initially. Maybe it is a failure of replication. Maybe it is autoimmune recurrence. There are many possibilities for studying this question.

Dr. Sherwin agreed that the basic problem is starting out with a marginal β-cell mass and then a number of factors contribute to the loss of function, be it failure to replicate, apoptosis, or core perfusion. It is not

really known if the islet normally is perfused inside-out or how it is perfused. More information also is needed on amyloid production. The fact that mild hyperglycemia develops with time, probably doesn't help the β-cell function; therefore, if even a successful transplant has not more than 30 and maybe only 20 percent of β-cell mass, it is not difficult to see how, over time, small effects quickly add up to produce insulin requirement.

Referring to the suggestion from Dr. Sherwin about using islets from obese individuals whose pancreases are otherwise not used, the comment was made that one thing that happens with obesity is that there is an adaptation that clearly includes an increase in β-cell mass. Using the obese persons' islets that have more β-cells actually may be a better answer than taking people who have been sick, who are on drugs, and who are insulin resistant, and transplanting them with an islet equivalent mass of what are thought to be healthy islets, but in which the β-cell is not able to replicate quickly enough.

Dr. Hering said he thought most programs do isolate islets from obese donor pancreases because they are available. In his opinion, the reason for late failure in transplantation is more immune-related than islet mass-related. The experience in islet autotransplantation indicates that patients who received a very low β-cell mass (2,000 or 3,000 islet equivalents per kilogram, or one-third of what an islet autograft recipient would receive) showed stable function long-term. In the Minnesota islet autograft data, late failure was seen in no more than one or two patients out of 110 transplanted so far; thus it was a rare occurrence.

In answer to Dr. Sherwin's question about allocating human donor islets to islet allograft recipients based on matched tissue antigens, Dr. Hering replied that it is probably helpful, but not very practical. If possible, Dr. Hering would do it, but it is difficult to accomplish. Most programs have a very small list of islet recipients and finding a patient with a 6-antigen match pancreas is very unlikely, so that is the limiting factor.

Dr. Jose Caro, Eli Lilly and Company, asked if there was a plan to develop collaborative arrangements among the transplant centers, employ a common protocol, and jointly accrue enough patients to obtain a reasonable amount of outcome data and then modify the protocol based on that outcome data. The question was based on the seeming lack of adequate outcome data possibly being related to the number of different centers that are using different protocols and the relatively small number of patients that each one of those centers had.

Dr. Hering responded that progress in any field in medicine is only possible if well organized and carefully designed multi-center clinical trials are organized to address clinically important questions. The very first multi-center trial has just been more or less completed, testing whether the Edmonton data can be confirmed at a number of additional sites. Results will be presented at the ADA meeting and at the American Transplant Congress later this year. One question is how to standardize and address roadblocks. With NIH's establishment of the islet transplant consortium, there will be many opportunities to promote collaboration between centers and address important questions. Dr. Hering added that designing an islet transplantation mega-study, involving a few hundred patients, as has been done in hypertension or in diabetes intervention, requires substantial resources not readily available. Dr. Hering recommended using a multi-disciplinary approach and focusing on a small subset of people with difficult-to-manage diabetes such as those with severe hypoglycemia-related problems. Well-defined, controlled, and consistent islet manufacturing processes would have to be in place. Once a process is licensed for this very defined subgroup of patients, additional resources through third-party reimbursement may become available so other clinical trials can be performed. Dr. Hering pointed out that the per patient cost for the type of trial under discussion is $100,000 to $150,000, which is difficult for even NIH or JDRF to sponsor.

Dr. Caro asked what FDA's position was about using a multi-center, collaborative arrangement with a defined patient population and agreed-on protocols to establish a defined starting point and then modify

the protocols based on outcomes. Dr. McFarland answered that he thought FDA would support such an attempt, in general, if it provided them with more clinical information. He reminded the group that an important point is the quality of the islets that would be used by the collaborative. FDA is currently involved in the INDs (Investigational New Drug Applications) process with the ITN multi-center trials.

In response to a question about the possible benefit of expanding the mass of the islets that are transplanted or supporting them after transplant with, for example, GLP or exendin-4 or DP- IV inhibitors, Dr. Hering said that any strategy that would accomplish this would be very helpful. Dr. Gordon Weir and his group at the Joslin Diabetes Center studied this in an animal model using GLP-1 and did not find evidence of a beneficial effect in the first study. Dr. Hering was not aware of any other studies.

Dr. Marcel Salive, Centers for Medicare & Medicaid Services (CMS), stated that CMS was very pleased to be directed by Congress to participate in the islet cell transplant trials under the Medicare Modernization Act. CMS has begun the process in coordination with NIH, FDA, and other agencies. Currently, CMS is providing coverage for Medicare-eligible patients who are participating in the clinical trials. In order to provide future coverage to Medicare patients, CMS needs to see clinical evidence of effectiveness rather than surrogate markers as endpoints. Dr. Salive asked Dr. Sherwin if the types of clinical trials he proposed would be designed to provide such data.

Dr. Sherwin said they would. A problem in clinical trials is the amount of duration required to show benefit. For people with severe hypoglycemia who are nearly incapacitated by that complication, Dr. Sherwin thought the answer would be easy and straightforward. These patients do not do well long-term and consequently would benefit. The patients who have kidney transplants can be followed for kidney outcomes and to see whether the islet graft prolonged kidney graft survival, which presumably would have an impact from the standpoint of Medicare. That is why Dr. Sherwin proposed trials with those two groups of patients. For the general patient with type 1 diabetes, longer trials would be required to validate that islet transplantation was an improvement over insulin therapy. Longer trials are more expensive. Dr. Sherwin expressed the idea that the short-term trials with the specialized subgroups would provide a valuable learning process and to help design a longer, more expensive trial. At this point in time, Dr. Sherwin said he doubted that one could prove that islet transplantation can provide a better survival benefit and any major complication differences for the majority of type 1 patients.

Dr. Hering agreed. The islet transplant community at this time is not expecting coverage of islet transplantation for just any patient with type 1 diabetes. Granted, coverage would be very helpful, for the patients and for the field, for patients that present with diabetes that cannot be managed satisfactorily by any other available treatment. This is the place to start. Then, as treatments improve with respect to islet manufacturing, or in particular, immunosuppression, and data from randomized clinical trials becomes available, additional patient groups could be considered.

The comment was made that diabetes and its treatment is more complex than dealing with a malignancy. To begin with, defining the patient at-risk is very subjective. The speaker liked Dr. Sherwin's suggestion of having a patient cared for by a committed diabetes care team for 6 to 12 months before deciding that this person had uncontrollable diabetes. Treatment advances in diabetes are happening all the time. There is uncertainty as to which patients to study; there is uncertainty as to what a good islet quality is; there is uncertainty about how to monitor outcome; and there is uncertainty in the immunosuppressive protocol selected. Designing a multi-center study that might be the very best design one can come up with today would very likely be quite different if designed 6 months later. This presents a very difficult conundrum.

Dr. William Tamborlane, Yale School of Medicine, said that the problem with long-term clinical trials is that by the time one arrives at an answer, the therapy is outdated. Dr. Tamborlane thought that a network

of transplant centers collaborating on targeted trials was a good idea. A single study cannot respond to all the transplantation issues. A multi-site effort would be more effective, in his opinion.

Dr. Caro added that the idea is not to get a protocol that is going to answer all the questions, but rather an evolving protocol that changes over time. Given the amount of information that is not known, it would be good to at least have a starting point and then, as more is learned, modify accordingly.

## Session V: Devices

*Moderator: Patricia Bernhardt, Office of In Vitro Diagnostics, Center for Devices and Radiological Health, FDA*

### Device Issues: Glucose ]Monitoring

***William V. Tamborlane, MD**, Professor and Chief of Pediatric Endocrinology and Diabetes, and Deputy Program Director, General Clinical Research Center, Yale University School of Medicine, New Haven, CT; Steering Committee Chair, DirecNet*

Dr. Tamborlane, whose background includes 25 to 30 years of working to achieve good control of type 1 diabetes in children and adolescents as well as being the current Steering Committee Chair of DirecNet (Diabetes Research in Children Network), noted that DirecNet is an NIH-funded collaborative study group of five centers, similar to what Dr. Caro suggested for islet cell transplants. DirecNet's objective is to critically evaluate the clinical usefulness of current and future glucose sensors in youth with type 1 diabetes. Dr. Tamborlane stated that one of the great strengths of the network is its outstanding coordinating center in Tampa, Florida, the Jaeb Center for Health Research.

Dr. Tamborlane explained that his presentation would try to answer the following two questions:

- What criteria should be used for approval of new glucose monitoring sensors?
- Can data from continuous glucose monitoring sensors be used as outcome measures for evaluation of the safety and efficacy of new diabetes treatments?

Dr. Tamborlane said the answer to both of these separate, but related, topics depends on sensor accuracy. This was the conclusion derived by the DirecNet study group when they designed their first study that focused on the accuracy of the two FDA-approved continuous sensing systems—the Cygnus Glucowatch Biographer II and the Medtronic MiniMed CGMS. For the DirecNet study, the investigators planned to recruit 90 youngsters ranging in age from 1 to 17 years, and were successful in recruiting 89 (ages 3 17 years) in the record time of only a few months. Dr. Tamborlane explained that each patient was admitted to one of the inpatient clinical research centers (CRCs) participating in the study for a 24-hour admission process that included serum samples for reference glucose measurements collected every hour during the day and every 30 minutes during the night. The samples were processed and mailed to Dr. Mike Steffes' lab, which was also the central laboratory for DCCT. The study participants wore at least one Medtronic MiniMed CGMS and one Glucowatch simultaneously, and some wore two Glucowatches and two Medtronic MiniMed CGMSs simultaneously. In addition to noting spontaneous fluctuations in glucose, there was the intent to stress the sensor systems by looking at their performance during acute hyperglycemia and acute hypoglycemia. The hyperglycemia subprotocol to cause a rapid increase in glucose involved a high carbohydrate liquid meal without a pre-meal bolus of rapid-acting insulin. In the older children, the equivalent of an insulin tolerance test also was done.

Dr. Tamborlane remarked that one of the wonderful advantages of working in pediatrics is how the children respond to these kinds of studies. The principle outcome of the DirecNet study was fairly standard point-to-point differences between the sensor and reference glucose values. Dr. Tamborlane pointed out that the differences can be looked at in multiple ways: simple, absolute, relative, and relative

absolute difference. Looking at the simple difference, if there is random error on either side of the reference value, then the difference should be close to zero. If there is a systematic bias, then there will be a consistent mean difference between the sensor and the reference values. Looking at the relative difference, which is the difference divided by the reference value expressed by a percent, one obtains a relative absolute difference, or RAD, which was the primary accuracy metric used in the DirecNet studies.

Dr. Tamborlane continued that another way to look at the performance of sensors as well as meters is by International Standards Organization (ISO) criteria, which says, "If the reference glucose is greater than 75 mg/dL, then the sensor reading should be within ±20 percent. If the reference glucose is less than 75 mg/dL, rather than a percentile, the sensor glucose value should be within ±15 mg/dL." DirecNet data were expressed as a percent of paired values meeting these ISO criteria.

Main results of the DirecNet trials as presented by Dr. Tamborlane were fairly consistent with published results for these sensors; however, the data do support the argument that these are first-generation devices. Their accuracy could be said to be analogous to the accuracy of the original glucose meters that were introduced 20 years ago. The Glucowatch reports glucoses every 10 minutes and the Medtronic MiniMed CGMS every 5 minutes. The mean relative absolute difference in the percent error for the Glucowatch was about 22 percent, and for the original Medtronic MiniMed CGMS, it was about 26 percent. Dr. Tamborlane said that, in looking at the overall dataset, the study investigators decided that mean was not the best metric to use, that median was a fairer test of the accuracy of these meters, because a few sensors were outliers that pulled up the average value. The median value RAD data was better: 16 percent for the Glucowatch and 19 percent for the original Medtronic MiniMed CGMS, with neither meter meeting ISO criteria consistently. Dr. Tamborlane explained that about 80 percent of the way through the study, Medtronic MiniMed modified the sensor matrix that they used, giving DirecNet the opportunity (albeit with a smaller number of subjects) to look at the accuracy of the modified sensor, which was much better (16% for mean RAD, 11% for median RAD, and within 72% of ISO criteria). Correlations between sensor and reference values also were better. Since the data for the later model was from only 1,120 paired reference and sensor values and only from one or two lots, Dr. Tamborlane recommended further confirmation of these encouraging results. While the children were on the research unit, Dr. Tamborlane explained that to make decisions regarding their therapy, the One-Touch Ultrameter, a more mature technology, was used. In 1,200 pairs, r-values between reference glucose and the Ultrameter values were 0.97, and the accuracy was between 6 and 7 percent.

In looking at the data, Dr. Tamborlane cautioned the audience to keep in mind that there is error involved with obtaining a reference value and sending it to a central lab, where there is the possibility of error as well. During the IV insulin test, the study measured and compared the Ultrameter measurements with measurements from YSI and Beckman instruments, which they had bedside for safety. Both sets of measurements were sent to a central lab during acute hypoglycemia, and there was no difference in the relative error between the instruments. Dr. Tamborlane stated that this was an impressive performance and indicated what the meter industry is currently able to produce for patients.

Looking at error as a function of plasma glucose level, both the Glucowatch and the Medtronic MiniMed CGMS had problems in the hypoglycemic range (25 to 40 percent error in glucoses under 60), which is an important issue related to FDA using continuous glucose monitoring as a safety index. The Ultrameter did fairly well even in the hypoglycemic range.

Dr. Tamborlane stated that, instead of just looking at point-to-point comparisons, the sensors were compared for ability to pick up a real hypoglycemic event and for incorrectly reporting a hypoglycemic event that was not real. The data collected during the IV insulin infusion test, where reference glucose dropped to values lower than 60 and hypoglycemia was usually achieved, the modified Medtronic

MiniMed CGMS appeared to do best, although there were too few events to ensure the results; the original CGMS did the next best; but only 12 of the 48 Glucowatches detected the episode.

The DirecNet study group was particularly interested in detection of hypoglycemia at night. With the Glucowatch, there were 18 events where the sensor said the patient had a night where the glucose levels fell below 60, but only 10 of those were confirmed by the actual reference glucose. The Medtronic MiniMed CGMS reported 26 events and only 8 were confirmed, and the modified Medtronic MiniMed CGMS was accurate with 3.

False alarms, either for hyper- or hypoglycemia, were considered a very important function for the sensors in relation to their use with children. A selling point of the Glucowatch is that it has both hypo- and hyperglycemic alarms. With the alarm set for a glucose under 60, the Glucowatch only picked 23 percent of actual hypoglycemic episodes, and had a 51 percent false alarm rate. Sensitivity was better at a setting of 120 (92 percent of real events) but the false alarm rate rose to 85 percent. Dr. Tamborlane reported that, in practice, patients tend to quit using the sensor at night after they, and their families, are repeatedly awakened with so many false alarms. The Medtronic MiniMed CGMS does not have an alarm system built into it; its sensitivity for real events was better at 49 percent, but it also had a high "false alarm" rate (58%).

In discussing metrics to use for analyzing the sensors, the DirecNet study group chose not to use the Clark error grid analysis or correlation analysis with R values for a number of reasons. In the Clark error grid analysis, there are zones, good and bad, and a reference glucose plotted against the meter or sensor glucose. The different zones are intended to distinguish clinically meaningful versus less important errors in glucose measurements. For example, when the grids were set up, if the blood glucose was between 50 and 250, treatment was not required, an easy decision. The correlate was that the grid divided glucose measurements into zones that distinguished increasing clinical significance of error, to ensure not mistaking hyperglycemia for hypoglycemia, and treating the patient with insulin. Sensor accuracy with the Clark error grid is usually measured by percentage of values within the A and B zones. The problem with this, Dr. Tamborlane explained, is that zones A and B are large enough that even inaccurate sensors will hit them the majority of times. Secondly, current insulin dosage adjustments are based on much smaller variations in glucose than when the grids were initially set up (e.g., there is now a difference between a 50 and a 250 and a correction dose is administered at 250). Third, one can get a misleading notion of sensor accuracy through chance agreement as in Dr. Tamborlane's example of randomly shuffling sensor and reference glucose pairings, which a statistician at the Jaeb Center did as a test, with 10,000 simulations. Even with these random pairings, the result was the average A and B zone accuracy was still 76 percent.

Dr. Tamborlane next discussed the problems with correlation analyses of r-values, beginning with the fact that r-values are so sensitive to the amount of variation in glucose levels that their reliance is limited. In correlation, variability is required. The DirecNet study group used the example of four hypothetical simulated sensors, each with identical accuracy, and 10,000 data pairs per sensor. Sensor value was equal to the "true" value or the reference value plus a normally distributed error with a standard deviation of 25 mg/dL. The actual mean of all the glucoses was 200. For the analyses, the range of true glucose values for each sensor was varied. The results were that if the reference values ranged between 175 and 225, the Pearson correlation R value was 0.5. With the same accuracy, if the range wais 50 to 350, the R value was 0.96.

Other limitations of point-to-point assessments of accuracy listed by Dr. Tamborlane included that methods developed for meters are single-point tests, which cannot capture the dynamic nature of continuous glucose sensors. Also, it is difficult to assess trends and there are issues about how to do accurate trend analyses to determine how well sensors characterize acute changes in glucose.

Dr. Tamborlane stressed that these are very important questions that, hopefully, smart mathematicians can address.

Dr. Tamborlane next discussed potential physiologic contributions to so-called error between reference values of plasma glucose obtained by a meter and sent to a central lab and sensor glucose values measuring interstitial glucose concentrations. It has been demonstrated that there is undoubtedly variability in the plasma and interstitial glucose gradients during the day. In a Yale study, euglycemic-hyperinsulinemic clamps were used at baseline and a sensor calibrated against baseline plasma glucose levels where nothing was infused. In this process, basically, the sensor is "told" what the plasma glucose level is, it measures a current coming off the interstitial glucose, and comes up with a ratio to account for the gradient between plasma and interstitial glucose. Next a euglycemic clamp was done with an infusion of high doses of insulin while maintaining plasma glucose unchanged, which lowered interstitial fluid glucose concentrations dramatically, measured by microdialysis, and the sensor followed the interstitial. This demonstrated that there are possible physiologic reasons why there is going to be some discrepancy between the reference blood glucose, or serum or plasma glucose, and the sensor glucose, which may actually be very important. Dr. Tamborlane said currently how to interpret these differences is unknown. In addition, in comparing a reference plasma glucose and an interstitial glucose, the interstitial is going to lag 10 to 20 minutes behind the plasma. If doing point-to-point assessments, one must find a way to account for that lag time.

For future studies of sensor accuracy, Dr. Tamborlane stressed the importance of studying children from diverse populations, especially type 1 diabetics post-transplant, those with hypoglycemic disorders, as well as type 2 diabetics and non-diabetics. When the Glucowatch and Medtronic MiniMed CGMS originally came out, there was a lot of interest in pediatrics to use these sensors to diagnose and manage hypoglycemia-related disorders. Unfortunately, the accuracy was insufficient, but there was still interest in seeing how well they performed with non-diabetic as well diabetic individuals. When these sensors, particularly the Medtronic MiniMed CGMS, were used with non-diabetic individuals, it was discovered that the algorithms developed to convert electrical current coming off the sensor into a plasma glucose level were based on type 1 patients with wide fluctuations, and those algorithms did not work in non-diabetic individuals where the fluctuations were much more modest, so algorithms had to be redone for non-diabetic studies.

Other areas for future studies recommended by Dr. Tamborlane would be frequent sampling in an inpatient study with Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory methods and also an outpatient study to investigate the accuracy of outpatient data using well-characterized meter methods as reference values. Beyond accuracy, Dr. Tamborlane called for testing the efficacy of using glucose sensors in clinical management to lower HbA1c levels, including whether this would lower or increase the risk of hypoglycemia. Dr. Tamborlane referred to a plan to do this in an outpatient study with one sensor as the therapy and the Medtronic MiniMed CGMS as an outcome measure, because one could mask the patients to the CGMS data. However, the CGMS is not a good outcome measure to determine the frequency of hypoglycemia in clinical trials due to insufficient accuracy in measuring glucose in the low glucose ranges. He added that the continued obstacle in looking at safety related to hypoglycemia that goes beyond clinically important events is that there is no simple test. There is no HbA1c for hypoglycemia, just as there was no HbA1c for hyperglycemia until 1980. Dr. Tamborlane noted that this inability to have a simple outcome measure for hypoglycemic exposure in patients obviously has important implications for islet cell transplantation as well as other therapies.

Another issue raised by Dr. Tamborlane was that not only do sensors need to be accurate and effective, they also need to be user friendly or patients will not use them. Also, how will patients and clinicians deal with the reams of data from 24x7 sensors? Who will provide the support to assess this data? Will the cost be reimbursed?

In responding to the question of whether current sensors are accurate enough to be used for outcome measures for diabetic therapy, Dr. Tamborlane said the answer depends on what is being measured.

- For mean glucose values, the average difference between the Medtronic MiniMed CGMS profile and the actual reference was 2 mg/dL, so the answer would be "Yes." However, the HbAlc values are still easier and better.

- For hyperglycemia, the answer would also be "Yes" since current sensors are reasonably accurate in the hyperglycemic range. With the CGMS, one can mask the patients to the sensor data, and a number of different metrics to do analyses can be used, such as meal-related excursions, AUC (area under the curve), or amount of time during the day above cut-offs.

- For glycemic variability, again "Yes," using day-by-day profiles, MAGE values, M-values, standard deviation scores, and so forth. The therapeutic question of particular importance to FDA is "Is postprandial hyperglycemia an independent risk factor beyond HbA1c for diabetic complications?" The answer is not known.

- For hypoglycemia, the answer is "No. They are not accurate enough."

According to Dr. Tamborlane, the real excitement about continuous monitoring is not only the present, but the promise for the future, especially the potential to combine sensors and pumps and develop a closed-loop artificial pancreas. Studies completed at the University of California at Los Angeles tested the Medtronic Guardian system, which is a wireless, continuous glucose monitoring system that sends real-time glucose readings from a sensor via wireless transmission to a computer that then drives a pump to respond to high and low glucose alarms. Ultimately, the sensor connected to the pump will have a computer in the unit itself.

In using such a closed loop system to regulate overnight insulin delivery to a patient with type 1 diabetes, the concern would be the sensor's reading higher than the true plasma glucose level, and therefore extra insulin would be infused when the plasma glucose was normal. Dr. Tamborlane said the solution is to set the target at 120 at night so that, even if the sensor is mis-reading plasma glucose by 50 percent, the pump will go back to basal insulin infusion when the glucose hits 80. If the error is 100 percent, there will be a back-to-basal insulin infusion when the glucose gets to 60. He stressed that such an overnight insulin delivery to control glucose in the type 1 patient would be a tremendous therapeutic advancement.

### Pumps: Hopes and Expectations

***Christopher D. Saudek, MD**, Hugh P. McCormick Family Professor of Medicine; Director, Johns Hopkins Diabetes Center; and Program Director, General Clinical Research Center, The Johns Hopkins University, Baltimore*

Dr. Saudek suggested that, broadly speaking, a cure for diabetes could be considered achieved if the person were able to forget that he or she has diabetes, and were able to live life normally, free of the complications of diabetes. Dr. Saudek said he thought it reasonable to consider approaches to "cure" as either biological approaches or mechanical. Today those present had heard about organ transplants and islet cell transplants as therapies and, although not mentioned, embryonic and adult stem cells also were possibilities. As a mechanical approach, "open loop" pumps have been around for a long time. There is an external open-loop pump and an implantable open-loop pump. With continuous sensing, the ultimate answer will be a closed loop external or implantable pump. All the approaches have to be assessed for efficacy and effectiveness within particular circumstances and timeframes.

The current conventional treatment of diabetes is multiple daily injections of a long-acting glargine and short-acting insulin preparations, which are adjusted according to meals and bedtime. Dr. Saudek said that subcutaneously delivered insulin response is affected by a whole series of variables such as the depth, the location, the surrounding tissue, heat of the tissue, and so forth., all of which contribute to making injectable insulin imperfect.

The theory behind external pumps and, in fact, implantable pumps is to establish a known basal rate that can be varied, but is relatively constant, as an infusion and to supplement that by specific boluses that are given by the patient choosing the dose and given precisely in the same spot as a relatively exact amount of insulin. The currently available external pumps have developed from the "Continuous Subcutaneous Insulin Infusion" (CSII) first accomplished with the Mill Hill Infuser. The new models of CSII are small, relatively convenient, but still injecting from a syringe housed in the external device, through a catheter into subcutaneous space. In the last year or so, Dr. Saudek said that telemetry from a glucose monitor has been one newly available approach, the pump then doing some of the arithmetic that patients ordinarily do when they calculate a bolus dose. This telemetry system, available as the Medtronic MiniMed Guardian device, can suggest an insulin dose based on the blood sugar. As mentioned by Dr. Tamborlane, Medtronic MiniMed has also developed— and had approved recently—the Guardian System, a telemetry system that takes a sensor reading and telemeters it to an alarm system. There are, then, continual improvements being made on the available external delivery and sensing systems.

External pumps are now a viable business and have been an available option since the 1980s for treatment of type 1 and unstable type 2 diabetes. Regarding indications for using a pump, Dr .Saudek commented that the distinction between type 1 and type 2 diabetes is, in some clinical respects, artificial since beta cell secretory capacity in type 2 deteriorates, and patients can end up so insulin-deficient as to be metabolically similar to type 1 diabetes. Insulin pumps may be indicated for unstable, labile diabetes, regardless of whether type 1 or type 2 diabetes is the underlying diagnosis. Well over 100,000 have been sold, produced now by at least four manufacturers (Medtronic MiniMed, Roche/Disetronic, Deltech, and Animus).

Dr. Saudek listed advantages and disadvantages of the external pumps. The external pump offers flexibility of meal and activity timing. The patient can choose a meal time, even skip a meal, and theoretically, with the right basal rate going, not have to worry about eating on time. Other advantages are freedom from multiple daily injections, more precise insulin delivery patterns, and true basal/bolus insulin delivery. Most of the evidence suggests improved glycemic control. A major limitation of external insulin delivery is that the patient must wear the device at all times, and some people do not like that, are truly phobic about it. Other disadvantages include occasional skin irritation, infection, need to change the site regularly, poor skin insert sites, and peripheral insulin delivery. Dr. Saudek stressed that therapies such as injectable insulin, external pumps, and even whole pancreas transplants deliver insulin peripherally, not hepatic portally.

When implantable insulin pumps (IIPs) were invented, the potential advantages included that there was none of this externality that many patients find very inconvenient. The maintenance or refill procedure is done only every 3 months, rather than every 3 days or so as required by external pumps. The implantable provides the more physiologic, hepatic portal insulin delivery, with the potential advantages of that for hepatic glucose handling, lipids, and so forth. Dr. Saudek referred to the latter as potential advantages because while the exact effects of portal delivery of insulin is an area of science he thinks is under-tapped, it does appear to have beneficial clinical effects.

Dr. Saudek noted that the history of the implantable pump is almost as long as that of islet cell transplantation. Dr. Buchwald started in the 1970s with the continuous rate pump. NASA in the late 1970s developed a little pump that landed on the Mars surface and became the basis of a so-called

Programmable Implantable Medication System (PIMS) developed at the Johns Hopkins Applied Physics Laboratory, which then became the basis of today's implantable pump. There have been a couple of other manufacturers of implanted pumps, but the present day Medtronic MiniMed pump is the one that has linearly descended from the PIMS.

Preclinical dog trials conducted by Dr. Saudek in the mid-1980s led to a proof-of-concept set of human implantations done in the late 1980s, with about 21 implanted pumps. These studies showed that a variable rate pump could work and could manage type 1 diabetes. The trials were greatly expanded in the 1990s and the incidence of pump implantations during the mid-1990s increased dramatically.

Between 1990-2000, Dr. Saudek said it was shown that IIP therapy was safe and effective on a large scale, that the refills were practical and safe, and that metabolic control and lipid metabolism could be improved with the IIP and hypoglycemia could be lessened. It also was found that the catheters and the insulin are vulnerable points that have to be taken very seriously in the evaluation process. Autoimmunity, pocket complications, refills, and flushes were manageable, but they also were issues, and battery programming needed to be improved. Dr. Saudek presented information on each of these positive points and areas of concern.

***IIPs are feasible on a large scale***. The number of IIP implants per year grew worldwide in the early 1990s. In the mid-1990s, there was a brief period of decline due to an insulin problem, which has been resolved, and now the field is back to more and more implants. Most active centers are in France because the French government chose to support and pay for pump implantations and the pumps; therefore, MiniMed spent a lot of its time working in France to develop the technology. In 2000, there were 340 active patients and in 2003, there were 365 in France and 59 in the United States for a total of 424.

***Refills are practical and safe***. The refill procedure involves a little scrubbing of the abdomen, some xylocaine in the skin, an introducer needle, and then a thinner needle going into the refill port of the pump, pulling the old insulin out, and then, with another syringe, putting new insulin in. Dr. Saudek explained that one of the key safety features of these Medtronic MiniMed pumps is that the pressure of the reservoir is negative relative to atmosphere, so that when the insulin is replaced, the "old" insulin must be pulled out but when the needle with new insulin is inserted, because of the negative pressure, the insulin is drawn into the pump, not pushed. This is a major safety feature when introducing about 6,000 units of insulin in the refill procedure; if the needle is not actually in the pump reservoir the insulin will not be injected; it will be drawn in only if the needle is properly in place. The refilling procedure is now routine, and takes about 10-15 minutes, done every 3 months.

***Metabolic control can be improved with IIP***. Dr. Saudek expressed some skepticism about the ability to prove superiority of any one method of insulin delivery over another, perhaps excepting fully closed loop delivery, noting that metabolic control can be improved with any variety of insulin delivery approaches. It can be improved by a diabetes team, an attentive endocrinologist, an external pump, an implanted pump, a transplant, and so on. It is not so much that measures of metabolic control are not important—they are. But in considering relative approaches to the management of diabetes, regulators should not consider improved blood glucose control the only parameter, since it is such a "manipulateable" feature, subject to all levels of bias in study design and investigator or patient involvement. This said, Dr. Saudek's Johns Hopkins data suggest that HbA1c is reduced and mean plasma glucose is reduced significantly (Udelsman R., H. Chen, K. Loman, H.A. Pitt, C.D. Saudek. 1997. Implanted programmable insulin pumps: 153 patient years of surgical experience. Surgery 122:1005-11).

A number of other studies of implanted insulin pumps also showed a decrease in mean blood glucose with IIPs and a drop in HbA1c and introduced the fact that the standard deviation of blood glucose came down very significantly in this study. The French consortium, Evaluation dans le Diabete du Traitement par

Implants Actifs (EVADIAC), has collected very good data on implanted pumps, comparing subcutaneous and multiple dose insulin with external pump insulin and with implanted pump insulin. Their experience also showed reduced HbA1c and a marked reduction in severe hypoglycemia.

***Hypoglycemia can be lessened***. A large, randomized, company-independent trial in the VA system was, in Dr. Saudek's opinion, the best and largest randomized trial done. The initial goal was to achieve equal glucose control with multiple dose therapy and implanted pump therapy. The goal was stated prospectively, to get equal measures and to look at other parameters. Dr. Saudek stressed to those who are involved in regulation of devices and evaluation, that if mean blood glucose is lowered without lowering the standard deviation, the result is what happened in the DCCT, there is an increase in hypoglycemia. If the mean glucose and the standard deviation are both lowered, then it can be proven medically or statistically that people are not driven into hypoglycemia. This can be seen in downloads of glucose meters and so on. He emphasized that in managing diabetes, it is very important to look at how variable the blood glucose is, whether you call it MAGE or whether you call it measure of standard deviation. Results in the VA trial demonstrated significantly decreased definite and suspected mild hypoglycemia. Results also showed decreased severe hypoglycemic reactions, although the number of events was not large enough to be significant.

***Lipid metabolism can be improved***. Dr. David Kelley measured free fatty acid data showing a more finely tuned regulation of fatty acid metabolism for patients on the implanted pumps than on subcutaneous insulin. Dr. Barbara Howard also published favorable changes in lipid status with IIP therapy.

***Portal absorption of peritoneal insulin delivery.*** Dr. Saudek presented older data from Schade to show that there is a portal peripheral gradient of tagged insulin, when you infuse insulin into the peritoneal space. This indicates, at least to some extent, that this insulin is absorbed into the hepatic portal system and there is a hepatic portal gradient established by peritoneally delivered insulin. Another study of Micossi et al. showed that the different routes of delivery—upper peritoneal, lower peritoneal, intramuscular and subcutaneous—all had different pharmacokinetic characteristics. Dr. Saudek commented that the millimeter differences between intramuscular and subcutaneous insulin can be a significant factor in the variability seen with glucose in response to conventional insulin injections. With IIP therapy, the free-floating intraperitoneal catheter tip may vary in its lower-versus-upper peritoneal cavity insulin delivery, although this has not been studied.

***Catheters and insulin are a vulnerable point.*** Dr. Saudek explained that in the first dog implantation, there was a vicious attack on the catheter by the peritoneum. The Johns Hopkins study group worked on catheter materials and came up with a much better result. Today catheter blockage is occurring at about 10 to 15 percent per year. A side-port catheter is used now that can be pushed through blocks.

The early dog trials showed that insulin precipitation in the catheter meant that the insulin was not going to go very far with a clot right in the middle of the catheter. A stabilizing factor worked; polyethylene polypropylene glycol stabilized the insulin very well. It was first used *in vitro* and then *in vivo* for upwards of 8 years without any indication of an insulin problem. Then, all of a sudden in the mid-1990s, the EVADIAC group noted that there was a systematic increase in the pump slow-down rates and problems such as catheter survivals that did not relate to how long the pump was going, but related to the stability of the insulin being used. Dr. Saudek explained that what happened was that, in the mid-1990s, Hoechst changed its insulin manufacturing technique, causing serious problems. The insulin was aggregating in the catheter and precipitating on the pump valves, causing some backflow and under-delivery of the insulin. Catheter flush and pump procedures were developed to handle the problem temporarily. Then Van Entwerp at MiniMed developed a technique for the rapid assessment of insulin stability, so it was not necessary to wait months to assess the stability of insulin preparations. In the

meantime, work was done to improve the insulin, so that the newer Aventis HOE 21 PH seems to be stable at this point. Today, the insulin being used is much better than in the mid-1990s.

***Autoimmunity, pocket complications, and refills/flushes are manageable***. Reported data indicate that the incidence of pump pocket infections varies from 0 to 28 percent per patient year, which is a very wide range. The mean was 7 percent. Dr. Saudek said the importance here is that it is difficult to clear if it happens. Usually, the device has to be explanted or changed entirely.

Autoimmunity has also been a long-time concern, sometimes bordering on obsession regarding anti-insulin antibodies in IIPs. One study showed an increase in insulin antibody titer. The amount of total antibody increase was divided up into so-called responders and non-responders, and obviously, the responders responded and had much higher insulin antibody titer. Dr. Saudek said he did not favor this type of study design. Over the years, the responders' levels tended to come back down, possibly indicating regression to the mean; however, in looking at the data, a wide range of insulin antibody levels were found. Then a syndrome appeared that seemed to suggest what were called "fasting lows." Even cutting the infusion rate way down overnight, people were still low in the morning. On looking at the antibody titer of people who were suspected of the syndrome clinically, it was, in fact, the people who were at the very high end of the antibody syndrome who had the fasting lows, indicating that antibodies can be induced in persons with a high affinity. There were no metabolic consequences overall, but Dr. Saudek said he thought that IIPs do occasionally cause high antibody titer and a prolonged insulin action that is rarely clinically significant.

Dr. Saudek remarked that when MiniMed became Medtronic MiniMed, the implants slowed down while the company went through its consolidation period, before resuming implantations in 1993. Now Johns Hopkins is implanting the new IIP model 2007, which Dr. Saudek showed in a slide. The new model has a much smaller and more efficient communicator, and the battery life is now up to 8 years.

In discussing the future of insulin pumps, Dr. Saudek stressed that he certainly hoped patients did not have to wait too long for a closed-loop system, but cautioned that it will take time to develop because it requires very high levels of safety and reliability of both the sensor and delivery systems. Nevertheless, it is too limited to think of the closed loop system only as entirely implanted. It could be developed as an external-to-external system, with an external pump and a subcutaneous sensor; or it could be a combination of an external sensor and an implanted pump; or implanted sensor with external pump; or both implanted. Dr. Saudek stated that developing the software to link the glucose monitoring with the insulin delivery will not be easy, but is do-able. Initial forays and initial trials into developing such a closed loop system are beginning, but Dr. Saudek sees the successful development of a safe and successful system as being some years away.

Dr. Saudek acknowledged the contributions of his collaborators at Johns Hopkins, the founding fathers and young contemporaries in the field, and, in particular, the research subjects who have been such an important part of the study projects to develop and test insulin pumps.

## Discussion

Ms. Bernhardt opened the discussion period by asking if Dr. Tamborlane and Dr. Saudek thought that before a closed-loop system could actually be used clinically that management of diabetes would have to change to be based on interstitial values rather than blood glucose values. Her question was based on taking into account the physiological differences between the interstitial glucose and the blood glucose, and the fact that current diabetic management is based on blood glucose measurements.

Dr. Tamborlane responded that he had raised the issue of interstitial versus blood glucose values because of small differences in accuracy. Another physiologic observation that may or may not have real clinical importance is that 10 minutes off may not make a big difference in how a patient is treated, but it may make a big difference in the error of the method used. For example, his group did a more complicated clamp study where there was a measurement at baseline and then at an acute euglycemic phase, a hypoglycemic phase, and an acute hyperglycemic phase, and there was a discrepancy. If all calculations were done at basal, aligning the gradient between the plasma and interstitial resulted in an abnormal sensor value. On the other hand, if measurements were calibrated throughout the four different phases of study, and the small changes in gradients were averaged out, the numbers came out quite well.
Dr. Tamborlane added that this is something to consider, but it should not have a major impact on use of the closed loop system.

Dr. Saudek commented that his group had done some studies of time-lag between subcutaneously measured glucose and blood glucose, finding also that there is a gap of between 9 and 12 minutes. They did not find a consistent difference dependent on whether the blood glucose is increasing or decreasing under insulin's effects, contrary to the findings of some others. In driving a closed-loop system, what may be more significant than the GLP issue is whether reproducing a "cephalic phase" of insulin secretion (i.e., the anticipation of an up-coming meal) is needed to normalize postprandial glucose. The patient would have to somehow signal the pump that he/she was going to eat, because the pump would have no way of knowing that (i.e., no way of reproducing a cephalic phase of insulin secretion). Dr. Saudek said that he doubts, however, that this is clinically significant, and emphasized that absolute normality of glycemic response is not necessary to control blood glucose between 90 and 110. Diabetic complications should be preventable with something a lot less fine-tuned than that.

Dr. Tamborlane added that the point is particularly relevant to the external-external model, where insulin is infused subcutaneously. Between the time the glucose is rising on the sensor and insulin is being augmented and delivered subcutaneously, there is that lag time. Two separate issues with the external-external are "How well can postprandial excursions be controlled and then what about overnight?" The overnight does not have to be extremely accurate. Gains on the algorithms can be adjusted fairly quickly to tell the pump how fast to infuse the insulin, so that even if there is not a perfect glycemic excursion—the peak values may go up into the low 200s—but 2 or 3 hours later they will be back to basal. Looking at postprandial hyperglycemia data in 56 youngsters with HbA1c of about 7.5, which is outstanding for children, 50 percent of postprandial glucoses were over 300.

Asked to expand on his concern about control of variability, particularly as it relates to postprandial glucose, and why this happens, given the tools available, Dr. Tamborlane answered that he supposed the normal pancreas does respond to cephalic phases. He related an anecdote about when he was a student in medical school. The students were required to fast for 24 hours, taken into a room and shown a big meal, and then had blood drawn to measure the increase in their insulin levels based on seeing the meal. That is probably the cephalic phase where the pancreas is primed to secrete insulin even before meal ingestion. Portal delivery may affect the post-meal excursion, but Dr. Tamborlane said he doubted this was clinically significant.

Dr. Fradkin asked Dr. Saudek for more detail about the differences in lipids that he saw when delivering the insulin portally versus peripherally and also, did he look at any inflammatory markers such as CRP or plasminogen activator inhibitor-1 (PAI-1). Dr. Saudek said they have not looked at inflammatory markers. In the VA study, Dr. Kelly did look at fatty acid metabolism and found free fatty acids to be more finely tuned with the implanted pump. Dr. Barbara Howard also has shown there is less atherogenic LDL with the implanted pump. A thorough fractionation of lipids has not been done, but he thought it would be interesting to see whether portal delivery makes any difference.

In reply to a question about whether anyone had put GLP-1 in a pump to treat type 2 diabetes, Dr. Saudek had not heard of this being done. He had received a call at one time about putting growth hormone in a pump for cattle, but to do this was too expensive. The regulatory process takes a long time, which is reasonable.

Asked if he thought the current sensor devices were accurate enough to be used to manage hypoglycemia unawareness, Dr. Tamborlane said he thought this would certainly be worth a study, especially in patients who suffer 5 or 10 treatable episodes a week that lead to serious defects in their regulatory responses.

Related to the issue of quality of life, as came up earlier in the islet transplant discussion, Dr. Tamborlane asked if the FDA ever put on the label, information about quality of life. For instance, given two hypothetical therapies, a standard therapy and a new therapy that had a non-inferior efficacy but superior quality of life, would this information be reported on the label? The reason for the question was the reimbursement problem that concerns most everyone. Fortunately, pumps in children are not a big problem, but there are artificial barriers put up by insurance companies unless one can show that the patient has failed every other therapy.

Dr. Orloff answered that a group at FDA is working intensely on quality of life issues and instruments to measure it. Within CDER, institutional procedures and policies are being developed to give guidance, essentially, to industry for developing products with quality of life measurements and thereby labeling them. If two products had non-inferior efficacy, or had equivalent efficacy, but there was a difference in some other aspect, then in that instance, to some extent, the quality of life would fall under the rubric of safety. The reason for this would be because, as an example, refractory problems with repeated hypoglycemia are ultimately a safety issue. Clearly, there is a quality of life aspect in terms of the psychological misery, but FDA is primarily interested in comparative safety of products that have essentially equivalent efficacy and would use that as a way of judging the overall merits of the therapy.

Dr. Tamborlane commented that this was very helpful, because there are aspects of quality of life that have to do with symptoms or adverse effects of the therapy, but there also are aspects that are simply quality of life that usually fall under the rubric of patient convenience, which is not looked on favorably by insurance companies. One could say that an aspect of what is being called convenience is that life is more livable with the disease when there is a better way of delivering a drug to a patient or monitoring control of the drug's action.

Dr. Orloff remarked that it was his impression that currently there is a change from the time when FDA would have said that greater convenience would have had to translate to greater efficacy by showing that, for example, people tended to adhere to the therapy better, compliance improved, and thus some meaningful clinical outcome was improved. Now FDA is saying it is comfortable with validated, tested quality of life instruments that are customized for the disease and the treatment being studied.

Dr. Tamborlane replied that diabetes care is really all about making life easier for persons with diabetes, but calling a therapy tool or measure a "convenience" is not usually understood in this light. He was very glad that FDA was interested in this. He also suggested that tools for measuring the quality of life of approaches and concepts were needed.

Dr. Orloff offered some observations he thought might be valuable in FDA and NIH interactions. Quality of life is an interesting rubric that has come to take on a lot of meanings, but what they were talking about here was quality of life specific to treatment. In other words, quality of life is a big area. Quality of a person's treatment for diabetes is specific. In clinical trials for drugs, quality of life is specific to that trial. In asking about the impact of one form of therapy versus another form of therapy, on how the patient perceives life as a person with or without, in this case, diabetes, Dr. Orloff said he would be cautious in

trying to get standardized instruments that would fit all possible scenarios, because that would be difficult to do, given the different kinds of profiles that drugs present in terms of how people react to them, how they incorporate them, and the symptoms that go along with them.

For Dr. Marrero, an important point was that quality of life is a moving target in relation to therapy. While initially a patient may not like something; later, with experience, the person may like it a lot. He cited his own experience with the insulin pump as an example. In the beginning, he did not like the pump at all. As mentioned by Dr. Saudek, it was an external device constantly attached to him. With time and experience, it became more agreeable. His assessment of his quality of life thus varied, based on his initial and then later experience. Questioned in the initial phase, his response would have been very negative. Six months later, his assessment would have been very different. This is an important issue, because a patient's decisions about treatment are based on the quality of treatment life—what it does to one's life and well-being in the long-term, what it does in terms of convenience of management of the disease, what the tradeoff is in terms of efficacy versus tolerability, and so forth. Dr. Marrero strongly recommended that this quality of life issue be amplified in the interface between FDA and NIH.

The first day's meeting was adjourned at 5:37 p.m.

## DAY 2: PERSPECTIVES ON THE FUTURE OF PREVENTION AND THERAPY

## Session VI: Prevention of Type 2 Diabetes

*Moderator: Sanford Garfield, PhD, Senior Advisor for Biometry and Behavioral Research Program, DDEM, NIDDK*

### The Metabolic Syndrome

***Robert H. Eckel, MD**, Professor of Medicine and Professor of Physiology and Biophysics, University of Colorado Health Sciences Center (UCHSC); Denver; Program Director, NIH-sponsored Adult General Clinical Research Center, UCHSC, Denver*

In the absence of Dr. Barbara Howard, who could not attend the meeting, Dr. Eckel's task for the day was to cover both her and his portions of the agenda. First, he discussed definitions, demographics, and disease risks related to the metabolic syndrome, particularly risks for cardiovascular disease and diabetes. Secondly, he spoke of the metabolic syndrome as a therapeutic target for the prevention of type 2 diabetes.

### Overview of Metabolic Syndrome

**Definitions**. Dr. Eckel presented the following major definitions of the metabolic syndrome as offered by (1) the National Cholesterol Education Program (NCEP) and the Adult Treatment Panel III (ATP IIII) guidelines; (2) the World Health Organization (WHO); and (3) for the American Association for Clinical Endocrinologists (AACE) and the Association of Clinical Endocrinologists, the insulin resistance (IR) syndrome:

**NCEP/ATP**

3 or more
Abdominal circumference
men > 40 in women >35 in
Triglycerides > 150 mg/dl
HDL cholesterol
men <40 mg/dl women < 50 mg/dl
Blood pressure >130 diastolic or > 85 systolic
Glycemia as fasting plasma glucose > 110 mg/dl

**WHO**

Hyperinsulinemia or fasting plasma glucose $\geq$ 110mg/dl
AND at least 2 of the following
Abdominal circumference:
Def. 1: W/H > 0.90 or BMI > 30 kg/m$^2$
Def. 2: Waist $\geq$ 94 cm (37 in)
Dyslipidemia
Triglycerides $\geq$ 150 mg/dl OR
HDL cholesterol < 35 mg/dl
Blood pressure. 160/90 OR on medication
Microalbuminuria, AER > 20 μg/min

**AACE/ACE**

Cluster of abnormalities
Blood pressure and lipid criteria of NCEP/ATP III
Abnormal glucose tolerance (i.e., if type 2 diabetes not present)
Fasting glucose of 110-125 mg/dl OR
2-hour post-glucose (75g) > 140 mg/dl
BMI and waist circumference increased risk but
Not a criterion
Needs to be adjusted for ethnicity
Other factors increasing risk
E.g., family history of type 2 diabetes

Dr. Eckel noted that the criteria for glycemia has been reduced to > 100 mg/dl, which will change the prevalence of the metabolic syndrome but only by a couple of percents, not 5 to 10 percent. He added that the NCEP/ATP definition is more CVD-driven whereas the WHO definition is more diabetes-driven. This difference is important when speaking of preventing diabetes. Hyperinsulinemia in the WHO definition is

defined as the upper quartile of the non-diabetic population. AACE urged glucose tolerance testing if diabetes itself were not already present. AACE allowed for ethnic differences in waist circumference. For example, African Americans tend to have a larger waist but the type of fat distribution varies (decreased visceral, increased subcutaneous).

In Dr. Eckel's opinion, the metabolic syndrome is more than these criteria. If one thinks of the metabolic syndrome as the insulin resistance syndrome, which is open to controversy, the following components that affect insulin resistance would apply:

- Cigarette smoking.
- Presence of small dense LDL and HDL particles.
- Increases in the following:
  - apoB, which reflects atherogenic dyslipidemia
  - uric acid.
  - fibrinogen, PAI-1, viscosity.
  - inflammatory markers as reflected by increased hsCRP, IL-6.
  - asymmetric dimethyllarginine (decreased nitric acid).
  - homocysteine.
- Decreases in adiponectin, reflecting insulin sensitivity.

**Demographics.** Dr. Eckel stated that the current emphasis on the metabolic syndrome is the result of the prevalence of obesity. According to the 2001 Behavioral Risk Factor Surveillance System (BRFSS), every State now has a greater than 15 percent prevalence of obesity, in spite of the inaccuracies of self-reporting body weight and BMI in a telephone survey. Data from National Health and Nutrition Examination Surveys (NHANESs) show that since 1999, there has been a 2½ to 3-fold increase in the prevalence of obesity as defined by a BMI > 30 $kg/m^2$. In fact, data for obesity in the United States projected by Dr. Peter Kopelman in 2000 (Kopelman, P.G. Nature Insight 404:637, 2000) were superseded by the later NHANES data. However, if Dr. Kopelman's slopes continue as projected, 42 percent of Americans will have a BMI > 30 $kg/m^2$ by 2025. NHANES data also show a dramatic increase in obesity in children and adolescents over the last four decades. Dr. Eckel noted this ensures we will have the metabolic syndrome with us for some time.

**Etiology of Obesity**. Dr. Eckel explained that the issue of obesity relates to the balances between energy intake and energy expenditure. The gene pool has not changed, although today there is awareness of monogenic syndromes and susceptibility genes. The environment is where most of the problem has arisen through increased food availability, especially energy-dense foods and larger portion sizes, and reductions in physical activity.

Dr. Eckel described an experiment asking what the effects of being sedentary for 24 hours had on substrate utilization and the energy intake/expenditure balance in people randomized to either a high-carbohydrate (60 percent of calories) or a high-fat diet (40 percent of calories), followed by a wash-out period, and then put on the opposite diet. The important part of this longitudinal study, supported by NIDDK, was the impact of this type of energy balance assessment on changes in fat mass and body weight over 4 years. Subjects included normal weight, overweight, and obese men and women and remained on the diets for several weeks and then had energy balance measured in the hold room calorimeter chamber where they lived and were inactive for 24 hours. These people were weight-maintaining before they entered the chamber. The calorimeter assessed oxygen consumption and $CO_2$ production, and because urinary nitrogen was known and protein balance can be determined, fat balance and carbohydrate balance could be calculated. On the high-carbohydrate and high-fat diets, subjects respectively had 800 and approximately 925 calories of positive energy balance. Those on the high-fat

diet had 400 calories of fat balance, whereas those on the high-carbohydrate diet were nearly zero for fat balance. Dr. Eckel said that this last data indicates that those on the high-carbohydrate diet, although overfed, did not convert the calories to fat within the 24 hours of inactivity. The CHO balance was understandably higher on the high-carbohydrate diet than on the high-fat diet, but protein balance was the same regardless of diet.

Over the 4 years of the study, fat mass measured by kg/year changed by 0.31 ± 0.15, a p value of 0.0477, and weight measured by kg/year changed by 0.29 ± 0.15, a p value of 0.0592. Dr. Eckel pointed out that this represents the importance of power analyses in predicting outcomes because they had powered a p value of 0.05 for weight gain over the 4 years. Dr. Eckel stated that the overall results of this study, after 4 years of subsequent analysis, showed that it was *how* people responded to carbohydrates that determined their weight and fat mass. In a 24-hour inactive state, if a person is in positive carbohydrate balance, then the person is protected from weight gain or fat mass gain.

Dr. Eckel said the overall prevalence of the metabolic syndrome is about 23-24 percent; however, NHANES reports differences in populations. African-American men probably have a lower prevalence because their triglycerides are lower and their HDL is higher. Hispanic women have a greater prevalence, probably due to a combination of waist circumference and fasting glucose. Of the components that lead to the prevalence of the metabolic syndrome, waist circumference is more prominent in women than in men; triglycerides are higher in white men, which probably drives the higher prevalence of the syndrome in white men. Men and women are about equal in HDL cholesterol (< 40 men, <50 women). Hypertension and fasting glycemia are higher in men than in women.

**Causes of Metabolic Syndrome**. Dr. Eckel pointed to obesity as possibly the foundation of the metabolic syndrome, but in discussing causes, there remains the issue of whether the metabolic syndrome represents an insulin-resistant state. He noted that Dr. Gerald Reaven had established the principles of the metabolic syndrome a decade before its definition by listing a number of covariants that are highly associated with each other and reflect inadequacies in insulin sensitivity. Free fatty acids (FFAs) are central to the development of the metabolic syndrome or to insulin resistance. One of the most sensitive impacts of insulin action is anti-lipolysis. Once there is an increase of FFAs, then lipolysis tends to be enhanced, which results in a vicious cycle of increased production of FFA and insulin resistance. The FFA burden then drives the prothrombotic state and the production of atherogenic lipoproteins, which are modified in density. The increase in FFA flux also drives the defect in insulin–mediated glucose disposal and the increased production of glucose by the liver and kidney, and in susceptible individuals, this leads to impaired glucose tolerance and hyperinsulemia. Dr. Eckel stated that the link between hypertension and insulin resistance is much more questionable and has generated considerable controversy. He cited an article by Dr. Gerald Reaven, Dr. Earl Ford, and others in the May 2004 issue of *Diabetes* (Diabetes. 2004 May;53(5):1195-1200),] that reported the results of steady state plasma glucose (SSPG) tests in more than 400 persons that identified the metabolic syndrome in about 20 percent. The study investigators did not find any relationship between SSPG and blood pressure. Dr. Eckel thinks that, therefore, the metabolic syndrome in part reflects insulin resistance, however if hypertension is to be included other factors must be involved.

**Metabolic Syndrome and Risk of Atherosclerotic CVD**. Dr. Eckel presented data from the Kuopio study that investigated the impact of the metabolic syndrome, using WHO criteria, for mortality, in 55-year-old men, from coronary heart disease, CVD, including stroke, and all other causes of mortality. The study showed that when the data was adjusted for cholesterol, smoking, and other known cardiovascular risk factors, there was an impressive relative risk of the metabolic syndrome impacting all three causes of mortality in the study subjects. Dr. Earl Ford in NHANES III presented a comparison of ATP III and WHO criteria and the prevalence of self-reported myocardial infarction and stroke in persons over the age

of 20 who had or did not have the metabolic syndrome. Dr. Eckel pointed out that Dr. Ford's data indicate that WHO and ATP III criteria are basically equivalent in predicting CVD.

Dr. Charles Alexander and Dr. Steven Haffner analyzed the impact on CVD of the metabolic syndrome, with or without diabetes, from NHANES III data for persons 50-years-old and older. They reported (Diabetes 2003;52:1213) that without the metabolic syndrome or diabetes, the prevalence of CVD in this group is 8.7 percent. When persons have diabetes without the metabolic syndrome, the prevalence of CVD is approximately the same (7.5%) as for those without either diabetes or the metabolic syndrome. Dr. Eckel stressed that having diabetes certainly implies the presence of the metabolic syndrome; however, if someone has diabetes and is not overweight and does not have high blood pressure or lipidemia, then the risk of CVD is nearly the same as that of someone without diabetes. When the metabolic syndrome is present without diabetes, the prevalence of CVD doubles (13.9%); however, when the person has both the metabolic syndrome and diabetes, the prevalence jumps to 19.2 percent, almost 3 times the risk for diabetes alone.

**Metabolic Syndrome and Risk of Diabetes**. Dr. Eckel emphasized that the literature is weak in this area and, although it shows that the metabolic syndrome is a predictor of new-onset diabetes, better evidence is needed regarding *how* the metabolic syndrome predicts diabetes. Based on literature published in the last 4 to 5 years, the risk of diabetes in someone with the metabolic syndrome is about 2- to 4-fold. To estimate the risk, one would have to apply the metabolic syndrome criteria to the study data on the cohorts from various clinical trials.

## Metabolic Syndrome as a Potential Target for Prevention of Type 2 Diabetes

In considering the particular components of the metabolic syndrome that would make the best therapeutic targets for prevention of type 2 diabetes, Dr. Eckel selected waist circumference, blood pressure, and glycemia. Physical activity for weight reduction seems to reduce waist circumference more than diet alone, although this has not been thoroughly substantiated. Based on this relationship to physical activity, he recommended keeping waist circumference on the target list. The rationale for blood pressure lowering relates to the increasing number of clinical trials in which ACE inhibitors or ARBs have proven to reduce the incidence of type 2 diabetes. Ways to reduce triglycerides relate to most of the elements of the metabolic syndrome, but aside from weight reduction, he set triglycerides aside as a target. Nicotinic acid is the only reasonable pharmacological target to raise HDL cholesterol, and this is not a promising intervention to reduce the incidence of diabetes in individuals with impaired glucose tolerance; in fact, it does the opposite. Dr. Eckel felt that there basically was not enough evidence for intervening with dyslipidemia as a target. The effects of statins and fibrates on type 2 diabetes incidence are modest at best and mostly absent. In fact, niacin can increase glycemia. Blood pressure and insulin resistance as reflected in abdominal obesity and impaired glucose tolerance were better targets.

**Treatment of Hypertension**. Dr. Eckel listed four classes of drugs commonly used to treat hypertension: diuretics, beta blockers, ACE inhibitors, and ARBs. Diuretics and beta blockers tend to increase the incidence of diabetes. There are only modest effects on insulin secretion. On the other hand, clinical trials have shown that ACE inhibitors (captopril, lisinopril, ramipril) and ARBs (losartan, candesartan) *do* reduce the incidence of diabetes, as *secondary* outcomes of using these blood pressure-lowering drugs. The overall effects in lowering type 2 diabetes incidence have been relatively modest but significant, with the exception of the SCOPE trial with candesartan (relative risk = 0.81, $p<0.09$). Dr. Eckel felt the effects were insufficient in impact to recommend these drugs as a primary strategy, but there was a rationale for using an ACE inhibitor or ARB as adjunctive therapy in the setting of the metabolic syndrome. Dr. Eckel said to keep in mind that the trials supporting this rationale were not conducted on the basis of the metabolic syndrome and prevention of type 2 diabetes.

**Treatment of Insulin Resistance**. A more fruitful area of intervention within the metabolic syndrome is "insulin resistance," particularly obesity/abdominal obesity and impaired glycemia. Dr. Eckel recommended converting abdominal android fat distribution to lower body gynoid fat distribution. He remains unconvinced that obesity in women that puts most of their fat below their waist leads to CVD and diabetes, but feels more evidence is needed to show whether or not this is true.

Weight reduction is the target to reduce waist circumference. Dr. Eckel briefly reviewed some clinical trials on weight reduction and its effects on diabetes. In the Finnish Diabetes Prevention study, 522 men and women, ages 55±7 years, with BMI of 31.2±4.6 kg/$m^2$ were randomized as a control group and a lifestyle intervention (diet and exercise) group and had a mean follow-up of 3.2 years with an oral glucose test to indicate diabetes. The lifestyle intervention diet included restricted fat, especially saturated fat, and increased fiber. The lifestyle intervention group had a 55-60 percent reduction in new-onset type 2 diabetes. The DPP (27 centers in the United States, 3, 234 men and women, ages 25-85, with an average BMI of 34 kg/$m^2$) was a 3.2-year ramdomized trial with three arms—placebo, lifestyle modification (goal 7 percent weight loss), and metformin (850 mg bid). A fourth arm was discontinued earlier due to concern over potential adverse events from the use of troglitazone. Lifestyle had the greatest effect on preventing type 2 diabetes, followed by metformin. Both of these strategies favorably modified insulin sensitivity and thus are strategies to use to target insulin resistance in the metabolic syndrome.

Dr. Eckel asked "How long will the weight loss last?" Even in the highly constructed and controlled DPP, weight was regained. He also asked, "How long will the prevention of type 2 diabetes last?" Both are crucial questions. He added that before considering pharmacological interventions to lose weight, it is important to remember that lifestyle changes do work. Dr. Eckel said it was also interesting that the diets used in the Finnish study and DPP were both diets that restricted fats, not carbohydrates.

Moving on to weight-loss drugs, Dr. Eckel noted that there are basically two choices in anorectics. Sibutramine is FDA-approved for weight loss; phentermine is not listed but is commonly prescribed because it is much less expensive. Dr. Eckel thought that in spite of the phen-phen issue, phentermine remains a major anorectic being used by physicians. The other choice as a weight-loss drug is orlistat, a lipase inhibitor. There are no clinical trials using these in the prevention of diabetes, but there is the XENDOS study in which orlistat plus lifestyle change resulted in more weight reduction than lifestyle change plus placebo. Again, there was the regaining of weight that always occurs. Orlistat plus lifestyle reduced the incidence of diabetes in subjects with IGT by 45 percent and in all patients by 37.3 percent compared to the placebo plus lifestyle.

Dr. Eckel listed other hypoglycemic therapies that might favorably modify insulin sensitivity: sulfonylureas, meglitinides, α-glucosidase inhibitors, metformin, and thiazolidinediones. There are no such trials with sulfonylureas or meglitinides. As mentioned, metformin was used fairly successfully in DPP. In the STOP-NIDDM (Studies to Treat or Prevent Type 2 Diabetes) trial, there was a dramatic impact of acarbose (an α-glucosidase inhibitor) on patients with IGT in reducing all CVD events, and especially myocardial infarction (from 12 events in the placebo group to 1 event in the acarbose group). Dr. Eckel added that there is some concern about the validity of the results of STOPP-NIDDM involving selection bias, inadequate blinding, bias in data analysis, and potential sponsoring bias.

Dr. Eckel cited Dr. Ronald Evans' review of work on PPAR compounds in *Nature Medicine* (Nat Med 2004 Apr;10(4):355-61) Thiazolidinediones do not cause weight reduction, but they change where body fat is deposited. For example, in a study by Dr. Miyazaki and colleagues (Miyazaki Y et al. JCEM 2992;87:2787) after 16 weeks of pioglitazone, there was dramatic redistribution of abdominal fat from the visceral depot to the subcutaneous depot. Data from that study also showed that changes in visceral fat contribute to improvements in insulin sensitivity, since the visceral fat area predicts the metabolic clearance rate of insulin and thus reflects insulin sensitivity. Likewise, Dr. Tom Buchanan's study of

troglitazone (Buchanan, TA et al. Diabetes 2002;51:2798) showed a long-lasting benefit in the prevention of type 2 diabetes in high-risk Hispanic women with gestational diabetes, even subsequent to discontinuation of the drug in the study. Dr. Eckel concluded that the PPAR class of compounds looks promising in the prevention of type 2 diabetes in patients with the metabolic syndrome.

The PPARs that are available, at least those targeted for reduction of insulin sensitivity, are largely the PPARγ class. Many pharmaceutical companies have bi-agonist drugs that combine PPARα/γ properties. The α properties reflect mostly changes in fatty acid metabolism and the γ relate to both carbohydrate and lipid metabolism. Dr. Eckel added that recently the PPARδ compounds or, theoretically, ligands that impact the PPARδ system, seem promising, as described by Dr. Ronald Evans' group (Yong-Xu et al., Cell 2003; 113:159-170). This study showed that by modification of the PPARδ system, fat metabolism could be altered in a way that enhanced fatty acid oxidation and prevented obesity and, ultimately downstream, in Dr. Eckel's opinion, type 2 diabetes and the metabolic syndrome that precedes it. This is an area in human biology, physiology, and pharmacology that there is not much information on yet, but a promising area of this PPAR class of drugs.

Dr. Eckel also listed other non-FDA-approved drugs that affect the metabolic syndrome by modifying weight first and then incidentally type 2 diabetes. These include anti-epileptics (topiramate, zonisamide), MCH-1 inhibitors, cannabinoid antagonists, GLP-1 and DPP-IV inhibitors, and other new players in the field. At this time, there are limited data on these drugs in terms of their application to patients with the metabolic syndrome and much less data on their application to the prevention of type 2 diabetes. Zonisamide has shown an impressive weight reduction in obese persons compared to placebo (Gadde, KM et al. JAMA 2003;289:1823) as has topiramate in a randomized trial (Bray, GA et al. Obes Res 2003;11:727). Dr. Eckel recommended that these compounds and their side effects be intensely studied.

In summary, Dr. Eckel said "The metabolic syndrome is upon us" and is going to increase its prevalence, and likely predict a much higher incidence of type 2 diabetes, as well as coronary heart disease and stroke. Lifestyle interventions should be the initial and sustained therapeutic approach. Some drug therapies already seem to work such as metformin, TZDs, ACE inhibitors, and ARBs. A variety of other therapeutic options appear to be forthcoming. As illustration of what can be done, Dr. Eckel showed a "before slide" of a patient who had all the components of metabolic syndrome plus type 2 diabetes and an "after slide" of this attractive patient after successful weight reduction.

**Discussion.** Dr. Garfield asked Dr. Eckel if he would be more optimistic regarding intervening to reduce triglycerides if future therapies such as use of adiponectin to promote fatty acid oxidation existed today. Dr. Eckel responded that he understood that adiponectin is being considered as part of the pharmacological "toolbox" to treat type 2 diabetes and IGT. The idea of modifying triglycerides as a target reflects opportunities to modify triglyceride production rates and/or lowering triglycerides by increasing removal of triglycerides from the system. The evidence is that increasing lipoprotein lipase (modifying clearance) is probably not the way to reduce triglycerides, but modifying production rates reflects that fatty acids are being partitioned into different pools. So if triglycerides are not going into triglyceride biosynthesis, because of this effect on AMP kinase they are going to oxidative metabolism, then here the PPARδs become particularly attractive. There is not much evidence that metformin, also an activator of AMP kinase, does much to serum triglycerides. Dr. Eckel said he thus thinks that targeting triglycerides will be an indirect method of altering fatty acids. He also suspected that insulin sensitivity would improve with triglycerides just being an innocent passenger.

The comment was made that metformin has not been studied enough yet to know how far up the dose response curve would go in terms of activating AMP kinase, and also what the effect of these and other tissues would be. Metformin per se may not do what is needed; we do not know for sure what the possibilities are of that mechanism, depending on how much and where it can be activated.

**The Diabetes Prevention Program and New Perspectives on the Metabolic Syndrome**
***Harry Shamoon, MD,*** *Professor of Medicine and Associate Dean for Clinical Research, Albert Einstein College of Medicine, Bronx, New York*

Dr. Shamoon stated that he would present a brief overview of the DPP data and some new analyses from the study that might shed light on the metabolic syndrome and the issue of should it be treated, and if so, how should it be treated. Dr. Shamoon acknowledged the contributions of the many DPP investigators, many of whom are now involved in the DPPOS. He noted that DPP was sponsored by several NIH institutes and offices in addition to NIDDK (i.e., National Center on Minority Health and Health Disparities; National Center for Research Resources, GCRC Program; National Institute of Child Health and Human Development, National Institute on Aging, and Office of Research on Women's Health), other Federal agencies (i.e., Indian Health Service, Centers for Disease Control and Prevention), the American Diabetes Association, and private industry (i.e., Bristol-Myers Squibb, Warner-Lambert, LifeScan, Inc, Merck &Co., Health O'Meter, Nike Sports Marketing, Hoechst Marion Roussel, Inc., Slim Fast Foods Co., Merck-Medico Managed Care, Inc., and Quaker Oats Co.).

**Primary Goal and Results**. Dr. Shamoon said the primary goal of DPP was to prevent or delay the development of type 2 diabetes in persons with impaired glucose tolerance. The study design included a randomized three-group clinical trial at 27 sites with a common protocol across all sites, staff training, and a data quality control program. The criteria to define a high-risk IGT population was a 2-hour post OGTT plasma glucose of 140-199 mg/dl and a fasting glucose in the non-American Indian population of 95-125 mg/dl, thus persons from the upper end of the glucose range. Other eligibility criteria were being 25 years of age or older and having a BMI $\geq$ 24 kg/m$^2$. Persons from all ethnic groups were recruited with a goal of up to 50 percent from high-risk ethnic populations. The study interventions, following randomization and the giving of standard lifestyle recommendations to all the subjects, were intensive lifestyle, metformin, and placebo (NEJM 346:393-403, 2002).

The DPP was very successful in recruiting ethnic minorities plagued with the problems of diabetes. The DPP population was 20 percent African American, 16 percent Hispanic, 5 percent American Indian, 4 percent Asian or Pacific Islander, and 55 percent Caucasian. There was a two-thirds (women) to one-third (men) gender distribution. Besides the 45-59 age group (49%), there were young people ages 25-44 (31%) and older people over 60 years of age (20%).

Dr. Shamoon said the primary outcome of the DPP was glucose: (1) annual fasting plasma glucose (FPG) and a 75 gm OGTT with the following criteria for a diagnosis of diabetes: FPG $\geq$ 126 mg/dl or 2-hour $\geq$ 200 mg/dl with either of these confirmed by a repeat test and (2) a semi-annual FPG of $\geq$ 126 mg/dl, confirmed.

The lifestyle intervention was a multi-component effort involving behavioral and medical components to achieve a minimum weight loss of $\geq$ 7 percent of body weight and maintenance of weight loss with a dietary fat goal of < 25 percent of calories from fat and a calorie intake goal of 1200-1800 kcal/day. In addition, sustained physical activity of a minimum of 150 minutes per week was encouraged and documented. Medication interventions were 850 mg per day of metformin escalating after 4 weeks to 850 mg twice a day compared to placebo.

Dr. Shamoon confirmed that the DPP subjects were an obese group. The average BMI was 34.0 ± 6.7 kg/m$^2$. Weight loss was a predominant effect of both lifestyle and metformin and was dramatically different initially in the lifestyle group, although some weight was regained after almost 4 years. At study end, there still was about a 4 kilo reduction in weight from baseline in the lifestyle group. Leisure physical activity was by self-report; it increased and was maintained by the lifestyle group in comparison

to the placebo and metformin groups. In terms of adherence to medication regimen, Dr. Shamoon reported that approximately 80 percent of participants took at least 80 percent of their prescribed placebo or metformin dose over the course of the study, with just slightly better adherence in the placebo group.

As has been reported often, Dr. Shamoon repeated that for the DPP participants as a group, the risk of diabetes was reduced 31 percent by metformin and 58 percent by the lifestyle intervention versus placebo. Secondary analyses show that lifestyle, followed by metformin, was similar for both men and women in lowering the risk for diabetes. By age, there were some differences. In the 25-44 age group, metformin and lifestyle were almost equally effective in reducing the incidence of diabetes. In the 45-59 years of age, metformin was intermediate. In the 60 years and older group, lifestyle was the most effective, with metformin and placebo being about equally effective.

Dr. Shamoon continued with the analyses by showing that in the least obese group (BMI 24-29), metformin was much less effective than lifestyle. In the most obese group (BMI $\geq$ 35), metformin was basically equivalent to lifestyle in reducing the incidence of diabetes. Dr. Shamoon said fasting glucose obviously plays a big role in the conversion to diabetes. His data showed that in subjects with the lowest range of fasting plasma glucose concentrations (95-109), the diabetes incidence rates were much lower than in the group with the higher glucose concentrations (110-125). Again, there was a stepwise effect, with metformin having an intermediate effect on the prevention of diabetes compared to lifestyle. Across all ethnic groups, the effects of lifestyle in reducing risk of diabetes was the most effective intervention, with metformin again being the second most effective.

Regarding adverse events, based on 100 person years, Dr. Shamoon reported that metformin was well tolerated. There were no differences in major adverse events. Gastrointestinal symptoms, not unexpectedly, were greater in the metformin group compared to the placebo or lifestyle intervention, and musculoskeletal symptoms were slightly higher in the intensive lifestyle intervention.

Following the reduction of incidence of diabetes, there was still a trend in the DPP cohort toward a rising fasting plasma glucose even with the two successful therapies. Dr. Shamoon said whether there is an inexorable change to developing diabetes, a possible question is "Is the effect of the drug, for example, transient?' The DPP tried to address this question with a 1-week withdrawal of metformin, followed by a re-challenge with an OGTT (Diabetes Care 26:977-980, 2003). The test showed that the rate of prevalent diabetes declined a little, but the summary conclusion of the analysis was that approximately one-quarter of the effect of metformin to prevent development of new diabetes can be attributed to an acute pharmacologic effect; after washout, metformin *still* reduced the incidence of diabetes by 25 percent compared to the placebo. Dr. Shamoon interpreted this data to indicate that lowering plasma glucose with metformin has its own effect beyond prevention of diabetes by mechanisms unknown.

Dr. Shamoon explained that the DPP was originally designed as a four-group study. Between 1996 and 1998, subjects were randomized to troglitazone (585 of the total of 2,345 subjects), as well as the other three arms. Due to emerging data on the hepatoxicity of troglitazone, and the death of one subject, the drug was discontinued in 1998 and ultimately withdrawn from the U.S. market 2 years later. Analysis of the data on diabetes incidence rates per 100 person years for the four groups up to discontinuance of troglitazone was not different than the final results. The lowest projected incidence was with the troglitazone; however, the safety of the drug precludes its use. Although troglitazone was highly effective, there was not a significant difference between it and intensive lifestyle as an intervention. Unlike Dr. Buchanan's Tripod Study, Dr. Shamoon said that DPP did not find a persistent effect of troglitazone on prevention of diabetes. Data on incidence of diabetes after troglitazone was discontinued in 1998 showed that, while there was no "catch-up" increase in incidence, the cumulative incidence basically followed the same trend as placebo, suggesting there was no persistent effect of that brief 9-month exposure to troglitazone.

***Conclusions and implications*** drawn by Dr. Shamoon regarding the two drugs used in DPP to prevent diabetes included the following:

- Metformin was safe and effective, particularly in younger and more obese persons; its effect did not wash out after 1 week, suggesting it did not simply "mask" hyperglycemia.

- Troglitazone markedly reduced diabetes incidence during its brief use, but the action did not persist after it was discontinued.

- The effect of troglitazone was due in part to improved insulin sensitivity with maintenance of insulin secretion. This same mechanistic effect was true for intensive lifestyle on the prevention of diabetes.

**DPP Secondary Goals and Results**. The secondary goals of the DPP as listed by Dr. Shamoon were to reduce CVD events, reduce CVD risk factors, and reduce atherosclerosis. The DPPOS will look at the data for these outcomes; Dr. Shamoon therefore said he would not directly address this data in the current meeting in discussing the metabolic syndrome. He posed the interesting question of whether the metabolic syndrome is related to CVD directly, not just to CVD as a complication of the diabetes developed following IGT.

**Metabolic Syndrome and DPP**. Many of the subjects in DPP had at baseline a family history of type 2 diabetes, a history of high cholesterol and hypertension, in addition to obesity and IGT, and, in women, a history of gestational diabetes. Dr. Shamoon pointed out that thus some members of this cohort were likely to have metabolic syndrome. Objectives of the new analysis were to determine the prevalence of the metabolic syndrome in this multiethnic DPP population with IGT and to evaluate the effect of the two interventions—intensive lifestyle changes and metformin—on the incidence of the metabolic syndrome in those subjects without the syndrome at baseline. Data were also analyzed on those who did have the syndrome at baseline. The definition selected to make the diagnosis of metabolic syndrome was that of the NCEP ATP III, 2001.

Only fifty-three percent (1,711 of the 3,234) persons had the metabolic syndrome at time of randomization. Prevalence did not vary by gender or age group, but did vary by ethnicity, being highest in Caucasians (57%) and lowest in Asians (41%). Dr. Shamoon explained that one of the reasons for this difference might be that the NCEP criteria were developed for Caucasians, or there may be other reasons for this. Prevalence of the components of the metabolic syndrome did vary by age group. The most frequent combination of components was high waist circumference + elevated triglycerides + low HDL. The least frequent combination of components was elevated fasting plasma glucose + elevated blood pressure + low HDL. In those with the metabolic syndrome, a waist circumference > 102 cm (40 in) in men or 88 cm (35 in) in women was true for all age groups. Low HDL cholesterol was clearly less important in the older age group and more important in the younger persons. Conversely, hypertension was more prevalent in the older age group and less so in the younger group. Triglycerides were about the same across all the age groups.

Looking at those *without* the metabolic syndrome at baseline, the DPP study group asked "What did the interventions achieve?" There were 1,523 subjects without the metabolic syndrome (490 in the placebo group, 503 in the metformin group, and 530 in the lifestyle group). In the 3+ years of the study, there was a risk reduction of about 17 percent in the metformin group versus the placebo group, 41 percent in the lifestyle group versus placebo, and 29 percent in the lifestyle intervention group versus the metformin group. The lifestyle reduction rate was therefore similar to that for prevention of diabetes, but not quite as potent.

Data presented by Dr. Shamoon for the 3-year incidence of the components of the metabolic syndrome for those *without* the syndrome at baseline showed that those in the placebo group had a 33-percent incidence of reaching the criteria for waist circumference, compared to a significantly reduced 15 percent and 8 percent, respectively, in the metformin and intensive lifestyle groups. Low HDL cholesterol was not affected by these interventions compared to placebo, and triglycerides were reduced in the intensive lifestyle group. As expected, occurrence of high fasting plasma glucose was prevented by intensive lifestyle and metformin. Hypertension was reduced only in the intensive lifestyle group.

In the subjects *with* the metabolic syndrome at baseline, the 3-year incidence data for the various components was very high in the placebo group as shown in Dr. Shamoon's slide of this data. Waist circumference was modestly but significantly reduced by both the metformin and lifestyle intervention. HDL cholesterol, interestingly, was about equally increased in both the metformin and lifestyle groups, and lifestyle also had an effect on triglycerides and blood pressure. Lifestyle also reduced fasting plasma glucose about 5 percent more than metformin, but both were significantly better than placebo, of course.

***Conclusions and Implications*** from Dr. Shamoon for this DPP volunteer cohort selected for the high end of IGT and treated for 3.2 years included the following:

- Over 50 percent of the cohort had metabolic syndrome at baseline in contrast to NHANES III data for persons over 20-years-old (22 percent) in the United States . (Ford E.S., Giles WH, Dietz WH. Prevalence of the Metabolic Syndrome Among U.S. Adults: Findings From the Third National Health and Nutrition Examination Survey. JAMA 2002; 287(3):356-359). Among people age 50 years and older with IGT, a recent analysis of the NHANES III data set suggests 33 percent have the syndrome (Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Diseases Among NHANES III Participants Age 50 Years and Older. Diabetes 2003; 52(5):1210-1214).
- Components of the metabolic syndrome varied by age, gender, and race.
  - — Waist circumference and low HDL criteria were more prevalent in the younger group; blood pressure was more prevalent in the older group; triglycerides were equivalent across all groups.
  - — Waist circumference and low HDL criteria were more prevalent in women; fasting plasma glucose and blood pressure criteria were more prevalent in men.
  - — In order of prevalence, the metabolic syndrome was more prevalent in Caucasians, then in African Americans, Hispanics, American Indians, and Asians.
- Metformin was not effective in preventing the metabolic syndrome in women and was less effective in persons with the higher fasting glucose; it was most effective in obese and younger men.
- Intensive lifestyle intervention prevented the metabolic syndrome by decreasing waist circumference and blood pressure, not by correcting dyslipidemia, surprisingly.

In summary, Dr. Shamoon emphasized that the DPP has provided a valuable reservoir of stored samples and biomarkers and information to help design new studies and chart the course in this complicated area of obesity and its effect on the metabolic syndrome and the risk for diabetes and/or CVD.

**Discussion**

In response to a question from Dr. Garfield regarding the possibility of there being a single target for drug action within the metabolic syndrome, Dr. Eckel said that, with the exception of hypertension, he thought the other components could be targeted by a single intervention, particularly if insulin resistance is considered the working paradigm. For example, C-reactive protein can be influenced by fibrins. Other inflammatory markers can be favorably modified. Prothrombotic components as risk factors for CVD can be improved by agents that improve insulin sensitivity.

Dr. Shamoon added that, independent of the data about preventing diabetes with metformin in DPP, enough data exists showing the effect of metformin on preventing and treating the metabolic syndrome components. The challenge to the community, including ADA, is to define a treatable subgroup of individuals who are most likely to respond to metformin. Dr. Shamoon answered Dr. Garfield's question about what research support would be needed from NIH and FDA to determine if the metabolic syndrome is an actual syndrome or a coincidental aggregate of several syndromes, by suggesting that NIDDK apply resources and mine new information from trials with children. One of the problems in studying the metabolic syndrome in adults is that aging and obesity complicate the analysis. For larger kinds of analyses of the pathophysiology of the syndrome, he believed that children or adolescents would be the best starting point.

Dr. Amy Rosenberg, FDA, noted that everybody recognizes there is a growing epidemic of obesity and type 2 diabetes in children. She pointed out that children are a captive audience. Most are in school until nearly 18 where there is a real opportunity to focus on lifestyle issues, such as exercise. Currently, the amount of time for recess and for physical education has been cut back. Dr. Rosenberg recommended that there be a major public health effort to evaluate the benefits of physical education programs in schools and perhaps to expand them so that children will be inculcated with the importance of diet and physical activity. She stressed the enormous benefit to be gained by preventing obesity in children, and therefore type 2 diabetes.

Dr. Shamoon agreed. His researchers had published some papers in collaboration with a Columbia University group analyzing 2- and 3-year-old Hispanic children, from upper Manhattan, in whom the biomarkers of insulin and C-reactive protein were already present and related to BMI.

Dr. Tamborlane referred to a paper being published in June 2004 by Dr. Caprio from Yale reporting that the incidence of metabolic syndrome is more than 40 percent for obese teenagers and obese pre-adolescent children, a real problem that supports the need for studies in children, not only for prevention, but also to look at management and interventions. Dr. Tamborlane suggested a MetNet, a network approach to not only do a very large study that would take years but also smaller studies focused on interventions such as proof-of-concept studies of therapies for children. DPP showed that in 20- to 49-year-olds, metformin *is* as effective as lifestyle. Similar studies are needed for children. Dr. Tamborlane stressed that researchers and physicians are focusing in pediatrics on the rising incidence of type 2 diabetes, but they believe it is only the tip of the iceberg—a warning signal for the future. What they will be seeing as these young people approach their 20s is an 18-year-old with a heart attack.

Dr. Garfield commented that shortly after publication of the DPP results, ADA presented a position paper in *Diabetes Care* on recommendations based on the DPP as well as other studies within a similar timeframe. The paper encouraged the lifestyle changes, but urged caution in prescribing drugs for those at risk. Dr. Garfield asked if the speakers thought we were now at a point when drugs could be recommended as part of NDEP's outreach efforts.

Dr. Shamoon noted DHHS Secretary Tommy Thompson's prescription to Americans has had at least a limited impact in encouraging the lifestyle intervention. As a national mandate or public health task, this is important, but difficult to carry out. Dr. Shamoon questioned, though, why 2 years after the publication of the DPP results, there is not an indication for the use of metformin. In New York at least, physicians are eager to treat patients at an earlier level of their glycemic history, and metformin's safety record is remarkable.

Dr. Eckel stressed that the public health issue before the American public and most of the civilized world is that the metabolic syndrome is set by obesity with CVD as the primary outcome, either directly or by way of diabetes. Educating the public about lifestyle changes is important for modifying obesity and for

good health in general, but this cannot be accomplished readily. Therefore, Dr. Eckel thought the pharmaceutical industry would actually be the one to accomplish this task better than healthcare professionals, researchers, or government agencies. Nevertheless, the message about eating better and being more active needs to continue to be promoted. A related issue to some extent is that even if a patient fails weight reduction, the person still can become more active and eat well. The quality of the diet also can potentially impact hard outcomes that relate to the consequences of obesity and the metabolic syndrome or diabetes. Dr. Eckel emphasized that these are messages that need to be forthcoming, but there also is a need to take a more aggressive approach through a pharmacological intervention in those patients who cannot modify the components of metabolic syndrome by lifestyle alone.

Dr. Bob Silverman, Merck and Co., Inc., asked if it would be useful to the therapeutic community if there were drugs available and indicated for the treatment or the prevention of metabolic syndrome.
Dr. Shamoon answered that if there were agreement on the criteria for the metabolic syndrome and the definition of the syndrome as a treatable entity, there already is an effective drug to prevent metabolic syndrome in some groups such as younger more obese men. The results suggest that if one targets the glucose component roughly described by the DPP cohort, metformin might be effective in reducing other components of the metabolic syndrome.

Dr. Eckel stated the pharmaceutical industry should think about targeting the metabolic syndrome as an intervention that could have long lasting and favorable consequences, not only for diabetes but particularly for CVD.

Dr. Richard Bradley inquired, "What does it mean to prevent diabetes with a drug that lowers glucose levels? Why not just treat patients who develop diabetes? What benefit is actually being accrued?" He also asked what would be the endpoint to prove that a drug impacted the metabolic syndrome.

Dr. Shamoon explained that in treating diabetes, one actually treated hyperglycemia, the salient feature of the disease. There are different components of hyperglycemia along the continuum of increased hepatic glucose production, postprandial hyperglycemia, plasma glucose per se, and other defects. A drug that prevents the rise in hepatic glucose production, which is metformin's major effect, prevents the occurrence of fasting hyperglycemia, which is the definition of diabetes. So it is somewhat circular in that sense.

Two outcomes suggested by Dr. Eckel would be either reduction in incidence of diabetes or, since the definition for the metabolic syndrome in the United States is based on atherosclerotic cardiovascular disease not diabetes, reduction in CVD events. He added that determining the appropriate outcome for a drug to be approved was an important question for discussion.

Dr. Harold Lebovitz, State University of New York, stated that the practicing physician requires more specific guidance. They are being told all about the metabolic syndrome and about CVD. They are being told about the severe consequences of diabetes. However, when it comes to an intervention, they are uncertain about what they can really do. They have known since 1960 that losing weight and exercising helps their patients prevent diabetes, but in the real world this has not been effective. Now two drugs are known to be effective—metformin and acarbose. They have been used for years and have excellent safety records. Dr. Lebovitz strongly recommended that these drugs be approved for use in treating patients with the metabolic syndrome.

Dr. Orloff said that the group would probably spend some time at the panel discussion on the issue of indication. In a discussion about indications, it will be important to look at who in fact is the target population, for a broad prevention kind of indication. First, insulin resistance seems to be a unifying mechanistic starting point for the CVD risk-related abnormalities that comprise the syndrome. For

diabetes, not everybody with metabolic syndrome develops diabetes and not everybody with diabetes has metabolic syndrome. Dr. Orloff asked how to reconcile what appear to be somewhat disparate results from the DPP with regard to prevention of diabetes with metformin and prevention of metabolic syndrome with metformin, given that the two are not 100-percent correlated in the current observational database.

Dr. Eckel said that over half of the DPP subjects already had the metabolic syndrome at baseline. It is therefore difficult to look at the database and the impact on diabetes versus the metabolic syndrome, when the majority already had the outcome.

Dr. Shamoon added that such secondary analyses are difficult. The question seemed to be based on the metformin and lifestyle interventions being less effective in preventing transition to the metabolic syndrome than they were in preventing diabetes, thus raising the issue of choice of a target. Dr. Shamoon said that is why he recommended targeting subgroups, since the DPP subjects were specifically selected on the basis of having high glucose resistance and therefore there may have been a group with the metabolic syndrome with no degree of fasting hyperglycemia.

Dr. Eckel commented that interventions that modify glycemia may in fact work through different mechanisms, so the metformin effect on insulin resistance, although it does improve insulin sensitivity, is mostly a hepatic effect, whereas the TZD class of drugs has a plethora of effects that involve potentially multiple tissues such as adipose tissue, muscle, and liver. The idea of modifying insulin resistance with drugs that have multiple mechanisms of action is very different than thinking about an intervention that is more glycemia targeted. It is necessary to understand drug action related to the indications for insulin resistance and glycemia, both separately and together.

Asked what would be appropriate endpoints for FDA to approve a drug for an indication of insulin resistance or metabolic syndrome, Dr. Eckel replied that perhaps the criteria would be that the drug favorably modifies at least two of the three out of five components of the metabolic syndrome. He added that this was a matter for discussion. Dr. Shamoon said that from a gluco-centric point of view, in a high-risk population like the DPP subjects, the lowering of triglycerides has to be done independently from treatment of hyperglycemia. Dr. Eckel added that only 15 percent of the subjects with the metabolic syndrome also had hyperglycemia, using the 110 cutpoint.

## Session VII: Industry and Advocacy Perspectives

*Moderator, Robert Meyer, Director, Division of Metabolic and Endocrine Drugs, FDA*

### Drugs

***Simeon Taylor, MD, PhD**, Vice President, Discovery Biology, Pharmaceutical Research Institute, Bristol-Myers Squibb, Hopewell, New Jersey*

Dr. Taylor listed the following objectives for pharmaceutical research and development (R&D): production of safe and effective drugs, addressing unmet medical needs, and, ultimately, extending and enhancing human life. Dr. Taylor stressed these objectives are not trivial undertakings faced with the challenges the industry faces such as the need for cost-effective drug development and for increased success rates, especially in the very expensive late stages of the R&D process. Learning which drugs "fail fast" in earlier stages is critical as well as being able to predict "go-no go" business decisions early on.

To illustrate the R&D process, Dr. Taylor presented a schematic depicting the two major phases: drug discovery and clinical development. Together, these phases tend to span nearly a decade. The drug discovery phase includes the following steps:

- Target identification.
- Target validation.
- Lead generation.
- Lead optimization.
- Pre-clinical safety.

Dr. Taylor stated that, during the basic research phase of drug discovery, novel target identification and validation depend on efficacy and the potential for mechanism-based toxicity, as with the PPARγ compounds and their tendency to cause edema. With the mapping of the human genome, the industry now has more potential targets for disease. Biomarkers provide evidence for inhibiting targets and are useful to predict dose-response in these. In addition, through DNA and blood tests, biomarkers identify the exceptional patients who may be at risk for toxic reactions to a drug. The practicing physician does not want to titrate the dose for each patient, as is necessary for the patient with diabetes. Of course, this principle of "one dose fits all" has to be different in prevention trials.

The second R&D clinical development phase is comprised of the following trials and elements familiar to those present:

- Phase 1: Safety
- Phase II: Efficacy
- Phase III: Registration
- Phase IV: Post-marketing

Dr. Taylor pointed out that during the translational research period of R&D, surrogate markers not only predict clinically relevant outcomes but are key to acceptance of the drug for regulatory approval. He stressed that the Phase I and II trials conducted by the Government and by academia are of great importance to the pharmaceutical industry in identifying surrogates and in establishing safety and efficacy of drugs. He particularly noted the large, longitudinal trials such as the DCCT, UKPDS, and the epidemiology of diabetes studies with the Pima Indians. Dr. Taylor suggested that such trials offer excellent opportunities for public-private partnerships in basic scientific research, translational research, and developing regulatory policy.

As an example of the benefit to the pharmaceutical industry of such studies, Dr. Taylor referred to the landmark DCCT study that demonstrated that HbA1c could serve FDA as a surrogate marker in predicting the efficacy of intensive glycemic control interventions to prevent the development and progression of complications in type 1 diabetes. Likewise, the DPP showed that metformin was very effective in preventing type 2 diabetes in high-risk persons with impaired glucose tolerance, especially in young obese men. Dr. Taylor asked how much benefit would need to be shown for FDA to approve the use of metformin in this subgroup.

To meet the objective of targeting unmet medical needs through development of new drugs, Dr. Taylor said he would select prevention of diabetes, the metabolic syndrome, and prevention of the chronic complications of diabetes, which are not being prevented as well as could be done with the knowledge we have gained. He emphasized that the pharmaceutical industry would be facilitated by the establishment of clear criteria for approval of drugs to address these unmet needs. Such criteria exist in other areas, but not for obesity and prevention of type 2 diabetes.

In summary, Dr. Taylor stressed that success could be achieved by the partnering of Government, academia, and the private sector in sharing the objectives to identify and develop safe and effective drugs that address unmet medical needs and enhance and extend human life.

## Biologics

***Alain Baron, MD**, Senior Vice President, Clinical Research, Amylin Pharmaceuticals, San Diego*

Dr. Baron defined biologics as those products that are often first-in-class drugs and/or novel therapies for which R&D (research and development) largely takes place in settings other than those of the large pharmaceuticals. Biologics include peptides, proteins, cytokines, monoclonal antibodies, and cell- or gene-based therapies. They tend to employ non-oral routes and target important unmet medical needs. The scientific community and technology are often advanced in the area of biologics far ahead of the regulatory guidelines for their use in the practicing healthcare community. Dr. Baron stressed that, therefore, regulatory risk and other uncertainties impede companies from investing in R&D programs in novel therapies.

Dr. Baron emphasized that industry takes decided financial, scientific, clinical, and developmental risks in translating basic research advances and bringing novel therapies to the marketplace. There is a clear value chain. Following the R&D stage, with its inherent risks, there is also the risk involved in the regulatory review stage. Finally, industry assumes a high degree of responsibility for the long-term safety and for the acceptability of such therapies following their introduction into the marketplace. Industry recognizes that innovation does not come without risk, but it must carefully define and implement risk controls at various levels of the process.

The previous day, Dr. Baron had asked where in the list of serious diseases one should place type 1 diabetes on a scale of 1 to 10, if cancer is an 8. He explained that the importance of the answer to this question is that the seriousness of a disease is a paramount factor in determining the amount of risk one is willing to take to develop a therapy and to use the therapy. His answer would be that type 1 diabetes and insulin-requiring diabetes are incredibly serious and require very serious therapies. Given the choice between type 1 diabetes at the age of 16 and stage 1 lymphoma with a 95-percent cure rate, Dr. Baron would opt for the lymphoma. He urged that diabetes be taken as seriously and with the same sense of urgency as cancer and AIDS, diseases for which patients undergo an incredible degree of therapy risk, as do patients who undergo pancreatic transplantation, islet transplantation, immunomodulation, and immunosuppression. Today, in spite of important advances in insulin therapy, glycemic control for the type 1 and insulin-requiring patients is not optimal. They do not achieve their glycemic goals. Dr. Baron said he would therefore place the emphasis in his presentation on the issue of risk and the need for a better glucose-lowering therapy.

Dr. Baron offered the hope that in time there will be a cure for type 1 diabetes through immodulation, stem cell, islet transplantation, islet growth, and gene transplantation therapies. Meanwhile, over the past 20 years, intensive insulin therapy with glucose monitoring has enabled patients to lower their glucose, but with increasing insulin dose the risk of hypoglycemia also increases. Dr. Baron noted that every new insulin coming on the market is associated with an increase in hypoglycemia or loss of control or both. The “sweet spot” for each person is highly individualized, which is why an insulin vial does not have a label specifying how to use it. The patient learns how to use it over time. With hypoglycemia, the patient backs off the insulin. With hyperglycemia, the patient adjusts the insulin dose. This can take place on a moment-by-moment basis. Clinics are staffed with nurses and diabetes educators to help patients with this. Adjusting the dosage takes time. Dr. Baron pointed out that, thus, patients have accepted this incredibly high risk of insulin therapy, which is actually a dangerous therapy.

In his opinion, while waiting for an actual cure, the greatest unmet need in type 1 diabetes and insulin-requiring type 2 diabetes is the need for a novel therapy to provide another control variable beyond the single-control variable we have today, insulin. While insulin is clearly necessary for life, it is not

necessarily sufficient to achieve optimal glycemic control. Risk and regulatory guidelines continue to be daunting problems to development of such a system, not just technical- and patient-related barriers.

Dr. Baron stated that the critical question then is "What is an acceptable risk-benefit ratio for novel therapies?" Also, if a second control variable is added to intensive insulin therapy, how can it be studied? This is a real challenge. If there is a partial cure, for instance with a cell-based therapy in which a little bit of insulin is coming out of the cell but not enough to make the patient insulin independent, how can the therapy be studied and the risk-benefit ratio be evaluated? Are blinded studies with a novel therapy appropriate—and safe—when the sweet spot is individualized for each patient and takes so much time to determine? Dr. Baron concluded that the insulin experience in a blinded study—all that had been learned about diet, exercise, insulin dose, monitoring, and insulin adjustment for each subject—would actually be lost in a blinded study testing a second control variable, making such studies impossible to do.

Another question raised by Dr. Baron was "Is superiority of HbA1c always necessary for approval?" Dr. Taylor had made the same point with regard to implantable insulin therapies (IITs). Variables other than HbA1c matter in patients with IIT, such as postprandial glycemic excursions. Although HbA1cs of 7 and 7.5 are achieved in patients treated with insulin, they have incredible excursions and anxiety over those excursions. So the HbA1c level really does not help in that regard. Patients want glycemic control that is more predictable, with fewer fluctuations and less hypoglycemia. Weight control matters to patients. Quality of life matters to them. Complications are a major concern. Dr. Baron recommended that the scientific community and industry listen to patients rather than being concerned only with validated instruments that might be had 20 years from now.

In discussing risk and a cure or partial cure, Dr. Baron raised questions about the value of insulin independence or partial independence at any cost. He asked who would determine the level of acceptable risk—patients, industry, FDA? Dr. Baron noted these are very difficult questions but ones that must be answered if innovation is to take place.

On the path to novel drugs and consideration of the value chain, Dr. Baron stressed that each partner has a large area of responsibility. FDA has to be basically dispassionate yet passionate. They have to be careful and also innovative. This is a very tight, tight balance. Dr. Baron said the solution requires risk management. Clearly, all the answers cannot be in place before going to the marketplace. The marketplace teaches us about a lot of things, as has been seen with insulin. Years of experience have made insulin acceptable in the marketplace. He continued that all innovation has risk, and there is a learning curve. Reducing regulatory uncertainties are essential to spur innovation. Ultimately, however, if these therapies are not brought to the marketplace, there will not be an incentive for any more research translation, and all will suffer; most of all the patients will suffer.

### Devices

***David Horwitz, MD, PhD,*** *Vice President, Medical and Clinical Affairs, LifeScan, Inc., Milpitas, California*

Dr. Horwitz explained that he was representing the device industry and, in particular, the Advance Medical Technology Association and the Blood Glucose Working Group. He planned to speak primarily about *in vitro* diagnostics and innovations in blood glucose monitoring, including home glucose monitoring and, with a liberal definition of *in vitro*, continuous glucose monitoring.

Dr. Horwitz pointed out that innovations in glucose monitoring systems have improved accuracy, speed of testing, sample size, the ability to sample from alternative anatomic sites, and the ability to gain more information from meters (data summaries, trend analysis, and so forth). Monitors are easier to use, are

more convenient, have safety features such as 24-hour patient hotlines, and have special features, including data analysis through interfaces with computers.

For the future, Dr. Horwitz foresees continuous monitoring, open-loop control of insulin pumps, the "artificial pancreas," (i.e., mechanical pancreas), and the ability to optimize and individualize diabetes management with actionable health information. Achieving these goals will require exploring and facilitating a number of research, regulatory, and reimbursement areas. Relevant questions include:

- How can we advance and enhance the regulation of *in vitro* diagnostics?
- How can we address the reimbursement challenge?
- How can we fund the research to move the field forward?"

**Regulation**. Dr. Horwitz commended the FDA's progressive efforts to aid the device industry. The availability of published guidance documents make the regulatory path clear and facilitate the ability to get products to market more quickly and cost-effectively. The new 510(k) paradigms enable industry to take a shorter loop for a less risky product or for measures that are not likely to affect product performance. For example, the regulatory path has been simplified by the ability to classify open-loop infusion pump controllers as Class II devices, even though they do not have a true predicate device. Another important regulatory advance cited by Dr. Horwitz has been the ability for *de novo* classification of a device as Class II when there is not a predicate device, instead of going the Pre-Market Approval (PMA) route, which has facilitated getting devices on the market.

The FDA Modernization Act (FDAMA) has enhanced communication with FDA through the ability to meet with FDA and solve problems ahead of time, instead of conducting a study, submitting the data, and then finding out that the wrong study was conducted from the FDA's regulatory point-of-view. This has also helped to get products to the marketplace more quickly. Dr. Horwitz remarked that the FDA Office of Combination Products is becoming more and more important as products become a combination of devices and biologics, devices and drugs, biologics and drugs, and so forth. In the area of *in vitro* diagnostics, the Office of *In Vitro* Diagnostics, which looks at products throughout their lifecycle, has eased the process of working with FDA.

In considering how FDA can prepare for new technologies, Dr. Horwitz said that one obvious area that FDA is currently engaged in is global harmonization of premarket reviews. He noted that industry must deal with differing requirements, types of studies, and device standards in different parts of the world, which increases costs and time for developing products and bringing them to market. Achieving global harmonization is a particularly important area for the industry. Another helpful area would be to develop criteria for device down-classification, such as reclassifying Class III devices without a predicate device down to Class II where the regulatory path is clearer and products can be on the market sooner. This is critical in the device area, particularly for *in vitro* diagnostics, where product lifecycles are often only 2 or 3 years long before the next generation comes out, unlike pharmaceuticals that often have a 10-year or longer lifecycle.

Dr. Horwitz noted that screening for diabetes has been getting a lot of attention. While there is some controversy over who should be screened, when screening is indicated, glucose test strips are not an approved indication for screening. Nevertheless, the device firms are constantly being asked for glucose test strips for screening. Dr. Horwitz said that resolving this issue depends on establishment of a public health policy for diabetes screening that considers and balances the tradeoffs between diagnostic accuracy standards and the accuracy of the test strips and establishes appropriate criteria. The clinical studies needed to establish this indication involve large populations that are beyond the scope of the industry to study and may benefit from NIH-sponsored studies.

The review of genetic diabetes testing was another area in which Dr. Horwitz felt FDA needed to develop criteria to regulate *in vitro* diagnostics test systems, test reagents, test kits, and related pharmacogenetic products that look at various genetic aspects related to diabetes. As more and more drugs and different mechanisms for the treatment of diabetes are considered, there is a need to choose what drug might be the most important and which genetic factors are most important. Dr. Horwitz suggested that some of the regulations today, such as those related to analyte-specific reagents, are perhaps no longer completely relevant given the new directions being taken in genetic research. He added this is an area that needs some advanced thinking to speed the regulatory processes as these diagnostics begin to reach the market.

**Reimbursement**. Dr. Horwitz pointed out that blood glucose monitoring equipment seems to be continually targeted for Medicare payment reductions, creating a major reimbursement challenge for the industry. As the incidence of diabetes grows, the cost of monitoring will obviously grow. The problem is being specifically called out now in Medicare legislation. Reimbursement limitations directly impact patient access to what, for many, is the most appropriate technology in managing their diabetes. Dr. Horwitz added that lack of reimbursement for this equipment has the potential to affect blood glucose monitoring compliance by patients, and the impact of non-compliance on blood glucose control has clearly been shown. Reimbursement issues also limit the availability of new technologies, because they are not reimbursable and thus not immediately billable. Obviously, from a business standpoint, reimbursement affects the willingness of companies to invest in additional R&D to provide new products and new services for the market and can inhibit development of new molecular tests and pharmacogenomic solutions, as well as new devices. As an example of the reality of the issue, Dr. Horwitz cited data showing that Medicare costs from 1982 to 2001 grew by 382 percent, while spending for *in vitro* diagnostics was essentially flat, which, as a proportion of overall Medicare expenses, indicates a significant decrease in spending for *in vitro* diagnostics.

Dr. Horwitz noted that there has been an increasing public health policy emphasis on the importance of diabetes as a public health measure and, as a result, an increase in awareness of diabetes. He stressed that today's meeting is evidence of the concern as are DHHS Secretary Tommy Thompson's frequent statements about preventing diabetes and its complications. At the same time, the Centers for Medicare & Medicaid Services (CMS) have had to enact policies that discourage diabetes testing and monitoring. More cuts are planned for the future. In noting this discrepancy in public policy, Dr. Horwitz said this is currently a major issue for the industry, and one that needs to be addressed through proper research on what really is cost-effective therapy.

In closing his remarks, Dr. Horwitz listed the following areas of needed research according to the device industry:

- Effectiveness of screening using blood glucose monitors, which is going to have more and more impact as the potentially diabetic population grows.
- Medical and economic benefits of tight glycemic control in type 2 diabetes. In type 1, this is clearly established. In type 2 diabetes, there is an important need to translate research findings into clinical practice, especially in the primary care community, where therapy targets are not being reached and where educational efforts are needed to provide the data that glycemic control *is* important.
- Optimization of ways to achieve the desired glycemic control, an area where research is significantly lacking.

Dr. Horwitz suggested the following research questions regarding optimizing ways to use self monitoring of blood glucose to achieve glycemic control: When should it be done? How should it be done? By whom should it be done? How should it be used to guide therapy? Is postprandial testing important? Is control of postprandial glucose important? Advances being made include advances in biomarkers and surrogate endpoints, which can certainly help in studies. Questions remain about non-glycemic or non-HbA1c

endpoints. There are also the quality of life issues that have been discussed at this meeting and frequency of hypoglycemia issues as indications for therapy,

***Recommendations for fostering innovation*** in diabetes care, presented by Dr. Horwitz for the industry, included regulations that facilitate the introduction of innovative products; payment systems that place emphasis on early detection and optimization of treatment to prevent complications; and increased research dollars to find ways to make living with diabetes easier by discovering solutions for better screening, better management, and better cellular, genetic, and pharmacogenomic therapies.

### American Diabetes Association

***Nathaniel Clark, MD, RD,*** *National Vice President of Clinical Affairs, American Diabetes Association, Alexandria, Virginia*

Dr. Clark acknowledged the collaborative relationship ADA has had with NIH, particularly NIDDK, and with FDA over a number of years. He noted that an important role of ADA, as the representative of the 18 million persons with diabetes and the increasing numbers of those who are at risk, is to be the translator of the research being funded. The ADA call center receives 20 thousand calls per month from persons asking questions about diabetes, questions about this drug or that, about treatment options, and so forth. ADA also receives 300 thousand visits per month through its website and requests for the books, magazines, and journals the association publishes. Dr. Clark stressed that this connection with the diabetic and pre-diabetic populations and their families and friends provides ADA with a tremendous opportunity to "get the word out." The overall question for him as he sits in meetings like this one is, "What is the word? What is the word that we should be getting out?"

The mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all of those affected by it. Prevention has obviously been in the press of late, and ADA has been very active in this critically important and highly challenging area. Dr. Clark cited CDC data that predicts that a child born this day has a one-in-three chance of developing diabetes in his/her lifetime. New numbers based on the redefinition of pre-diabetes are that perhaps 40 million Americans have pre-diabetes. When researchers and clinicians came together and discussed defining a normal blood glucose level in the fasting state as less than100 mg/dl, not the previous 110, Dr. Clark wondered if the full significance of that decision was clear to everyone. This simple change doubled the number of people with pre-diabetes. The public health impact of doubling the group was not a major topic in the scientific discussions about whether the data warranted this redefinition. How to treat 40 million persons with pre-diabetes is now a primary issue for research translation and thus an issue of major concern for ADA.

As mentioned earlier, ADA saw the impressive DPP as a proof-of-concept study and put out a position paper addressing the DPP results. Dr. Clark said the main message from the DPP was that lifestyle change is very effective in preventing or delaying progression to diabetes in those at high-risk, roughly twice as effective as using a medication such as metformin. The main issue for ADA was how to translate that result, what should be done to operationalize it. The National Diabetes Education Program's Small Steps, Big Rewards and other programs that Secretary Thompson has supported have helped advance the cause of diabetes prevention. ADA has supported these.

As a Registered Dietitian, in addition to being a physician, Dr. Clark wondered if the prevention of diabetes through lifestyle change concept was still being undersold. It is very difficult to receive reimbursement for dietitian services or for increasing a patient's physical activity level. On the other hand, there is a drug that works, and so the question is raised, "Why not approve this drug for prevention and use it?" As a physician, Dr. Clark admitted it is much easier to write a prescription than it is to get patients to undergo lifestyle changes. On the other hand, the benefits of losing moderate amounts of weight and increasing physical activity are so enormous globally—across a person's complete health

spectrum—compared to the relatively small gains of simply improving blood glucose levels with a medication. He added that these obviously are controversial areas.

Dr. Clark explained that the reason ADA interpreted the DPP the way they did (emphasizing lifestyle change over medication) was because of their deep concern that once that study was published and people saw that metformin worked, practitioners would immediately move to the drug option and ignore the lifestyle option. This concern continues and a recent example of their reason for it was an interesting article in the *Washington Post* about pre-disease. The article spoke of an endocrinologist in Washington, D.C., who prescribed metformin for a 15-year-old girl, even though her laboratory results of blood glucose levels did not qualify for pre-diabetes by any criteria, new or old. He put her on the drug because he felt that her insulin level was somewhat elevated. Dr. Clark stressed that responses such as this to research results clearly raise questions about indications for use of a drug, about endpoints, and about the goals of treatment.

Referring to Dr. Nathan's earlier concern about not appropriately using the drugs we have now for treating diagnosed diabetes, Dr. Clark raised the issue of diverting attention from this valid concern by talking about drugs for pre-diabetes. In the field of diabetes, there also are already many drugs to treat hyperglycemia, hypertension, and dyslipidemia to prevent complications in diabetes, yet these are not being used optimally to treat these problems. While it is important to support approval of new therapies by FDA, there is also a need to promote better use of existing, proven therapies.

Dr. Clark introduced the problem that ADA and the public face in trying to interpret research studies that are done in very different ways. The DPP was an excellent, randomized, long-term, controlled trial that produced excellent data. Dr. Clark though is repeatedly asked by the media to comment on other studies being published by colleagues. He is presented with such questions as "Is it true that Oolong tea prevents diabetes? That drinking five to six cups of coffee a day prevents diabetes? That eating peanut butter prevents diabetes? That having your blood tested for an increased iron level predicts diabetes?" The public is being challenged to compare a study done by correlating numerous variables using a computer to show that five to six cups of coffee prevents diabetes with the DPP that showed that lifestyle change and metformin prevent diabetes. The public's attempt to compare and interpret results from such disparate study designs is a challenge for the ADA, the FDA, and NIH in terms of their prevention translation efforts.

The second part of ADA's mission is seeking a cure for diabetes. Dr. Clark said this begins with supporting good research. Along with NIH's expansive efforts, ADA provides seed grants to encourage young researchers and to enable them to collect the data to apply for an NIH grant. Islet cell research is an area about which ADA receives many questions.

The largest area that Dr. Clark is personally involved in has to do with improving the lives of those with diabetes, including the development of ADA's evidence-based clinical practice guidelines. Dr. Clark emphasized that defining the cutpoint for HbA1c or LDL or any of the diabetes-related factors has to be based on good research. ADA largely relies on NIH for this basic and clinical research.

In the area of medication, ADA obviously relies on the FDA in terms of what gets approved. ADA and FDA have collaborated well to date and plan to continue doing so in the future in looking at how drugs are used and what problems might occur. For example, a working group assessed the effect of glitazones in terms of edema and congestive heart failure. As the manufacturers came through and presented their data, a member of the FDA staff was present to comment on the validity of the data and assist the working group in preparing their paper. At a recent meeting on antipsychotic use and the development of diabetes, an FDA representative was invited to present the agency's experience in this area. Lastly, Dr. Clark said that, at the request of FDA, a future working group would be looking at hypoglycemia,

including to what extent hypoglycemia should be used as an endpoint in new drug approvals and equipment approvals and if there is there is special relevance of night-time hypoglycemia.

Dr. Clark noted that there has been an explosion over the last 10 years in the number of drugs to treat diabetes, specifically new insulins, new oral medications, a number of drugs for dyslipidemia, and also a number of ACE-inhibitors and ARBs for treating blood pressure. This plethora of new drugs, along with what we know about diabetes and risk factors, has led to the issue of whether simply having diabetes is a sufficient indication to be on all these pills. Also, is there a need to develop what has been called the polypill—a single pill that contains, for example, aspirin, an ACE inhibitor, and a statin and is prescribed upon diagnosis of diabetes? Dr. Clark added that then the question would become if for those with pre-diabetes or the metabolic syndrome, who are also at risk, should these drugs be introduced earlier and earlier into people's lives, even though all these drugs have potential side effects?

According to Dr. Clark, there also are current questions applicable to laboratory tests. ADA is very proud of the HbA1c standardization program using a reference range, which was largely based on data from the DCCT. The Association is interested in trying to standardize the insulin assay, so that this assay can be used more effectively. They are also looking at the same issues with regard to C-peptide. Dr. Clark explained that a very important question that comes up now is in regard to home testing of HbA1c and of lipids. Once a laboratory test is moved out of the clinical arena where there is a physician or other experienced healthcare provider to determine when to get the test and to interpret the test, costs may increase while benefits may not change or decrease. For example, to what extent is it a good idea for patients to check their HbA1c once a day, once a week, or once a month as current guidelines suggest checking 2-4 times per year? Will such home testing provide the patient with any truly useful information?

In summary, from the American Diabetes Association's perspective, Dr. Clark said they take very seriously the responsibility to dispense reliable information, to help those with diabetes whom ADA serves, and to work closely with NIH and FDA. Certainly, together the three organizations can accomplish more than any one group can separately.

### Juvenile Diabetes Foundation International

***Robert Goldstein, MD, PhD,*** *Chief Scientific Officer, Research Department, Juvenile Diabetes Research Foundation International, New York*

Dr. Goldstein said he was really a pinch-hitter for either an articulate child with diabetes or a mother. JDRF is run by dedicated volunteers who would be very interested in everything that was discussed at this meeting. He stressed that, in addition to NIH, FDA, academia, and the pharmaceutical industry, the future also depends on foundations and advocacy groups.

The mission of JDRF is to find a cure for type 1 diabetes and its complications through supporting research. Cure is defined as restoring blood sugar to normal, preventing complications, and preventing diabetes. Dr. Goldstein explained that over the past 6 or 7 years, JDRF has been becoming increasingly focused, as opposed to becoming increasingly broadened, in its research agenda for a cure. He listed the following significant outcomes on a 5-year path toward a cure:

- Generate permanent euglycemia by islet transplantation without chronic immunosuppression.
- Generate a replenishable, stable, universal source of glucose-responsive beta cells and insulin-secreting cells that resist immune attack for human transplantation and begin Phase 1 trials.
- Restore euglycemia and insulin independence by activating endogenous beta cell regeneration and inducing immune tolerance to beta cells in animal models of autoimmune diabetes. (Dr. Goldstein remarked that regeneration with a capital R is becoming a topic for a variety of disorders.)

- Create permanent euglycemia and prevent complications with a closed mechanical loop artificial pancreas.
- Encourage novel approaches to predict and novel therapeutics to prevent and treat complications.
- Accurately predict the risk of type 1 diabetes and develop novel therapeutics to prevent diabetes, including a vaccine to prevent this disease. JDRF is working with a variety of NIH institutes, as well as governments outside the United States, to accomplish this.

Dr. Goldstein explained that although it is not a typical cure item, the closed loop artificial pancreas is a goal that responds to children and parents wanting their lives to be better in terms of their ability to manage and control their disease and, thus, they would settle for a device to help them do that while waiting for the promised cure. JDRF has stopped funding this area of research and secured funding of approximately $4 million from the Department of Defense specifically to promote innovative work to accomplish this goal.

After 9/11, JDRF's funding leveled off somewhat. In FY 2003, the association's $81 million research budget was divided up approximately into 57 percent for achieving euglycemia, 27 percent for prevention of complications, and 16 percent on prevention of type 1 diabetes. Dr. Goldstein said that this year, JDRF will spend approximately $93 million on research.

Presenting a pie chart depicting where JDRF research funds are spent, Dr. Goldstein noted that 38 percent of the 2003 money was allocated outside the United States. JDRF has partnerships with medical research councils in 10 to 15 countries that advocate for type 1 patients and promoted enhanced activity on their research and public health agendas in their respective countries. He pointed out that both Finland and Sweden, where there is a tremendous amount of type 1 diabetes, have wonderful healthcare systems that permit JDRF to do clinical trials that probably would be more difficult to do in the United States. They collect enormous amounts of phenotypically well-characterized patient specimens that JDRF is trying to bring together so that other researchers will have access to them. When clinical trials are conducted outside the United States, the study groups look to FDA for ultimate guidance. This is also true for the EU regulatory system, and so forth. Dr. Goldstein assured those present that JDRF's funding of research outside the United States has not been in order to work where the rules were less difficult, but to go where there are excellent patient resources and dedicated physicians.

Dr. Goldstein stated that JDRF is sponsoring clinical trials in islet transplantation—a cooperative clinical trial with NIDDK and another one with CMS and NIH in Medicare recipients, which will provide a post-kidney transplant opportunity. JDRF also is organizing its five largest European groups to complement this U.S. activity. Dr. Goldstein said that over the past couple of years since the Edmonton protocol publication, the focus of attention has been on freeing patients from having to take insulin shots. He stressed that, unfortunately, many of the publications have emphasized insulin-independence and have under-emphasized the ultimate therapeutic benefit of islet transplantation itself. Over time, insulin-independence drops off; however, the therapeutic benefit remains. Dr. Goldstein recommended that more attention be paid to documenting and observing this ultimate benefit. Taking some insulin would not be a terrible imposition on the patient population currently receiving transplants.

New onset type 1 diabetes immune intervention represents a frustrating paradigm for JDRF, according to Dr. Goldstein. JDRF has a study group working with CD3. The group is based in Brussels, but the Principal Investigator overseeing the trial is in France. The research reagent was not permitted to cross the border from England to France, but was allowed to go from England to Brussels. The government of Belgium supports a diabetes registry and tracks the patients. This is an example of the kind of opportunities that exist overseas. In the United States, JDRF is sponsoring anti-CD3 trials in new onset type 1 diabetes. Anti-CD3 has shown a potentially reasonable effect, but given over a period of time, it also has some toxicity issues. To date, Dr. Goldstein feels the issue of issue of trials in children,

particularly prevention trials in at-risk children who are quite healthy, has not been adequately addressed. This partially explains why most type 1 prevention studies are being done with insulin, because a lot is known about insulin and about its safety. Dr. Goldstein emphasized that working with the next generation of therapeutic agents is a huge challenge in efforts to move forward. Many, if not most, of the current approaches to immune modulation involve toxicities that the scientific community is not used to and thus do not know whether these toxicities are theoretical or real. Dr. Goldstein stressed that a way must be found to deal with this issue if the field is to advance.

Other clinical trials supported by JDRF include advanced glycation endproduct (AGE) inhibition for which the group has seeded a grant that is blocking RAGE receptors and trying to work on complications. An issue in this clinical trial is the difficulty of obtaining high quality material. Dr. Goldstein explained that there is not a lot of venture capital available for these very early novel therapies. The FDA in particular does not like the use of research grant-level material; the agency wants higher quality material. Dr. Goldstein commented that this was another area for future discussion.

Dr. Goldstein also raised the issue of collecting ell-characterized patient populations in order to begin to stratify and find subgroups, particularly for genetic studies or therapeutic trials in molecular medicine, genomics, and proteomics. He stressed that this is a resource that all groups currently need. NIDDK has made a commitment to accept the challenge of assembling these critical patient populations in a manner suitable for researchers to gain access. This often requires re-consenting people from international studies to have modern and up-to-date consent to do new studies. Once this resource is freed up, Dr. Goldstein is optimistic that the work will go forward more quickly in type 1 than in some other disease areas where such resources do not exist.

Regarding stem cell research, Dr. Goldstein stated that JDRF took the position, politically and scientifically, after August 2001, that more work was needed than could be done in the United States at NIH. Therefore, JDRF has partnered with half a dozen countries in an effort to derive new stem cell lines, characterize existing lines to study beta cell development, promote information exchange and research according to the highest ethical standards, and make the stem cells freely available to researchers by removing the constraints that currently exist with the NIH lines. The effort is being carried out by the International Stem Cell Forum, which was organized in the United Kingdom by the Medical Research Council and is made up of groups from numerous countries, including NIH from the United States. Additional information about the Forum and its objectives is available at http://www.mrc.ac.uk. Dr. Goldstein announced that within the next 6 to 9 months, the Forum will be characterizing about 50 new cell lines, including ones with human fetuses. He acknowledged that for FDA and for anyone wanting to do therapeutics based on embryonic stem cells, the challenge will be how to bring potential therapeutics from outside the United States into the United States; however, it is JDRF's hope that this will occur, ultimately, but not next week, of course.

Dr. Goldstein concluded by saying JDRF also has a program for supporting small companies, usually headed by academics who have come up with a novel idea. It is sort of a pre-SBIR (Small Business Innovation Research) type program.

**Discussion**

To lead off the discussion, Dr. Meyer noted that the industry speakers had presented a litany of challenges and areas of therapy requiring research. He asked Drs. Clark and Goldstein if they saw the gaps or failures to achieve optimal therapy in clinical practice being driven by lack of adequate therapies and/or devices or by inadequate use of the therapies currently available.

Dr. Clark responded that, in general, his feeling and that of ADA was that there are an enormous number of tools that are not being used effectively at this time. There clearly are gaps, and ADA supports and looks forward eagerly to new drug and device development. Meanwhile, his and ADA's wish would be for better utilization of what already exists rather than waiting for the creation of something new.

Dr. Goldstein declined to give an answer for JDRF, but personally, he agreed with Dr. Clark that the United States is not doing all that it could do. In Scotland, for example, all persons with diabetes are registered in a database, along with every laboratory test, x-ray, prescription, and so forth. Of course, Scotland's population is around 5 million people. Anyway, 4 or 5 years ago, the database showed that insulin-dependent diabetics were not getting eye exams, so they instituted a mandatory eye check and achieved a 95-percent compliance. This did not increase their costs because they had a basic infrastructure in place. Dr. Goldstein said one had to be amazed at a functioning healthcare delivery system that could accomplish this type of thing. In other countries, particularly ones interested in islet transplants, their quality control and their ability to achieve tight control is exceptional. In Finland, for instance, it does not matter who the patient is, access to all the specialty information is available for anyone with type 1 diabetes. That is not true in the United States.

Dr. Taylor agreed that delivery of the healthcare technology that exists is imperfect, but was unsure if that presented an either/or choice regarding development of new therapies versus application of current ones. Type 1 patients who receive the absolutely very best care available in the world with the best utilization of the technology still do not achieve normal HbA1c. They still have diabetic complications, which is why JDRF is looking for a cure. Similarly, with metabolic syndrome, cardiovascular risk, and type 2 diabetes, people who receive the very best available medical care still have problems controlling their weight. Dr. Taylor suggested that the issue may be that therapies need to be more user-friendly in order to do a better job of getting people to use the available therapeutic modalities. An implantable closed-loop pump, for example, or an artificial beta cell, would make patient compliance much easier. Dr. Taylor said there would still be economic issues to address, but outcomes would be better.

Dr. Clark commented that there might be more success in diabetes clinics if there were fewer meters or monitors available, which were selected based on patient and provider characteristics. Today, for example, some children have three or four different types of meters, and there is therefore no easy ability to download results effectively because every instrument requires its own software program. When the different manufacturers are asked about standardization, the answer is that there is no possibility at this time of standardizing the technology.

Dr. Tamborlane brought up the reimbursement challenge in attempting to run a large-scale treatment program for youth with Type 1 diabetes. He said the fee-for-service model to pay for intensive diabetes care for 1,000 children is just not a doable operation. As a result, his group must subsidize the care with money from whatever source they can. Dr. Tamborlane stressed that other reimbursement models were needed, such as global fee models or disease management models. He suggested that this was a target for the advocacy groups to pursue. He mentioned that JDRF has a committee and a grant to look at how to pay for the personnel required to implement advanced technologies.

Dr. Goldstein responded that JDRF had not solved the problem yet but were continuing to work toward a solution. The association's focus has been on research so it has been difficult to shift to paying attention to fixing the healthcare system.

Dr. Clark added that even though we have good meters and good insulins, there is not a willingness to reimburse the time of healthcare professionals that is needed to help patients make maximum use of these existing technologies. For example, physicians and their staff members spend a lot of time going over glucose levels with patients, particularly over the telephone, and there is no reimbursement for this. The

reimbursement issue is an important point in physicians' better applying what is known about diabetes care.

A member of the audience asked what processes were available to help investigators and evaluators make conscious, deliberate use of the unique expertise of patients. More to the point, in order to provide patients with access to therapies that have ambiguous results in terms of being safe and effective for average patients in a static protocol, what can be done to enable patients to conduct their own personal clinical trials to determine what is safe and effective for them. As background to the question, the inquirer said that when her daughter was diagnosed with type 1 diabetes 15 years ago, the Chief of Pediatrics at Joslin Diabetes Center told her that once she learned to care for her daughter under his tutelage, she would know more about her care than he would know. This statement was confirmed by many other professionals over the years until now, at 19, the patient knows better how to care for herself than any physician does. In looking at the development of new therapies and in designing clinical trials, how are procedures decided for evaluating whether the new therapy is right for an average patient and whether the therapy will have the proper effect on average levels of blood glucose, granting that there is no such person as an average patient? New trials and evaluations are based on fixed protocols. Her daughter's protocol changes every day, sometimes every hour. Use of HbA1c was a huge advance for research, but it is wrong to call it a gold standard because there is never an average blood glucose.

Dr. Baron responded that on the device side, glucose meters, in particular, are largely a consumer-driven market. Market research begins at the user level. Different users clearly have different desires, different wants, and different preferences. That is one reason why there are so many multiple products. Dr. Baron suggested that large databases are obviously needed to obtain the statistics for the "average" patient. A challenge that must be dealt with is how to deal with small numbers of persons in special situations. Should this be part of the practice of medicine or part of the regulatory process?

Dr. Horwitz commented that patients make choices all the time. For some investigators, pumps are the ultimate form of delivery of insulin. Currently there are approximately 120,000 to 150,000 patients on pumps. Clearly, most patients with diabetes have opted not to use pumps. Others have opted to discontinue the pump and to go on to Lantus therapy. Others have discontinued regular insulin and gone to newer insulin analogs. Dr. Horwitz agreed that all patients are different and all of them have their own paradigm of what is best for them. Mean values do not respect the individual. With respect to type 1 diabetes, Dr. Horwitz believes it is such a devastating disease, that patients do need to be listened to more carefully.

Dr. Taylor remarked that industry and regulatory agencies do work together to ensure that compounds meet minimal standards of safety and efficacy before they are made available for patients in clinical trials. Once a drug is approved, there is in effect a post-marketing clinical trial to further monitor the drug's safety. In exceptional cases, where early data are especially encouraging, the FDA and the industry partner work to make a product available on a compassionate use basis if it is believed that there is value in making it available to people who would otherwise be harmed by preventing early access to the product, even if the product has not met the normal regulatory standards for approval. There are many controls involved in this early availability, but the practice does recognize the issue that for some patients, this is an appropriate course of action.

Dr. Taylor went on to say that it is sadly true that, for the most part, patients with either type 1 or type 2 diabetes must be viewed as a more or less homogenous group, Physicians are taught to treat the average patient. However, Dr. Taylor said that over the next 10 or 20 years, genetic ways, for example, will be found to identify patients who vary from the average and who have special characteristics. These patients will then be treated, not necessarily as absolutely individualized patients, but as members of a definable group of patients for whom particular treatment regimens have been identified as being safe and

especially effective. He added that this is one of the important areas for contributions from Government and private-sponsored research.

Dr. Horwitz added that gene identification of subtypes of type 1 and type 2 diabetes is needed. There are patients with type 1 diabetes who can achieve reasonable glycemic control and not gain a massive amount of weight. Others cannot. This needs to be recognized, rather than simply telling the weight-gaining patients they are not doing the treatment correctly. Residual C-peptide secretion in a patient enables that patient to get better control. Not everybody has the same degree of residual C-peptide secretions. Dr. Horwitz recommended identifying patients who have particular needs. He said it is wrong to ignore the fact that there are highly motivated people who cannot achieve the results from a therapy for which other people are successful.

Dr. Alex Szidon, DARA BioSciences, asked the panel to identify elements or hallmarks to keep in mind that would foster preclinical and early clinical development of new diabetes and obesity drugs further down the road. This would be a valuable benefit to take away from the symposium, along with the discussions about clinical outcomes and endpoints.

Dr. Horwitz responded that it is difficult to ask that investments be made in targets that are uncertain with regard to the risks and the regulatory process. In the drug development industry currently, it is better to be number two in coming up with a novel class of medications because you can piggyback on number one's risks and experience. This happened with statins. Dr. Horwitz thinks this will also be true with ACE inhibitors. The ability to take a novel chemical entity or a biological therapy all the way to the marketplace is so daunting today because of the uncertainties that, in order for choices to be made early on, there needs to be a better sense of the risk-benefit ratios in terms of what patients want and what the FDA thinks is in the best interest of patients, rather than what is the easiest regulatory door to get through. Dr. Horwitz recommended that the FDA continue to aggressively initiate conversations with industry about better risk management methods. Otherwise, he believes it will be very difficult for people to invest in true innovation early on.

Dr. Taylor disagreed slightly. It is partially true that to get a drug approved that is the nth in its class is appealing because of the lower risk. On the other hand, to get a drug that is say 5$^{th}$ in its class but that truly adds value, that really distinguishes itself, that is going to make a real difference for patients, is extremely challenging. For the most part, people in the industry try to balance the risks. If there is a class of drugs that are seen as having benefit but there is a problem with the drug, people will try to improve it. There needs to be room for improvement with any drug to make a difference with patients and have a commercial success. It does make life easier if some of the risks are known, if a company knows what kind of data will be needed to have a new class of drug approved. This allows the company to make a fair and reasonable assessment of its risks. It is the unknown and unmeasurable risks that are particularly discouraging.

Dr. Horwitz said that Dr. Taylor's statements were correct. In a big company with a portfolio of risk, there can be four or five versions of a drug that is known to work and that people have accepted. The difficulty is when people look for go-no-go decisions and the regulatory path is unclear. This makes for a very risky situation in the minds of the business people. Dr. Horwitz stressed that for true innovation to occur, and it is happening, industry does have to be bold. They are very capable when the science is there to be harnessed. Industry has to be convinced that the need is serious, for instance for better type1 treatments. They are aware of this seriousness for AIDS and for cancer, where in a sense the risk is minimal because death is the other outcome. To deal with the epidemic of diabetes in children, where the level of incidence of children with type 2 diabetes is replacing the level of those with type 1 diabetes, is going to require bold thinking on the part of research and industry. It is a daunting task. There are many tough decisions that all parties must make—the Government, industry, academia, advocacy groups,

patients, healthcare professionals, third-party payers, policymakers and decisionmakers, and the general public who ultimately pay the bills.

## Session VIII: Targeting Safe and Effective Prevention and Treatment: Steps Forward by FDA and NIH

*(Moderators: David Orloff, MD, FDA, and Judith Fradkin, MD, NIDDK)*

**Panel Members:** *Drs. Robert Eckel, Christopher Saudek, Harry Shamoon, Robert Sherwin, William Tamborlane, and Simeon Taylor*

Dr. Orloff convened the panel and expressed his appreciation to Dr. Garfield and to Dr. Fradkin for their assistance in organizing this meeting. He particularly wanted those present to be aware of Dr. Fradkin's clarity of insight about this area and her knowledge of the people at the forefront of the issues.

Dr. Fradkin responded that the partnership with Dr. Orloff had been excellent and expressed her appreciation for those who had come together to share their knowledge, perspectives, recommendations, and commitment to the goals of the meeting. She noted that the speakers had presented eloquent descriptions of both the public and the private burden of diabetes. As stakeholders, they had offered a wide range of perspectives. Dr. Fradkin acknowledged that selecting targets and moving forward was a challenging task for all and, in particular, for NIH and FDA.

Dr. Fradkin asked the panel to comment on two issues:

- What might NIH and FDA do to further enhance the research climate and to enable industry to translate the discoveries coming from academia into new therapies?
- What is a meaningful outcome for prevention and treatment studies in diabetes?

With regard to the second question, Dr. Fradkin listed insulin independence or increased beta cell function or C-peptide preservation as choices for outcomes for islet transplantation. She added that a meaningful outcome for treatment or prevention of the metabolic syndrome is also important, since the syndrome is becoming a large, emerging problem as a collection of risk factors for CVD and diabetes.

Dr. Shamoon responded that the workforce issue is one that NIH could be addressing. Referring to NIH's Roadmap Initiative, he remarked on the enormous number of targets, possibilities, and opportunities that fundamental science has created in the last 20 years. The gap now is the lack of trained clinical investigators to carry the science forward. He emphasized that an important task of the next generation of clinical investigators is to take the up these problems in a way that addresses public health. Dr. Fradkin commented that NIH recognizes this need and continues to be active in encouraging medical students to pursue research careers.

Dr. Tamborlane stated that for youth with type 1 diabetes, he would encourage industry to move forward in the technological development of artificial pancreases as a key area. New sensors are overcoming obstacles that stood in the way for the past 20, 30, or 40 years. Dr. Tamborlane thought it likely that the artificial pancreas will be a successful mode of treatment well before the problems and risks from islet transplants and immuno-suppression are resolved in children.

Regarding meaningful outcomes for type 1 diabetes, Dr. Tamborlane listed HbA1c, reduced risk of hypoglycemia, improved quality of life, and reduced treatment burden. He said that the 900 type 1 diabetes patients at the Yale clinic are doing so well with an HbA1c of 7.5 that he tells them that, for the most part, they have beaten diabetes. This control of their hyperglycemia will have a tremendous impact

on late complications. The problem is that they must beat diabetes every day. That is the burden, and that is what exposes them to risk. Dr. Tamborlane stressed that this daily struggle is the top problem that needs to be solved.

Dr. Sherwin said that an important area for NIH support would be development of drugs, particularly a vaccine for type 1 diabetes. This is not area that is on the radar screen of the large pharmaceutical companies because of the size of the market. In clinical trials, NIH could help determine the risk-benefit ratio for islet transplantation once the procedures move ahead sufficiently for it to be potentially more readily available; identifying the risk-benefit ratio would help with reimbursement and product development issues. In reducing the risk of CVD, trials are needed to answer what extent lowering glucose in people with the metabolic syndrome contributes to the equation of treating dyslipidemia and lowering blood pressure to optimal levels, along with aspirin treatment. Dr. Sherwin's bias is that hyperglycemia does have an impact, but FDA would need evidence of this as an endpoint for the metabolic syndrome. Meaningful endpoints for type 2 diabetes are first, prevention of CVD; second, prevention of complications of diabetes; and third, achieving a sense of well-being, which is hard to define but is relevant.

Dr. Sherwin continued that the daunting task is identifying surrogate endpoints. There are valid endpoints for cholesterol, blood pressure, and glucose. He asked if there was a valid endpoint yet for treating insulin resistance, as this would be a major problem for FDA in relationship to the metabolic syndrome. Dr. Sherwin stressed this was an area that needed further discussion and debate in a larger forum to resolve. Other issues to be discussed further include endpoints for treatment of persons with pre-diabetes and pre-CVD. Something other than CVD itself is needed. Dr. Sherwin recommended that preparing a position paper for FDA on these subjects was in order.

Dr. Taylor stated that preventive medicine is a huge challenge. If someone has pneumonia, the person is given penicillin and gets better—a very short-term endpoint. Whereas preventive medicine has much longer time spans. DCCT required about a decade. He explained that it is difficult for a pharmaceutical company that has a patent clock ticking to consider trials in which the patient may well expire by the time the outcome study is done. Dr. Taylor said it would therefore by very helpful if there were validated surrogate markers, like HbA1c, viewed as an outcome rather than as a kind of risk factor. He suggested that Phase II studies could identify biomarkers that could help industry assess risk and make decisions early on, even if they were not FDA-approved biomarkers. For example, once HbA1c and LDL were validated as mechanisms for insulin and statins, respectively, then industry knew that any mechanism that changed these biomarkers was going to predict a good outcome. This is not known for HDL. If it was known that HDL is truly the good cholesterol and that raising it would be beneficial, then HDL as a surrogate marker would stimulate industry to seek ways to raise it.

Dr. Eckel pointed out that raising HDL per se could not be the endpoint because of other factors equally important to an outcome. For example, one of the ways to raise HDL cholesterol the most is eating the Atkins diet. On the other hand, a diet of high intake of saturated fats and cholesterol will likely not provide a satisfactory outcome for CVD.

A panel member commented that NIH needs to continue to investigate the genetic, molecular, cellular, and pathophysiologic causes of disease. It is not NIH's job to develop drugs but the institutes can assist the process through clinical trials like those suggested by Dr. Sherwin. It was noted that NIH sponsors workshops for medical students to teach them clinical research skills and introduce them to clinical research as a potential opportunity for their future. Also, through its K-series awards, NIH has several mechanisms to develop clinical support for the transitional scientist. What was needed was support for R01 investigators who must compete with cellular and molecular biologists. The speaker suggested that in investing in clinical research, which is the pathophysiological basis of drug development to some extent

through helping to understand the mechanisms by which drugs work, NIH is assisting the industry. Another role NIH plays is in training those who have the tools and capability of understanding the mechanisms of disease operation.

A panel member spoke about the major issue of long-term weight maintenance after weight loss. He said he was not actually convinced that there was a health benefit to weight reduction if the weight loss is not maintained, although all the biomarkers say there is. Current clinical trials have demonstrated the transient nature of weight loss. Once a person is obese, that person tends to maintain that body weight against most odds. The speaker stressed that the public message of prevention of weight gain is what should be heeded. NIH's LookAHEAD is an important clinical trial to show whether or not people at high risk of CVD can, under the best of circumstances, not only lose weight, but maintain the weight loss over years and gain a long-term benefit with respect to cardiovascular outcomes.

In reference to raising HDL by different mechanisms, a panel member referred to a recent article in the *New England Journal of Medicine* about cholesteryl ester transfer protein (CETP) inhibitors that showed that CETP inhibitors raise HDL and lower LDL and triglycerides (Broussau, ME et al. NEJM 350:1505-1515; April 2004). He raised the concern that the mechanisms by which HDL changes and how the changes relate to the atherosclerotic process are unknown. For instance, if HDL is raised by modifying its clearance, then the HDL is being raised in a mechanism that does not relate to its ability to reverse cholesterol transport. It is the lipid-poor HDL that binds membranes in reverse cholesterol transport. It is not modified clearance.

Dr. Taylor stressed that his earlier comments about the need for support for research in biomarkers for atherosclerotic disease or the metabolic syndrome was not specifically about HDL but about how critically important these problems facing the Nation are with respect to the growing numbers of obese youngsters. If the country must wait for a decade-long clinical trial, the epidemic of heart disease in 20- and 30-year-olds will already be taking place.

Dr. Saudek commented that as FDA moves forward in the management of diabetes, the agency will have to increasingly think of the burden of the disease. Established biomarkers can show that something is effective in managing HbA1c or managing biomarkers for CVD and so forth. He stressed that the burden of treatment is a major factor today. While there are patients who are excellent at managing their treatment regimens, there are many more who are not and are not capable of doing so. Type 1 diabetes involves dozens of interventions every day. Anything that eases that burden of treatment is going to pick up another small percentage of people who will be successful in managing their disease.

Dr. Saudek continued by saying that for type 2 diabetes, losing weight is critical. Losing weight and getting active is a major need for a large portion of the population of the United States; however, this fact has not penetrated very far. Given this situation, Dr. Saudek asked what criteria are being set up for approval of, for example, obesity drugs. He said that he sat in on a discussion for a company a few years ago and learned that FDA had a criterion for effectiveness in managing diabetes that was independent of blood glucose lowering. In his practice, the first thing he did for overweight diabetics was institute a weight management program. Thus, would not an effective weight reduction medication be valid as a treatment for diabetes regardless of whether it had been shown in animals or in people that it had an independent effect on blood glucose? Other items that have been on the back burner, such as insulin antibodies, also should be continuously addressed.

Dr. Taylor suggested that major opportunities existed to help in understanding new targets and to identify what would be good targets, including genetic markers or other kinds of biomarkers to define subpopulations that are particularly likely to benefit in terms of efficacy or safety from a particular mechanism. In the areas of drug development and a regulatory path for drug approval, he said that

important questions for prevention of type 2 diabetes have followed the excellent work of the DPP. The DPP showed that there is a statistically significant impact of lifestyle and/or metformin. This statistic is important from the viewpoint of science-based evidence, but it does not clarify the question of whether or not a person should be treated prior to developing diabetes to delay the onset for a year or a little longer. Is that year delay really important? Does something irreversible happen during that year? Other questions are "Should glucose be lowered even earlier? Are beta cells irreversibly destroyed during that time period?" Dr. Taylor stressed that if FDA had data showing there was a particular window of opportunity for lowering the glucose before there was irreversible damage, then people would take notice. In other words, there are policy implications for therapy beyond showing a statistically significant difference in an endpoint.

Dr. Shamoon reminded those present that the design of clinical trials frequently creates an artificial situation. The assumption often is that what happens in the clinical trial can be extrapolated to the broader population, such as translating the interventions from DPP to other persons with IGT, without conducting further trials. Dr. Shamoon said that some of the frustration about having scientific-based evidence that is not being put into practice is caused by setting the bar too high. It is very difficult to cost-effectively transition into everyday clinical practice the results of a carefully designed clinical trial. The subjects in the DPP cohort who had all the CVD risk markers and transitioned to diabetes were already close to becoming diabetic. However, in this high-risk IGT cohort, 40 percent of those in the intensive lifestyle group and 30 percent of those on metformin had normalized their 2-hour and fasting glucoses after 1 year. After 4 years, 30 percent of the intensive lifestyle group had normal glucose tolerance. In those who went back to normal, all surrogate markers improved in a favorable direction.

Dr. Taylor said that he was not questioning the validity or importance of the DPP results in suggesting learning more about the window for irreversible harm to the beta cell. His question was based on the burden the regulatory and public health agencies face before spending the money needed to try to prevent type 2 diabetes in all those considered at risk or subjecting them to even the small risk of taking a medication. His intention was to suggest that further information would be helpful to them in making their decisions.

Dr. Orloff agreed that additional information would be helpful. He said that the discussion so far clearly indicated that, regardless of what part of the process a group is involved in, the concept of prevention is very complicated. FDA's responsibility in this area is as complex or more complex, perhaps, than in any other area of the agency's work. He presented some of the principles under which FDA works and described how they come into play in some of the practical aspects of FDA's job. FDA is charged through the Food, Drug, and Cosmetic Act with labeling of drugs for safe and effective use. The mandate involves generating and translating into labeling an enumeration of the expected benefits and risks for an intervention. He reiterated that this is extremely complicated in the context of prevention. Some of the issues in the prevention of type 2 diabetes involve determining which endpoints truly assess benefit. Another key issue is identifying the target population for the drug—who will definitely benefit, who may possibly benefit, and who will not benefit.

Dr. Orloff stressed that in prevention versus treatment, the bar actually has to be raised with regard to requirements for safety. Even though a drug may have been shown to be exceedingly safe for other indications, there are always risks associated with drug treatment and their relative importance obviously increases with decreasing risk of development of the target condition, as exists in disease prevention.

Dr. Tamborlane commented that when he has participated as a consultant on Phase III trials with children and questioned why the pharmaceutical company was doing things a particular way when he thought it should be done a very different way, the feedback was "This is what FDA wants." When asked if the study group had had an opportunity to discuss this issue with FDA, the response was usually "No."

Dr. Tamborlane asked Dr. Orloff what was the best way to deal with such a situation, where a company calls in a consultant with particular expertise in design and conduct of these types of trials and runs into this kind of obstacle.

Dr. Orloff answered that one of the things that has come out of the new legislation has been an easier and more enforceable process for formal interactions between FDA and industry. In addition, there are also many informal interactions. FDA gives guidance on the agency's *current* best thinking on an issue. Dr. Orloff explained that his position and attitude is that "current" is a keyword meaning that everything is always open to change as more information is brought to bear on an issue. He assured those present that he would certainly listen if a drug company came to him and said they thought there was a better way to do something based on expertise gained from other similar trials by using a different method than the FDA-specified one that would not only answer the questions FDA considered important but answer other questions that may be even more important. Dr. Orloff added that bringing effective, safe products to market is an enterprise where reasonable people have to come to agreement. Sometimes reasonable people will disagree, and that is life, but there is always a way to come back and say, "Tell me where you think I am wrong and tell me why, and then we will continue the conversation."

Regarding FDA's policy of calling together a panel of experts—very reliable experts— to review the final product of studies and advise FDA, Dr. Tamborlane suggested that perhaps there could be a mechanism for meeting earlier on with an impartial panel, perhaps from NIH or academia, to provide advice to both sides on evaluation of products and study designs and so forth..

Dr. Orloff responded that part of the process of guidance development involves, or can involve, open public hearings. That is what has been done in the past and what is intended for future guidance development in obesity, osteoporosis, and diabetes. In addition, there is a Notice and Comment process, whereby notice of the existence or issuance of a draft guidance document is made in the *Federal Register* and comments are requested. To the greatest extent possible, the FDA guidance system is an open process.

Dr. Orloff next addressed the advisory process that Dr. Tamborlane had referred to that reviews individual products. This process is to some extent constrained due to the availability of limited information and limited expertise not only on the subject matter, but in making the bridge to regulatory decisions, which is complicated. Advisors are not expected to have regulatory experience. Referring back to the separateness of the guidance process for establishing the required criteria, Dr. Orloff stressed that no one wants to get to the point of an advisory committee to discuss a particular product unless some ground rules have been laid previously so those present understand the basic rules for approval of this type of product.

Dr. Saudek raised the issue that in these 2-day advisory meetings, a great deal of information is shared. Could not that process become integrated, not as a formal regulatory-related process, but as a way to get ongoing conferencing with staff at FDA by objective, outside people who are not linked to the company submitting the product? This could make the guidance development process less passive. People have to initiate contact when something is put in the *Federal Register*. Dr. Saudek suggested that a special panel be brought together to discuss important study design issues related to prominent subjects in public health, as for instance, the studies to evaluate drugs for type 2 diabetes in adolescents. Input from the academic community might have improved those study designs.

Dr. Richard McFarland, Center for Biologics, FDA, agreed with Dr. Orloff's remarks about FDA having an open door. In the Center for Biologics that deals with many novel products that stretch the regulatory paradigm, there is an advisory committee that meets to discuss issues in the realm of translation between science or clinical trials and regulation. This committee, which does not review products for licensure,

meets two, three, or four times a year. Public forums on held on various topics that have generated substantial disagreement. The committee is composed of standing members and supplemented with members of other FDA advisory committees and other people in the particular field under discussion. FDA members also participate. Transcripts of the meetings are on the FDA website. These meetings contribute to the development of FDA's current way of thinking that Dr. Orloff mentioned.

Dr. Taylor added that industry frequently discusses their relations with FDA and he had never heard anybody say that FDA people were not willing to meet with them. There may be times when industry thinks it knows what FDA has said and does not think another meeting would be productive, or there may be delays in scheduling a meeting that interfere with a timeline and make the meeting unnecessary later. However, Dr. Taylor said he would agree that the door has always been open.

A symposium participant commented that a lot is known about the risks for heart disease, and preventing a myocardial infarction (MI) is common practice. When talking about pre-diabetes, people are really referring to pre-myocardial infarction. When someone is in the pre-myocardial infarction state or has had a prior myocardial infarction, the person is treated with a statin to lower high cholesterol. The Scandinavian Simvastatin Survival Study (Lancet 344:1383, 1994) studies and data from other studies on cholesterol lowering clearly show that when cholesterol was lowered in patients with IGT, the risk of MI was lowered and mortality was lowered. In spite of all the data that has been accumulated, the current recommendation for treating IGT is basically to watch it, unless the person has elevated blood pressure or elevated glucose, then the patient is treated for each of those problems. Much of the discussions about preventing diabetes are largely about preventing microvascular disease, while these patients are currently at risk for macrovascular disease. The speaker thus recommended that if cholesterol were treated in the IGT patient, even if the patient had a "normal" LDL of 130, then the patient would be treated the same as a patient with a prior myocardial infarction or a patient with diabetes. In response to a comment from Dr. Tamborlane that there is no current evidence-based data showing that lowering glucose is going to prevent cardiovascular disease in the IGT group at high-risk for diabetes, the speaker said he was referring to giving the IGT patient a statin not a glucose-lowering medication.

The symposium participant continued that not everybody with IGT develops diabetes. Although patients with diabetes tend to have macrovascular disease and most will die of macrovascular disease, diabetes is a microvascular disease. He noted that many patients are so elderly that they never will suffer from microvascular disease, even when they develop diabetes. Meanwhile, there is a large body of data showing a huge impact is possible on CVD in these patients, and it is not being done. The participant's point also was that a clinical trial is not needed to answer every question that comes up, when there already exists good data from other trials that can be analyzed and applied. He urged the group to mine the data that they had, stressing that the approaching epidemic is serious enough to call for such measures.

Dr. Sherwin said that in the consensus data, he believed there was a recommendation to treat this high-risk population for cholesterol.

Dr. Fradkin stated that studying the metabolic syndrome from the viewpoint of treating glycemia in persons with pre-diabetes or the metabolic syndrome did not seem to be the practical direction to take. Therapies studied in relationship to the metabolic syndrome would likely affect multiple components of the syndrome, rather than a specific component such as glycemia. On the other hand, the DPP interventions clearly did not exert their effects solely on glycemia.

Another member of the audience followed up on the issue of the amount of accumulated data that exists. Researchers in CVD are conducting large outcome trials and pooling the data in very large registries to find out more about the natural history of cardiovascular disease. The speaker recommended that academia, NIH, and FDA do the same in diabetes. This could enable the sub-phenotyping of patients and

increase understanding of how these sub-groups respond to different drugs. There are not a lot of incentives for individual pharmaceutical companies to partner with one other to do this, and this is not likely to happen; however these companies do have quantities of data that are left behind as they move on to other therapies. Dr. Fradkin noted that this was a good suggestion.

Dr. Tamborlane said that if IGT is defined as a disease, the outcome for prevention would be a normal fasting glucose. In DPP, the lifestyle intervention was the most effective, but metformin was also highly effective in restoring glucose to normalcy. In the metabolic syndrome, lowering blood pressure to normal would apply.

A participant stated that defining a disease requires that there are specific problems related to that disease. Other than by testing for IGT itself, there are no symptoms of IGT in a patient. It is unknown what complications, if any, are associated with IGT. In discussing biomarkers, the speaker noted that they had not discussed the question of what biomarkers are pathogenic and what markers are not. In IGT, there is a glucose abnormality that associates with cardiovascular disease. The question is whether or not IGT is the cause of early cardiovascular disease or just a marker for it. It was suggested this was the type of question that an NIH study could address. To call IGT a disease, it would have to be shown that in itself IGT causes morbidity, not that it is just associated with another disease. Biomarkers have to be identified as to whether they are a cause of a disease or whether they are an association of the disease. Which raises the question about obesity. Is obesity a disease? Or is it only associated with disease.

Dr. Shamoon responded that he had no doubt that obesity is a disease.

On the other hand, Dr. Eckel said he would call obesity a disorder, a physiology of an expanded fat mass, the consequences of which are diseases such as hypertension, dyslipidemia, glucose intolerance, diabetes, obstructive sleep apnea, pulmonary hypertension, and so forth. There is reasonably good evidence that in the early 20$^{th}$ century, through World War I and World War II, being fatter allowed for greater survival when famine ensued. As a survival advantage, obesity has gone astray today because people live so much longer.

Dr. Orloff remarked that the overall goal for all those present—industry, academia, advocacy groups, and the government—was to extend life and to improve health for type 1 and type 2 diabetes patients. Based on the recurrent message heard at today's meeting that tools currently available were not being used optimally, he asked those present if they felt an NIH consensus conference on prevention would now be appropriate to address the issues raised in this meeting. Dr. Orloff commented that unconflicted, NIH consensus conferences had historically been successful in moving fields forward at a practical level in instructing physicians in how to manage their patients and use the tools that they had available.

Dr. Saudek agreed that consensus was particularly needed regarding what to do about the metabolic syndrome and about IGT. He added that it would take a good deal of work to arrive at such a consensus.

Dr. Fradkin explained that, in general, consensus conferences are held when the data is at a point to ensure a consensus can be reached. She said she believed that many of the important questions raised in today's meeting needed to be addressed and answered before there would be sufficient clear data for a consensus conference on, for example, longer-term transplants. The joint ADA-NIH group that looked at interpreting the DPP essentially was a consensus conference that assessed the current state of the data. There really has not been much additional data beyond the DPP at this point that would justify holding a consensus conference.

Dr. Taylor agreed that there are many questions left to be answered about current and potential future therapies and suggested that there would be some value in reaching consensus on what are the most

important questions to ask. This would help in developing a plan for obtaining answers. Dr. Fradkin agreed that clarifying the questions and the steps needed to answer them would be a good approach before trying to arrive at consensus on therapies based on current answers.

Dr. Orloff and Dr. Fradkin thanked the speakers, panelists, organizers, and participants for their contributions to an excellent and successful meeting.

The meeting was adjourned at 12:40 p.m.