Diabetes Mellitus Interagency Coordinating Committee Meeting

National Institutes of Health Campus
Natcher Conference Center, Conference Room A
Bethesda, Maryland
February 25, 2003

The Metabolic Syndrome

Summary Minutes

Dr. Saul Malozowski, Executive Director of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), convened the meeting and presented Dr. Allen Spiegel, DMICC Chair and Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). Dr. Spiegel welcomed the speakers, committee members, and guests. He stated that they were an important body of persons with the opportunity to coordinate manifold activities as representatives of agencies of the U.S. Department of Health and Human Services (DHHS), along with important stakeholders such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE).

Dr. Spiegel noted that there are critical issues to be addressed regarding the metabolic syndrome. These include definition issues, the etiology of the metabolic syndrome, risk factors represented by the syndrome, and implications for prevention and treatment of the syndrome. Since a major definition was developed by the National Heart, Blood and Lung Institute's (NHLBI's) National Cholesterol Education Program's (NCEP's) Adult Treatment Panel III (ATP III), the group was fortunate to have Dr. Peter Savage present today representing NHLBI's membership on the DMICC. Dr. Claude Lenfant, NHLBI Director, regretted not being able to attend but was looking forward to hearing the results of the meeting.

Dr. Savage, Director, NHLBI Division of Epidemiology and Clinical Applications, joined Dr. Spiegel in emphasizing that today's meeting provided the group with a major opportunity to discuss the metabolic syndrome and its relationship to diabetes and to cardiovascular complications in non-diabetes. He agreed that there were many questions to be answered regarding the definitions and the magnitude of the problem. An overview of these issues would be presented by three speakers very active in the field—Dr. James Meigs, Dr. Steven Haffner, and Dr. Scott Grundy. Following these overviews, DMICC agency representatives and members of ADA and AACE would present their groups' perspective on the metabolic syndrome. (Dr. Haffner's and Dr. Grundy's slide presentations are available at http://www.niddk.nih.gov/federal/dmicc/Haffner.ppt and http://www.niddk.nih.gov/federal/dmicc/grundy.ppt. For informational purposes and due to the need of further analyses only part of these presentations are available. Dr. Meigs slides could not be posted because they contained data that has not been published yet.)

James B. Meigs, MD, MPH, Assistant Professor of Medicine, General Medicine Division, Harvard Medical School, and Massachusetts General Hospital, Boston.

Definitions of the Metabolic Syndrome and Related Risk of Heart Disease and Type 2 Diabetes

Dr. Meigs introduced the NCEP ATP III definition, developed in 2001, and the World Health Organization (WHO) definition of 1999 (see box), which differ in trait thresholds and inclusion criteria.[1] Regardless of the definition used, the metabolic syndrome is very common, according to Dr. Meigs. Those with the syndrome, again regardless of the definition, are more insulin resistant and at greater predicted risk for coronary heart disease (CHD) and diabetes. Presence of the metabolic syndrome doubles the risk for CHD events and dramatically increases by as much as 10-fold the risk for type 2 diabetes. Specific clustering of traits may better predict the risk or burden of CHD or type 2 diabetes than the presence of any three individual traits. According to data from the Framingham Heart Study, in which Dr. Meigs has been a key participant, prevalence of the NCEP-defined metabolic syndrome increased from about 15-20 percent in men and 7-16 percent in women from the late 1980s to the mid-1990s.

NCEP ATP III (2001)	WHO (1999)
3 or more of:	(IFG or IGT, or DM) and/or IR* plus 2 or more of:
Waist circ >40" (M) or 35" W)	BP ≥140/90
TG≥150	TG ≥150 and/or HDL <35 (M) 39 (w)
HDL <40 (M) or 50 (W)	WHR >0.9 (M) or 0.85 (W) and/or BMI >30
BP ≥130/85	UACR ≥30/
FPG ≥110/	

*IR=clamp-assessed glucose uptake <25 percentile
[1]Definition of acronyms
NCEP ATP III *JAMA* 2001:285:2486-97

Prevalence by Definition. Based on the National Health and Nutrition Examination Survey of 1999-2000 (NHANES III), the metabolic syndrome as defined by NCEP tends to be heterogeneous across racial/ethnic populations, is more common in men than in women, and prevalence increases with age. Population-based comparisons of the data from NHANES III, the San Antonio Heart Study, and the Framingham Offspring Study indicate that, of the components of the NCEP definition, hyperglycemia was the least common trait. Components varied across populations and tended to be most prevalent in Mexican Americans. It was interesting that both whites and Mexican Americans had a higher prevalence of the syndrome than white Finnish males in the Kuopio IHDRF Study, possibly because the Kuopio men are relatively slender. Comparing the prevalence of the WHO metabolic syndrome traits in populations from the Framingham Offspring Study, the San Antonio Heart Study, the Botnia Study, and the Kuopio IHDRF Study, hyperglycemia with or without insulin resistance (IR) was nearly as common in white Finns from Botnia as it was in the San Antonio Mexican Americans as was the prevalence of the syndrome, with 46 percent of the Botnia subjects and 49 percent of the Mexican Americans having the syndrome.

[1] Waist circ = waist circumference; TG = triglycerides; BP = blood pressure; FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus; IR = insulin resistance; WHR = waist:hip ratio; UACR = urinary albumin creatinine ratio

Issues in Defining the Syndrome. Dr. Meigs listed several uncertainties that arise in considering any definition of the metabolic syndrome. Should simple trait counting be used or empiric weights or clusters? Are insulin levels being measured or insulin resistance? Should high glucose or diagnosed diabetes be included as part of the definition or as an outcome? Which is a better indicator, BMI or waist circumference? What about microalbuminuria or C-reactive protein (CRP) and other inflammatory markers? Finally, which thresholds should be used—NCEP or WHO? Comparison of waist circumference versus waist:hip ratio is not the same measure and NCEP does not include BMI, fasting glucose, or diabetes.

In counting traits, rather than clusters, Dr. Meigs said it is important to note that the individual syndrome traits do not have equal predictive power. On the other hand, factor analyses show that certain traits tend to cluster, suggesting physiological trait clusters exist, and that the most common clusters include from two to four factors. This may indicate a need to define the syndrome by requiring selection of traits based on their specificity for insulin resistance. For instance, requiring that a large waist circumference and low HDL/high triglyceride dyslipidemia be present may increase the specificity of the diagnosis of metabolic syndrome. Comparisons were made of Framingham Offspring and San Antonio Heart Study subjects with factors added, such as BMI and empiric clusters to the NCEP and microabluminuria to WHO. Dr. Meigs pointed out that overall prevalence and the degree of HOMA-IR (homeostasis model assessment of IR) between whites and Mexican Americans is highly similar regardless of the alternative definition used, except for slightly higher rates according to the WHO definition, especially for Mexican Americans. Also, the prevalence drops dramatically when the NCEP definition is applied with empiric clusters, although subjects remain quite insulin resistant and at elevated predicted CHD risk even by this definition.

Metabolic Syndrome and Risk for CHD and Diabetes. The risk for coronary heart disease (CHD) based on the Framingham Heart Study Risk Score is also similar, regardless of alternative definitions used, with both whites and Mexican Americans who have the metabolic syndrome being at much higher risk. The 11-year adjusted relative risk for CHD and all-cause mortality associated with the metabolic syndrome, regardless of definition, was also true for Finnish men in the Kuopio IHDRF Study. The relative risk for CHD and cardiovascular disease (CVD) in the Framingham Offspring Study participants showed slight differences between those who had two versus three traits of the metabolic syndrome, but with three traits certainly increasing the risk. Dr. Meigs emphasized that, on the other hand, the presence of any two or three traits was a powerful indicator of risk for diabetes.

Dr. Meigs next described the population-attributable risk percent (PAR%) formula, or the burden of disease that can be attributed to a given condition, as a clinically useful indicator for public health. He stated that, in the Framingham Offspring Study, the 8-year age-adjusted relative risk and PAR% for CHD was always highest for those with a three-way combination that included lipid and waist traits. For type 2 diabetes. the PAR% was very high for any three-way combinations, with those including fasting glucose and waist traits being the highest for both relative risk and PAR%.

The risk of CHD was higher in those with the fasting plasma glucose and waist combination and increased in those who had any three-way combination, any two-way combination, or the HDL-

blood pressure combination. The burden of CHD increased as persons had any two-way combination of traits and increased with any three-way combination or HDL-blood pressure combination.

For diabetes, the risk increased beginning with the fasting plasma glucose trait in combination with any other one or two traits and the risk increased or was equal to this with any two- or three-way combination of traits. The public health burden for diabetes was predictable given any three-way or two-way combination of traits and increased with the presence of the HDL-waist combination.

Steven M. Haffner, MD, MPH, Professor of Medicine, Department of Medicine/Clinical Epidemiology, University of Texas Health Science Center, San Antonio.

Etiology(ies) of the Metabolic Syndrome and Variations Across Racial/Ethnic Groups

Dr. Haffner presented the risk of CHD and/or of diabetes as one criteria for comparing the NCEP and WHO definitions of the metabolic syndrome. A second possible criteria is the relation of the syndrome to IR, and a third is the prevalence of the syndrome in the community and by different racial/ethnic groups. The metabolic syndrome is associated with increased risk of heart disease, although the increased risk may not be entirely due to increased IR. On the other hand, most subjects with the metabolic syndrome do not have type 2 diabetes. African Americans tend to have low triglycerides and high HDL; therefore, the prevalence of the metabolic syndrome in this population is lower according to the NCEP definition and is higher according to the WHO definition, a peculiarity that Dr. Haffner felt deserves consideration. He stated that another thing to consider is the simplicity or understandability of the definition in order to apply it in the general population not just discuss it as a theoretical aspect.

Dr. Haffner addressed the prediabetic state as a model for the metabolic syndrome; insulin resistance, insulin secretion, and subclinical inflammation as predictors of the metabolic syndrome; the relation of inflammation to increased insulin resistance and decreased insulin secretion; factor analyses from the Framingham and the Insulin Resistance Atheroscerlosis Study (IRAS); the metabolic syndrome, diabetes, and coronary heart disease prevalence in the NHANES and other database populations; and identification of persons with insulin resistance and beta-cell dysfunction using alternate definitions of the metabolic syndrome. Dr. Haffner's presentation was based on data from five studies: the San Antonio Heart Study (SAHS), IRAS, the Mexico City Diabetes Study, the Framingham Study, and NHANES

Literature on the Eiology of the Metabolic Syndrome. Dr. Haffner said the question of clustering of cardiovascular risk factors has been talked about for at least 35 years. The concept was developed by an Italian group in the late 1960s, and in the 1970s there were a variety of papers on the subject. A group in East Germany led by Hanefeld talked about clustering of cardiovascular risk factors and about insulin but because the literature was in German and the wall was still up, this received little publicity.

Reaven began the discussion about an insulin resistant syndrome, calling it syndrome X (*Diabetes*, 1987), and Ferrannini (*Diabetologia*, 1991), and Haffner (*Diabetes*, 1992) added to

this. Reaven's discussion was based on non-obese persons with insulin resistance. Some people objected to this because in the United States and other western countries, the syndrome occurred primarily in obese persons. John Despres referred to the hypertriglyceridemic waist (triglycerides at 176 mg/dL and a 90 centimeter waist in men), and Peter Wilson discussed the presence of weight gain in multiple metabolic disorders (*Arch Int Med*, 2000) from the Framingham Study, while not referring to the metabolic syndrome. Glycemia in the non-diabetic range was given as the primary cause by Gerstein, who called it the dysglycaemic syndrome, and glycemia was also presented in the DECODE data. There remains an issue that needs further study about whether the syndrome is related only to the risk factors within itself or to cardiovascular risk factors. Subclinical inflammation has also been presented as a factor.

Prediabetic State as Model of Metabolic Syndrome. A prediabetic syndrome was an early attempt at looking at the metabolic syndrome. Basically, the suggestion was that increased cardiovascular risk factors preceded the onset of type 2 diabetes. An issue was whether it was glucose or insulin that increased the CVD risk. In nondiabetic subjects, people who are insulin resistant always have slightly elevated glucose levels. United Kingdom Prospective Diabetes Study (UKPDS) data suggest that the relationship between glucose concentrations, while clearly significant related to myocardial infarction (MI) is a lot more modest than its relationship to microvascular disease. Dr. Frank Hu reported (*Diabetes Care* 2002:25(7):1129-1134) that in the Nurses Health Study, not only those who were diabetic at the beginning of the 20-year followup had a five-fold increased risk of cardiovascular disease, but those who were prediabetics had a three-fold risk prior to diagnosis. In each of the populations cited in the literature, cardiovascular risk factors were all higher in prediabetic subjects. Dr. Haffner explained this is important as part of the intellectual basis for prevention of type 2 diabetes as an important strategy as opposed to screening for diabetes and then managing it with tight control.

Insulin as a Predictor of the Metabolic Syndrome and CHD. Dr. Haffner next addressed insulin resistance, insulin secretion, and subclinical inflammation as predictors of the metabolic syndrome and noted that there is some controversy about insulin levels as a predictor of CHD, although most of the data indicates a positive correlation. He stated that it is known that insulin concentrations predict the metabolic disorders and also predict multiple metabolic disorders. High absolute concentrations of LDL are not related to baseline insulin levels, but high insulin concentrations predict the development of small dense LDL.

In the San Antionio Heart Study, people with normal glucose tolerance were followed to see whether they developed type 2 diabetes. At baseline, they had higher tryglycerides, higher HDL, higher systolic blood pressure (BP) than prediabetics, slightly higher glucose levels but the differences were really very small, although significant, and much higher insulin concentration. The argument was that it was hyperinsulinemia and IR that drove this pre-diabetic issue. After Gerstein's data came out, the San Antonio data was reviewed and an attempt made to develop a model for IR versus glucose. From a San Antonio cohort, where there was information on surrogates of IR and low insulin secretion, and from earlier studies of the Pima Indians and data from Joslin, it was shown that low insulin secretion and IR do predict the onset of type 2 diabetes. Furthermore, when these factors were combined, there was about a 20-fold excess of incidence of type 2 diabetes.

Next the SAHS investigators looked at 105 individuals before they became diabetic and compared them according to IR and insulin secretion and traditional cardiovascular risk factors—triglycerides, HDL cholesterol, and systolic blood pressure. Fifty-four percent were IR, 29 percent were IR but had fairly good stimulated insulin secretion based on the change in insulin and in glucose over 30 minutes of a glucose tolerance test, about 16 percent had low insulin secretion, and a little less than 2 percent had neither defect, although the latter data has some difficulties. These subjects were Mexican Americans and non-Hispanic whites in four groups with identical glucose tolerance, which allowed matching for glucose control and comparison of those who developed type 2 diabetes. The data is very similar across the ethnic groups. Analysis of the data strongly suggests that among prediabetics as a model, it is IR, not small changes in glucose levels, that predicts type 2 diabetes.

The two groups with matched glucose and with high IR had higher rates of conversion to diabetes and much higher tryglycerides than those with low insulin secretion who converted, even when stratified and controlled for weight differences. Those with low insulin secretion who converted to diabetes had tryglycerides similar to non-converters. There was a similar pattern with HDL cholesterol and systolic blood pressure, in that those with low secretion tended to have similar blood pressure and HDL levels to those who did not convert. These low secretion converters and the nonconverters had lower blood pressure and higher HDL levels than those with IR who converted. LDL data on these groups also was similar. Dr. Haffner also presented data from a 25-year followup study reported by Pyorala et al. (*Circulation*, 1998; 98:398-404) that showed that nondiabetic men with the highest IR are at greatest risk for a major CHD event.

Subclinical Inflammation as a Predictor of the Metabolic Syndrome and CHD. With regard to CRP, Dr. Haffner referred to a 1992 consensus conference sponsored by the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC). The participants discussed the relative risk of CVD as predicted by markers of inflammation. Their recommendations (see Pearson et al., *Circulation*, 2003; 107:499-511) adopted the following CRP cutpoints: high-sensitivity as 3 m/L or higher (in mg/dL this would be 0.3 mg/dL), low as less than 1 mg/L, and average as 1 to 3 m/L.

In the IRAS study with nondiabetics, data adjusted for demographics (age, sex, clinic, ethnicity) and smoking (because smoking is related to high CRP levels and some people think it is related to IR as well), showed a strong correlation of CRP with obesity and waist circumference, a positive association with fasting insulin levels, a significant but weaker relationship with systolic blood pressure and fasting glucose, and an inverse relationship with insulin sensitivity directly measured by frequently sampled intravenous glucose tolerance tests. The original comparison was made prior to the NCEP definition, but was redone using the NCEP definition and the WHO definition, with similar results—the higher the CRP level, the greater the number of metabolic disorders.

Dr. Haffner also referred to six studies on the 5-year incidence of type 2 diabetes stratified by quartiles of three inflammatory proteins—fibrinogen, CRP, and PAI-1—that showed that high CRPs predict type 2 diabetes, in some circumstances independent of fasting insulin, although not significantly when adjusted for IR. PAI-1 (plasminogen activator inhibitor-1) levels were a

stronger predictor, but Dr. Haffner said PAI-1 is unlikely to be used for clinical purposes because of collection and measurement issues.

Effect of Insulin-Sensitizing Interventions on Reducing CRP Levels. Dr. Haffner cited Diabetes Prevention Program (DPP) unpublished data presented at an AHA meeting in 2002 that showed that two insulin-sensitizing interventions, modest lifestyle changes and metformin, reduced CRP levels by 58 percent and 31 percent, respectively, in this impaired glucose tolerance cohort. Lifestyle changes caused the most lowering of CRP levels in both genders, but were most significant in women who tend to have higher levels than men. The lowering of CRP by lifestyle and metformin continued to increase for women over the 12-month period. Dr. Haffner indicated that, although the data covers only 1 year, it suggests that lifestyle changes that produce greater changes in type 2 diabetes may also have greater effects on CVD. The use of rosiglitazone, a TZD (thiazolidinedione), with diabetics, a different population than that of the DPP, showed a 25 percent reduction in triglycerides, similar to most statin studies (see *Circulation* 2002;106:679-684).

Elevated CRP Levels as Predictors of the NCEP Metabolic Syndrome. Data from the Mexico City Diabetes Study indicates basically no relationship in men between CRP levels and development of the metabolic syndrome and a very limited relationship to development of type 2 diabetes. In women, those in the lowest quartile of CRP levels have about a 7 percent chance of developing the syndrome over a 6-year period, whereas those in the higher quartile have about a 3.5-fold increase in risk. CRPs predict the metabolic syndrome in both lean and obese women, indicating that obesity, whether determined by BMI or waist circumference, plays a strong role as a predictor aside from CRPs. Dr. Haffner recommended that additional studies with other populations be conducted to examine whether testing for CRP would be helpful in determining risk of developing the metabolic syndrome in women, independent of BMI and HOMA-IR.

Relationship of Inflammation to Increased IR vs. Decreased Insulin Secretion in the Pre-Diabetic State . Dr. Haffner noted again that in the IRAS, those with high IRs who converted to type 2 diabetes had high CRP levels The high IR/high CRP group was also more overweight than the other two groups. There was basically no difference in CRP levels in those with low secretion but no IR who developed diabetes regardless of their BMI. However, the non-converters with high BMI also tended to have higher CRP levels, though not as high as the converters with high IR. Because glucose levels were similar in all the groups, Dr. Haffner said this strongly suggests that IR is the major factor in predicting type 2 diabetes, but this is a complicated area because most people think that among the principal determinants of subclinical inflammation (CRP is produced by the liver) are cytokines produced in adipocytes such as IL6 and TNF-alpha but many of the interventions that lower CRP do not actually decrease IL6 in studies, possibly for measurement reasons.

Factor Analyses From the Framingham Study and IRAS. The basic conclusion from factor analyses of the Framingham study reported by Dr. Meigs in *Diabetes* in 1997 and the IRAS analyses described by Dr. Anthony Hanley in *Diabetes* in 2001 is that hypertension is a separate factor not associated with IR. Framingham also included a glucose factor. In IRAS, there was a metabolic factor that included adiposity, triglycerides, and glucose levels. IRAS also concluded that, along with hypertension, there was PAI-1 that entered into the metabolic factor and a

separate inflammatory factor with CRP and fibrinogen. According to Dr. Haffner, it does not look like IR is responsible for all of these factors, such as hypertension..

Prevalence of Metabolic Syndrome, Diabetes, and CHD Based on NHANES III and Other Study Data. Dr. Haffner said that according to a paper by Charles M. Alexander et al. to be published in *Diabetes*, of which Dr. Haffner is an author, 85 percent of diabetics have the metabolic syndrome based on NHANES III. The overall risk for CHD appears to be intermediate between diabetes with and without the metabolic syndrome. In the NHANES population, the risk of CHD in those with metabolic syndrome but no diagnosed diabetes is approximately 14 percent and approximately 19 percent in those with both the syndrome and diabetes. The risk without the syndrome or diabetes is 8.7 percent and without the syndrome, but with diabetes, the risk is 7.5 percent. Of interest to Dr. Haffner was the relatively small number of diabetics who do not have the metabolic syndrome and whose risk of CHD is very close to that of nondiabetics without the syndrome. This is probably not a surprise, since hypertension is a well-known risk factor for CHD among diabetics.

Four other databases, including data from a large European and American pharmaceutical study in new diabetics called ADOPT (A Diabetes Outcome Progression Trial), whether one uses the NCEP or the WHO definition, indicate that somewhere between 75 and 80 percent of diabetics have metabolic syndrome. These numbers appear to be equally true in populations where obesity is less common than in the United States, as in some areas in Europe.

Prediction of CHD based on multivariate logistic regression analysis of NHANES data do not show that the metabolic syndrome predicts CHD independently of its individual components. However, the individual components that have a higher correlation as risk predictors are low HDL, high blood pressure, and diabetes, which is similar to the information provided by Dr. Meigs' Framingham data. Therefore, some of the components of the metabolic syndrome may be more related to CHD than are other components.

Comparison of characteristics among the U.S. population age 20 and older with and without the metabolic syndrome are similar whether the WHO or NCEP definition is used and the IR is similar to Framingham data. Although the 1998 WHO definition includes HOMA-IR data and the 1999 definition involves IR as clamp-assessed glucose uptake, the comparisons are based on HOMA-IR because no one had clamp data. When a different measure of insulin sensitivity is used, there is a different answer, as discussed below.

Identification of Subjects With IR and Beta-Cell Dysfunction Using Alternate Definitions of the Metabolic Syndrome. In IRAS, Dr. Haffner said data on the lowest quartile for insulin sensitivity in three different population groups of nondiabetics—African Americans and non-Hispanic whites and Hispanics, all of whom were actually Mexican Americans—were examined to determine how well the metabolic syndrome identified persons with IR but without diabetes as a criteria for comparing the NCEP and WHO definitions. Unlike the Framingham and NHANES data that look at surrogate measures, direct measurement of insulin sensitivity presented a different study. The group with the lowest sensitivity met neither definition. About half the population with insulin sensitivity met both definitions, and about one-quarter with sensitivity met one or the other definition. Combining the criteria of the definitions made no difference. The

WHO definition was better than the NCEP in identifying persons with IR. Overall, the direct measurement of insulin sensitivity was better than HOMA-IR or any of the NCEP or WHO surrogate measures in identifying those with IR.

In looking at the measure of insulin secretion in IRAS nondiabetics, the metabolic syndrome did predict people with low insulin secretion, with NCEP being a better predictor than WHO. Dr. Haffner pointed out that of special interest in this data is that the NCEP definition identified a group of nondiabetic African Americans with insulin secretory defects, and there is literature that indicates that not only does this population have IR as a cause for their increased rate of developing type 2 diabetes, but there may be lower glucose effectiveness and lower insulin responses in African Americans. Dr. Haffner suggested further analysis is needed in this area.

In conclusion, Dr. Haffner remarked that the characteristics of the metabolic syndrome need to be reexamined based on the data from the IRAS. Using directly measured IR across three different ethnic groups, the WHO definition was better than the NCEP as a predictor of IR, but whether this is significant enough is another matter. Obesity is a significant factor in the United States, IR has data that suggests it is and is not important, and subclinical inflammation appears to be important according to experimental work in epidemiology. IR is certainly not the cause of the entire syndrome, but it does seem to be a contributing factor, according to Dr. Haffner.

Scott M. Grundy, MD, PHD, Director, Center for Human Nutrition, Professor of Internal Medicine, Chairman, Department of Clinical Nutrition, University of Texas Southwestern Medical Center at Dallas

Issues for Prevention and Treatment of the Metabolic Syndrome

Dr. Grundy served as Chair of the NHLBI's National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of Blood Cholesterol in Adults (Adult Treatment Panel III). He opened his presentation by explaining that the NCEP ATP II committee and panel members involved in developing LDL cholesterol guidelines to prevent and treat coronary heart disease (CHD) were concerned about a nutritional approach along with the drug treatment approach that clinical trials had shown could reduce the risk for CHD. ATP II thus addressed obesity and physical inactivity, but this was not really noticed. The increasing evidence that obesity and physical inactivity leads to CHD prompted the ATP III members to take a new approach. Concerned that the NCEP guidelines would be seen as only drug treatment guidelines for LDL, they decided to define a set of medical conditions related to obesity, physical inactivity, and nutrition and define these conditions as a metabolic syndrome. Based on the prevalence of CHD and its mortality rate in those with type 2 diabetes, the panel also elevated type 2 diabetes to a CHD risk equivalent or high-risk condition. The intention was to get physicians to pay more attention to their patients at risk for both CHD and diabetes because of lifestyle-related problems. Therefore, the guidelines addressed high LDL, the cluster of medical conditions termed metabolic syndrome, and type 2 diabetes that tends to result from or accompany the syndrome, as being high-risk factors for CHD. Dr. Grundy stated that by defining a syndrome, rather than merely further emphasizing obesity and physical inactivity as CHD and diabetes risk factors, ATP III has successfully moved forward in acquiring attention about these risk factors.

Dr. Grundy stated that it is known through the literature reports of clinical studies that therapeutic lifestyle changes do correct or at least modify all of the metabolic syndrome risk factors (excess fat in adipose tissue and abdominal fat, high blood pressure, high triglycerides, low HDL, insulin resistance, high PAI-1, and high CRP). These reports also show that drug treatment is a potential approach to managing the individual components such as using aspirin and hypertensive drugs for the prothrombotic state, the insulin-sensitizing drugs such as metformin and the TZDs for insulin resistance, the lipid-lowering drugs to reduce the proinflammatory state , and drugs besides statins for patients with atherogenic dyslipidemia. Factors in favor of drug therapy for the metabolic syndrome would be high-risk individuals such as those with established CVD and/or type 2 diabetes, persons with multiple risk factors, and also moderately high-risk patients who have a 10-year risk in this range according to ATP III guidelines.

Issues for Prevention and Treatment of the Metabolic Syndrome. Dr. Grundy listed public health and clinical strategies as key issues for the prevention and treatment of the metabolic syndrome. In clinical strategies, it is important to know about risk assessment in patients with the syndrome, selection of patients for interventions, both lifestyle, which was made the major part of the ATP III guidelines related to metabolic syndrome, and pharmacological intervention. Prevention and therapy issues include defining the syndrome, determining its prevalence, identifying the metabolic components or risk factors and potential treatment targets, assessing the health consequences of these components, and understanding the pathophysiology of the syndrome.

What Is the Metabolic Syndrome? Dr. Grundy noted that definitions of the metabolic syndrome have come from several areas, each of which has particular implications for prevention and treatment of the metabolic syndrome.. The syndrome has been defined according to clinical outcomes (CHD and diabetes), in relation to underlying causes such as insulin resistance or obesity; by its metabolic components as in the ATP III clustering of metabolic cardiovascular risk factors, and according to clinical criteria as in the NCEP definition based on cardiovascular disease (CVD) risk factors and the WHO definition based on insulin resistance as an underlying cause.

Implications for Therapy and Intervention Based on Definitions of the Metabolic Syndrome. Dr. Grundy stated that how the metabolic syndrome is defined has implications for therapy and intervention in patients identified with the syndrome. When defined by insulin resistance as the underlying cause, the metabolic syndrome is often called the insulin resistant syndrome. When lifestyle, especially obesity, is considered the major underlying cause, the concept is known as the metabolic syndrome. Each viewpoint results in different treatments.

Implications Based on Clinical Outcomes. The cardiovascular area sees the metabolic syndrome as primarily a precursor or risk factor for cardiovascular disease and treats it to prevent CHD. Those in the diabetes field view it as mainly a precursor or predisposing factor for type 2 diabetes and look on it and treat it as pre-diabetes. (Dr. Grundy acknowledged that this is not the ADA definition for pre-diabetes.) For lifestyle interventions, each viewpoint's therapeutic

implications are much the same, but for pharmacological interventions, there is generally divergence of these two pathways.

Implications Based on Components or Risk Factors. A variety of components have been identified as being associated with metabolic syndrome, such as those in the ATP III definition: atherogenic dyslipidemia (high triglycerides, perhaps increased apoliprotein B (apo B), small LDL, and low HDL); raised blood pressure; insulin resistance with or without hyperglycemia; a proinflammatory state; and, increasingly, the prothrombotic state, which many people see as the dominant component, whereas from the cardiovascular point of view, these other factors are equally important. Therapeutic implications according to this definition see all these components as potential targets of treatment and management, independent of the underlying causes. For instance, in addition to treating high triglycerides, low HDL, and blood pressure, there is a great deal of current interest in directly targeting the proinflammatory state as a separate approach to reducing cardiovascular risk. It is also known that through aspirin or any platelet therapy, the prothrombotic state can be reduced.

Implications Based on Underlying Causes and Clinical Criteria. The NCEP ATP III definition was based on obesity, especially abdominal obesity, as the primary factor that gives rise to the other four components as a CVD risk, whereas the WHO definition emphasized insulin resistance as the underlying cause. Although not specifically requiring abdominal obesity as a requirement, the ATP III definition's clinical criteria and therapeutic strategy was meant to focus on obesity and its treatment, and the public health strategy was to prevent obesity in the general population, which is the approach of the NHLBI/NIDDK Obesity Education Initiative. However, there has been a developing interest in the field in focusing on treating the individual metabolic components, which has implications for the use of drug therapies. The WHO definition's clinical criteria places more emphasis on the genetic basis of the syndrome, rather than obesity. The WHO requirement of IR or one of the glucose abnormalites (IFG, IGT, diabetes) for the diagnosis places the therapeutic focus on the use of drugs to treat patients with the metabolic syndrome. Dr. Grundy noted that this use of drug therapy concerns many people in discussing the value of the metabolic syndrome as a means of identifying CVD metabolic risk factors and of recommending interventions to prevent development of the disease.

Implications of Including Type 2 Diabetes in the Definition. Dr. Grundy noted that inclusion of type 2 diabetes in the definition of the metabolic syndrome also has important therapeutic implications. The NCEP and WHO include it. The American Academy of Clinical Endocrinologists (AACE) and Framingham analysis do not. If included, clinical intervention will be emphasized more, including greater emphasis on drug therapy for the CVD risk factor components once the patient has developed type 2 diabetes. Clinical trials have provided evidence of the benefits of such drug therapy. This also raises the question of when should drug therapy for the individual risk factors be introduced in the pre-diabetic state.

Prevalence of the Metabolic Syndrome and Implications for Therapy and Intervention. NHANES III data reported by Dr. Earl Ford of the Centers for Disease Control and Prevention (CDC) in the *Journal of the American Medical Association* (*JAMA*) (Ford et al. *JAMA* 2002;287:356-359) shows the rising prevalence of the metabolic syndrome by age regardless of gender. Dr. Grundy pointed out that, although the prevalence of individual components varies,

the magnitude of the problem and the relevant issues for clinical management and public health are evidenced by the fact that approximately 24 percent of 47 million U.S. citizens have at least three of the abnormalities defined by the metabolic syndrome. Some populations, such as Hispanics, Mexican Americans, Asians, particularly South Asians, and African-American women, have even higher prevalences. In the NHANES III period between 1990 and 1999, diabetes rates as an outgrowth of the metabolic syndrome increased at an alarming rate, particularly in young adults. Dr. Grundy stated that there are as many people with diabetes in the United States as with established CHD, making these two diseases basically equal for development of metabolic and cardiovascular complications in the U.S. population.

Implications for Intervention. The fact that 47 million people have the metabolic syndrome and 18 million have type 2 diabetes appears to indicate that one-third or more of persons with the metabolic syndrome will develop diabetes, which has serious public health and therapeutic implications. This is true for young adults, older adults, ethnic populations, and women.

There is a relatively high prevalence of the metabolic syndrome among ***young adults*** and, in the decade of 1990-1999, there was a 76 percent increase in type 2 diabetes in adults between the ages of 30 to 39. Dr. Grundy directed the audiences' attention to the CARDIA study that points out the dangers of early development of the metabolic syndrome and its risk factors. He stated that the current 35-45 percent prevalence of the metabolic syndrome in ***middle-age and older people*** indicates the need to focus attention on public health strategies that target adolescents and young adults to reduce the burden of the syndrome in the future. It also means clinical strategies are needed to identify and provide interventions for the substantial number of persons already affected by the syndrome, and it may possibly indicate the need for public health strategies for this group.

Dr. Grundy urged that more attention be paid to the health consequences of the metabolic syndrome in the ***ethnic populations*** who appear to be prone to the syndrome and that additional research be conducted on interventions for these high-prevalence groups. With regard to CVD, Dr. Grundy said he suspects that the metabolic syndrome may be a dominant cause of cardiovascular disease in ***women*** in all ethnic groups. The Framingham Heart Study indicated that although women are at lower risk for CVD, the metabolic syndrome is very common among women who develop CVD. NHANES indicates that the metabolic syndrome is equally prevalent in men and women, and the risk for type 2 diabetes in those with metabolic syndrome is also about equal.

Components of Metabolic Syndrome and Relationship to CVD. From accepted guidelines, it is known that the intensity of any therapy should be proportionate to the level of risk. Therefore, it is extremely important to know the risk of the metabolic syndrome for both development of CVD and diabetes. Each of the components of the metabolic syndrome are connected in some way but vary in their relative risk for developing CHD and work through different mechanisms. Dr. Grundy noted that there is increasing evidence that each of the metabolic syndrome components are in some ways a separate risk factor for either atherogenesis or acute coronary syndromes. If that is the case, then each of the components as a metabolic risk factor is a potential target for a lifestyle or drug therapy intervention.

According to Dr. Grundy, this is an area that needs a lot more investigation. The data may already be contained in the Framingham study and other studies, but it needs to be mined, analyzed, and studied to better understand the absolute risk associated with the metabolic syndrome for these two conditions. Framingham suggests that people with the metabolic syndrome are perhaps at 2 to 3 times higher risk for CHD, although this needs to be analyzed in more detail. The results of the Finnish study also indicate that coronary mortality is much higher in patients with the syndrome than in those without it (Laska et al., *JAMA* 2002; 288:2709-2726). In a study reported by Norhammar et al. (*Lancet*, 2002; 359:3140-2144), the majority of acute myocardial infarctions (MIs) occur in people with unrecognized abnormal glucose tolerance. Dr. Grundy says this needs to be confirmed but is of great interest. In the Norhammer study, among 200 patients admitted to a Swedish hospital with acute MI, 20 percent had established diabetes, another 33 percent without known diabetes actually had diabetes according to an oral glucose tolerance test (OGTT), and another 31 percent had impaired glucose tolerance. Only 35 percent of the so-called normals (those without known diabetes) actually had normal OGTTs. Dr. Grundy pointed out that this report indicates there is a high prevalence of metabolic disorders in patients who have acute coronary syndromes or MI, and it illustrates the importance of glucose and insulin abnormalities in patients with CVD, factors that should certainly help bring the two fields together.

Metabolic Syndrome and Risk for CVD. Dr. Grundy spoke of the confusion that exists about the ATP III guidelines and the metabolic syndrome as a risk for CVD. He said it is important to clarify this because of the possible pharmaceutical versus lifestyle interventions that would result based on a misconception. Some people mistakenly believe that the ATP III defined the metabolic syndrome as a CHD risk equivalent, which it did not do. ATP III did identify type 2 diabetes, or diabetes in general, as a high-risk condition for CHD. Dr. Grundy recommended further study of Framingham and other databases to determine the absolute risk of CHD among patients with the metabolic syndrome.

Type 2 Diabetes and Risk for CHD. One of the reasons ATP III identified type 2 diabetes as a high risk condition for CHD is that CVD is the number one cause of death in type 2 diabetes and probably in type 1 diabetes also. Furthermore, there is a high 10-year risk in diabetics for developing CHD, a high lifetime risk, and nearly twice the risk of mortality after MI compared to nondiabetics after MI.

Relationship of Diabetes to Obesity. NHANES III showed that as the body mass index (BMI) increases in U.S. adults ages 20-49, so does the prevalence of diagnosed diabetes, especially when the BMI is 35 or more. In adults over the age of 50, 23 percent of those with a BMI equal to or greater than 35 have diabetes. There is also a very high incidence of IR in those with obesity, somewhere in the range of 85-90 percent. Not all of these persons will develop the beta cell dysfunction that leads to hyperglycemia and type 2 diabetes, perhaps only 15 to 20 percent. The relationship between obesity and type 2 diabetes is certainly not universal, as it appears to be with IR, because it requires a second factor. This has implications for intervention. Dr. Grundy stressed that although the majority of people with obesity and IR do not develop type 2 diabetes, nonetheless prevention of obesity in the general population will reduce the prevalence of type 2 diabetes and this is a worthy goal. He added that the relationship of diabetes to obesity perhaps

also indicates the need for early detection of glucose intolerance to aid in the selection of patients for prevention of type 2 diabetes beyond just the identification of the obese individual.

Pathophysiology of the Metabolic Syndrome and Implications for Intervention. Dr. Grundy divided the pathophysiology of the metabolic syndrome into two major areas—upstream abnormalities such as underlying causes, particularly adipose-tissue disorders, and downstream abnormalities such as the responses in the risk factors to the underlying causes, possible risk factors specific to genetic abnormalities, and ethnic characteristics that determine the expression of the metabolic syndrome in the presence of these upstream underlying causes.

Adipose tissue disorders include (1) excess fat in adipose tissue (obesity), (2) lipodystrophies where there is a deficiency of adipose tissue, (3) abdominal fat distribution (abdominal obesity), and (4) primary IR of adipose tissue, which is a separate and perhaps genetic factor that may or may not be present in people with these other disorders. There is a public health approach for the general population dealing with ***excess fat*** or obesity and clinical therapeutic guidelines for lifestyle changes in the NHLBI/NIDDK Obesity Education Initiative, which did not have as a primary focus the subsequent risk factors associated with obesity, although there was more emphasis on clinical intervention in overweight people when risk factors were present. Since a third of overweight/obese Americans have the metabolic syndrome according to NHANES III, Dr. Grundy believes these patients need special attention for clinical detection and probably more intensive intervention.

Dr. Grundy said that ***lipodystrophy***, which comes in several forms, is an interesting model for the metabolic syndrome. When there is a deficiency of adipose tissue, there is a redistribution of fat between adipose tissue that in many ways serves as a storage or even protective organ and fat distributed into muscle and liver, which gives rise to the syndrome. Patients with lipodystrophy usually manifest the metabolic syndrome. The congenital, rare lipodystrophies have been studied at NIDDK and by Dr. Abhimanyu Garg at the University of Texas Southwestern Medical Center. There are also partial lipodystrophies (lamin A/C mutations, PPAR (peroxisome proliferative-activated receptor) gamma mutations, HIV lipodystrophy) that are associated with the metabolic syndrome. The HIV lipodsytrophy associated with the metabolic syndrome is quite common and presents a therapeutic dilemma for physicians taking care of HIV patients. Dr. Grundy said that research is needed in this area from a clinical viewpoint and also may provide important information about how to approach the metabolic syndrome in other situations.

In speaking of ***fat distribution*** patterns, Dr. Grundy said there is a lot of clinical evidence that patients with lower body (gluteofemoral) obesity have a lower prevalence of the metabolic syndrome than those with upper body obesity. Different kinds of upper body obesity is perhaps related to different metabolic syndrome components and different implications for therapy. Some people who have upper body obesity and predominantly subcutaneous fat are at increased risk for diabetes. Those with predominantly visceral fat also are at increased risk and more prone to develop dyslipidemia. Dr. Grundy stressed that if abdominal obesity as a risk factor for the metabolic syndrome is important, then there is a need to encourage waist measurement in the clinical setting to help identify these high risk patients. He added that perhaps there also is a need for intensive testing for the presence of the metabolic syndrome with abdominal obesity and, if present, then more aggressive intervention for weight reduction and treatment of risk factors.

Next Dr. Grundy addressed ***primary IR of adipose tissue*** and generalized IR that extends to adipose tissue. When this occurs, often on a genetic basis, there is an excessive release of NEFA (non-esterified fatty acids) in circulation and other adipocyte products associated with mild obesity, which gives rise to this syndrome. Certain populations are at high risk for this type of abnormality, particularly South Asians, who are very insulin resistant on a genetic or racial basis and who have the metabolic syndrome, premature CHD, and diabetes at exceptional rates. Studies also show that offspring of diabetic parents tend to be insulin resistant and manifest the syndrome even with mild obesity and patients with primary hypertriglyceridemia probably also have an underlying IR and adipose tissue that leads to this hypertriglyceridemia. So there is a high prevalence of the metabolic syndrome even in the presence of mild obesity, which illustrates the problem of using obesity as the only factor in identifying the metabolic syndrome in some individuals. Dr. Grundy stated that it remains to be seen how far to stress this in the clinical area. Perhaps there is a need to identify IR with minimal abdominal obesity in a subpopulation of people or perhaps in certain population groups because even mild obesity in persons who have IR by this mechanism accentuates their risks and should be a target for treatment by weight reduction and possibly even TZDs, although he did not advocate the latter.

According to Dr. Grundy , genetic factors contribute to all the metabolic syndrome components—atherogenic dyslipidemia (high triglycerides, high apo B, small LDL, low HDL), hypertension, hyperglycemia, the proinflammatory state, and the prothrombotic state.

General Discussion of the Morning Presentations

The general discussion that followed the presentations addressed the definitions of the metabolic syndrome and its etiology, prevalence of the syndrome, the relationship of the syndrome to risk for CVD and diabetes, and implications for prevention and therapy. An overall major issue was the heuristic value of the syndrome.

Definition of the Metabolic Syndrome and Its Etiology. Dr. Peter Savage, NHLBI, remarked that it was likely that there are multiple causes of the metabolic syndrome, which may be difficult to identify, and even the possibility of the chance concurrence of common risk factors in a given individual. On the other hand, data from the CARDIA study indicates that people who have multiple risk factors tend to persist in having multiple risk factors over time. So from a pragmatic point of view, regardless of the etiology, the metabolic syndrome has significance by defining the development of risk later on in life. Dr. Savage said that a pragmatic definition is therefore important and useful, even without universal agreement on what the exact criteria of the metabolic syndrome should be.

Dr. Judith Fradkin, NIDDK, suggested that perhaps rather than defining the cluster of risk factors as the metabolic syndrome, the same purpose of achieving recognition and attention for the clustering might be accomplished by using the data to develop a continuous and individualized risk engine. Persons could then view their personal risk engine and learn what losing 10 pounds by walking could do in reducing their own risk of developing diabetes or heart disease. This might motivate people as much as presenting them with a syndrome.

Dr. Grundy replied that NCEP tried very hard to get physicians interested in using Framingham risk scoring and even made it the core of their guidelines. However, his impression is that the metabolic syndrome has generated a lot more interest. He is now hoping that Framingham will include the risk factors from the metabolic syndrome. He believes there is something about the simplicity of the idea of the metabolic syndrome that seems to appeal to many people who have not yet accepted the Framingham risk scoring, even though it is a very powerful tool in defining cost-effective and appropriate therapies.
Dr. Grundy added that another possible component of the metabolic syndrome might be stone disease. It is related to obesity and insulin resistance and there is a lot of data on the mechanisms. He felt that if an expanded view was to be developed, then it would fit in as one of the complications like fatty liver.

Dr. Vinicor commented that viewing the metabolic syndrome as a concept or a vehicle to increase attention by the practitioner was one thing, but the use of the word "syndrome" or "disease" creates a different issue. What is required to move from a concept to a statement that something is a syndrome or a disease is determined by experts in nosology who classify diseases. While he agreed that consensus on a definition was worthwhile, he felt that it was also important to consider what is necessary to identify this cluster of conditions as a syndrome because this has huge policy and financial implications that go beyond a conceptual or methodological viewpoint. He urged the group not to move too easily or quickly from an area that may be intellectually important or may become clinically important to an area that is practically, financially, and public policymaking important without a clear understanding of the implications. He referred to conversations he has had with persons from the Centers for Medicaid & Medicare Services about why hypertension is a disease and high cholesterol is not. However, whether a condition is a risk factor, a syndrome, or a disease does have very important implications.

Dr. Grundy said that the NCEP panel had similar issues in defining individual risk factors. Is hypertension a symptom or a sign or a disease? Is diabetes a syndrome or a disease? He agreed that defining this concept does present problems but thinks they are built on top of existing underlying problems.

Dr. Haffner added that an interesting implication in establishing guidelines is that if hypertension is a disease then treatment is not based on the global risk over the short-term, whereas if cholesterol is a symptom, then global risk is calculated and considered in treating it.

Dr. Jay Everhart, NIDDK, asked if there was data on serum leptin in regard to the metabolic syndrome, particularly since leptin is both a marker of adiposity and a marker of inflammation. Dr. Haffner replied that there must be, but he could not actually remember seeing it.

Prevalence of Metabolic Syndrome. Dr. Frank Vinicor, CDC, asked what was the role of the aging U.S. population in the increased prevalence of the metabolic syndrome based on the Framingham and NHANES III data. Dr. Haffner answered that it would be necessary to use broad cohorts to actually look at that, but it would be interesting to do an analysis by different age groups to acquire an idea of the magnitude of this increasing problem.

The Metabolic Syndrome and Risk for CVD and Diabetes. Asked why people who have MI, both acute and long-term, and diabetes have a mortality rate that is double that of nondiabetics with MI, Dr. Grundy replied that it was probably due to the presence of multiple factors such as more hypertension, advanced atherosclerotic disease because of their diabetes, and diabetic caridionmiopathy, which is a complex condition. One reason it is important to prevent heart disease in the first place in patients with diabetes is that they are at higher risk for heart failure once they develop established CHD and have a very high risk of dying from the CHD.

Dr. Richard Kahn, American Diabetes Association (ADA), asked if anyone had studied the metabolic syndrome in a population, such as the Framingham cohort, by adding CRP to the other components and identifying which of the components had a greater effect on development of CVD. Dr. Haffner replied that a report by Dr. Paul Ridker's group based on the Women's Health Study, which is a very low-risk population, only about 0.2 percent per year, indicated that CRP was basically independent of the metabolic syndrome as a risk factor. This may indicate that CRP is not caused by the metabolic syndrome as stated in many papers. Dr. Haffner's data suggests that CRP is a fairly good risk factor for diabetes, not as good as glucose levels, but probably as good as waist circumference. He added that, ironically, some people think CRP is easier to measure than the waist.

Dr. Meigs explained that the Framingham risk score is calculated as points for the presence of incrementally elevated risk factors even within the normal range, so that a blood pressure that is mildly elevated gives a little bit of extra risk. Age is a major driver of the Framingham risk score, and what happens with the metabolic syndrome and age is unknown, other than that the prevalence increases considerably. Framingham only considers total cholesterol or LDL cholesterol, but not high triglycerides. Also the main published use of the Framingham risk score only considers established diabetes, not impaired fasting glucose or post-challenge glucose.

Dr. Meigs said that Framingham is working on the question of what is added by including the metabolic syndrome criteria to the Framingham risk score. They should have an answer in another month or two. Dr. Meigs does not consider the current Framingham risk score as the right tool to measure whether the metabolic syndrome increases risk because the metabolic syndrome captures a different set of risk factors than the Framingham risk score. He thought it entirely plausible that adding the metabolic syndrome criteria to the Framingham risk score would increase the predictive capacity fractionally because of these additional components.

Dr. Haffner stated that the Framingham risk score handles HDL and blood pressure very well as CVD risk factors, better than the metabolic syndrome, because they are separate categories. Although Framingham does not include any individual glucose information, just the presence of diabetes, that data and low HDL may be unimportant in calculating CHD risk. Framingham does include waist circumference but not BMI. Dr. Haffner wondered if including BMI or weight would have served as a tool to teach people about the importance of lifestyle changes.
Dr. Haffner agreed with Dr. Meigs that, to his knowledge, there was no data that tested any population adding the metabolic syndrome to the global risk within strata to determine increase in risk, which would be key to determining implications for therapy.

In response to a question from Dr. Kahn about the integrity of risk levels associated with the metabolic syndrome based on the different components and the levels of the individual components, Dr. Grundy pointed out that there is a consensual similarity between the metabolic syndrome and the Framingham risk score in that they are both mult-risk factor concepts. Framingham risk scoring includes one set of risk factors; the metabolic syndrome has an overlapping relationship to Framingham scoring, but goes beyond it by including obesity and triglycerides. These additional factors are increasingly common in the population, and many people believe they are truly independent risk factors. The PROCAM (**Pro**spective **Ca**rdiovascular **M**ünster Heart Study) algorithm being used in Europe includes weight and triglycerides as independent risk factors. Using the PROCAM algorithm for patients with the metabolic syndrome results in an absolute risk somewhat different from that of the Framingham score. Incorporating weight and triglycerides into Framingham would be a big service in Dr. Grundy's opinion.

Dr. Meigs addressed Dr. Kahn's question by saying that different trait combinations do confer risk for different endpoints in Framingham. For example, people with normal blood pressure but a larger waist may have a different risk than people with elevated blood pressure and a normal waist. Another issue is that measurement of thresholds are quite variable; an individual would certainly require at least two glucose measurements for the establishment of diabetes. However, a fasting glucose of 127 mg/dL twice would be clinically diagnosed as diabetes even though it is likely that the patient has a normal hemoglobin A1c. The situation is still taken seriously because it is known that eventually the patient is going to have more hyperglycemia and resultant complications. It is just the timeframe that is longer than for a person with a higher threshold. When thinking about metabolic risk factors, this diabetes analogy is helpful to consider. The CARDIA study also shows that even a person who is very, very mildly abnormal, when tracked over time, is identified as a person in the early stages of cardiovascular risk.

Dr. Kahn stated that ADA is looking at another kind of modeling of the various risk factors and examining the effect caused by reducing one or the other. For example, instead of looking at a continuum, the model will examine a group of people who have blood pressure or fasting glucose levels that are borderline but not severe, such as 130 to 140 or 110 to 125, respectively, and evaluate risk. The model will also evaluate risk based on whether an individual has one or more risk factors that are at high levels versus one or more risk factors that are at low levels.

Dr. David Orloff, FDA, had a question about prevalence data of the metabolic syndrome, the risk of CVD prior to clinical diagnosis of type 2 diabetes, and prevention versus screening and aggressive treatment of diabetes: Dr. Haffner answered that slides have limitations in presenting data: The Nurses Health Study was a very large study but diabetes was self-reported so the actual onset was probably earlier. Also, the data were only for women. The lifetime risk was approximately a 20-year risk. About 25 percent of the risk of CVD might actually occur prior to clinical diagnosis. That is not trivial and could be an impetus for prevention, especially if it is believed that lifestyle interventions have an effect on decreasing CVD even in people who do not develop diabetes. NHANES and Framingham data might also be calculated to determine the population-attributable risk of people who eventually develop type 2 diabetes. Economic analyses could also be done. The data needs to come from populations of both genders to decide

on an optimal strategy between early screening and aggressive treatment versus prevention strategies.

Dr. Spiegel commented that the followup to the Diabetes Prevention Program (DPP) will look at data on this well-characterized population in which the exact onset of overt diabetes is known and will also look at the CVD influence. Dr. Haffner agreed that the DPP data is very important and that hopefully within a year there will also be atherosclerosis data based on carotid artery intima-media thickness (IMTs), which may provide a hint of what is happening in this area.

In response to a question from Dr. Spiegel regarding type 1 diabetes, macrovascular complications, and inflammation, Dr. Haffner said that there would be an NIH workshop on this subject in a couple of months. He stated that the ideal way to study this, and possibly NIDDK is funding this, is to look at type 1 diabetes in adults in Scandinavia where there is a relatively high rate of type 1 diabetes in adults, and using registry data, match persons who develop type 1 and type 2 diabetes at the same age and then follow them prospectively. The problem with studying this issue in children is that it takes a long time to develop and the risk is very low. It could be done with atherosclerosis studies, since there is so much type 2 diabetes starting to occur in adolescence in the United States and the progression of atherosclerosis is known. Dr. Haffner assumed that those with type 2 diabetes would have more disease because they are much more obese than persons with type 1 diabetes when matched for age. In the Diabetes Control and Complications Trial (DCCT), the early data on IMTs did not show a difference between those with type 1 diabetes and normal controls. The progression data may now be showing an acceleration, but Dr. Haffner is not on that review panel and so does not have that data. Dr. Fradkin added that surrogate measures from DCCT do indicate clear differences between the treatment groups in terms of progression.

Implications for Therapy. Dr. Malozowski noted that even in patients with established diabetes, long-term compliance with lifestyle changes is difficult to achieve. For persons who have the metabolic syndrome but have not been diagnosed with diabetes or CVD, he asked what interventions are necessary and practical. Even though lifestyle changes have been shown to be an excellent approach, the potential of using different medications has also been discussed. Among these are the TZDs, which provide improvements in some of the metabolic aspects but are known to increase weight gain, sometimes substantial weight gain.

Dr. Haffner replied that the TZD issue is two issues: the diabetic issue and the non-diabetic issue. The diabetic issue is less problematic to some degree because the TZD does lower glucose. While all diabetes drugs have their own limitations, if you use conventional definitions of the metabolic syndrome, whether WHO or NCEP, TZD, in spite of the weight gain, will improve the metabolic syndrome. They raise HDL, are slightly beneficial or neutral for triglycerides, claim to lower blood pressure, and clearly improve insulin sensitivity. Several studies, some of which are NIH-funded and some that are pharmaceutical studies, are looking at the long-term effects of TZDs on diabetes. BARI2-DM (Bypass Angioplasty Revascularization Investigation and Diabetes Mellitus) will presumably collect information on weight gain and will compare sensitizing versus insulin providing drugs. ADOPT (A Diabetes Outcome Progression Trial) is probably the clearest in terms of weight gain and waist circumference and will resolve some of the issues that measure lipids in the components. However, this does not mean that these agents

are better for CVD, according to Dr. Haffner, which is a real limitation for their use. There are very few trials, here or abroad, competently looking at this issue of paying to take a medication that may or may not be more effective than lifestyle modification for diabetes and may not be effective for CVD. Dr. Haffner said that he thought the Food and Drug Administration (FDA) should require companies to do endpoint studies if they want to treat non-diabetics with insulin sensitizers rather than rely on a "leap of faith."

Dr. Jay Everhart, NIDDK, inquired whether the DPP has looked at changes in the metabolic syndrome constellation following the lifestyle intervention. In terms of the public health aspect, it would be very attractive to show an effect of lifestyle intervention on this constellation. Dr. Haffner referred to a paper submitted to ADA by Dr. Robert Ratner that presents statistically significant blood pressure, triglyceride, and HDL changes but does not calculate the metabolic syndrome at the beginning and end of the study. The prevalence of the syndrome in the DPP cohort was about 60 percent. The study subjects had to have impaired glucose tolerance (IGT) and a fasting glucose of 95 mg/DL or higher. Dr. Haffner assumed that the numbers went down with the lifestyle intervention. Dr. Kahn said the biggest change was in triglycerides; blood pressure went down a fair amount in the first year but less at the end of the 3 years when the subjects regained some weight.

Heuristic Value of the Metabolic Syndrome. Dr. Spiegel remarked that the metabolic syndrome is basically a concept involving a very heterogeneous set of disorders with undoubtedly many underlying genetic sequence variations and environmental interactions. He noted that much of this will become clearer after Dr. Francis Collins of the National Human Genome Project provides the sequence on a chip. Meanwhile, based on the current definitions of the syndrome, Dr. Spiegel asked what is the real heuristic and practical value of the metabolic syndrome. The syndrome presents a constellation of treatable abnormalities, whether they be lipid abnormalities, hypertension, or glucose abnormalities. Is this an issue of defining different cutpoints that would then lead to treatment with drugs? What is being learned? What is the practical significance of this concept of a metabolic syndrome?

Dr. Grundy responded that one of the reasons the metabolic syndrome was introduced or emphasized in the ATP III guidelines was to get physicians to pay more attention to the medical aspects of obesity and its complications, which were being ignored. Obesity had tended to be considered as something one could do little about in a clinical setting. If the metabolic syndrome could draw attention to people who have risk factors that converge and emerge from the presence of obesity, then physicians might begin to internalize this idea, pay more attention to it, and make it more meaningful in their practice.

Dr. Haffner spoke of the many databases that include the components of the metabolic syndrome or the modified metabolic syndrome, but few papers that discuss the interrelationship of these components. He added that people pay little attention to behavioral aspects, but if they become convinced that this is an important syndrome whatever their actual risk, and if lifestyle interventions are relatively more effective for this syndrome than are drugs, which he thinks is likely to be true, then they just they might do the right things, even if not exactly for the right reasons, which would make this a useful concept. The concern Dr. Haffner sees people

struggling with is whether this is this going to lead to a huge explosion of drug therapy and the use of new drugs in non-diabetic patients because they have the metabolic syndrome.

Dr. Meigs, as a primary care doctor and researcher, said he thinks the value is two-fold. First, defining the metabolic syndrome helps to focus attention on the importance of mildly elevated risk factors in combination as being important targets for some form of intervention, rather than ignoring mildly elevated blood pressure or mildly abnormal lipid levels. Defining the syndrome also crystallizes the concept of multiple risk factors occurring together as being worthy of some form of intervention. It provides a handle on obesity as a target for intervention in terms of treating the related risk factors as defined by the metabolic syndrome. Historically, obesity is difficult to deal with and clinically doctors tend to view it as not their problem. For these reasons, Dr. Meigs felt it was valuable to move toward a consensus definition. on how to actually define it. Secondly, the etiology of the syndrome seems to derive largely from lifestyle issues that arise in childhood and adolescence. It is, therefore, important to address these issues early. The issue of treating basically asymptomatic, otherwise healthy people with drugs to prevent development of a disease 10 or 20 years in the future requires serious evaluation, especially in the setting of emerging data that lifestyle changes are so effective in preventing at least diabetes.

Agency Presentations

National Institute of Diabetes and Digestive and Kidney Diseases, Judith Fradkin, MD, Director of Division of Diabetes, Endocrinology, and Metabolic Diseases

Dr. Fradkin stated that NIDDK is not specifically investigating the metabolic syndrome, but the Institute is conducting programs indirectly related to it such as the Diabetes Prevention Program (DPP). In February 2003, the National Diabetes Education Program (NDEP), funded by NIDDK and CDC, launched the Small Steps, Big Rewards campaign based on DPP results. DPP showed that a modest weight loss and 30 minutes of exercise 5 days a week reduced the risk of developing type 2 diabetes and the complication of CVD in subjects who were overweight, had impaired fasting glucose, and a family history of diabetes. NDEP is working with its partners to develop materials for physicians and patients based on the DPP lifestyle intervention. As part of their campaign to put these tools to physicians and patients, they have established a Web site (http://ndep.nih.gov). The Web site has links to and now we will talking with partners in trying to get those materials into the hands physicians and patients. The website has inks to NHLBI and to the Obesity Education Initiative that NHLBI helped develop. NIDDK is also increasing its efforts with regard to obesity research from trying to identify new potential targets for therapy from molecular research to clinical research related to prevention and intervention.

NIDDK also is developing a school-based prevention study for type 2 diabetes. Currently in its pilot phase, the study will collect baseline data on height, weight, waist circumference, blood pressure, glucose tolerance testing, and lipids from students in middle schools with at least 50 percent minority populations. Investigators will use the baseline data to define metabolic outcome measures for the intervention, not just a weight loss outcome, for the clinical trial. Dr. Fradkin said these pilot studies will provide a lot of population-based information about the prevalence of the components of the metabolic syndrome in early adolescent children. She added that she would be very interested to hear from other groups about the metabolic syndrome in

children, including what definitions are being used, in order to coordinate the outcome measures NIDDK is developing. This would likely make the results of the trial more relevant to the syndrome as defined and used by others.

Finally, NIDDK is talking with the National Center on Health Statistics about potentially restoring the oral glucose tolerance test (OGTT) to NHANES. She explained that it was done this way in NHANES III but when the yearly NHANES began, it was dropped, largely to tie in with the ADA recommendations for using fasting blood glucose to diagnose diabetes. With the increasing prevalence of type 2 diabetes and the DPP and other data related to the risk factors for CVD, the decision to use the 2-hour OGTT is being reconsidered. Dr. Fradkin said the earliest the change could happen would be in 2005, but she was interested in the group's opinion on how useful this would be. Drs. Grundy and Haffner agreed this was an interesting idea.

National Heart, Lung, and Blood Institute, Peter Savage, MD, Director, Division of Epidemiology and Clinical Applications

Dr. Savage announced that NHLBI in collaboration with the American Heart Association will conduct two conferences on the metabolic syndrome, one in April on the definitions and one in September on treatment issues. Dr. Grundy will chair both meetings.

Dr. Savage presented opportunities for investigating the metabolic syndrome through NHLBI-funded cohort studies including the Framingham Original Cohort and Framingham Offspring studies, the Honolulu Heart Program, Atherosclerosis Risk in Communities (ARIC),Cardiovascular Health Study (CHS), and the and the Coronary Artery Risk Development in Young Adults (CARDIA). Like NIDDK, his Institute is not directly studying the metabolic syndrome but NHLBI does have studies related to it and data sets that provide an opportunity to look at questions, some of which had been discussed today.

CARDIA is a study of approximately 5,000 (5,115) 18- to 30-year-old African American and white young adults initially examined in 1985-86. Metabolic syndrome defined by ATP III was rare, about 4 percent. Therefore, the investigators defined a pre-metabolic syndrome to look at those who were above the gender-specific 90th percentile at the baseline exam for three or more of the risk factors used by ATP III and below the 10th percentile for HDL cholesterol.

The group was relatively unique in its balance by race, sex, education, and age within centers. There were five examinations over time with a substantial followup. Seventy-four percent (74%) returned for the Year 15 examination. What we found was that the frequency of risk factors increased fairly strikingly over the 15-year period in these young adults. The prevalence of the syndrome rose from 4 percent at baseline to 21 percent. It was highest in those at year 15 who were already overweight at baseline versus those who were normal at baseline, 41 percent versus 11 percent. Although all the group gained some weight, the prevalence was higher in those who gained 15 kilograms or more versus those with little weight gain, 44 percent versus 25 percent. Young adults with the pre-metabolic syndrome at baseline were much more likely to have the full-blown ATP III syndrome at the end of 15 years. Now the young adult years between ages 20 and 40 are relatively silent years. Disease progresses during that time, but the individuals tend to feel well and do not have much in the way of symptomatic disease. These are people who are

still healthy in young adulthood and yet they are well on their way to developing the abnormalities that are likely to lead to clinical disease sometime in middle age or early older years.

Dr. Savage next offered data sets available through NHLBI to address some of the questions about the metabolic syndrome. In addition to the cohort studies he listed at the beginning of this presentation, Dr. Savage noted there is also data from current clinical trials (Asymptomatic Cardiac Ischemia Pilot (ACIP); Intermittent Positive Pressure Breathing (IPPB), Post-Coronary Artery Bypass Graft Study (Post CABG), Thrombolysis in Myocardial Infarction Study (TIMI II), Lung Health Study (LHS), Digitalis Investigation Group (DIG), Beta Agonist in Mild Asthma (BAGS), Antiarrthymics Versus Implantable Defibrillators (AVID), and Colchicine in Moderate Asthma (CIMA)). There is data on almost 50,000 people who have had longitudinal exams, multiple racial/ethnic groups, men and women, ages ranging from about 18 to 100. Dr. Savage explained that NHLBI is planning to gradually make more and more data from the large studies available.

Researchers may collaborate with existing study investigators or request a public access data tape to work on at their own pace. He pointed out that collaborating with the primary study investigators on an issue as complex the metabolic syndrome has many advantages such as the knowledge of the investigator, the assistance in doing complex analyses provided by the statisticians of the coordinating center, and access to the most recent data. The rights of the primary investigators are protected by giving those doing epidemiology studies a 5-year period after the close of an examination and a 3-year period after publication of the primary paper and the clinical trial. So for access to the most recent, complex longitudinal data sets, it is important to try and work with the study group. There are also a set of rules to protect participant privacy and procedures about what can and cannot be done with the data. To obtain data sets directly from NHLBI, researchers must agree to follow certain rules and procedures to protect both the rights of the investigators and the participants.

NHLBI's Web site (www.nhlbi.nih.gov/resources/ deca/default.htm) provides data documentation, distribution agreement forms, information about Institutional Review Board (IRB) approval, and the overall policies that NHLBI has developed. The data is provided at no cost to the applicant.

Centers for Disease Control and Prevention, Frank Vinicor, MD, Director, Division of Diabetes Translation

Dr. Vinicor stressed the importance of having science-based evidence before launching a public health program as opposed to a clinical program related to a disease or a syndrome. There is general consensus that the 17 million persons diagnosed with diabetes deserve treatment, not only for the their glucose problem but for all the components included in the metabolic syndrome definitions. In NDEP and in other public health efforts, obesity, cardiovascular risk factors, and so forth are addressed. In taking a broad view of diabetes, however, CDC's Division of Diabetes Translation is asking: When does the diabetes clock start ticking? There is some question whether CDC should be looking for the missing roughly 6 million people with present but undiagnosed diabetes, an issue that will have to be decided at the policymaking level more than

at the scientific level. Next, there is a cohort of about 16 million persons who presumably have what is now called pre-diabetes. That group is reasonably defined by IFG and/or IGT based on several randomized controlled trials indicating that primary prevention should work and the question is how to make it work. The fact that there is good science underlying this gives us the moral, ethical, and programmatic responsibility to take a public health program forward. Those we call pre-diabetic presumably emanate out of the cohort of 45 million people identified in Dr. Earl Ford's study as having the metabolic syndrome as defined by ATP III. Dr. Grundy indicated today that there are a lot of people with metabolic syndrome who do develop pre-diabetes and then diabetes. Finally, there is the issue of the fetal programming mentioned by Dr. Grave that may precede development or contribute to the development of the metabolic syndrome.

Dr. Vinicor listed CDC's public health activities as involving basically three areas—surveillance activities, epidemiology and translation research, and pubic health programs. As evidenced by Dr. Ford's surveillance work, CDC is using national data sets to examine the prevalence and associated factors of the cluster of conditions called the metabolic syndrome. The nature of the utility of these national surveys varies. For example, the Behavioral Risk Factor Surveillance Survey (BRFSS) is a self-report so to the degree to which people do not know about the syndrome, they cannot be asked "Have you ever been told you have the metabolic syndrome?" There is slightly better reliability in administrative data, such as discharge data. Finally, NHANES, where the components are actually measured, actually provides a sense of the prevalence of the factors associated with the metabolic syndrome. Surveillance is typically not hypothesis driven.

Epidemiological and translation research is more hypothesis generated. For example, the SEASRCH study with CDC's colleagues at NIDDK will hopefully identify people with type 2 diabetes and might be an opportunity in a prospective way of looking at whether or not elements of the metabolic syndrome exist in this group. Similarly, Dr. Rodolfo Valdez who was involved with the Bugalosa Heart Study in Louisiana and Dr. Henry Kahn of CDC are looking at ways to more easily define the metabolic syndrome from a public health standpoint.

As a framework for public health programs, Dr. Vinicor listed six progressive, interrelated steps delineated by Dr. Detsky of Canada and his colleagues in 1990. The initial step is fundamental research. Next is an efficacy trial, such as the DCCT, followed by determining the intervention's effectiveness, efficiency, availability, and distribution in the real world—it works but at what financial cost, is it affordable, are policies such as reimbursement in place to allow to happen, and can it be distributed in Small Town, Indiana, as well as in Bethesda, Maryland. Dr. Savage reiterated that all these steps are involved in thinking about what can be done from a public health perspective to help people. He said that, in his opinion, the field is at the fundamental research stage with regard to the metabolic syndrome and cautioned against leaping over the intervening steps between research and availability. He felt it important to determine if it will make a real difference to identify persons with the syndrome rather than simply treating the individual components, which no one would argue with as being reasonable and necessary.

CDC is interested in participating in the fundamental research and through surveillance to understand the syndrome better. The agency is not ready to develop public health programs and policies based on the metabolic syndrome. First, the case definition needs to be clarified and

examined by the nosology experts to officially identify is as a syndrome. Second, there needs to be more science-based evidence comparable to that from DCCT or DPP upon which to build a public health perspective. Thirdly, public health policy can not be determined by the tails of the distribution curve; it appears to be a heterogeneous condition, it is not clear how common it is, and whereas unusual cases can determine a clinical viewpoint, they cannot determine public health policy. Finally, currently, CDC has many competing priorities. The Division's mission is to help people who have diabetes and now, for those with pre-diabetes, to prevent diabetes. While the group is interested intellectually, conceptually, and scientifically, there simply are no resources to deal with the metabolic syndrome as a public health program.

Dr. Vinicor's opinion was that "there is real gold out there" but the definition needs to be clarified and a consensus reached on just what the metabolic syndrome is. He saw value in finding a way to identify people at a younger age who might have or develop the components and go on to develop diabetes or cardiovascular diseases, but the science is not yet there from a CDC public health perspective. Dr. Vinicor emphasized once again that CDC is interested from an investigative or scientific stance, but his viewpoint is that it is a mistake to launch public health programs unless there is solid science behind them.

In the discussion that followed, Dr. Vinicor agreed with Dr. Grundy that obesity is a public health concern. However, in studies with different racial/ethnic populations, the sequence of events regarding obesity and hyperinsulinemia varies greatly. Therefore, he believed it premature at this time to view obesity together with the metabolic syndrome from a public health point of view. NDEP is focusing its efforts on that portion of the total obesity population that is pre-diabetic, not a small group, some 16 to 18 million persons. Other programs at CDC and at NIH are focusing on the broader obesity issues for the entire population. The CDC Division of Diabetes Translation is part of that team but not taking the lead. That is the role of a sister division.

American Association of Clinical Endocrinologists (AACE), Helena Rodbard, MD

Dr. Rodbard discussed the results of the American College of Endocrinology (ACE) conference held in the summer of 2002 and convened to address the growing epidemic of the metabolic or insulin resistance syndrome. The conference's consensus statement will be published in the March issue of *Endocrine Practice.* The previous year, ACE had developed guidelines for treatment of type 2 diabetes with emphasis on the prevention of macrovascular disease and its comorbidities. The ACE Task Force on the Insulin Resistance Syndrome was co-chaired by Dr. Daniel Einhorn and Dr. Gerald Reaven. Dr. Earl Ford of CDC was also a member. Dr. Rodbard said that ACE also championed development of the CPT code (277.7) for the metabolic syndrome, which helped to put the syndrome on the map, particularly for third-party payers and to legitimize the syndrome as a real clinical concern.

The first issue at the conference was what to call the syndrome. Different names were proposed, such as the metabolic syndrome, the dysmetabolic syndrome, and syndrome X. Finally, insulin resistance syndrome was agreed on based on the rationale that it was a more encompassing name and addressed the pathophysiology of the disease. Diabetes, as Dr. Grundy pointed out, previously was not part of this syndrome, but was considered as another risk factor for CHD. At

the center of the equation as the main concerns were heart disease and stroke. Although the vast majority of the people did not have diabetes, some of them actually would develop diabetes, as well as the other complications associated with CVD.

The components of the insulin resistance syndrome as defined by ACE are a constellation of factors including some degree of glucose intolerance, although not overt diabetes; abnormal uric acid metabolism; dyslipidemia, particularly with elevated triglyceride levels, low HDL, high concentrations of the small dense LDL, and the high lipidogenic particles; hemodynamic changes, with hypertension being at the core of those; prothrombotic factors, PAI-1 being one of them, and fibrinogen; markers of inflammation, such as CRP, endothelial dysfunction, and other markers of inflammation; polycystic ovary syndrome (PCOS), a frequent concomitant of this syndrome, and non-alcoholic fatty liver disease (NASH). The concept is very emperic, but the main concern is to decrease the incidence of CAD in the population, primarily through lifestyle modifications rather than pharmacological therapy.

Screening of people most likely to develop the insulin resistance syndrome and be at high risk would include those who have coronary heart disease, hypertension, PCOS, or acanthosis nigricans. Dr. Rodbard said this latter symptom is particularly important to clinicians as an indication of the syndrome that can be easily seen when the patient walks into the room. Other indications are a family history of type 2 diabetes, hypertension, or CVD; women with a history of gestational diabetes or individuals with glucose intolerance; ethnic minorities; people with sedentary lifestyles; a BMI greater than 25 kg/m^2; and age, particularly people over the age of 40.

Particular hallmarks, the clinician would be looking for as a definite for the diagnosis, would be triglyceride levels greater than 150 mg/dL, HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, blood pressure greater than 130/85 mm/Hg, and fasting glucose between 110 and 126 mg/dL, people who would be candidates then for a OGTT. A lesser factor, but one of the components, would be increased microalbumin or urinary albumin excretion. Dr. Rodbard remarked that in Renoir's time, abdominal obesity might have been a mark of beauty, but today concepts have changed. We know that it is not healthy. She said it is incumbent on the leaders of medicine in the United States to join forces and fight this growing epidemic..

In the discussion that followed, Dr. Rodbard explained that the CPT code for the metabolic syndrome is a combination of mostly clinical criteria, a combination of phenotypes, and some laboratory tests as well. The CPT panel were not too specific. The existence of a code was to make it implicit that there is such a syndrome and there should be some type of reimbursement for diagnosing and treating it, because there is no reimbursement for obesity, per se, unfortunately. Obviously, not everyone who is obese has this syndrome, but if they have obesity and they have some of the components of the syndrome, this code would be applicable.

Dr. Rodbard agreed with Dr. Vinicor that establishment of a code by the American Medical Association CPT Editorial Panel does not guarantee reimbursement for screening or for treating something as a syndrome by, for instance, the Centers for Medicaid & Medicare Services (CMS).

Dr. Grundy suggested that when this metabolic condition is called the insulin resistance syndrome and requires a glucose abnormality, it is likely to lead to a focus on drug treatment of insulin resistance and treating persons with insulin-sensitizing drugs prior to their developing diabetes. Also, it would almost have to require glucose tolerance testing on a large number of people to make the diagnosis. Who those people would be is another issue—would it be just overweight people, or since overweight is not a factor, would every patient be tested as is commonly done now for cholesterol and blood pressure?

Dr. Rodbard replied that therapeutical approaches will be the subject of a future conference. At this time ACE was simply trying to identify people with the syndrome because of concern for the coronary risk factors and comorbidities associated with it. The primary approach will probably be educating the patients and encouraging them to be less sedentary, lose weight, do lifestyle modification, rather than medical therapy. She said they did not have much data to justify pharmacological therapy. It would not make sense to putting everybody on TZDs or another form of insulin-sensitizer without having the data to show that would be effective.

American Diabetes Association, Richard Kahn, PhD

Dr. Kahn announced that ADA is in the midst, along with some collaborators, in developing a paper on the metabolic syndrome for publication in and ADA journal and across,at least two or three other journals that reach different disciplines. The purpose of the paper is to provide a perspective and address questions such as "To what extent is the definition of the metabolic syndrome based on data?" A number of components have been named by ATP III and WHO and Dr. Rodbard added a few more from the ACE definition. The issue, he said, is what is the basis for choosing these components,. On what basis are the cutpoints chosen? Are there data to suggest that one cutpoint is better or worse than another cutpoint for any of the components? How does a risk factor become a part of the definition? Why, for example, is not LDL or age a risk factor? Age is as metabolic as blood pressure.

The second issue the paper will address is do all combinations of the factors imbue the same risk? Are the risks of adverse outcomes the same between all ages, all races, and at all levels of any of the risk factors? Dr. Kahn said this is important before screening and treating a population based on the syndrome.

The third major topic in the paper will be the etiology of the metabolic syndrome. Is it really all insulin resistance or to what extent is it insulin resistance versus something else. As Dr. Grundy pointed out, there are different therapeutic ramifications depending on what the underlying etiology is? Is enough known yet to even say what the underlying etiology is?

Last and most importantly, in Dr. Kahn's opinion, is what is the appropriate therapy for someone with the metabolic syndrome? Is there any clinical evidence to support any therapy for the syndrome itself—not hypertension, not diabetes, not dyslipidemia, but the general metabolic syndrome? Are there any clinical studies that show CVD or diabetes can be reduced by identifying someone with the metabolic syndrome? The closest there is to that is the results of the lifestyle interventions in the DPP and the Finnish study, but they are not definitive for the metabolic syndrome as defined.

Dr. Kahn stated that these questions important for three reasons. First, the concept of a metabolic syndrome has grown from a very interesting, probably important, epidemiological finding of clustering into a disease in and of itself. As Dr. Rodbard pointed, it has a treatment code and potentially could cost billions of dollars in health care costs. Instead of turning into a strategy to reduce obesity, it has become a disease to be treated. Patients are not only receiving pharmacological therapy , it has become a gold mine of insulin assays for laboratories and referrals for specialists. The practitioner is unaware of the uncertainties and problems regarding the syndrome that are being discussed in this meeting.

Second, definitions tend to become cemented and are very difficult to change even when new data arrives, as ADA has experienced in the area of diabetes. It is critical not to define anything in a relatively arbitrary manner.

The third factor is the adding on of layer after layer of things for physicians to do and for consumers to do, which may divert attention from what may be the most important things to do. For example, a recent article in *Diabetes Care*, reported that only 3 percent of diabetic patients treated by endocrinologists in an academic medical center were reaching their hypertension, LDL , and hyperglycemia goals. If additional items are added on, clinicians and consumers are likely to become more and more frustrated. Dr. Kahn's recommendation was to "try to hold the train back a little bit," while continuing with additional research.

Dr. Kahn's comments elicited considerable discussion. Dr. Savage commented that there is not evidence that the metabolic syndrome is a disease or that it should be treated in any specific way. On the other hand, there is an epidemic of obesity in the United States; millions of people are becoming overweight, and data from the last 25 to 30 years shows an alarming growth of obesity-related problems in children and young adults. There are many questions to be examined. However, one relatively clear message is that obese people are at markedly increased risk of developing diabetes and at an increased risk of developing heart disease. Therefore, the public and those delivering health care need guidance to deal with the problem and prevent the full-blown metabolic syndrome from developing in large numbers of people.

Dr. Kahn responded that the conclusion that obesity is a predominant, if not the most predominant, risk factor, could have been reached 3 or 4 years ago. He went on to say that organized medicine as it exists today is not going to help the obesity problem, because physicians by and large have no training and no time to do what it takes and there are no interventions that work in the long-term from the medical perspective. In addition, there are billions of dollars of marketing money favoring obesity. It is possible to draw attention to obesity as a public health problem, and this must be done, but what is going to change the situation in the absence of a pharmaceutical agent is really mass social reengineering.

Dr. Savage agreed that a cultural change was needed before physicians could intervene in a way that would change the problem in millions of people. He added that people who gain a lot of weight, particularly during the years from 20 to 50, tend to be the people who also have a much higher risk of developing multiple risk factors and the complications that follow. This means that an attempt needs to be made to promote a cultural change in the public that will result in

behavior changes. On the other hand, if someone has full-blown risk factors, they need conventional medical therapy.

Dr. Spiegel said that one of the most compelling presentations he had heard was by Lawrence Green in speaking of the smoking problem at a translation session.. Although the obesity challenge is even more daunting, there are applicable comparisons to smoking, including the billions of marketing dollars targeted at the U.S. population and the fact that physicians alone cannot be the sole solution to the problem. A possible lesson can be learned from the Surgeon General's report on smoking and cancer that was the impetus; it was clear cut. And even though, the country is not "home free" and everything is not all solved and perfect—young women are lighting up at increasing frequency—nonetheless, there has been a tremendous shift culturally. Today's stigma associated with smoking needs to be avoided where obesity is concerned. Still, once there is scientifically based data comparable to that of the Surgeon General's on smoking, then the public message can be that obesity is not a moral problem, it is not a cosmetic problem, it is a health problem. Dr. Spiegel stated that getting to the dimensions of it as a health problem in the most rigorous, precise way is what this discussion was really about.

Dr. Kahn agreed but drew attention to the fact that, in spite of the intention to focus the issue on the clusters of risk factors, or obesity's relation to them, the unintended consequence has been the rise of a whole medical industry focusing on laboratory tests and drugs at a time when the definitions are not firm and the interventions are unclear. Although there is a huge problem with obesity, the most telling aspect is that if one looks at attendees at annual scientific sessions or any group of people who should know about obesity, are they really any different from the population at large?

Dr. Spiegel replied that there is a difference. If you look at the behavioral risk factor surveys, there is a totally inverse correlation between education and diabetes, particularly type 2 diabetes, and obesity. There is a whole segment of the population that has access to health clubs and so forth. The other thing is that only a few decades ago, a significant number of those present at a scientific gathering such as this meeting would have been smoking. That no longer happens. Eventually if the science is there and the public health message is presented appropriately, substantial differences will be seen in overweight and obesity. That is not a Pollyanna point of view.

Dr. Grundy added that when cardiovascular guidelines were being developed, similar criticisms were voiced about definitions and other imperfections. The same was true with cholesterol and blood pressure. His other point was that although there are separate guidelines dealing with blood pressure and cholesterol, patients tend to have the same cluster of conditions—hypertension, dyslipidemia, and obesity. In fact, there has been criticism for not unifying the guidelines. The metabolic syndrome is a first attempt to look at the whole patient and to recognize all the different components that make up the constellation. It is a step in the direction of bringing together and synthesizing a total risk package for the patient.

Dr. Kahn raised another issue taken from the world of diabetes. People have suggested that the 1997 definition for diabetes based on the so-called "gold standard" of the OGTT as being 140 for IGT and 200 for diabetes should be changed based on current data. The problem with doing that

is that too many papers have been written based on the old definition. As more and more people relate to the definition of the metabolic syndrome and base their research and analyses on, for instance, the NCEP definition, if data comes along demonstrating that a cutpoint should be higher or lower or that a component should be added or subtracted, there will be a point where people will say, "We can't do that. It would be too disruptive even if the data shows this is not right or should be modified." This is what happened with the OGTT.

Dr. Haffner stated that changing from doing OGTTs had some beneficial effects in identifying more undiagnosed diabetic subjects. The use of the metabolic syndrome has not suggested new pharmacological therapy. It has suggested that there be a focus on those risk factors for which there are already guidelines. It also has focused on behavior. The NCEP ATP II also recommended behavior modification, but the problem was that the behavioral effects on LDL cholesterol were not that much, so people wrote off the suggestion. The ATP III is being taken more seriously. The definitions are probably not perfect. More research is needed. There continues to be a need for standardization of insulin concentrations, which was agreed to 5 or 6 years ago but has not happened. Interest in the metabolic syndrome may stimulate that. One of the reasons that people dislike the WHO definition is because they do not know what insulin concentrations mean..

Dr. Kahn told the group that ADA has a committee that will meet soon on standardizing the insulin assay. He also pointed out that although the intentions of the ATP III definition were clear, the consequence has been a growing number of pharmaceutical companies approaching ADA and fundamentally saying they want their drug, no matter what it is, to be associated with the metabolic syndrome. Some companies have said they even do not want their drug associated with lowering a particular parameter such as blood pressure or glucose or weight; they want it positioned as affecting the metabolic syndrome.

Dr. Vinicor spoke of the power of science that was experienced though the experience of DCCT. DCCT created not just a medical change but a cultural change in thinking about the importance of glucose control. This power facilitated social-cultural change beyond the doctor's office; it affected policymaking, Congressional appropriations, third-party reimbursements, and the CMS. This is also true for the DPP and the Finnish study. He urged that the power of good science not be underestimated. If a good study showed that addressing weight in 20-year-olds in a rigorous way improved even intermediate outcomes in lipids and blood pressure after 5 years, that study could then change society.

Dr. Savage said that treating individual endpoints would probably yield a slight incremental benefit, but he felt that treating the metabolic syndrome abnormalities as a whole would result in the most benefit. It would be important to do an intervention study in healthy young adults to see whether or not there was a relatively cost-effective way of changing the pattern of development of obesity and risk factors before they are clearly established, rather than just continuing to document their prevalence in more and more populations.

National Institute of Child Health and Human Development (NICHD), Gilman Grave, MD, Chief, Endocrinology, Nutrition, and Growth Branch

Dr. Grave referred to the growing numbers of adolescents with type 2 diabetes, obesity, and high blood pressure. NICHD is very interested in the early origins of the clustering of these factors of the metabolic syndrome and the heuristic value of looking at these in childhood, especially the fetal origins of the syndrome. The NICHD National Children's Study will look at fetal origins of adult disease to learn when it is first possible to detect the appearance of the cluster, to closely track it into adulthood, and to assess its implications. Referring to a study by Dr. Boyd Metzger and the late Dr. Norbert Freinkel, both of Northwestern University, Dr. Grave noted that it will be interesting to see if study subjects who are now in their 20s and are the offspring of women who had gestational diabetes show evidence of the clustering since the study showed earlier that the level of amniotic fluid insulin in their mothers highly correlated with the incidence of the children's obesity at 10 years of age. NICHD also is very interested in the genotype-phenotype correlations and what the environmental interactions are because so many women with obesity do not have this clustering.. He invited those present to participate in an NICHD workshop on June 30-July 1 that will address the same questions presented here: What is the etiology? What are the definitional issues? What are the cutout points, especially by age in children? How does puberty affect insulin resistance?

Food and Drug Administration, David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products

In his presentation of FDA's perspective on drug development in the metabolic syndrome, Dr. Orloff noted that the idea of the metabolic syndrome as a target for therapy in and of itself has great appeal to the pharmaceutical industry. He also stressed that if the syndrome is to have public health implications, a consensus definition must first be established. While FDA shares the public health goals of the other DMICC members, their mandate is sometimes incongruous in their duel role of protecting the public health and also regulating and even promoting commerce in presumably safe and effective drugs. FDA challenges sponsors to develop safe and effective treatment and preventive agents, conducts a guidance and review process and regulatory actions to bring new drugs to market, and then partners in the public health arena to label the drugs or treatment and preventive agents appropriately with regard to expected risks and benefits. Dr. Orloff said that expected risks and benefits is a very important concept in drug labeling and to ensure "balanced promotion."

The agency's current position on what would be required for a "treatment for metabolic syndrome" and a drug label is that diagnostic criteria is needed that identifies a population in which negative outcomes attributable to the syndrome can be reliably predicted. There would need to be a central pathogenetic mechanism or combination of mechanisms, a drug or combination of drugs impacting this mechanism that predictably ameliorates the spectrum of metabolic and physiologic abnormalities of the syndrome, and finally evidence based on hard outcomes of a role for drugs in the management of CVD or another potentially mortal risk. Short of meeting these criteria, FDA would say treat the components of the syndrome, or without a consensus definition of the syndrome, treat the known established cardiovascular risk factors for which there are effective interventions as demonstrated by the impact on intermediate or

surrogate measures or evidence of impact on overall hard outcomes. FDA agrees that the metabolic syndrome comprises a constellation of cardiovascular risk factors and that there is plentiful evidence suggesting these should be addressed therapeutically. However, absent a unifying pathogenetic mechanism and evidence of a salutary effect on outcomes of the intervention on that mechanism, drug target(s) remain the components of the syndrome not the syndrome itself. Obesity interventions, such as lifestyle modification, that do not involve drugs do not come under the purview of the FDA.

Dr. Grundy commented that one of his concerns has been that in treating the components physicians sometimes concentrate on one component and ignore others. This is highlighted in patients with diabetes where physicians may focus on treating glucose because the patient has diabetes but fail to treat the hypertension that almost all patients with type 2 diabetes have, do not treat lipids appropriately, and do not recommend aspirin and things like that. An advantage of looking at the syndrome is that it considers all the components and points to the need for each one requiring the appropriate intervention, either drugs or not drugs.

Dr. Orloff agreed but said there is not universal agreement on this at FDA. However, for a long time, the agency has included in the labels for the lipid-altering drugs, the National Cholesterol Education Program guidelines and information on multiple risk factor intervention. Dr. Orloff proposed that similar information could be provided on labels that would be appropriate and applicable to patients who have a constellation of cardiovascular risk factors, such as the components of the metabolic syndrome. To include such directions in labeling, the expected benefits of the intervention must be specific and have been shown to impact a particular outcome. Once that is well-established and a consensus reached on how to predict risk in patients with a constellation of risk factors and how to guide them therapeutically, then such information could be included on labels.

Indian Health Service, Kelly Moore, MD, Clinical Specialty Consultant, National Indian Health Service Diabetes Program

Dr. Moore reported that as a clinical care system, IHS plans to provide training to its clinicians and administrators on the metabolic syndrome and in applying the additional $50 million received under the special diabetes grant program for prevention and treatment of diabetes in its patient population, the agency will be looking at screening for diabetes and for the metabolic syndrome. She said there is a sense of the metabolic syndrome among IHS clinicians, and there have been a number of training sessions on the diagnostic criteria and on interventions related to some of the components. Patients do not have much knowledge of it.

Dr. Moore's presentation focused on the risk factors for the metabolic syndrome in the American Indian and Alaska Native (AI/AN) population based on the epidemiology of diabetes and obesity in this group, particularly those who have diabetes but also AI/AN youth at risk. IHS has developed state-by-state maps, similar to CDC's obesity maps, to show an increasing age-adjusted prevalence of diagnosed diabetes among AI/AN persons age 20 years and older. Clearly there is an epidemic. The rate of high prevalence in 1991 that existed in only four states—Florida, Nebraska, Maine, and Mississippi—in 2001 existed in 18 states, Arizona, Colorado, Iowa, Kansas, Maine, Michigan, Minnesota, Mississippi, Montana, Nebraska, New Mexico,

North Carolina, North and South Dakota, Texas, Utah, Wisconsin, and Wyoming. Comparing prevalence in 1991 versus 2001 by age group shows alarming increases in the younger age groups. There has been a 106 percent increase in diagnosed diabetes in the 15- to 19-year-old adolescent population. There was also an increase in prevalence of overweight and obesity from 1994 through 2001 in the patient population with diabetes. In a study of overweight AI youth from a large tribe in the Southwest, children of 6 years of age are already well along the trajectory towards developing diabetes (Elsenmann, 2000).

IHS does not have good data on the metabolic syndrome in AI/AN groups; their best data is from the annual audit of the patient population with diabetes. The 2001 diabetes audit showed that nearly 40 percent of men and 30 percent of women under the age of 45 who have diabetes were taking lipid-lowering drugs. Over the age of 45, the percentage increased to nearly 50 percent for men and a little over 40 percent for women. There has been significant improvement in blood pressure control. However, IHS is limited in data collection to patients voluntarily seeking care so there is not any national aggregate data on the general population. For example, there is very little data about men from age 20 to mid-40s because they do not often access the health care system..

An intertribal heart project was reported by Kurt Greenland et al. in *Diabetes Care* in 1999 that looked at a cluster of risk factors associated with insulin resistance including hypertension, diabetes, high triglycerides, and low HDL, among three communities in Wisconsin and Minnesota. Prevalence estimates based on the study were approximately 10 percent for AI men and 6 percent for AI women. Generally, the percentage of individuals with each trait increased as the number of other syndrome traits increased. In both men and women, the number of syndrome traits was related positively with age and inversely with education level and unrelated to their Native American ancestry.

A small study was conduced in the state of Montana that screened youth from seven schools on two reservations from 1999 through 2000. Fifty-five percent were from 6 to 11 years of age and 43 percent were 12 to 19 years of age. The majority of children were AI youth. In terms of risk factors for diabetes among this population, 31 percent were overweight, 33 percent had acanthosis nigricans, and 61 percent had a family history of diabetes. Compared to NHANES III data for youth in the same age groups in the general U.S. population, the AI youth had a 30-31 prevalence of overweight compared to the 13-14 percent of their U.S. counterparts.

Veterans Health Administration (VHA), Thakor Patel, MD

Dr. Patel was unable to attend the meeting as planned, but he submitted a set of slides that were included in the participants' program package. The slides presented VHA clinical user demographics and implications for the metabolic syndrome. Key points were that the prevalence of the syndrome in VHA is unknown, but data suggests that the prevalence is likely very high given the age of the clinical population, which is increasing along with the increasing number of minority groups. Diabetes prevalence is increasing at younger ages in both women and African Americans of both genders. In fiscal year 1999, there was an overall prevalence of diabetes of 16 percent, a 40.4 percent prevalence of hypertension in the VA population as a whole, and a 65.6

percent rate of hypertension among patients with diabetes. Veterans with diabetes also tend to have numerous comorbidities and disabilities that may limit lifestyle interventions.

Closing Remarks

Dr. Malozowski summarized the meeting by saying that a consensus on a definition of the metabolic syndrome was needed, there are many opportunities to find answers to the questions raised at the meeting, some through mechanisms available at NIH, and opportunities to pursue additional research in the metabolic area. He thanked the participants and the three speakers, and he thanked Dr. Savage for being active in organizing the meeting.

Dr. Spiegel also thanked the attendees and added that there exists today an underlying vision of prevention and of change in the health care system from being reactive to being proactive. This is a major reason why groups are grappling with issues like those discussed at this meeting, why more research is needed, and why ultimately understanding of the genotype-phenotype correlation and gene-environment interaction will be forthcoming.

Dr. Fradkin noted that all the major groups—NIDDK, NHLBI, CDC, ADA, ACE, NCEP, NDEP—are presenting basically the same message with regard to hypertension, hyperlipidemia, and hyperglycemia and the prevention of cardiovascular disease and the complications of diabetes based on evidence from a large number of clinical trials. In discussing the metabolic syndrome, the consensus heard around the table today was that the public is receiving a very confusing picture. Each group has different names for the syndrome and defines it differently. Most importantly, there is not a research base to know specifically what to do about the syndrome. The most productive course of action at this point, according to Dr. Fradkin, would be for the group to define a research agenda related to the metabolic syndrome and not get too far ahead of itself in terms of a public health message. She emphasized that it certainly had been very helpful for those present to come together and share their perspectives.

The meeting was adjourned at 12:52 p.m.