Joint National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Food and Drug Administration

Predictors, Pathogenesis, and Prevention of Insulin Resistance and Type 2 Diabetes Meeting

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National Institutes of Health
Bethesda, Maryland

Meeting Summary

WELCOME AND OPENING REMARKS, GOALS OF MEETING

Judith E. Fradkin, MD; Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, Maryland

Dr. Fradkin welcomed guest speakers, panel members, and attendees. She noted that it has been 5 years since the results of the Diabetes Prevention Program (DPP) were announced. The American Diabetes Association has developed a position statement based on the findings of the DPP, and a major public health campaign focused on the incontrovertible evidence that lifestyle factors can prevent or delay the impact of type 2 diabetes has been launched by the NIH and the Centers for Disease Control and Prevention (CDC) through the National Diabetes Education "Small Steps, Big Rewards" Campaign. Despite these and other research findings and outreach efforts, the rates of type 2 diabetes in the United States continue to increase. Current efforts are underway through the DPP Outcomes Study to assess the long-term benefits of lifestyle factors and metformin. In addition, NIDDK has a robust program to develop more cost-effective lifestyle interventions. More recent research has identified genetic factors associated with the risk for diabetes, and the DPP has shown that individuals with the major genetic risk factor for type 2 diabetes respond to the DPP lifestyle intervention. However, it is not clear how or when to incorporate these molecular findings into practice. Although lifestyle was effective in all subgroups, relative efficacies of lifestyle and metformin drug interventions varied within subgroups (e.g., by age) in the DPP. The impact of the combination of lifestyle plus drugs on risk remains largely unknown. Dr. Fradkin pointed out that metformin has not yet been presented to the FDA for a prevention indication largely because it is a generic drug. However, given recent findings, the FDA is expected to be questioned about indications for pharmacologic prevention of diabetes.

The current meeting, which was co-sponsored by the NIDDK and the FDA, was a follow-up to a meeting held 2 years ago. Participants and attendees are asked to consider the state of the science of diabetes prevention research within the context of the goals of the meeting, which are to:

- Share the latest information about predictors for type 2 diabetes and discuss obstacles and solutions for widespread use of a predictor system;

- Explore potential common etiology pathways for development of syndromes associated with insulin resistance, obesity, and type 2 diabetes and translation of this information into clinically relevant interventions; and

- Reexamine the adequacy of the current data to support an indication to treat for prevention of diabetes.

Through information presented and discussed during the panel Q&A sessions, the key questions to be answered by the end of the meeting are:

- What important, unanswered issue(s) can only be answered through a large clinical trial?

- Is there any area that is not being explored that could benefit from targeted funding opportunities?

- What is considered sufficient evidence to justify a pharmacological treatment to prevent or delay the onset of type 2 diabetes?

SESSION 1: PREDICTORS OF TYPE 2 DIABETES

Moderator: Myrlene Staten, MD, NIDDK

Current Status of Predictive Models—Known Key Variables

Michael Stern, MD, University of Texas at San Antonio

The Framingham model for predicting coronary heart disease (CHD) risk (Wilson et al., *Circulation* 97:1837-47, 1998) has been validated in a number of independent studies. Factors identified as influencing CHD risk include age, sex, total and high-density lipoprotein (HDL) cholesterol, cigarette smoking history, systolic blood pressure, and presence or absence of diabetes. Results of the San Antonio diabetes predicting model found that many of the same factors for CHD risk, including age, sex, HDL cholesterol, systolic blood pressure, and family history of diabetes, in addition to fasting glucose and ethnicity predicted risk for diabetes (Stern et al., *Ann Int Med* 136:575-81, 2002). Since this initial report, the findings of the San Antonio study have been validated in three published reports: the Mexico City Diabetes Study (Stern et al., *Diabetes Care* 27:2676-81, 2004), the Japanese American Community Diabetes Study (McNeely et al., *Diabetes Care* 26:758-63, 2003), the Atherosclerosis Risk in Communities (ARIC) Study (Schmidt et al., *Diabetes Care* 28:2013-8, 2005), and in one as yet unpublished study, the Insulin Resistance-Atherosclerosis (IRAS) Study.

Dr. Stern provided a demonstration of a diabetes risk calculator based on the Framingham CHD model and the San Antonio diabetes model to identify high-risk patients. The prototype uses an Excel spreadsheet and can be used in a doctor's office or clinic or public health setting. Patient data for each of the risk factors (i.e., age, sex, HDL cholesterol, height, weight, blood pressure, etc.) are entered, and the system calculates the person's 10-year risk for both CHD and diabetes. Data entry is relatively quick and simple, and the calculations are instantaneous. By modifying

the information entered (e.g., decrease in weight or blood pressure), the risk level will change accordingly. Thus, the model can be an effective patient counseling tool by showing patients "before" and "after" calculations of risk with a change in their weight, blood pressure, or other measure. In an example of an overweight 51-year-old male smoker with hypertension, elevated cholesterol and TG, a fasting glucose of 90, a BMI of 33.5 kg/m^2, and a family history of diabetes, Dr. Stern demonstrated that one change—a loss of 30 pounds (from 220 to 190 pounds)—dropped the patient's 10-year risk of diabetes from 38.9 to 31.3 percent with no change in his 10-year risk of CHD (21.4 percent). A decrease in the patient's blood pressure combined with this weight loss resulted in an additional reduction in his diabetes risk, to 27.4 percent, as well as a drop in his CHD risk to 17.3 percent. Dr. Stern showed how additional changes in HDL and total cholesterol can decrease risk of diabetes and CHD even further.

Despite the apparent ease and ability to produce results quickly, these predictive models do not approximate the level of popularity of tools such as an impaired glucose test (IGT), which requires a 2-hour glucose tolerance test, or assessment of metabolic syndrome, which is not standardized and is based on a selection of dichotomous cut points rather than a complement of continuous values. Dr. Stern argued the superiority of the risk calculator (and similar tools) using diabetes and heart disease incidence data from studies such as the San Antonio Heart Study (n = 5158) and the Mexico City Diabetes Study (n = 1353) (for independent validation of the diabetes data) in conjunction with statistical tools, such as receiver operating characteristic (ROC) curves. A series of comparisons to estimate diabetes and CHD risk showed that in each case, the predicting models alone yielded a greater sensitivity or lower false positive rate than the metabolic syndrome assessment alone and thus appeared to be better predictors of future disease. Adding the metabolic syndrome to the predictive models did not improve the predictions further. In one example, applying the diabetes prediction model to the Mexico City Study data while holding the false positive rate constant (at 38.7 percent) produced a sensitivity of 76.0 percent for the predictive model alone, 74.4 percent for the combination of the model and the metabolic syndrome, and 62.4 percent for the metabolic syndrome alone.

Dr. Stern also explored operationalization of a public health strategy for preventing CHD that incorporates metabolic syndrome, specifically in response to the statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI): "The metabolic syndrome is a secondary target for reducing cardiovascular events" (Grundy et al., *Circulation* v. 112, 2005). This exercise compared a two-stage strategy that considers those at increased risk for CHD (based on Framingham score) plus those not at high risk according to Framingham, but with the metabolic syndrome, with a one-stage strategy that merely relaxes the Framingham risk threshold in such a way as to generate a target population of similar size as generated by the two-stage strategy. Applying the standard Framingham score of a 10-year, 20-percent CHD risk cutoff to the San Antonio study cohort identified 193 participants (4.3 percent of the population) with a specificity and a sensitivity of 24.5 and 97.0 percent, respectively. Adding patients with metabolic syndrome *or* relaxing the Framingham score threshold to 8.4-percent 10-year risk identifies similar-sized target populations (n = 1041, or 23 percent of the cohort)that have increased sensitivity but reduced specificity compared with the more stringent Framingham score. However, application of the relaxed Framingham score yields a greater sensitivity (65.9 percent vs. 54.8 percent) and specificity (79.6 percent vs. 78.9 percent) than the two-stage strategy incorporating the metabolic syndrome. In all combinations tested, the relaxed

Framingham score strategy outperformed the combined strategy that includes the metabolic syndrome.

Fundamental to a robust predictive model is an acceptable area under the ROC curve (aROC). An aROC above 80% is generally considered quite good. The aROC may be interpreted as the probability that someone who develops a disease will have had a higher baseline risk score compared with some who did not develop the disease. Thus, an aROC of 80% means that 80% of the time the individual who later developed the disease will have had a higher risk score at baseline than the individual who remained free of the disease, and 20% of the time it will be the latter individual who has the higher baseline risk score. Dr. Stern identified the following requirements for establishing new risk factors with added value in predicting models: (1) A suitable data set for model development, namely, a prospective cohort study that includes measurement of the proposed new risk factor (e.g., CRP) along with conventional risk factors at baseline, and measurement of outcomes of interest at follow-up to determine whether the novel risk factor significantly improves the aROC (e.g., >85 percent); (2) an independent validation data set(s) with the same requirements as the data set for model development; and (3) the cost of measuring the new risk factor. Dr. Stern also identified several barriers to the adoption of predictive models in clinical and public health practice as follows: (1) The absence of naturally occurring cut points for action (i.e., continuous variables), (2) although the cut-off points for other risk factors (BP, cholesterol, metabolic syndrome, etc.) tend also to be arbitrary, they have been "hallowed by time" and thus are widely accepted as "calls to action" for intervention; and (3) the need to develop action points for risk scores, perhaps through an international conference of experts.

In conclusion, Dr. Stern noted that researchers and clinicians need to recognize the availability of validated models for predicting CVD and diabetes that outperform the metabolic syndrome. In addition, whether the incorporation of new risk factors into these models improves their performance needs to be documented. Finally, barriers to adopting these models in clinical and public health practice exist, but they can be overcome.

Potential New Predictors of Insulin Resistance and Type 2 Diabetes—Leveraging New Scientific Insights
Jorge Plutzky, MD, Brigham & Women's Hospital

Dr. Plutzky described the discovery and investigation of novel predictors of insulin resistance and type 2 diabetes based on a model that integrates the vector of time preceding clinical indications of diabetes, biomarkers and surrogates associated with altered metabolic pathways, and genetic mechanisms of very early perturbations in the pathophysiology of this disease. The model also includes drivers of atherosclerosis and obesity as contributors to the development of insulin resistance and diabetes. The key organizing principles for this research framework include insulin resistance and new predictors that involve molecules that modulate resistance, excess central adiposity and adipogenesis, and the external forces that influence energy balance (intake, expenditure).

Given the fundamental role of endothelial dysfunction in insulin resistance and diabetes, atherosclerotic risk factors are considered possible predictors of these two conditions.

Abnormalities in the microvasculature, where metabolic processing of TG-rich lipoproteins occurs, may involve dysfunction, while abnormalities in the endothelium of the macrovasculature may explain why atherosclerosis and dysmetabolism are closely linked. A nested case-control study within the Nurses Health Study found that the risk of confirmed diabetes was significantly increased in association with baseline levels of endothelial markers (e.g., RR of 3.56 for ICAM); risk was independent of inflammation and insulin and persisted after adjustment for early diabetes and early CVD (*JAMA* v. 291 April 28, 2004). Whether insulin resistance in diabetes and the early onset of disease are based in the endothelium requires further investigation.

The role of inflammation in the vasculature as a possible unifying factor for atherosclerosis and diabetes has been explored, with C-reactive protein (CRP) and IL-6 representing only two of many potential predictors. Analysis of data from the Women's Health Study shows significant associations between IL-6, CRP, and type 2 diabetes, even after adjustment for BMI (Festa et al., *Circulation* 102:42-47, 2000; Pradham et al., *JAMA* 286:327-34, 2001). Stepwise changes in CRP levels are observed with the addition of components associated with diabetes and insulin. These findings suggest that CRP may have a role as a biomarker and surrogate in assessing diabetes risk in addition to its association to atherosclerotic risk.

Another area of investigation involves insulin resistance in three tissue beds: the liver, skeletal muscle, and adipose. Recent clinical data indicate abnormal deposition of lipids in these settings, particularly the liver. Among the possible new predictors are liver function tests, which have been correlated directly with fasting insulin, fasting glucose, and waist circumference and inversely with insulin secretion (Hanley et al., *Diabetes* 53:2623-2632, 2004). In this study, the strongest correlations were found for ALT and AST. In another study, the DREAM trial, rosiglitazone had a favorable effect on liver function tests (*Lancet* 368:1096-1105, 2006; *NEJM* 355:1551-1562, 2006). Possible mechanisms for altered liver function include insulin resistance in nonalcoholic fatty liver disease, in which lipid deposition in the liver accounts for resistance; hepatic changes as a reflection of systemic insulin resistance and fat deposition in other parts of the body, such as the muscle; and inflammation resulting from hepatic fat deposition, which, in turn, triggers an acute response by cytokines, CRP, and factors originating in the liver.

Other biomarkers include quantification of visceral fat using new technologies; improved measures of insulin (e.g., pro-insulin); improved characterization of pathways of adipogenesis, fat deposition, and relative fat depot deposition; and the role of the PPAR-gamma-regulated target adiponectin in skeletal muscle bioenergetics (Civitarese et al., *Cell Metab* 4:75-86, 2006). Many drugs such as rosiglitazone were discovered serendipitously, and the natural ligands for these agents are not known. It is hoped that taking a pathways approach to these questions will facilitate identifying natural receptors and, in turn, to the discovery of defects in pathways that lead to syndromes that can be treated with, for example, thiazolidinediones. In one study, Dr. Plutzky and his colleagues identified through lipolysis mechanisms three nonoverlapping pathways that can generate endogenous PPAR activation and suggests a possible anti-inflammatory role for lipoprotein lipase (Ziouzenkova et al., *PNAS* 100:2730-2735, 2003). Pathways-based research also has led to the identification of natural molecules through carotenoid- and retinoid-modulated responses, and to studies of drugs that have adverse effects (e.g., thiazides, protease inhibitors) and can induce diabetes or lipodystrophies, or that have

unanticipated positive effects on the metabolic environment that favors increased adiponectin and decreased food intake (e.g., endocannabinoid receptor antagonists). Of growing interest are studies of retinoid signaling indicating that serum retinol binding protein 4 (RPB 4) may be associated with the development of diabetes through glucose transport mechanisms, specifically reduced expression of glucose transporter 4 (GLUT4) in adipocytes, which is an early feature of insulin resistance (Graham et al., *NEJM*, 354:2552-2563, 2006).

Less common genetic phenotypes, such as genetic lipodystrophies, have informed certain pathways to diabetes; for example, a specific mutation in PPAR-gamma leads to a unique form of lipodystrophy that results in insulin resistance and diabetes. Recent work on a variant of the transcription factor 7–like 2 gene (*TCF7L2*) on chromosome 10q revealed an association with type 2 diabetes; initial analysis indicates that this variant accounts for 21-percent attributable risk for the disease among carriers (*Nature Genetics* 38:320–323, 2006). Genome-wide scanning of Framingham samples led to the discovery of an association between obesity and a variant of a common gene, *INSIG2*, which is present in an estimated 10 percent of individuals (*Science* 312:279-283, 2006).

Integrating the complement of potential risk factors and strategies will be achieved through advances in technologies and analyses spanning the array of data from genetic assays, animal studies, clinical trials, and observational findings. This approach will assist in validating results from different sources and harnessing the existing tools and findings in a precise manner, leading to fundamental insights with direct relevance to clinical interventions and new early-stage targets for further investigation.

Inhibitors and Motivators for Prevention of Diabetes: Understanding Them Through Research
K.M. Venkat Narayan, MD, MSc, MBA, Emory University

Clear evidence-based policy and guidelines that integrate the patient, provider, and health-care system are needed for developing an effective public health program to prevent diabetes. Fundamental to this effort is determining (1) what is being prevented (diabetes or CVD); (2) the types of interventions (lifestyle, societal, or drug, or a combination thereof) being targeted; (3) in whom prevention is sought (all high-risk people, those with IFG and/or IGT); and (4) the evidence supporting prevention interventions for the sub-population targeted. Clarifying these issues should help develop targeted messages and interventions that translate research findings into practice.

Although not all factors associated with the development of type 2 diabetes and CVD overlap, interventions built around common factors for both diseases (elevated TGs, elevated glucose, low HDL, elevated blood pressure) would likely reach the greatest number of affected people as possible. A clear understanding of the size and characteristics of the target population(s) is also essential. For example, data for U.S. adults at least 60 years old suggest that about 20 percent have diabetes (diagnosed and undiagnosed), an additional 20 percent have pre-diabetes (IFG >110 mg/dL and/or IGT), 40 percent are at high risk (based on BMI, family history, ethnicity), and about 20 percent fall into an "other category," Thus, up to 80 percent of this population have or are at increased for diabetes. The impact of changes in the definition of disease and pre-disease also must be considered. For example, the shift in the impaired fasting glucose (IFG) cut

point from 110 to 100 mg/dL increased the estimated affected U.S. population (40–74 years old) from 20 million to up to 41 million. Risk-benefit assessments are also essential. A review of available data on lifestyle interventions from randomized clinical trials (RCTs) and cohort studies indicates that of four RCTs targeting IGT alone, the benefit size for preventing diabetes ranges from 25–58 percent. While the harm associated with lifestyle changes in diet and exercise in general are low, the costs associated with effective implementation would be significant. No trials exist on the impact of lifestyle changes on IFG, but extrapolation to IGT suggests similar harm and cost profiles. Post-hoc analysis of MRFIT data of persons at high risk (e.g., family history) for diabetes but without dysglycemia suggest an 18-percent reduction in risk through lifestyle changes, low harm, and very high costs to implement a prevention program targeting this large group.

Balancing available evidence with potential harm and costs will drive the intervention strategy. The best scenario involves cost-effective interventions and messages and a target population for whom the benefits are strong and harm is minimal. The readiness of the health-care system and society to deal with the challenge of pre-diabetes, which would double or triple the current burden on the health system, must also be taken into consideration. In the United States, despite direct costs of approximately $90 billion for care of persons aged 20 and older with diabetes, the level of implementation of good, simultaneous control of three key risk factors (blood glucose, blood pressure, and total cholesterol) is poor: only 10 percent of the affected population achieve this goal. The economic realities of competing priorities of the health-care system and society, cost effectiveness, implementation costs, willingness to pay, and identification of payers all contribute to decisions regarding final products and policies.

The potential impact of effective lifestyle interventions on diabetes prevention is great. Analyses based on cumulative incidence of diabetes over the lifespan suggest that implementation of beneficial lifestyle habits and activities can delay the onset of diabetes within the U.S. population by approximately 11 years. Further analysis of DPP findings shows that compared with the placebo intervention, the DPP lifestyle costs about $1,100 per QALY (quality-adjusted life-years) over a lifetime, while waiting to treat the disease can cost multiple times that amount. However, even a low lifetime expense involves cost and is not usually viewed by health-care vendors and systems as a high-value investment over time. One study found that if private insurers covered the costs of lifestyle interventions for persons between ages 50 and 65 years old, after which time Medicare would cover the costs, the incremental cost per QALY is approximately $10,000 for the private insurer and cost-saving for Medicare would occur because fewer persons with diabetes would be expected to enter the system (*Diabetes Care* 26: 2518-2523, 2003). Based on this analysis, cost-sharing strategies that offer the DPP lifestyle intervention to eligible persons between ages 50 and 64 could provide a financial return-on-investment for private payers and long-term benefits for Medicare. It was suggested that Medicare consider seeking authority to offer the DPP lifestyle intervention to eligible adults prior to age 65. Strategies to implement such a plan require further study and detailed discussion.

At the level of the individual, studies indicate that most people at high risk for diabetes would be unwilling to pay full program costs. However, studies also show that approximately three-quarters of at-risk individuals are unaware of personal risk in part because of the failure of health-care providers to discuss risks and solutions with their patients. Key to overcoming these

barriers include understanding how co-payments will influence patients and systems, determining how costs will be reimbursed, and ensuring effective risk communication in delivering the key findings of the DPP.

Any large-scale intervention plan needs to locate and identify the target population(s) (i.e., through clinics, private practice, etc.); ensure that appropriate system capacity and infrastructure are in place for screening and intervention; and ensure that providers possess the attitudes, skills, and resources consistent with the proposed lifestyle interventions. The costs associated with all components also must be assessed and secured. At the clinical interface, the most meaningful statistic is the positive or negative predictor value of the test, which is sensitive to the prevalence of the condition. Ideally, the test will be simple and useful across populations.

Many important lessons can be applied to diabetes prevention based on studies designed to improve diabetes care, such as the TRIAD Study (http://www.triadstudy.org/index.shtml). This multi-center study includes six Translational Research Centers and five additional VA sites that collaborate with 10 health plans and 66 provider groups serving a combined total of approximately 180,000 patients with diabetes. TRIAD results indicate that overall the study's process indicators are poor predictors of outcomes. Because the choice of indicators can drive the system, it may be preferable to replace indicators with more sensitive intermediate outcome measures for pre-diabetes prevention programs or studies. The study also found that education and income levels influenced delivery of care, even after adjustment for confounders, including health-care coverage. A future system will need to determine how to overcome these barriers to ensure more equitable delivery of care. Several clinical care strategies thought to be helpful, such as keeping a diabetes registry and physician reminders, did not appear to affect outcomes in the TRIAD (e.g., improved A1c level/glucose control). Processes of care rates and intermediate outcomes were significantly higher for the VA system compared with commercial providers. The basis for this difference needs to be explored further to deliver better prevention strategies to the larger population outside the VA. A review of 160 physician interventions in 99 trials identified reminders, patient-mediated interventions, outreach visits, opinion leaders, multifaceted activities, and audits and feedback as the most effective strategies to change physician behavior, whereas formal CME conferences were the least effective (Davis, *JAMA* 274:700-705, 1995). Dr. Narayan also reviewed several behavioral theories that may be useful in affecting change in patient behaviors regarding diabetes prevention. Research on the application of these theories to diabetes prevention is very limited, and further investigation is warranted.

Questions for shaping the next phases of intervention research and public policy development include: Should a network of translation research centers of excellence be created to promote primary prevention (e.g., with focus on policy, behavioral science, strategies for screening, etc., to stimulate change)? Should the use of alternative delivery systems for lifestyle interventions be considered (e.g., YMCA, weight loss programs such as Weight Watchers and Jenny Craig)? Should an evidence-driven national diabetes prevention plan with political buy-in be developed, and who would assume leadership of such a program?

Panel Discussion
Dr. Staten, Dr. Stern, Dr. Plutzky, Dr. Narayan

Dr. Stern was asked whether he has incorporated any of the newer markers (e.g., as described by Dr. Plutzky) into the diabetes or Framingham predictive models and if so, how changing the markers, whether old or new, affected the aROC? Dr. Stern encouraged researchers with access to suitable databases (i.e., that meet the criteria described in his presentation) to develop and incorporate markers of interest into the predictive models to determine if they outperform the standard set of variables. The key is to systematically select variables (e.g., through logistic regression) and to include conventional risk factors in the model. It is also important to consider all of the costs associated with use of any new markers proposed for use in screening. Dr. Stern added that that while many accessible data sets exist, he doesn't have access to the data or information on many of the risk factors described by Dr. Plutzky. For example, Dr. Stern noted that he hasn't yet explored the role of CRP in these models. Because baseline specimens from the San Antonio Diabetes Study, which started in 1980, are nearly exhausted, it is unlikely that new markers will be isolated from this cohort. He noted further that feasibility is a concern when developing predictive models. For example, insulin was deliberately left out of his team's model as a candidate predictor because measurements are not yet standardized. A cautionary note was that models may "max out" once five or six predictors have been incorporated. Dr. Plutzky noted that for any test, the issues of validity, reproducibility, and cost must be addressed. The molecular work provides the rationale for identifying potential risk factors and predictive variables. Tests exist to identify causal relationships between phenotype and genotype. Subsequent comments made the point that information is lost when continuous variables are reduced to dichotomous variables and that when definitions of cut points or variables change, some misclassification will occur. However, similar points can be made with respect to an 80-percent aROC, which will include some false-positives while missing some true cases. The extent of misclassification can be characterized though the use of ROC curves.

Dr. Narayan made the following points regarding prediction: (1) The addition of variables needs an *a piroi* reason for inclusion in a model. For example, when BMI or waist circumference is included in a model, the effect of CRP is negligible. It is not clear if CRP is an independent variable. Thus, it is important to weigh the etiologic and pathophysiological bases for considering the potential value of a variable. (2) As noted by Dr. Stern, adding variables to a model beyond five or six will generally have minimal impact on discriminating between high and low risk individuals. (3) Distinctions should be made regarding the role of predictive models for communicating risk versus identification of persons or groups who might benefit from an intervention.

Barbara Hansen made a suggestion to add longitudinal data to the predictive models to describe the time curve of changes in variables, which is critical to interpretation. Use of longitudinal data, in turn, reflects the need for the collection of samples over time. A request was made that NIDDK take stronger leadership on standardization of an insulin assay, as was done with the lipid clinics. Insulin should be a standard variable in these models, but this is not possible, as Dr. Stern pointed out, because of the wide variability among assays. Even with a standardized, reproducible insulin assay, it is important to remember that insulin changes follow an inverted U-

shaped curve. Thus, use of a single insulin value cannot be used as a reliable predictor. Although values on the down slope of the curve are excellent predictors, such an assessment as to direction cannot be made with only one measure. An additional comment focused on the duration and termination of the DPP, specifically, that the trial was cut off at the point of maximum efficacy and that an additional 5 years of actual intervention (not just follow-up) are needed to evaluate the effect of lifestyle over the long term. It may be that the efficacy of weight loss, including the amount of weight lost and the duration of sustained weight loss, is the key predictive variable. Finally, the role of appetite regulation and the physiology of appetite regulation should be part of the discussion and assessment of risk and prevention. Regarding insulin assays, Dr. Stern pointed out that the ADA (America Diabetes Association) has a major initiative underway to standardize insulin assays. Dr. Scott Campbell, vice president of research for the ADA, commented that the manuscript describing this effort is expected to be published in the near future in *Clinical Chemistry*. A follow-up paper is planned on the potential use and application of a standardized assay. In addition, funds may be allocated to expand the study to include a reference method and a reference material for insulin in the next 6–9 months.

Dr. Knowler noted that he and his colleagues have found risk prediction engines and calculators such as Dr. Stern's, to be good motivational tools. However, because the risk factors used in the model usually do not change independently, the team is still trying to determine how best to use it. Development of a more sophisticated subpredictor informational model may prove useful, for example, in estimating the extent to which lipids improve if the patient loses a specific amount of weight. Dr. Stern commented that use of these models as a counseling tool is to give patients an impression of how and to what extent they can modify their risk for diabetes (or CHD), either favorably or unfavorably. The science behind the models is founded on their predicting ability, not their potential use as an adjunct to counseling. As with other statistical measures, there is an error variance associated with the predictions. A key use of these models is within a public health context to identify target or high-risk populations for interventions.

Dr. Yudkin commented about the point of reversibility of disease risk not being 100 percent, noting, for example, that once a person has developed hypertension, risk will not revert to a level comparable to that associated with a "normal" blood pressure level, even when the condition is well controlled. He also echoed the opinion of others regarding the lesser predictive value of the metabolic syndrome compared with the Framingham model because of the use of dichotomous rather than continuous variable. In addition, using any three of the five variables as the threshold for assessment of metabolic syndromes incorrectly assumes that each of the variables or criteria carry the same weight or have an equivalent effect. Further, the most important variable for CHD, age, is not one of the variables in the metabolic syndrome. For predicting diabetes, glucose is the most important variable and thus should not be given equal weight against other measures. Regarding prevention, researchers and clinicians need to consider why the goal is to prevent diabetes. A key factor is that patients with this disease develop both micro- and macrovascular complications. Although halting or delaying the progression from IGT or IFG to diabetes places patients below the threshold for diabetic retinopathy, nephropathy, and neuropathy, their CVD risk is still increased, and they are not in an environment of cardiovascular prevention. In conjunction with these points, Dr. Yudkin asked about the status of the DPP CV outcomes associated with lifestyle interventions. He noted further that researchers need to question whether pharmacological interventions are actually preventing diabetes or otherwise disguising the

disease and when the medications are stopped, the clinical manifestations of diabetes will become apparent. Investigators also need to consider the DPP finding that one case of diabetes is prevented with pharmacological treatment of seven persons; specifically, what is the true likelihood that the six other patients would have gone on to develop frank diabetes. The other significant challenge is that prevention efforts in this country increasingly face overall trends that counter these efforts and increase diabetes and CHD risk, such as higher BMIs and an aging public.

Dr. Ratner noted that data on cardiovascular events in the DPP were published approximately 1.5 years ago in *Diabetes Care*. The findings indicated an incident rate of 0.6 events/100 patient-years within the control group. This was comparable to the rate of 0.5 events/100 patient-years in the DREAM Trial. Thus, while there is an increased relative risk for CV events in patients with IGT and IFG, the absolute risk is relatively small. To power a study to find an effect on CV events is not feasible (i.e., follow 20,000 patients over 10 years). The Diabetes Prevention Program Outcome Study should provide an indication of the long-term impact on CV events. Another attendee commented that the complications and difficulties associated with any medical condition (CNS changes, stroke, and surgical interventions) will be worse in the presence of diabetes and may be related to hyperglycemia. Thus, although the CV event incident rates and risks have been determined in these studies to be low, it might be prudent to consider a large-scale diabetes prevention study to better assess the risk of CV events in this population.

Regarding reversibility of risk, Dr. Plutzky commented that once a sufficient number of very precise predictors (e.g., within a genetic context) are available, a more accurate prediction of reversibility of risk may be possible; at that point, individuals may have a greater range of options as to when to commence an intervention to prevent or reverse increased risk. He noted that explaining the results of the DPP with his patients has proven to be a very successful motivational tool; showing the potential positive effects of something as simple as walking can be powerful. With respect to the possible masking of drug interventions, Dr. Plutzky pointed out that data from TRIPOD and animal model data suggest that TZDs may offer beta cell protection, with some alteration of the natural history of the disease, although this remains to be proven in humans. Dr. Plutzky also noted that washout data from the DREAM study will be closely analyzed to consider this although this remains a hot topic of discussion as to the meaning and importance of washout data. Dr. Stern added that washout data from the DREAM study are expected to be released at some point in the future, which may help clarify if the drug interventions used delay the onset of diabetes or mask disease progression.

Dr. Li (University of Pennsylvania) asked Dr. Stern about use of growth factors and other surrogates as predictors of insulin resistance or type 2 diabetes, in the absence of a standardized insulin assay. Dr. Stern commented that many are good predictors; however, it is not clear whether in combination they are superior to insulin. When added to the predictive models, these factors do not alter the overall performance of the model; for example, the AUROCs remain in the low 80-percent range.

Dr. Eckel commented that lipid accumulation in the liver, through its potential effects by not-yet-well-understood mechanisms, raises the issue of TGs as possibly differentially transmitting information (versus free fatty acids), as reflected in the lipoprotein data presented by Dr. Plutzky.

A recent knockout study demonstrated the inability of the liver to regenerate in the absence of accumulation of extrinsic fatty acids; however, when the animals' cells were loaded with glucose, TG synthesis occurred, liver regeneration proceeded. The islets may operate similarly; that is, when too little or too much TG is present, insulin secretion is adversely affected.

Further support was voiced for the need for a standardized measurement for insulin because the islet cells are critical to the development of type 2 diabetes. Without this key component, how reliable or accurate are the predictive risk models? A second point stressed the importance of adopting lifelong changes to prevent crossing over the threshold to increased risk for micro- and macrovascular complications of diabetes. The science of genomics and proteomics needs to be integrated more completely into these discussions not using a reductionist model but as a component of systems biology approaches. Dr. Narayan commented that an assessment of interactions between variables needs to be built into the analysis of how the overall system predicts.

Dr. Ratner commented about Dr. Narayan's proposed shift from process measures to outcome measures based in part on the findings of the TRIAD Study. Dr. Ratner noted that the VA system has made significant changes and advances in the past 20–30 years and that it can serve as a highly informative model to study those changes and their justification. Dr. Narayan cited a paper that described the transformation of the VA medical system and the results of this transformation in terms of care for chronic diseases (Jha et al., *NEJM* 348:2218-2227, 2003). The paper identifies four key changes: (1) Institution of strong electronic medical records documentation, which included registration of high-risk patients that allowed risk-stratifying reminders and notes; (2) a shift in some financial incentives from utilization to rewarding quality of patient outcomes; (3) institutionalization of patient education; and (3) production of new guidelines and mechanisms for implementation of the guidelines. The changes have been in place since the mid-1990s and reflect a systems approach to care that takes into account the lifetime of the patient. Several other papers have validated the superiority of the VA system.

Dr. Phillips asked about three key factors driving the concept of preventing diabetes—the beta cell, "buying time," and "the long view"—with the ultimate prevention strategy realized through a system of vigilant detection and management. The progression from insulin resistance to frank diabetes is tied primarily to the beta cell. However, the only good marker of the status of beta cell function is glucose, and available treatments do not appear to be able to impart a lasting effect because they cannot reverse beta cell changes or restore function. The goal of the DPP was not necessarily to prevent diabetes but rather to delay the onset of the glucose intolerance and disease. The long view is to avoid the serious consequences of diabetes, including blindness, dialysis, and amputations, which may be delayed or prevented through treatment and close monitoring. Dr. Phillips requested feedback on these issues, including the cost effectiveness of available treatments to achieve these goals. Dr. Narayan noted that at least one paper from the DPP published in *Diabetes* showed that lifestyle factors did influence beta cell function. He added that it is generally agreed that in a "genetically susceptible" population, insulin resistance triggers a diabetes epidemic; however, the specifics of this genetic susceptibility, and whether there is any association with beta cell mass or function, are not clear and warrant further study. Challenges include how to best measure cell mass and function and identification of

interventions that might effectively restore function. Another issue to consider is whether simple measures such as fasting glucose correlate with beta cell function.

SESSION 2: COMMON ETIOLOGICAL PATHWAYS FOR SYNDROMES ASSOCIATED WITH OBESITY AND INSULIN RESISTANCE

Moderator: Phil Smith, PhD, NIDDK

Overview of the Currently Proposed Etiological Pathways and How They Might Intersect and How Nuclear Receptors Fit into the Picture

Mitch Lazar, MD, PhD, University of Pennsylvania

The dual epidemics of obesity and diabetes are of growing concern not only in the United States but also around the world. The two conditions are connected through the development of insulin resistance in the muscle and liver in the presence of excess adipose and the eventual progression to the "metabolic syndrome" and type 2 diabetes. As individuals becomes more obese, they become insulin resistant; their body initially compensates for this phenomenon by increasing circulating insulin to keep blood glucose levels normal. Over time, as the beta cells fail, hyperglycemia ensues and diabetes develops. Understanding the mechanisms of insulin resistance is important not only in the development of effective therapeutics but also in identifying biomarkers and predictive risk factors for disease prevention. Ultimately, research may shape a unified field theory to answer the question: How does obesity cause diabetes?

At the cellular level, insulin resistance occurs when insulin fails to function normally through a complex signaling pathway in its major target tissues of liver, muscle, and fat. In the liver, insulin resistance leads to increased lipid storage and decreased glucose production and glycogen synthesis. In muscle and fat, there is an increase in glucose uptake mediated by GLUC4 that also leads to lipid storage and glycogen synthesis in the muscle. Dr. Lazar noted that insulin resistance rarely results from insulin receptor defects. He pointed out that the normal effect of insulin is lipid storage; paradoxically, lipid storage (fatty liver) is a hallmark of insulin resistance, suggesting that the liver may not be resistant to the lipid-related effects of insulin but is affected to a much greater degree to effects on carbohydrate storage. What is not known is whether the defect in insulin resistance rests in the efficacy, or maximum effect, of insulin; its potency (half the maximal effect); or both. It also is not certain whether the defect is similar in all insulin-responsive tissues. Further, although evidence indicates some within-tissue differences (e.g., in the liver), additional research is needed to confirm whether all metabolic effects in a given tissue equally defective. The lack of clear answers to these questions makes predicting who will develop insulin resistance and diabetes, as well as treating and preventing these conditions, very difficult.

Dr. Lazar described some of the more prominent proposed mechanisms for insulin resistance. The FFA flux theory posits that in obesity, there is an increased influx of FFAs to tissues, a decrease in glucose oxidation, and reduced glucose uptake. The specific steps of this theory have been challenged, but the fundamental concept of FFAs inducing insulin resistance remains viable. A variation on the FFA flux theory is the ectopic fat storage theory, which suggests that increased fat storage in muscle and liver in obesity leads to increased FA metabolites that inhibit insulin signaling. FFAs either directly or through another agent (e.g., DAG) activate a kinase pathway (e.g., PKC) that affects the insulin signaling pathway, possibly at the level of serine

phosphorylation, which ultimately impairs the action of insulin in the target tissues. Another theory, the endocrine (humoral) theory, proposes that the production or secretion of adipocyte-derived molecules, such as adiponectin, resistin, FFAs, and cytokine-like molecules, is changed, thereby altering the insulin signaling pathway. The cell-autonomous theory involves multiple perturbations in signaling mechanisms associated with mitochondrial dysfunction and leading to the accumulation of cellular ROS. Increased cellular ROS and FAs induce the endoplasmic reticulum stress pathway, which has been linked to obesity, insulin action, and type 2 diabetes.

Dr. Lazar also discussed the effects of the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR-gamma) and members of the nuclear receptor superfamily. PPAR-gamma was first identified in 1990, and FFAs were the first natural ligands discovered for this receptor. In 1995, Lehman and colleagues suggested a wide range of effects of PPAR-gamma, including an increase in FFAs; a reduction in insulin-sensitizing factors (e.g., adiponectin); and an increase in insulin resistance factors such as TNF-alpha, IL-6, RBP-4, and resistin (*JBC* 270:12953-56, 1995). These changes, in turn, lead to an improvement in insulin status. Subsequent studies have suggested a possible role of PPAR-gamma in protecting against atherosclerotic disease and possibly cancer. FFAs are a key component in several mechanisms associated with PPA. As a ligand in type 2 diabetes, FFAs affect movement of fat from the liver and adipose tissue into the cell, ultimately affecting adipocyte differentiation, FA uptake, and FA retention. Increased cytokine production is associated with the nature of obesity, which may be considered a chronic inflammatory state. Adipocytes act as macrophages "in crisis" that store lipids. In diabetic (type 2) mice, the action of PPAR-gamma is inhibited and levels of resistin, which plays a significant role in the development of hepatic insulin resistance, are increased.

Macrophages, Inflammation and Insulin Resistance
Anthony Ferrante, MD, PhD, Columbia University

Inflammation is implicated in multiple obesity-induced complications, including atherosclerosis (affecting endothelial and smooth muscle cells), insulin resistance (hepatocytes, myocytes, and adipocytes), reactive airway disease (smooth muscle cells, pneumocytes), non-alcoholic fatty liver disease (hepatocytes), and cancer (ductal cells, hepatocytes). Obesity-associated inflammation acts through intercellular inflammatory signals, intracellular inflammatory signaling pathways, and immune system cells. One key component of this overall system is the adipose-tissue macrophage (ATM), which studies have shown accumulate in various tissues of obese mice and humans.

The role of ATMs in metabolic phenotypes and complications of obesity is under investigation. Clinical data collected over the past 2–3 years show that ATM content increases with obesity and adipocyte size, ATMs produce many of the inflammatory signals released by adipose tissue in obesity, ATMs are bone marrow-derived, ATM content is dynamic, and macrophage number is depot dependent (*Diabetes* (a)53:1285-1292, 2004; (b)54:2277-2286, 2005; (c)55:1554-61, 2006). Although potentially informative, these findings need to be considered with caution given the following caveats: most studies included only a small number of subjects, patients had overt metabolic diseases (e.g., diabetes, dyslipidemias) and were morbidly obese (average BMI, 47), and in many cases results were based on only a single measurement. Studies preferably will include patients whose status is not complicated by treatment, a range of adiposity, a validated

measure of adiposity, multiple types of measurements of ATM content, and use of hyperinsulinemic-euglycemic clamp assessment of insulin sensitivity.

The NIDDK has supported a long-term metabolic study of the Pima Indians in Phoenix, Arizona, which sought to determine whether ATM content predicts adiposity and/or insulin sensitivity in healthy young people, chemoattractant expression predicts ATM content or insulin sensitivity, and endothelial activation predicts ATM content or insulin sensitivity. The study population included young adult Pimas (n = 66) and Caucasians (n = 14) between 18 and 45 years old who had no diabetes, cardiovascular disease, renal disease, or liver dysfunction, and who were taking no medications. Measurements included body composition by whole body imaging; hyperinsulinemic-euglycemic clamp studies; fasting measures of glucose, insulin, and lipids; periumbilical adipose tissue analyzed; immunohistochemistry to determine ATM content; and gene expression studies of macrophage markers, endothelial cell activation, leptin, and adiponectin.

Although correlations were shown between ATM content and three markers of macrophage gene expression (CD68, CSF1R, CD11b), no single entity clearly defined the macrophage in adipose tissue. Additional results of this metabolic study showed that in subcutaneous adipose tissue, macrophage content correlated significantly with adiposity (percent body fat) even after adjustment for factors known to influence body composition, including age, gender, and ethnicity. Further analysis found that subcutaneous adipose tissue macrophage content was correlated with leptin expression and percent body fat, even after correction for sex, age and ethnicity. However, subcutaneous adipose tissue macrophage content was not convincingly correlated with insulin sensitivity, after correction for percent body fat.

Results of insulin sensitivity studies in animals and humans indicate that ICAM expression correlates with measures of adiposity in mice and human subjects; ICAM expression is correlated with ATM content in subcutaneous adipose tissue but not convincingly after correcting for percent body fat; and ICAM expression is strongly inversely correlated with all measures of glucose homeostasis, particularly insulin sensitivity ($r = -0.50$, $p < 0.0001$), even after correcting for age, gender, ethnicity, and adiposity. Although ICAM expression occurs primarily is in the endothelium, it also occurs, albeit to a lesser degree, in macrophages and leukocytes.

In sum, ATMs appear to have multiple roles in obesity. They modulate adipocyte metabolism by inhibiting further lipid accumulation, support adipocyte maintenance and viability, are involved in remodeling tissue as part of maintaining and remodeling the vasculature, and act to clear cellular debris including excess lipids and apoptotic cells.

Inflammation, NFκβ and Insulin Resistance
Steven Shoelson, MD, PhD, Joslin Diabetes Center

Exploration of the connection between obesity and diabetes has sought to determine whether obesity-associated inflammation is simply correlated with insulin resistance and diabetes or whether proposed markers of inflammation are pathogenic mediators of these conditions and possible pharmacological targets for prevention and treatment. Dr. Shoelson described a small

number of cases dating back to as early as 1875 suggesting that diabetes mellitus might be treated with an anti-inflammatory agent, salicylic acid. Additional case reports and small studies published through the 1950s demonstrated the efficacy of high doses of this agent or aspirin in the treatment of type 2 diabetes. In one report, use of 5–8 g aspirin/day reduced fasting glucose levels from approximately 200 to 90 mg/dL within 1–2 weeks in a group of eight diabetics taken off insulin for the study (Reid et al., *BMJ* 2:1071, 1957). An effect on insulin secretion was proposed but was not investigated further until more recently. In 2001, Dr. Shoelson and his colleagues published a paper on the effects of a 3-week regimen of high-dose aspirin in Zucker fatty rats, which have a defect in the leptin receptor and impaired glucose resistance (*Science* 293:1673, 2001). Results indicated notable improvements in insulin, TGs, and circulating FFA levels. Similar outcomes have since been reported in humans.

Numerous investigations have pursued the molecular target(s) of high-dose salicylates. The target appears to be distinct from that for low doses of aspirin, which inhibit COX enzymes. Data suggested that the most likely targets of high-dose salicylates were NFκβ and/or the enzyme that activates NFκβ, IκB kinase-β. Subsequent experiments by Dr. Shoelson's group found that the effect of glucose lowering in insulin resistance and diabetes also was mediated through NFκβ inhibition. NFκβ is a transcription factor activated by a variety of inputs, including pro-inflammatory cytokines, pattern recognition receptors, and cellular stresses. Once activated, NFκβ induces the transcription of a host of different genes, many of which have been independently implicated in the pathogenesis of insulin resistance and/or CVD. NFκβ–targeted genes encode cytokines (IL-6, IL-1β, TNF-α, resistin) and their receptor genes; chemokines (MCP-1/CCL2); and other factors or compounds such as PAI1, SAA, and CRP. Thus, small increases in NFκβ activity might induce small changes in the expression and concentration of a large number of potential mediators of inflammation, whereas small decreases in activity might, in turn, induce small changes in the expression of a large number of genes that might decrease inflammation and perhaps have a beneficial effect on disease risk. Primary tissue targets of inflammatory activation are liver and adipose; cell types include macrophages and other immune cells, endothelial cells, and parenchymal cells in fat and liver. Inflammatory effects might be initiated at these sites and signal to other tissues, including the muscle and beta cells.

Inflammation in specific tissues is demonstrated through gene expression studies that track upregulation of direct and indirect targets of interest following development of insulin resistance. Histochemical studies can also be used to show infiltration of immune cells and factors in various tissues. Results of these studies suggest that recruitment of immune cells targets certain fat cells more than others. Cells that have died would most likely be surrounded by macrophages as part of necrosis. Viable adipocytes might produce inflammatory substances and chemokines that recruit more macrophages than other cells or groups of cells. Investigations to better understand these mechanisms are ongoing.

A model for a possible mechanism in fat cells suggests that the cell initially swells to induce the recruitment of mononuclear inflammatory cells, which cross the endothelium into the fat tissue (*J Clin Invest* 116:1793-1801, 2006). The mononuclear cells and the adipocytes subsequently both secrete pro-inflammatory substances, thereby acting together to activate the vasculature of the endothelium further. These substances may have not only local but also distal effects following secretion into the circulation. This scenario provides a mechanism by which adipose

tissue in obesity might influence insulin resistance in the muscle. These same substances, secreted from the adipose tissue, also might promote vascular disease at distant sites. A similar mechanism and model may explain obesity-related "inflammation" in the liver (*Nature Medicine* 11, 183-190, 2005). NFκβ is activated in liver by obesity, as reflected though steatohepatosis or through the secretion of substances from abdominal fat to the liver. In either event, inflammation occurs and cytokines are produced by both parenchymal cells and resident immune cells.

A very different effect—severe wasting—is seen in muscle tissue upon activation of NFκβ by cachexia-inducing factors (e.g., cachectin) that activate the synthesis of MuRF1, which, in turn, targets muscle proteins for degradation (*Mol Cell* 14, 395, 2004; *Cell* 117, 399; *Cell* 119, 285-298, 2004). This process of muscle atrophy can be inhibited through growth factors (e.g., IGF1). Salicylate reverses the metabolic path to muscle wasting, suggesting that this compound can inhibit NFκβ.

Drugs having anti-inflammatory side-effects are currently in use as treatments for atherosclerosis, for example, TZDs and statins. Dr. Goldfine and Dr. Shoelson are targeting obesity-induced inflammation directly by using salsalate in small trials to ask whether this influences insulin resistance, diabetes, and CVD (manuscript submitted). Unlike aspirin, this compound, which is two esterified molecules of salicylic acid, does not cause GI irritation, nor does it inhibit cox enzymes.

Although promising and informative, these preliminary studies were not designed to answer two major compelling questions: Is salicylate (salsalate) a potential new treatment for patients with T2D? And, is the IKKβ/NFκβ axis a potential new therapeutic target for efforts in drug discovery in the areas of T2D and metabolic syndrome? To address these issues appropriately and adequately, a placebo-controlled, multi-site study with a run-in period has been launched. The name of this NIH/NIDDK-sponsored trial is Targeting Inflammation with Salsalate in Type 2 Diabetes, or TINSAL-T2D. Dr. Shoelson is the study PI, and Drs. Allison Goldfine and Vivian Fonseca are co-PIs. Stage I of this trial is a 14-week multi-center, double-masked, placebo-controlled dose-ranging study in which subjects will receive placebo or 3.0, 3.5, or 4.0 g salsalate/day; an estimated 240 patients will be screened to randomize 120 subjects to each arm (30/arm). Stage II of the trial will randomize 282 patients into one of two arms: placebo or the optimum salsalate dose group, based on the results of the first phase of the study. Stage II will run for 26 weeks as a multi-center, double-masked, placebo-controlled study. A companion study sponsored by NIH/NHLBI, TINSAL-CVD, will assess the effects of salsalate in 900 patients with CDA+ metabolism; subjects will be randomized to one of three study arms (salsalate, placebo, or life-style modification) for 30 months. Subjects will have a multidetector CT angiography (MDCTA) at study entry and at the end of the trial; the primary endpoint is calcified plaque. A third study, TINSAL-IGT, is being sponsored by the Phoenix VA in collaboration with the Boston VA.

Inflammation, Insulin Resistance, and Atherothrombotic Vascular Disease
John Yudkin, MD, University College London

Dr. Yudkin opened his presentation by noting that like visceral adipose tissue, fat surrounding the vasculature—whether larger vessels such as the coronary arteries or smaller vessels such as

resistance arterioles—is an important factor in risk for insulin resistance and atherothrombosis. The key themes of his talk were that the clustering of risk factors in the metabolic syndrome is better explained by low-grade inflammation than by insulin resistance; low-grade inflammation is a consequence of adipose tissue-generated proinflammatory cytokines; low-grade inflammation is associated with insulin resistance and endothelial dysfunction; many of the metabolic effects of adipocytokines may occur through local paracrine and 'vasocrine' mechanisms rather than endocrine action; and perivascular fat may play an important role both in hemodynamic physiology and in cardiovascular pathology.

The concept of "syndrome X" was first described in 1988 with three primary characteristics, dyslipidemia, hypertension, and glucose intolerance. Since that time, a range of other phenomena have been incorporated into this syndrome, with strong associations with pro-insulin-like molecules, plasminogen activator inhibitor 1 (PAI-1), low-grade inflammatory molecules, perhaps unexpectedly microalbuminuria and endothelial dysfunction, and central obesity and physical inactivity. In 1999, Dr. Yudkin and his colleagues proposed a different paradigm for this syndrome based on data collected on 107 healthy subjects using eight different measures associated with the condition. Four additional acute-phase factors, TNF-alpha, IL-6, CRP, and fibrinogen, also were measured. Even with these very crude measures, a sufficiently strong correlation was found between insulin resistance syndrome and acute-phase activation. Correlations also were found between measures of endothelial dysfunction activation and inflammatory markers, with the strongest associations between TNF-alpha and tPA antigen, vWF, and albumin excretion rate. The revised concept identified proinflammatory cytokines, rather than insulin resistance and hyperinsulinaemia, as the central drivers of the syndrome, capable of influencing lipids, blood pressure, endothelium, low-grade inflammation, and insulin sensitivity. Thus, in this model, insulin resistance is a *consequence* of low-grade inflammation rather than central to the clustering of effects. Subsequent research has supported a central role of inflammation in insulin resistance, including in the liver in response to suppressed glucose output and increased glycogen synthesis and in the muscle.

Further analysis sought to identify the source of inflammation in this model in humans. Possible correlations with infectious agents putatively related to CHD were not strong. Anthropometric measures of obesity were found to have much stronger relationships with inflammatory markers, with BMI, waist-to-hip ratio, and subscapular-triceps ratio accounting for about 20 percent of the acute-phase score. These data suggest that obesity may be the major contributor to low-grade inflammation in this model. The next question focused on determining how the fat signals to the liver, muscle, blood vessels, and other tissues differ in the obese versus the non-obese state. Common fat-generated circulating signaling molecules, including NEFAs (nonesterfied FAs), adiponectin, IL-6, resistin, leptin, retinol binding protein 4 (RBP4), and TNF, were considered as possible endocrine factors. Fasting arterial and venous concentrations of agents across an adipose tissue bed were measured, and IL-6 was found to be three to four times greater in venous versus arterial blood ($p < 0.0001$). However, there was no net production of fasting TNF-alpha, suggesting that this compound is not acting as an endocrine signal.

The concept that fat is deposited abnormally in obese persons as well as in persons in positive-energy balance may include "ectopic fat" as having a role in impairing insulin action in insulin-sensitive tissues. In the liver, this translates into steatohepatosis, whereas in the muscle,

intramyocellular lipid may serve as a source of intramuscular TG-free FAs. A similar component of the vasculature may also exist in the form of perivascular fat. Measurements of limb blood flow show that after exercise and eating, there is a rapid shift to the nutritive capillary bed within a few minutes before any effect on net blood flow occurs; insulin is implicated in this shift. Experiments show that the effect of insulin is to induce a six-fold increase in nutritive blood flow in the fasting state and a two-fold increase in the fed state. In the presence of various stimulating agents in a normal rat cremaster muscle model, insulin in conjunction with inhibition of PI3-kinase (wortmannin) constricts the arteriole by approximately 20 percent. Inhibition can be blocked with the addition of inhibitors of ERK1/2 to this system, whereas insulin in the presence of ERK1/2 inhibition but not wortmannin causes vasodilation, suggesting a dual effect of insulin on vasoreaction. (Insulin alone does not induce dilation or constriction in this model.) Thus, there appear to be two parallel paths for insulin-responsiveness in blood vessels, with vasodilation proceeding through a PI3-kinase–NO pathway, and vasoconstriction through an ERK1/2–endothelin pathway. In obese rats, insulin alone produces net vasoconstriction, which can be blocked with an endothelin inhibitor, in contrast with the response of a lean rat, in which there is no net response. Thus, the obese animal appears to be missing the vasodilatory effect of insulin and instead exhibits unopposed endothelin, ERK1/2-mediated vasoconstriction. Molecular studies show that expression of endothelial NO synthase in the vessels of the obese rats is markedly less than that in lean rats.

Conducting the same experiments in the presence of TNF-alpha and an endothelin inhibitor shows that the vessels of the obese rat act as if there is an excess of TNF-alpha causing an unopposed PI3-kinase inhibition and thus unopposed vasoconstriction. Further anatomical analysis of cremaster muscle vessels of the Zucker rat suggests that there may be a downstream effect of TNF-alpha to access the nutrient artery circulation. There is localized accumulation of fat at the branch point of the arteriole that appears to have a vasoregulatory role.

On the basis of the complement of findings from these studies, Dr. Yudkin and his colleagues have proposed a concept of ‘vasocrine’ actions of perivascular fat as a characteristic of vascular insulin resistance. He explained that under normal circumstances, insulin acting on the endothelial cell via PI3-kinase and ERK1/2 pathways through the lumen of the blood vessel (i.e., as in the above model), with a relative balance between the pathways. However, in situations where muscle blood flow is increased by insulin, the PI3K-NO-mediated vasodilatation would be expected to predominate. In obesity, adipocytes accumulate around the muscle and secrete a series of molecules (e.g., TNF-alpha as a paracrine molecule, IL-6, NEFA) that specifically inhibit the PI3-kinase–NO pathway, thereby reducing the effect of insulin on nutritive blood flow and possibly contributing to insulin resistance. Putative consequences of perivascular fat around conduit arteries and arterioles include altered vasoregulatory signalling and insulin resistance, and for epicardial tissue the potential effects include vascular inflammation, atheroma, and coronary calcification. In humans, epicardial fat depot size (as measured by ECHO) is highly correlated ($r = 0.84$, based on an n of 77) with visceral fat mass (measured by MRI). Putative consequences of perivascular fat in other tissues include microalbuminuria in the kidney from effects on local renal arteries, and atheroma in pelvic vasculature. The possible role of perivascular fat in the retroperioneal and omental regions is not clear.

Panel Discussion
Dr. Smith, Dr. Lazar, Dr. Ferrante, Dr. Shoelson, Dr. Yudkin

Dr. Phillips noted that not all individuals with insulin resistance become diabetic, and those who do often have a family history of the disease. This suggests a genetic susceptibility that is aggravated by the environment. Given the commonality of inflammation as described, Dr. Phillips asked about the critical mediators of the effect of the expanded adipose organ on the beta cell that lead to dysfunction that might initially be transient and reversible but subsequently becomes permanent. He also inquired about the role of oxidative stress, which is thought to be a component of beta cell dysfunction. In response, it was noted that genetics could explain why persons who are obese and develop insulin resistance do not become diabetic. However, the factors and processes contributing to these conditions and to disease progression are complex. For example, there are many pro-inflammatory lipid mediators such as FFAs and TGs that appear to contribute to the disease process. Many of the specifics are still unknown, and the question remains open and under investigation. Dr. Lazar pointed to ER stress, noting that in humans, mutations in ER stress pathways result in a phenotype characterized primarily by loss of beta cell function. Given the pathophysiology of insulin resistance, it is conceivable to understand the additional stress of having to produce more insulin in the beta cell leading to the death of the cell. Dr. Yudkin pointed out that the different degrees of insulin resistance among obese persons provide an additional clue, that is, that obesity-associated adiposity by itself might cause the initial steps in the process (hepatosteatosis), which may, in turn have constitutive differences across individuals that may or may not be genetic in origin. This concept may also apply to pancreatic fat infiltration. Dr. Yudkin noted further that concordance of diabetes in monozygotic twins is very strong for type 2 diabetes, and lesser so for type 1 diabetes. Some evidence suggests that the difference in birth weight predicts the delay, absence, or presence of diabetes in identical twins discordant for the disease.

A question to Dr. Yudkin focused on perivascular fat-angiotensinogen expression described in the late 1980s, which is likely fully characterized by now and could contribute to vasoactive regulation. Would (or does) inhibition of RAS play any role in the studies vasoregulation studies described? In addition, the pro-inflammatory action of fat appears to simply increase the number of macrophages and monocytes; with inhibition of NFκβ, MCP1, and other factors, the numbers in the fat decrease. Should therapies thus aim to control these numbers? Finally, what factor or factors actually regulate insulin-mediated glucose uptake in fat tissue, and are signaling pathways downregulated in the muscle if there are high numbers of monocytes in the fat tissue? Dr. Yudkin commented that the local activity of RAS in the perivascular fat is an interesting concept. The suggestion that obesity represents Cushing's disease of the omentum and that local activity may produce cortisol in locations where fat deposition occurs is intriguing, with the recognition of interplay between local endocrine function of adipose tissue and systemic effects. Dr. Ferrante added that macrophages probably have many functions in adipose tissue that have not yet been identified or described. He suggested that based on available information, it is more likely the function of different macrophages/monocytes rather than the number that influences regulation. Subpopulations of cells are beginning to be characterized by manipulating various

inflammatory pathways. *In vitro* experiments show that macrophages can communicate with adipocytes but whether this also occurs (or occurs in a similar fashion) *in vivo* is not clear.

A question to Dr. Lazar asked about the consistency in the finding of a reduction in tumors with PPAR-gamma agonists, given apparent data discrepancies regarding this effect. Do species or strain differences, for example, play a significant role? Dr. Lazar replied that there could be several possible explanations for discrepancies in the data in the reviewed literature compared with the information submitted to the FDA. One possibility is that academic researchers don't publish results that fail to fit their hypotheses; on the other hand, academic investigations tend to conduct hypothesis-directed research, while the FDA receives data on all possible tissue examined without any particular hypothesis associated with those findings or that information. Such research can, in turn, lead to spurious conclusions. Still another possibility is that because the size ("n") of pharmaceutical trials is often much greater than that of studies done in an academic setting, some findings may only be detected within the context of the larger study. Still, the dichotomy between what is in the published scientific literature and what was presented to the FDA, which forms the basis upon which the agency makes its decision, is striking.

Parallel pathways are activated by pro-inflammatory stimuli, including the JNK and NFκβ pathways. Inhibition of either pathway has a beneficial effect on sensitizing, which raises the questions of the underlying mechanism of this outcome and what might be the outcome of inhibiting both pathways. Inhibiting one pathway might cause the cells to spontaneously inhibit the other arm to avoid a disbalance, which could result in cell death. However, to date, this hypothesis has not been proven. By continuing this argument, inhibition of both pathways might be less beneficial than anticipated, but a study to demonstrate the impact of this intervention has not been done.

In response to another question, Dr. Yudkin stated that although there have been some CRP-lowering effects of insulin treatment, it is unlikely that insulin is beneficial in stress. Some studies (e.g., the Vandenberg studies in Belgium in ICU patients) have suggested an insulin regimen to control hyperglycemia and reduce mortality in the ICU; however, a subsequent study by the same group to replicate the earlier findings in larger numbers of patients was not successful. In addition, closer examination of the original results indicates that the metabolic effect of reducing ambient glucose levels rather than the insulin molecule itself that appeared to be associated with the stated benefit. The differences in results must also be considered within the context of an acute response versus potentially proatherogeneic effects in a chronic situation.

Dr. Shoelson was asked whether the effects of salsalate specific to this agent, or are they seen with other anti-inflammatory drugs. He also was asked about the time until initial response and the duration of the response. Dr. Shoelson noted that most other NSAIDs (e.g., low to moderate doses of aspirin, ibuprofen, naprosyn, etc.) are a different class of drugs that target cox-1 and cox-2 enzymes, in contrast with salsalate, which targets NFκβ. Thus, the effects of these different classes of drugs also differ, and glucose-lowering effects do not occur with cox inhibitors. The effect of salsalate is seen within a few days to a week, with a maximal effect within 2 weeks.

Dr. Lazar was asked about lessons that might be learned from experiences such as that with muraglitazar that showed biomarkers moving in one direction (i.e., potentially beneficial) and clinical events in another (i.e., increased risk of major CV events and death based on data from five clinical trials submitted to FDA). Muraglitazar was the first dual PPAR (alpha and gamma) to reach the FDA. In response to this query, Dr. Lazar noted that he was not familiar with all the details of the muraglitazar and that some of the controversy over this drug may be related to some of the specific populations in which it was being studied. What may be of benefit is knowledge gained about nuclear receptor biology; specifically, not every ligand will have the same function on the receptor and that agents should not automatically be reduced to classifications as "agonist," "antagonist," or "partial agonists." Some agents may be gene-specific, while others may have more targeted effects on anti-inflammatory pathways, such as NFκβ. One position is that given the complex pharmacology of nuclear receptors, additional caution is warranted. Another perspective might be to consider the significant body of information on nuclear receptors and regulation of their function, compared with many other types of targets.

The lifestyle arm of the DPP resulted in relatively modest sustained weight loss. Can this size weight loss have a significant impact on inflammatory mediators? Is it likely that weight loss will be added to the list of predictors given the wide variance among people at risk? Results of animal and human studies suggest that weight loss has beneficial effects on circulating inflammatory markers and potential mediators and expression levels in particular tissue depots. It would be necessary to extrapolating from the study findings to predict the effects of greater weight loss, but assuming a continuum, the effect would also be expected to be larger. In brief, it would probably be reasonable to expect benefits that are proportional to the degree of weight loss. To have more precise predictive data, however, will require a large study cohort. Dr. Yudkin added that in the DPP, weight loss is expressed consistently through BMI in a group in whom physical activity is increasing and who are in negative energy balance, which appears to have an independent anti-inflammatory and insulin sensitizing effect. Thus, there may be greater effects on insulin action and low-grade inflammation than anticipated, especially if weight loss continues.

REGULATORY PERSPECTIVES ON GUIDANCES

Robert Misbin, MD, FDA

Twelve years ago, physicians had only two treatment options to offer patients with type 2 diabetes: sulfonylureas or insulin. The sulfonylureas had been used since the 1950's, and as late as 1994, were the only oral agents available to treat type 2 diabetes. This situation changed in 1995. First came the approval of metformin, then acarbose and, subsequently, miglitol, troglitazone, rosiglitazone, pioglitazone, repaglinide, nateglinide, and exenatide. Troglitazone was removed from the market in March 2000 because of hepatotoxicity. The DPP4 inhibitors are under review at the FDA.

The key event that permitted this dramatic rise in approvals of drugs for type 2 diabetes was the publication of the results of the DCCT study. This established HbA1c as a surrogate end point for microvascular disease in type 1 diabetes patients treated with insulin. As a result of this

milestone study, a consensus emerged in the 1990s that treatment of hyperglycemia was important to prevent the complications of both type 1 and type 2 diabetes, and that the benefit would follow from any effective treatment, not just insulin. In recognition of this consensus, the FDA accepted use of HbA1c as the basis of approval for oral agents to treat type 2 diabetes.

In comparing two drugs that are very different pharmacologically, pioglitazone (a long-acting insulin sensitizer) and nateglinide (a short acting insulin secretagogue), Dr. Misbin pointed out that the basis of FDA approval was the same for both drugs: reduction in HbA1c. However, more than a decade after the breakthroughs of the 1990s, the prominence of HbA1c as the basis for approval of diabetes drugs is being questioned. This concern is greatest with respect to prevention of macrovascular complications, which seem to be less well correlated to changes in HbA1c than prevention of microvascualar complications. But despite his concern, Dr. Misbin does not anticipate a change in this standard any time soon.

Although several antidiabetic medications have been reported to prevent or delay the diagnosis of type 2 diabetes, there are no drugs that are labeled for this indication. The safety of a possible drug candidate would likely determine its approvability. Recognizing that patients with IGT/ IFG will not necessarily develop diabetes, the FDA will apply a more stringent safety standard for prevention than for treatment.

A major obstacle to the approval of a drug to prevent type 2 diabetes appears to be lack of a sponsor to prepare the application and submit it to the FDA. Metformin has been reported to prevent type 2 diabetes. But lacking patent protection, pharmaceutical sponsors have little incentive to try to market metformin for a new indication. If there were a serious threat to public health, the FDA would be able to request a labeling change. But with respect to the use of drugs to prevent type 2 diabetes, Dr. Misbin does not believe that the current circumstances warrant circumvention of the usual drug approval process. He went on to say that the FDA might be willing to act on its own if faced with a strong consensus among scientists and clinicians that patients with IGT/IFG should be treated with antidiabetic medications. Of primary importance would be the need to show that early drug treatment of those patients destined to develop diabetes justifies the risk/cost of treating other patients with IGT/ IFG, most of whom will not necessarily develop diabetes.

SESSION 3: PREVENTION OF TYPE 2 DIABETES

Moderator: Robert Misbin, MD, FDA

Prevention of Type 2 Diabetes: Overview of Published RCTs

Fred Brancati, MD, MSH, John Hopkins University

Dr. Brancati highlighted findings of randomized controlled trials (RCTs) of primary prevention of type 2 diabetes, including results of the DREAM trial and some secondary analyses of studies in which the development of diabetes was not the primary endpoint. The basis for primary prevention is that diabetes is a large and growing public health burden. Treatment of the disease is good but diagnosis is commonly delayed; drugs are often costly and have side effects; and optimal treatment is not completely efficacious, nor is it usually achieved. The benefits of early

intervention may include not only prevention or delay in the onset of diabetes but also weight loss, blood pressure reduction, and an improved lipid profile or CVD risk.

The impact of tolbutamide and/or dietary intervention on the incidence of type 2 diabetes in men with IGT was assessed in the 1980 Sartor study (*Diabetes* 29:41-49, 1980). A first-generation sulfonourea, tolbutamide induces the release of insulin from beta cells. Contraindications include DKA, monotherapy in type 1 diabetes, and hypersensitivity, and serious adverse events (SAEs) include CVD death and hypoglycemia. The current retail cost of 3 months' worth of a standard dose (1,500 mg daily) of tolbutamide is $240. Intention-to-treat analysis showed that the combination of tolbutamide plus diet was associated with the greatest reduction in risk of type 2 diabetes (cumulative incidence of 10 percent), compared with diet plus placebo (12.5 percent) and placebo (22 percent). Although the addition of tolbutamide to diet had a low marginal impact on reducing diabetes risk, long-term follow-up suggested some overall benefit on mortality (*Diabetologia.* 1997 Jun; 40(6):680-6).

The Da Qing study screened 110,660 Chinese adults, of whom 577 (0.5 percent) were found to have impaired glucose tolerance (*Diabetes Care* 20:537-44, 1997). Those with IGT were randomized by clinic (n = 33) into four groups (control, diet, exercise, or diet + exercise); advice on diet and exercise was provided for both clinicians and study participants. The cumulative incidence of type 2 diabetes at 6 years was 67 percent. The adjusted relative risks (vs. controls) were 0.69 ($p = 0.028$) for diet; 0.54 ($p < 0.001$) for exercise; and 0.58 ($p = 0.001$) for diet plus exercise. Of note is that this study was designed to assess effectiveness of interventions in primary care, compared with others designed to test efficacy in highly selected individuals.

Dr. Brancati noted that one of the first high-impact diabetes prevention studies of note was a Finnish study that tracked diabetes-free survival in 506 adults with IGT who followed specific lifestyle interventions (*NEJM* 344:1343-50, 2001). After 6 years, 40 percent of the control group was free of diabetes and 15 had developed diabetes, compared with the intervention group, in which 73 percent of subjects remained diabetes free and 5 percent were diagnosed with diabetes. Interim data show that the lifestyle intervention group was more physically active, consumed fewer calories, and lost more weight (as percent of baseline) at years 1 and 3 compared with the control group (*Diabetes Care* 26:3230-6, 2003).

Among the many drugs investigated for its prevention potential is acarbose, an alpha-glucosidase inhibitor that acts through competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase hydrolases. Acarbose also reduces absorption of carbohydrates. Contraindications include cirrhosis, colonic ulcers, malabsorption, inflammatory bowel disease, and obstruction. No SAEs are reported for acarbose; common nonserious AEs are bloating and gas. Retail cost of a 3-month prescription (100 mg tid) is $250. The STOP-NIDDM Trial looked at the effect of acarbose (50-100 mg tid) on risk of incident diabetes in 1,368 overweight adults between 40 and 70 years old with IGT (*Lancet* 359:2072-77, 2001). Results showed that study participants receiving acarbose had a 25-percent reduction in risk diabetes (adjusted RR = 0.75, $p = 0.0022$), which was highly significant but less than for lifestyle interventions. A subsidiary analysis of the STOP-NIDDM Trial found a 49-percent reduction in risk ($p = 0.03$) of any CVD event; most of the reduction in risk was driven by differences in MI rates, with one event in the acarbose group and 12 in the placebo group (*JAMA* 290:486-494,

2003). This finding is of interest because of the anticipated reduction in diabetes-associated cardiovascular complications with primary prevention of the disease. One issue raised regarding many diabetes prevention studies is that they are not, or have not been, sufficiently powered to detect CVD events.

Another drug, metformin, is a biguanide that decreases hepatic glucose production, decreases intestinal absorption, and increases peripheral glucose uptake and utilization. Contraindications include CHF, exposure to iodinated contrast media, renal impairment, and a history of metabolic acidosis. Metformin's SAE of lactic acidosis has a black box warning. A 3-month prescription (for 850 mg bid) costs $140. The DPP sought to determine the impact of metformin and lifestyle on incidence of diabetes type 2 in 3,000 adults with IGT (*NEJM* 346:393-403, 2002). Lifestyle had the greatest effect on diabetes prevention; metformin had a substantial but lesser effect in reducing risk of the disease. Participants in the lifestyle group were significantly more physically active than those in either the placebo or metformin group, which had similar levels of activity. The greatest weight loss (about 7 kg) occurred in the lifestyle group within 6 months of starting the trial; some recidivism occurred, with an eventual loss of about 3.5 kg in years 3 and 4. A smaller loss of 1–2 kg was reported for the metformin group.

The DPP also initially included a troglitazone arm. Not long after the DPP started, results from the TRIPOD study were published, showing that risk of incident diabetes was reduced (RR = 0.45) in a small group of women with IGT and a recent history of gestational diabetes (*Diabetes* 51:2796-03, 2002). The 55-percent reduction in risk in the TRIPOD study was comparable to that for the lifestyle intervention group in the DPP. When data from the shortened troglitazone arm of the DPP (before the drug was withdrawn) were compared with the arms that went through completion, including the lifestyle intervention arm, troglitazone showed the lowest cumulative risk over the first 1.5 years of the study (*Diabetes* 54: 1150–1156, 2005). Further analysis suggested a lasting effect of troglitazone for several years after its use had been stopped.

The lipase inhibitor orlistat is a reversible inhibitor of intestinal lipases that also acts to reduce absorption of dietary fat. Contraindications of orlistat include cholestasis and malabsorption. No SAEs are reported for this drug, although it can cause bloating, gas, and leakage. The cost of 3 months' of treatment (120 mg tid) with orlistat is $590. The XENDOS Study examined the effect of orlistat on incident type 2 diabetes in 3,305 obese adults with or without IGT at baseline (*Diabetes Care* 27:155-161, 2004). Among all subjects, the combination of orlistat plus lifestyle intervention produced a 37-percent reduction in risk. An even greater reduction in risk (45 percent) was observed for the combination of orlistat plus lifestyle intervention in subjects with IGT.

The HOPE Trial, which had a primary endpoint of CVD prevention, generated interest in a possible role for ACE inhibitors in diabetes prevention based on secondary analysis of study data. This analysis showed a significant benefit of ramipril on the risk of incident diabetes compared to placebo (RR = 0.66, $p < 0.01$) in the initial 4.5-year study period (*JAMA* 286:1882-85, 2001). This benefit was extended in the years after which the blind was broken. Ramipril, which was included in the DREAM Trial, is an ACE inhibitor that acts to treat hypertension by preventing the conversion of angiotensin to angiotensin II, a vasoconstrictor, thereby decreasing vasopressor activity and aldosterone secretion. Contraindications are angioedema and pregnancy,

and SAEs include ACE-induced angioedema; liver failure, which is rare; and fetal death in the second and third trimesters, for which there is a black box warning. Retail cost for a 3-month prescription (15 mg daily) is $380. The DREAM Trial also studied the effects of rosiglitazone, a thiazolidindione that acts as an insulin-sensitizing agent by activating PPAR-gamma nuclear receptors, thereby enhancing peripheral glucose utilization and improving glycemic control. In addition, rosiglitazone is involved in the regulation of fatty acid metabolism. The only contraindication is hypersensitivity, and SAEs include CHF; pulmonary edema; cholestatic hepatitis; hepatotoxicity, which is rare; and diabetic macular edema, which is very rare. The retail cost of 3 months of rosiglitazone (8 mg daily) is $515.

Dr. Brancati described the DREAM Trial, a multi-site study on five continents that enrolled 5,269 adults at least 30 years old who were at risk for type 2 diabetes based on fasting glucose (*Diabetologia* 47: 1519-27, 2004). The study used a 2 x 2 factorial design that compared ramipril 15 mg qD versus placebo, and rosiglitazone 8 mg versus placebo. No interactions between arms occurred, and results of each arm have been analyzed as a separate trial. The primary endpoints were type 2 diabetes or death, and the study was powered at 90 percent to detect a 22-percent reduction in relative risk at 4 yrs of follow-up. Analysis of findings in the ramipril arm showed nonsignificant decreases ($p = 0.15$) of about 9 percent for the overall primary composite outcome and risk for diabetes overall and based on fasting glucose and 2-hour post-load glucose tests (*NEJM* 355:1-12, 2006). Regression to normoglycemia, a secondary endpoint in this study, improved by 16 percent ($p < 0.01$) in the ramipril group compared with placebo. Analysis of findings for another secondary endpoint, CV events, indicated no difference between ramipril and placebo. Thus, for ramipril, the overall assessment suggested largely negative results. In contrast, relative risk for type 2 diabetes or death was reduced by 60 percent (RR = 0.40) in the rosiglitazone group (11.6 percent) compared with placebo (26 percent) (*Lancet* 368:1096-1115, 2006). A difference between the two groups was evident starting about 1 year into the study. The reduction in the composite primary outcome was due almost exclusively to a reduction in type 2 diabetes (10.6 percent vs. 25 percent for placebo, RR = 0.38). However, risk of all CV events was higher in the rosiglitazone group (2.9 percent) compared with placebo (2.1 percent), with a relative risk of 1.37 (ns). This outcome was driven by a significantly higher occurrence of confirmed CHF, a known SAE of rosiglitazone, among those receiving rosiglitazone (0.5 percent) versus placebo (0.1 percent) (RR = 7.03). Weight gain also occurred with rosiglitazone over the duration of the study.

Dr. Brancati commented that regarding effectiveness of these interventions, from a public health research perspective, the average person in the population generally is not comparable to persons entering a randomized controlled clinical trial, in terms of attendant co-morbidities, readiness to modify lifestyle, and/or willingness to adhere to a treatment regimen and tolerate side effects. In addition, he noted that none of the trials described were specifically designed to address economic implications of the study interventions. However, given differences between a highly selected study population and the general population, cost-benefit analyses done as part of a clinical study may not accurately reflect the economic impact outside the context of the study. For example, two recent cost and effectiveness estimates of DPP interventions were highly divergent in their assessments (*Ann Intern Med.* 142:323-332, 2005; *Ann Intern Med* 143: 251-264, 2005).

In conclusion, Dr. Brancati stated that even with the strongest interventions across these studies, there is a graded increase in the cumulative risk of diabetes over time. For example, the lifestyle intervention arm of the DPP showed the greatest effect on reducing disease risk; however, 20 percent of individuals in this arm converted to type 2 diabetes after 4 years. A key question for clinicians promoting healthy lifestyle behaviors and also considering drug interventions is properly assessing the status of each patient and anticipating changes in a failing intervention strategy to provide the greatest benefit for the patient. Thus, it is important to see intervention as a dynamic process over time.

Point–Counter Point: Are the available data sufficient to support an indication for treatment to prevent Type 2 Diabetes for currently studied drugs?

Yes, They Are Sufficient
David Nathan, MD, Massachusetts General

The rationale for screening for prevention of any disease, as adapted from the treatment model proposed by Frame and Carlson in 1975, is that the disease has (1) significant morbidity and mortality, (2) a high enough incidence to justify cost of screening, (3) an asymptomatic *(pre-disease)* phase during which detection and treatment reduce morbidity or mortality, and (4) methods to detect disease *(pre-disease)* in the asymptomatic phase. In addition, there should be an acceptable therapy (*prevention*) available, and sufficient evidence should exist showing that treatment (prevention) of disease during the asymptomatic phase yields results superior to that obtained by delaying treatment until (the disease) symptoms appears.

The key points to consider for diabetes prevention include the magnitude of the epidemic, issues related to screening, options for intervention and, finally, the role of drugs.

The epidemic: With regard to the magnitude of the epidemic, four years ago the total number of Americans with diabetes was 18 million; 16 million had type 2, and about 1.1 million new cases were diagnosed each year. In 2005, the CDC estimated that 21 million Americans have diabetes, approximately 1 million with type 1 and almost 20 million with type 2, including 6 million undiagnosed cases. Gestational diabetes accounts for about 75,000 cases, or 3 percent of all pregnancies. An additional 42 million are estimated to have prediabetes. As the U.S. population grows, these numbers are expected to continue to increase.

Morbidity and mortality and economic burden: Diabetes is accompanied by major morbidity and mortality: it is the most common cause of blindness, amputations, and end-stage renal disease (ESRD) in adults. Diabetics have a 2 to 5-fold increased risk for CVD compared with nondiabetics. In addition to the human consequences and suffering associated with diabetes, the economic burden of this disease is significant. In 2002, the ADA determined that in the aggregate, the costs attributed to diabetes total more than $132 billion dollars per year for the United States. Without a significant intervention to slow or reverse the current trends, these burdens and consequences will continue to rise as the U.S. population expands and ages.

Screening methods and opportunities: Key issues to consider with respect to screening to prevent diabetes include the ability to identify accurately the population(s) at risk using a low-cost, low-

risk method or strategy. Dr. Nathan noted that in most of the major prevention studies conducted thus far, at-risk subjects were identified based on age, OGTT, and BMI. Data from the DPP, DREAM, STOP-NIDDM, and Finnish DPS trials indicate that about 10 percent of the at-risk groups develop diabetes per year. In a 2002 editorial in *European Heart Journal* (v. 23, p. 1229), Dr. Barrett-Connor stated that, "[the oral glucose tolerance test] … remains our most valuable tool for the early recognition of persons with diabetes or who are at increased risk for diabetes and heart disease." In general, the OGTT is considered the most sensitive means of determining glycemic status. Risk-factor predicting engines, such as the San Antonio Diabetes/CVD Predicting Model (Modified), the Diabetes Risk Score Test, and the Framingham Offspring Study Screening Tool, may be used in lieu of the OGTT for screening purposes. The Framingham Offspring Study Screening Tool uses three models: a "personal" model that includes age, sex, parental history of diabetes, and BMI; a "basic clinical" model, which adds the presence of hypertension, low HDL, increased triglycerides, and IFG to the personal model; and the "complex clinical" model, which adds IGT and increased fasting insulin (or HOMA IR) to the basic clinical model. The area under the ROC based on the personal model is approximately 0.75, whereas the area under the ROC for both the basic clinical model and the complex clinical model is 0.85 (*Diabetes* 54 (suppl 1):A91, 2005). Thus, as with the OGTT, a validated screening tool or predicting model can be used to identify with a high degree of accuracy persons at increased risk for diabetes. These tests are all relatively inexpensive, especially if fasting glucose and fasting lipid tests are done routinely, as recommended by the ADA and the AHA.

Interventions: A variety of effective options are available for diabetes prevention, including lifestyle interventions in the form of diet, exercise, or a combination of both; weight loss medications; weight loss surgery, which has not been discussed at this meeting; and other medications. The DPP looked at the widest variety of interventions in a diverse population that was the most relevant to the United States. The study's four arms included intensive lifestyle interventions; metformin; troglitazone, which was discontinued early after an average 9 months of treatment; and placebo. Dr. Nathan briefly reviewed the relative benefits, risks, and costs of the drug interventions. Lifestyle was the most effective intervention, reducing risk of diabetes by 58 percent, the same reduction reported in the Finnish Diabetes Prevention Study. Reduction with metformin was 31 percent. Risk appeared to be reduced by the greatest amount by troglitazone, even compared with lifestyle. The recently reported 3-year results of the DREAM study confirms the DPP findings with troglitazone and suggests that TZD (i.e., rosiglitazone) reduces of the risk of developing diabetes by approximately 60 to 70 percent. Thus, data from controlled clinical trials provide a range of effective interventions for the prevention of diabetes, with lifestyle and the TZDs offering the greatest and relatively equivalent benefits.

Despite the apparent success of drug interventions, these results were de-emphasized while lifestyle interventions were headlined and formed the basis for the "Small steps, big rewards" campaign to prevent type 2 diabetes. Dr. Nathan commented that the relative magnitude of effects for metformin and lifestyle in the DPP likely played a role, combined with cultural enthusiasm for the idea of lifestyle intervention to address lifestyle problems (obesity, inactivity, fast food). The emphasis on lifestyle may also have been founded on the suggestion, which was undocumented at times, that lifestyle interventions may have pleiotropic beneficial effects, whereas metformin would yield only a single effect. Another contributing factor may have been

that metformin is unlabelled for a prevention indication. Finally, there is a general reluctance to use medications to prevent disease despite the popularity and marketing of statins, for example.

Further analysis of data from the DPP has suggested additional benefits of lifestyle on cardiovascular risk factors (hypertension, TG levels), while metformin had no effect. HDL and LDL levels were improved with both lifestyle and metformin, and CRP was reduced 12 to 14 percent with metformin. Thus, there are additional extraglycemic benefits from metformin in persons at risk for diabetes, including weight loss, improved atherogenic dyslipidemia, and reduced CRP. The DPP was underpowered to assess the independent effect of metformin on CVD events, but the available data suggest a possible reduction in risk. This preliminary findings is supported by data from the UKPDS, which demonstrated a decrease in CVD outcomes with metformin monotherapy. Observations in the DPP have been extended for an additional 10 years, which will include the impact of metformin on CVD outcomes.

Used around the world for more than 40 years, metformin has an excellent safety profile, as documented during the DPP based on 3,000 patient-years of experience. Severe adverse events associated with metformin (e.g., lactic acidosis) are exceedingly rare. Metformin also is generally well tolerated, with about 5 to10 percent of patients stopping use of the drug because of GI side effects. Substantial discrepancies in the estimated costs of lifestyle interventions to prevent diabetes have been reported, depending on the health economic models used. However, the two major economic models have come to very similar conclusions regarding metformin, estimating QALY costs between $30,000 and $35,000 for the branded drug. Economic models with generic metformin yielded a QALY of only $1,800. Several additional published economic analyses have supported metformin as "affordable," "cost-effective," or as being associated with "cost savings or minor increases in costs."

Further questions regarding pharmacologic interventions for the prevention of diabetes, including the longer-term impact of diabetes "prevention" and the impact of diabetes prevention on cardiovascular disease, are being examined in the DPP Outcome Study (DPPOS).

In closing, Dr. Nathan argued that although questions remain, as shown in his presentation, the available data are sufficient to support an indication for currently studied drugs, and metformin in particular, to prevent diabetes. The risk—for edema and CHF, in particular—and expense of the TZDs seem to mitigate against their use at the current time.

No, They Are Not Sufficient, More Data Are Needed
Elizabeth Barrett-Connor, MD, University of California at San Diego

Dr. Barrett-Connor acknowledged the complexity and challenges of this issue and the importance of discussing and debating it. Dr. Barrett-Connor opened her presentation by identifying several key questions for consideration of pharmacologic prevention of type 2 diabetes, including how to screen (with prediabetes markers or other measures and which ones), who to screen (age, risk markers, etc.), the number needed to screen (uncounted cost), whether efficacy is less important than safety in prevention of disease in otherwise healthy people, and the downside to implementation of pill prevention (i.e., uncounted costs including discarding diet and exercise). Dr. Barrett-Connor noted the following assumptions as part of this discussion: that

the medication will not be universal, that those at high risk be identified for the intervention, that pre-diabetes screening will be required, and that prevention by medication targeted at overweight or high waist girth may require no screening for pre-diabetes.

Possible risk markers for type 2 diabetes that could be used in screening include obesity, which could reflect up to one-third of the U.S. population; central adiposity, which is associated with but can also be independent of obesity; age >45 years old; family history of type 2 diabetes; personal history of gestational diabetes; physical inactivity; high TGs; low HDL-cholesterol; and nearly all non-Europid racial or ethnic groups. Thus, the potential at-risk population is very large.

Issues that need to be addressed when considering screening parameters and processes include whether the risk marker and disease are common; the disease has a known natural history, with a premorbid lag phase identified by marker; the risk marker is treatable; and early detection changes the prognosis. The screening method itself should be cheap and simple, accurate and repeatable, adequate sensitivity and specificity, and acceptable to the population.

Although many of these features such as prevalence of the predictive markers (obesity, IGT) are applicable to diabetes and prediabetes, one significant drawback is that a validated risk marker screening test for *prediabetes* with a presumptive identification of an asymptomatic risk factor by a rapid method that separates persons probably at increased risk for the disease from those probably not is not available at this time. The baseline entry criterion for studies of prevention of diabetes is based on IGT with or without IFG measured at least twice. The many other risk markers discussed over the course of this meeting have not been used as entry criteria for diabetes prevention trials. Screening for diabetes prevention must use two OGTTs, which is not practical for widespread screening; other options might include three metabolic syndrome risk factors, or race- and ethnic-specific obesity and waist girth criteria; however, neither has been used in diabetes prevention studies. Dr. Barrett-Connor suggested considering the use of anthropometric measures and no blood testing for the eligibility screening test. Baseline and annual glucose and insulin levels would be obtained, to exclude persons with diabetes, but would not be otherwise included for eligibility.

Acceptability of a screening test is important. Physicians do not regularly order OGTTs. In addition, there currently is no simple patient-initiated screening test for diabetes or prediabetes, as exists for cholesterol and blood pressure (i.e., “Know your number” campaigns); adding to this factor is that the accepted “normal” value for glucose changes relatively often. In an effort to overcome the obstacles associated with the OGTT and include persons with elevated 2-hour hyperglycemia, the diagnostic fasting glucose level has been reduced from 140 to 126 mg/dL. However, even with this reduced value, about half of older persons with diabetes remain undiagnosed. Fasting glucose testing is simpler and less expensive that the GTT; it is also more acceptable to patients and providers, less dependent on age and obesity, and more reproducible. However, patients consistently fail to remember to fast in anticipation of this test. In addition, there is some question regarding whether fasting glucose reflects a later rather than an earlier stage in the predisease process.

Often overlooked in the evaluation of a screening test is the true cost of all the components of the testing. Ideally, every individual in whom the condition is detected also benefits from the intervention. However, in the "real world," everyone who has a risk factor does not receive the intervention, and not everyone who receives the intervention benefits from it. Thus, cost-benefit analyses usually make assumptions that are incorrect. Moreover, determining the actual number needed to screen can be cumbersome.

The DPP included a two-part screening process. An initial phone screen was done to identify individuals at least 25 years old with at least one of three additional criteria (overweight, family history of diabetes, or personal history of diabetes or gestational diabetes mellitus). Those meeting the requirements of the phone screen were invited for in-person visits to be screened for additional criteria, including BMI (cut point, ≥ 24 or ≥ 22 for Asians) plus IFG and IGT on two occasions, no diabetes by OGTT, and 26 additional exclusions. From the initial 158,177 persons screened, 4,080 met all the inclusion criteria for enrollment—a very low yield. While the DPP is the best study to date demonstrating the ability of a medication to reduce the risk of diabetes, using this full complement of steps and tests to screen the general public would be highly problematic, very expensive, and impractical if not impossible.

Post-hoc analyses from the DPP might provide additional insight regarding the use of currently studied drugs for diabetes treatment. In assessing DPP outcomes by intervention and age, the data indicate that metformin is as effective as lifestyle only among older OR YOUNGER persons (i.e., ≥60 years old). However, this group is the most likely to already have diabetes (diagnosed or undiagnosed), versus being at greatest risk for developing the disease. Diabetes incidence rates by BMI show that metformin affords greatest protection for a BMI ≥35. These two DPP observations combined suggest a prevention intervention using metformin could target younger obese persons (i.e., those <45 years old) with a BMI of at least 35. The most common side effect of metformin is GI discomfort; however, data from the DPP show that about one-third of subjects on placebo also had GI problems. With improved lifestyle behaviors, these side effects can be reduced significantly.

Results of the DREAM Trial suggested an impressive performance of rosiglitazone on reduction of risk for diabetes. However, the study also showed an increased risk of heart failure from both ramipril and rosiglitazone, which is of great concern when considering widespread use of a drug for disease prevention often in asymptomatic people.

It may be prudent to shift the prevention target for diabetes to obesity. A comprehensive integrated plan that lowers calories, increases exercise, incorporates behavioral modification strategies, and provides for pharmacological interventions as needed and appropriate might affect changes that would help normalize dyslipidemia, hypertension, and impaired glucose—some of the same parameters being considered as predictive markers for prevention of diabetes. Drugs for other indications that could be considered for management of obesity and prevention of diabetes include pramlintide, exenatide, bupropion, topiramate, and zonisamide.

In closing, Dr. Barrett-Connor argued that the available data do not support use of drugs to prevent diabetes in the larger population. One at-risk group for which sufficient data exist who might benefit from pharmacological intervention is obese persons ≤45 years old with a BMI of

35 or greater. The complement of evidence indicates that preventing obesity to prevent diabetes seems to be the most attractive option, although more research on obesity etiology and medications is clearly needed. Ultimately, she said, a good lifestyle is the best revenge.

PANEL DISCUSSION: WHAT OTHER DATA NEED TO BE GENERATED, IF ANY?
Robert Misbin, MD, Moderator; Elizabeth Barrett-Connor, MD; Fred Brancati, MD, MSH; Robert Eckel, MD; David Nathan, MD; William Knowler, MD, DrPH, NIDDK, Phoenix

Dr. Stern commented on the comparison of treatment of prediabetes with that of hypertension and hyperglycemia. He noted that these comparisons must be made with the understanding that treatment of the latter two conditions were validated in RCTs with bone fide health outcomes as endpoints, including heart attack, stroke, congestive heart failure, revascularization, and death. The prediabetes prevention studies sought to prevent a condition that is asymptomatic and not associated with any concomitant manifest morbidity. How do such studies assess quality of life? In a commentary on preventive pharmacology that he wrote in 1999 for *Diabetes Care*, the safety requirements for treating otherwise healthy persons for whom a benefit cannot be provided must be set very high. He advocated for a trial of early versus late treatment that includes endpoints such as cardiovascular events and mortality. Interventions would be done early in the prediabetic period or delayed until diabetes becomes manifest. Dr. Nathan commented that in this construct, early treatment must be demonstrated to provide as good as or better benefit than waiting to treat. The outcome measures associated with diabetes prevention *per se* are not equivalent to outcomes in treatment studies, as noted. However, the presumption of the argument for prevention of diabetes is that delaying diabetes is predicated on pushing back the burden of diabetes that would otherwise occur, including micro- and macrovascular complications. Although direct evidence demonstrating this outcome is not currently available, the DPP is collecting data on micro- and macrovascular effects, and the findings are expected within 3–5 years.

Dr. Barrett-Connor proposed reframing the discussion to determine whether metformin should be studied further in a prevention trial or whether it is time for the FDA to consider prevention as an indication for this drug, given the growing epidemic.

Dr. Ratner referred to the discussion of continuous versus dichotomous variables, which also applies to determining the "cut off" between prediabetes and diabetes. He pointed to the retinopathy findings in the DPP and suggested that an argument can be made that therapies for diabetes could be started for treatment of diabetes diagnosed at an earlier stage of the disease. Dr. Nathan cited a recent consensus paper on initiating care of type 2 diabetes that recommended starting lifestyle changes and metformin at the same time. Thus, if further consensus is reached on this recommendation, the distinction between prediabetes and diabetes becomes less clear. Regarding CVD, there appears to be general agreement that a continuum of atherosclerosis risk for inflammation. These issues seem to point to treatment of a "glycemic condition" and raise the questions of how a disease versus "pre-disease" are defined and whether or when to start treatment along this continuum. In response to a comment that reframing the definition of "prediabetes" might also simplify the regulatory component given the many drugs already approved to treat diabetes, Dr. Nathan stated that if this were the case, he would prefer to retain the dichotomy because of heightened safety concerns associated with otherwise healthy persons

taking diabetes medications in the prediabetic period. Dr. Misbin suggested that the regulatory burden would be increased, not decreased, with a revised definition of diabetes because prior trials testing the safety and efficacy of currently approved drugs were conducted using a distinctly different definition and clearly different criteria of the disease.

The current screening recommendation is to focus efforts on people over 45 years old. However, for possible indications in younger persons, based on subgroup analyses, how would younger individuals or groups who might benefit from a preventive intervention be identified? Dr. Barrett-Connor noted that data from the DPP suggest that some under-50 high-risk subgroups would be at low risk for renal and other complications and drug side effects; thus, metformin would be "safe" while delivering a benefit to this population. Dr. Knowler commented that the rationale for the ADA's recommendation for diabetes screening for persons over 45 years old is not clear. Subsequent to the formulation of the ADA's recommendation, the CDC Diabetes Cost-Effectiveness Study Group and others performed cost-benefit analyses of diabetes screening and detection. They concluded that the benefit of detecting undetected diabetes in younger adults was greater than detection in older persons, given the longer time a younger population would live with the health complications and co-morbidities resulting from the disease, if undetected or poorly controlled (JAMA 280: 1757-1763, 1998). Although the issue of whether to screen for diabetes, IFG, IGT, or other measures is complex, continuing to focus or limit screening to those over 45 does not seem prudent. Secondary analyses within the DPP support Dr. Barrett-Connor's assessment that obese, younger persons benefited the most from metformin; however, this finding, while suggestive, must be taken in consideration of the limitations of secondary analyses and needs independent confirmation.

Dr. Brancati reflected on the types of messages to physicians regarding the clear benefit of lifestyle factors to prevent diabetes in a climate where drugs that appear to prevent the disease also exist. While he supports a prevention study powered to detect more rigorous endpoints, he also wondered whether such high standards would be required for a prevention indication for diabetes drugs, citing the example of calcium channel blockers that received FDA approval and won large market share before having been tested in trials taken to hard CVD end points.

One attendee asked about use of A1c as a screening tool, which is not included in the ADA's recommendation, although it has some favorable characteristics, such as standardization across U.S. laboratories and positive predictive value (for individuals). He does not do fasting glucose testing in his practice because most patients do not follow the requirements for fasting. He does test for A1c, however, and noted that an A1c value of 5.8–6.5% is cause for further consideration. He asked why use of A1c in screening appears to be problematic but once a diagnosis of diabetes is made and the A1c threshold is reached, it is commonly used. In response, it was noted that epidemiologic studies and analyses of predictors of CVD risk indicate that A1c captures ambient glucose better than other glucose tests. However, in this context, the value of A1c was considered as part of an assessment of persons who respond abnormally on a stress test but whose fasting glucose or non-stress glucose test results are normal. A1cs were collected on all participants in the Framingham offspring study and the San Antonio Diabetes Study, both of which also tracked incident diabetes; thus, an analysis on the predictive value of A1c in these populations could be done, if it has not already been. Another participant stated that the AUROC for A1c to detect previously unrecognized diabetes or IGT is between 0.6 and 0.65, indicating

that it does not have adequate screening characteristics. The average A1c for persons with impaired glucose tolerance is 5.5%. In practice, if the goal is to demonstrate slight improvements, it may be useful to test A1c values. However, to minimize risk, glucose levels must be obtained, and A1c is not sufficient for this purpose. In addition, although within-person A1c values are highly reproducible and serve as a reliable marker of average glucose levels, the wide range of "normal" A1c values (approximately 4–6 percent) precludes its use for screening in the general population as a predictive tool. Dr. Barrett-Connor pointed out that an A1c test costs about four times more than a fasting glucose test. Dr. Yudkin stated that it is important to understand glycemia in the context of diabetes; specifically, that there is a threshold of risk for glycemia for microvascular complications and a linear relationship beyond this threshold. For every 1-percent drop in A1c, there is a 25-percent decrease in microvascular risk consistently for type 1 diabetes and type 2 diabetes. The threshold for macrovascular disease in diabetes is lower than the cutoff for "dysglycemia." The clusters of factors associated with IGT more than with IFG may turn out to be better predictors of risk because persons with an impaired 2-hour glucose also have characteristics such central obesity, increased waist circumference, and low-grade inflammation.

One intervention study to reduce glucose macrovascular events is the 6-year United Kingdom Prospective Diabetes Study (UKPDS). Ultimately, a primary goal of preventing or delaying diabetes is to prevent the complications of the disease. If studies are underpowered to detect whether diabetes complications are prevented, then several hundred people (instead of a handful) may need to be treated with lifestyle changes and/or medication to prevent heart attack or other cardiovascular events. Another participant mentioned the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study, which will examine the impact of three medical interventions on CVD complications and mortality in more than 10,000 patients with type 2 diabetes. One of the study's secondary hypotheses involves treatment effects on and differences in microvascular outcomes. In addition, one study group, efforts will be made to reduce A1c levels to as close to the nondiabetic range as possible, whereas in another study group, A1c will be approximately 7.5 percent. The STOP-NIDDM Study examined the effect of acarbose on preventing or delaying the onset of diabetes in approximately 1,400 persons with impaired glucose tolerance. The study also looked at cardiovascular events, and results indicated significant reductions in the risk for CV events and hypertension. Further assessment of STOP-NIDDM suggested that this study was significantly underpowered, perhaps by 100-fold, and identified some consistencies in the findings. Acarbose appears effective in reducing risk of type 2 diabetes in high-risk subjects; however, its effect on CV events needs to be confirmed. Assuming similar safety and efficacy to prevent diabetes, the use of a specific drug is probably most closely associated with tolerability.

Three questions were posed regarding use of a drug in a diabetes prevention strategy: First, in what situations would metformin best apply? For example, one group that might benefit is obese, younger, high-risk subjects, as suggested by Dr. Barrett-Connor. This group would likely also benefit from lifestyle interventions. Second, does the addition of metformin to lifestyle interventions have an additive or synergistic effect on outcomes? Should this drug be recommended as a complement to lifestyle or as a stand-alone, and to which groups? Third, to date, lifestyle interventions have demonstrated the greatest effect in preventing diabetes in at-risk groups. However, 5 years after these results of the DPP were announced, implementation

remains suboptimal. What is the likelihood that recommending a drug as a complement to lifestyle interventions will deflect the emphasis and real benefits of lifestyle? What safeguards can be put in place to promote a drug as a complementary intervention without compromising aggressive lifestyle intervention. Dr. Barrett-Connor restated her concern that patients with pharmacological and lifestyle interventions may be overly impressed with the value of the drug and abandon the lifestyle recommendations. However, lifestyle interventions must continue to be stressed because of benefits beyond preventing diabetes, such as improvement in risk factors for CVD (HDL, TGs, pulse rate, hypertension). This holistic approach thus takes into account both diseases.

The ability of physicians to assess lifestyle behavior and then to affect changes in their patients' behaviors represents a very practical aspect of translation of research findings. However, data suggest that less than 15 percent of primary care physicians ask patients about nutrition and/or physical activity. In contrast, about 70 ask about tobacco use. It appears that when a medication can be given despite the existence of an equally or more effective lifestyle intervention, the doctor and patient tend to err in favor of the drug. The availability of medication seems to be "easier" although not necessarily better for both clinicians and patients. Modifying physician behavior is complex and involves time, interest, education, reimbursement, and other issues and factors. This remains an important issue to the medical profession as a whole as well as to the general population, especially given the "toxic" environment of poor nutrition and inactivity that is contributing to obesity, diabetes, and cardiovascular disease in this country. The ability to overcome these environmental and societal pressures seems to be increasingly difficult. For example, despite billions of dollars spent each year on diet and exercise products, programs, and informational/educational campaigns, the ability to sustain long-term weight loss and healthy behaviors or stem the tide of near-epidemic levels of obesity and diabetes on the population level does not seem possible. On the other hand, some segments of the population have embraced better eating habits and regular exercise, suggesting that behavioral changes are possible and perhaps sustainable beyond the level of the individual. Another participant acknowledged the importance of being able to offer patients a range of options, advice, and suggestions regarding lifestyle interventions, but pointed out that in the normal practice setting there is neither time nor incentive to follow this approach. To determine how to proceed, it might be helpful to consider identifying the limits and barriers to changing physician behaviors, assessing the impact of physician intervention and risk communication on patient behavior, and identifying successful strategies targeting physicians and the physician-patient relationship. One suggestion was to identify a multidisciplinary approach that might include financial incentive or reimbursement for doctors to recommend lifestyle changes and then follow patients.

Trends in obesity, BMI, and diabetes that are limited to the past 25 years fail to convey the impact of the current epidemic on evolutionary history. Estimates of BMIs over the last two millennia suggest that humans generally were in the range of 20–22. In just two generations, the mean BMI has jumped to about 30. This dramatic shift translates into a public health emergency; the government, industry, and physicians who recommend policy need to intervene to move beyond treatment of the individual domestically and globally as well. Studies, programs, and policies also need to address equity issues. People at lowest risk for obesity are generally those who exercise, have access to regular medical care, are better educated, and have higher incomes,

while ethnic minorities, the poor, and unemployed are likely to suffer the most from this epidemic.

The nutritional content of the diet also needs to be addressed with respect to lifestyle interventions. A low-carbohydrate diet that is rich in fruits, vegetables, and grains and that limits saturated and trans fats but is not overly restrictive in total fat intake may be best to address the prediabetic state. Several controlled studies have compared the nutritional value, health outcomes (e.g., weight loss, cardiac risk factors, insulin resistance, etc.), and adherence associated with various diets and eating plans in persons with or at risk for diabetes.

In an effort to shift the focus of the discussion, Dr. Brancati and Dr. Nathan pointed out that beyond considering the beneficial lifestyle behaviors to counteract the growing epidemic of diabetes, one purpose of this meeting was to review the state of the science of drug regimens that may be used to prevent or delay the onset of diabetes. Thus, the charge to the panel included assessing the evidence for the possible role for pharmacological interventions to prevent diabetes and providing guidance as to whether any of these drugs might be acceptable for use at this time as a preventive agent. Questions and issues to consider further: What are the attributes of the available medications and that might be developed? What are the subgroups or cohorts that might benefit from these agents? What is the justification for their use in these groups?

Another participant commented that drugs that are safe and effective should be used when indicated, even when effective lifestyle interventions are available. In certain situations, for example, if a patient's LDL is <70, dietary modifications independent of or in addition to pharmacological intervention may confer no further benefit. Many other examples exist in medicine (e.g., antihypertensives) and have benefited millions of patients, and it may be helpful to consider use of drugs to prevent or delay the onset of diabetes within this context.

A participant expressed concern about the inappropriate and relatively widespread use of metformin at all stages of prediabetes in the pediatric population. While the use of metformin is acceptable to treat type 2 diabetes in pediatric patients, there are no data demonstrating the efficacy or safety of this drug in children for non-diabetes indications. Despite this lack of evidence, pediatricians and physicians in family/general medical practices have adopted the use of medication to treat obesity, insulin resistance, and risk of diabetes, often in children with a normal OGTT. It was noted that the DPP is frequently sited as evidence of the efficacy of this drug.

Another participant echoed the concern and posed a follow-up question regarding age cutoffs in drug studies, given the explosion of insulin resistance and type 2 diabetes in children and adolescents. Practitioners thus often face a conundrum as to how to best treat these patients. He asked whether any completed trials have included children of elementary through middle school age, if there are any plans for a trial in children in this age group, or if any other special provisions exist to study diabetes prevention in this group. Dr. Misbin commented that FDA takes this specific issue very seriously. For each new drug considered, the FDA addresses the issue of appropriateness of pediatric use and trials, and the agency makes a decision based on this assessment. However, there is a tension between ensuring appropriate and adequate treatment for pediatric patients against the ethical and safety concerns of medicating children

with an experimental drug that may never be approved. That said, several trials of antidiabetic agents have included children with type 2 diabetes, and the results of these studies may be helpful in addressing some of the questions raised.

The pharmaceutical industry is developing and marketing, and FDA is considering, a class of drugs that, based on results from animal and tissue culture studies, offer the biological possibility of altering the natural history of diabetes. This class of drugs exploits GLP-1 analogs and DPP-4 inhibitors, and research to date suggests that these agents increase beta cell proliferation and decrease beta cell apoptosis. Given that changes in beta and alpha cell function and mass are the key pathophysiologic points in determining whether insulin resistance progresses to hyperglycemia, these efforts and findings should be much more visible in ongoing discussions. However, to date, it appears that no studies of, for example, DPP-4 inhibitors in persons with IGT or IFG have been conducted. Support for early-phase trials to assess the efficacy of these agents in the prevention and delay in diabetes should also be part of the discussions in the clinical and research communities, including Federal agencies such as the FDA and NIH. A more proactive stance in proposing studies based on cutting-edge or novel research findings, rather than on standard or conventional metrics by which FDA generally judges new drugs (e.g., drop in A1c in diabetes treatment), will likely be needed to affect a shift at all levels. To assist this effort, the FDA was asked revisit its criteria for approval of clinical studies and identify new outcomes considered acceptable to demonstrate early disease prevention in either already-approved or experimental drugs. Dr. Misbin commented that a considerable part of the challenge for FDA in defining acceptable clinical variables, end points, and criteria is the lack of consensus among experts in a field or consistency in available data to inform the agency. It was noted that many potential parameters were identified during the prior NIDDK-FDA meeting 2 years ago. A measurement of continuous changes in the glycemic index (for more diabetes-specific complications) or reduction in CV risk factors could be developed for application in diabetes prevention trials. Dr. Misbin relayed that in 1997, the FDA began to develop guidance to move this field forward; this effort is still ongoing. Thus, changes in the drug approval process and policy are often difficult and slow. Dr. Misbin subsequently sought to clarify when the FDA considers secondary analyses appropriate and inappropriate. He explained that for the FDA, if the primary outcome of a clinical trial is negative, subset analyses are not accepted by the agency. However, if the primary endpoints are positive, it would be appropriate to perform subset analyses, which can help direct the practice of medicine, and submit the results of those analyses.

Dr. Dobrestov suggested using a staircase approach for making decisions regarding diabetes prevention interventions. The first stage involves lifestyle and behavioral changes. If these changes do not yield the desired outcome(s) and the patient is at high risk for complications, medication could be prescribed, as indicated. Further recommendations could be made depending on the patient's progress and continued risk. Dr. Dobrestov noted his support of additional trials targeting various subgroups (e.g., different prediabetes stages/categories, different age groups, obese children) with a range of outcome measures, such as glycemic control, CV risk factors and events, and risk of neuropathy.

SUMMARY AND CLOSING REMARKS

Robert Eckel, MD, University of Colorado

Dr. Eckel recognized the many challenges and complexities in determining how best to address the increasing concerns regarding this public health issue and the prevention of diabetes and its correlates with pharmaceuticals. He noted that the meeting presentations and discussions reflected many of these difficulties and uncertainties.

Obesity and the *resultant* type 2 diabetes are reaching epidemic levels in this country, with evidence suggesting that approximately 75–80 percent of type 2 diabetes is associated with obesity. This additional factor may be critical in determining whether public health and medical interventions should focus more on obesity prevention and treatment than diabetes in the shorter and longer term. At the very least, obesity should be a significant component in efforts aimed at preventing type 2 diabetes.

Although predicting type 2 diabetes is not a simple task, several promising tools such as the risk calculator described by Dr. Stern at the start of this conference are available to assist in identifying those at greatest risk of developing the disease. Further development and validation of predictive models and tools should be considered. Dr. Barrett-Connor identified challenges and issues of glucose tolerance testing, especially for use in a doctor's office. Physician reluctance, level of acceptability of the glucose solution by patients, and the time required to complete the test all contribute to the difficulties surrounding this measure. Fasting glucose may be sufficient in assessing function and status. Time spent with patients is essential to their accepting the need for testing, understanding the real risks of and associated with developing diabetes (and co-morbidities), and being motivated to make and maintain lifestyle changes to reduce those risks.

The importance of inflammation and its relationship to obesity, insulin resistance, and type 2 diabetes was demonstrated in the meeting presentations. However, while evidence suggesting that metformin reduces CRP by 12–14 percent is impressive, lifestyle interventions are clearly more effective. A great deal more research in this area is needed before proceeding to discussions about pharmacological interventions for diabetes prevention. Investigations focused on paracrine, autocrine, and/or endocrine effects of cytokines in disease development, progression, and prevention are warranted if inflammation is the outcome sought in terms of risk for diabetes.

The benefits of and challenges associated with sustained lifestyle interventions were reviewed and discussed in detail during the meeting. Without adequate understanding of the importance of lifestyle in maintaining health and preventing disease, medication consistently supersedes the need for important lifestyle behaviors. Thus, the impact of the indication or approval of a drug to prevent type 2 diabetes on lifestyle must be considered very carefully. Dr. Eckel stated that available data do not adequately address this concern. Related to this discussion is the issue of the relative contribution of weight reduction, diet and nutrition, and physical activity to long-term benefit. Adaptations to significant weight loss in obese persons are significant biologically, psychologically, and socially. Data show that appetite increases in weight-stable, reduced-weight obese persons, which reinforces patients' perceptions of feeling hungrier following weight loss. Preference for high-fat, high-sucrose foods also increases, which substantiates the types of foods

people often choose to consume after losing weight. The amount of lean mass drops and basal metabolic rate falls with weight reduction, translating into lowered caloric requirements at the lowered body weight. Observation of persons who have had significant weight loss suggests that they become less physically active, which, in turn, influences energy efficiency. This group also has increased insulin sensitivity, which is associated with increased amino acid/protein, lipid, and glucose uptake and storage, increased lipogenesis, and reduced muscle mass. Tissue-specific changes in LPL leads to increased carbohydrate oxidation and reduced fat oxidation. The metabolic characteristics of this type of environment in reduced-weight obese individuals puts them at increased risk for weight re-gain. The take-home lesson for diabetes prevention is that lifestyle-based interventions may or may not have a sustained effect because weight often returns to baseline and the change that may have the greatest impact is not diet or exercise *per se* but weight reduction.

Regarding the issue of pharmaceuticals, Dr. Eckel explored whether a metformin trial for diabetes prevention is needed, or if it is time for a prevention indication. Questions for further consideration include: Would a metformin prevention trial ever be supported? Can the FDA be sufficiently petitioned to provide an indication for metformin as a type 2 diabetes prevention agent based on current evidence and criteria? Are data adequate for translation into a broad prevention intervention when it appeared that only one subgroup in the DPP study responded? Should the results of the DPP be repeated in a larger trial to document the impact of metformin in reducing the incidence of type 2 diabetes? Should such a trial target only the subgroup of younger obese at-risk subjects? Dr. Eckel argued that with evidence of clear benefit from a clinical trial, the FDA might approve a prevention indication for metformin even without a drug company championing the agent. Regarding other diabetes drugs, the key issue for a TZD clinical trial is long-term safety; it may be difficult to proceed at this time given this safety profile. On the other hand, nateglinide and related agents are safe but have relatively modest effects, act via mechanisms that increase insulin, and have no weight benefit. Injectables such as GLP agonists are not appropriate for a clinical trial to prevent prediabetes. DPP-4 is in a class of drug for further consideration. Drugs not yet approved for the treatment of obesity also should be considered because of their potential to reduce substantially the risk of type 2 diabetes.

ADJOURNMENT

Dr. Fradkin thanked guests and participants for attending and taking part in this important meeting. The meeting was adjourned at 12:10 p.m.