American College of Endocrinology
Position Statement on the Insulin Resistance Syndrome*

*By the American College of Endocrinology Task Force on the Insulin Resistance Syndrome.
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Executive Summary

INTRODUCTION

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The work presented in this *Endocrine Practice* report reflects the commitment of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) to provide leadership and guidance on public health issues that involve clinical endocrinology. This material was originally presented at the National Press Club in Washington, DC, on August 27, 2002.

The Position Paper presents the official position of AACE/ACE, authored by the members of the Task Force appointed by the AACE President. Faced with an absence of definitive studies, the Task Force used the best available evidence to make its recommendations.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) definition of the Metabolic Syndrome has been extremely successful in popularizing the concept of the clustering of blood pressure, lipid, glycemic and obesity risk factors and the implications of this cluster. The Task Force adopted the blood pressure and lipid criteria. However, the Task Force suggested modifications to other parts of the definition, including:

- recognizing the limitations of the fasting glucose
- recognizing the value of the 2 hour post-challenge glucose
- adding BMI as a measure of obesity
- classifying obesity as a risk factor rather than a criterion
- adjusting obesity criteria for ethnicity
- expanding the list of individuals considered at risk
- expanding the list of associated disorders.

The 2 hour post-challenge glucose is recommended when individuals at risk (Table 2 of the Position Paper) do not meet sufficient other criteria for IRS (Table 3) and a more sensitive test may be needed. It is not suggested for use in mass screenings or in every individual at risk.

There were numerous issues beyond the scope of the Task Force. For example, is there any evidence for treatment of the IRS beyond treating individual components, e.g. elevated blood pressure, dyslipidemia, etc.? Should the cut points for treatment of individual components be lower when IRS is present? Should treatment strategies for individual components be different if IRS is present? What might be the implications for an individual's health or life insurance if they carried a "diagnosis" of IRS? Are there any promising new diagnostic tools for IRS? What surrogate markers are of value in IRS?

The Task Force agreed that there was important clinical value in identifying an individual at risk for IRS. The potential benefits include: early and more aggressive lifestyle intervention with nutrition and fitness, closer and more focused medical follow-up, identification of family members at risk, treatment for individual components as soon as cut points are crossed, enrollment into research studies and, possibly, prevention of the disease consequences of IRS. The potential role of pharmacology was reviewed, and remains one of the more challenging questions.

Due to the complex and rapidly evolving nature of this field, the Task Force recognized it could not issue definitive clinical "guidelines" in the usual sense until more data were available. Therefore, as a complement to the Position Paper, a Conference on the Insulin Resistance Syndrome was convened in Washington, DC, August 25-26, 2002. The proceedings of that conference will be published separately; the presenters and participants are listed in the Appendix.

Special thanks to Drs. Gerald Reaven and Earl Ford for providing leadership in development of the paper, and Dr. Yehuda Handelsman for organization of the Conference.

Finally, the Task Force acknowledges a great debt to the many colleagues and friends of AACE/ACE who gave informal advice, and who have helped advance the understanding of insulin resistance.

EXECUTIVE SUMMARY

Question 1. What is the Insulin Resistance Syndrome (IRS)?

IRS describes a condition that is characterized by decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion. This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences, including cardiovascular disease and type 2 diabetes, polycystic ovary syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD), and other illnesses.

Question 2. What is the clinical impact of the Insulin Resistance Syndrome?

One in three to four American adults has IRS; most are able to produce enough insulin to maintain non-diabetic glucose levels. Some of these individuals will go on to develop overt type 2 diabetes. The majority will not develop diabetes, but yet will remain at significant increased risk for cardiovascular disease and other diseases. Over 90% of the 16 million Americans who have type 2 diabetes are insulin resistant. One in ten women have PCOS, another manifestation of IRS. The current epidemic of obesity among children and adolescents puts them at increased risk for IRS and its complications.

Question 3. Who is at risk to have the Insulin Resistance Syndrome?

The more risk factors an individual has, the greater the likelihood of having IRS.

- Overweight: a Body Mass Index (BMI) >25 or a waist circumference of >40 inches for men, >35 inches for women (10-15% lower for non-Caucasians)
- A sedentary lifestyle
- Age >40 years
- Non-Caucasian ethnicity (e.g., Latino/Hispanic American, African American, Native American, Asian American, Pacific Islander)
- A family history of type 2 diabetes, hypertension or cardiovascular disease
- A history of glucose intolerance or gestational diabetes
- Acanthosis nigricans
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease

Question 4. How can the Insulin Resistance Syndrome be detected in clinical practice?

Individuals at risk for having IRS can be identified by history, physical examination and laboratory evaluation. The following are the characteristic abnormalities of the IRS (Table A). There is no single definitive test for insulin resistance available for use in clinical practice. Standardized assays for plasma insulin are not available for routine use. Note that the post-glucose challenge plasma glucose provides a more sensitive indicator of insulin resistance than fasting plasma glucose measurement.

The "diagnosis" of IRS should be considered in any individual with risk factors and abnormalities from Table A, and we did not want to focus on an arbitrary numerical scoring system until there are data to justify it. For epidemiological purposes, however, we concluded that 2 or more abnormalities from Table A (corresponding to Table 3 in the Position Paper) in an individual with risk factors (Table 2 in the Position Paper) constituted the IRS.

Table A
Characteristic Abnormalities of Insulin Resistance Syndrome

Plasma glucose	
Fasting	110 - 125 mg/dL
120 min post-glucose challenge (75 g)	140 - 200 mg/dL
Triglycerides*	> 150 mg/dL
HDL cholesterol*	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure*	> 130/85 mm Hg

* Levels based upon NCEP/ATP III Guidelines, JAMA, May 16, 2001.

Question 5. What is a reasonable approach to managing the Insulin Resistance Syndrome in clinical practice?

A discussion of treatment considerations for patients with IRS must begin by differentiating between efforts focused on improving insulin sensitivity itself and those aimed at treatment of any of the specific manifestations of IRS.

Efforts to improve insulin sensitivity

There is consensus that individualized lifestyle modification is appropriate for all patients who are considered at risk to have IRS. The panel encourages research into other approaches, including pharmacologic therapies, to address insulin resistance directly.

Treatment of the components

Evidence-based guidelines exist which support the appropriate use of pharmacologic agents to treat the individual components of IRS. Individuals identified as being at risk should be treated as soon as thresholds are met and then followed closely, in anticipation of development of the other components of the syndrome.

Question 6. What should be the priorities for the future?

The panel identified four key areas of particular interest.

1. Development of a better diagnostic test for insulin resistance.
2. Targeted testing for individuals and families at risk.
3. Research into pharmacologic therapies to improve insulin sensitivity.
4. Convening a conference to gather leading researchers and clinicians to establish the best current understanding of IRS (Appendix).

SUMMARY

The Insulin Resistance Syndrome Task Force attempted to provide a means of understanding the Insulin Resistance Syndrome and a practical clinical approach to identifying and managing individuals at risk. By necessity, we had to limit discussion to outline form only, especially with regard to treatment. While we have accepted the lipid and blood pressure guidelines from NCEP ATP III, we do recommend certain differences to identify individuals with IRS. These differences may be summarized as follows:

1) The Insulin Resistance Syndrome is used to describe the cluster of abnormalities that are more likely to occur in insulin resistant/hyperinsulinemic individuals.
2) The Insulin Resistance Syndrome is differentiated from type 2 diabetes.

3) BMI, as well as waist circumference, is used as the index of obesity, and viewed as a physiological variable that increases insulin resistance, rather than as a criterion for diagnosis of the Insulin Resistance Syndrome. Any measure of obesity must be adjusted for ethnicity.
4) Ethnicity is introduced as an important risk factor for insulin resistance, and non-Caucasian ancestry identified as increasing risk of the Insulin Resistance Syndrome.
5) Other factors have been identified that increase the risk of developing the Insulin Resistance Syndrome, including a family history of type 2 diabetes, hypertension, CVD, as well as a personal history of CVD, PCOS, gestational diabetes, and acanthosis nigricans.
6) Fasting plasma glucose concentration is used primarily to identify individuals with type 2 diabetes. The plasma glucose concentration 2 hours after a 75-g oral glucose load is introduced as a more sensitive measure of risk for the Insulin Resistance Syndrome.

We are supportive of current concepts in medically supervised therapeutic lifestyle change, efforts directed to the treatment of obesity, and strategies for increasing physical activity. Further research into pharmacologic interventions for the treatment of the Insulin Resistance Syndrome appears very promising. We fully concur that the emergence of the Insulin Resistance Syndrome is among the most pressing problems of public health in the developed world, and many diverse talents and resources will need to work together to meet this challenge. As the Position Paper states, this is an area of rapid evolution consisting of many small incremental steps, of which the work of our Task Force is but one.

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INTRODUCTION

The clinical consequences of insulin resistance and compensatory hyperinsulinemia, the Insulin Resistance Syndrome, are increasingly appreciated as posing a major public health problem. Currently recognized clinical manifestations of the Insulin Resistance Syndrome include atherosclerotic cardiovascular disease (CVD), hypertension, polycystic ovary syndrome (PCOS), and nonalcoholic steatohepatitis, and the list continues to expand. Despite the recognition of the importance of this syndrome, identifying individuals who have the Insulin Resistance Syndrome is difficult, as there is no simple clinically available test to diagnose it. Important contributions have been made by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in their publication of criteria for diagnosing the "Metabolic Syndrome." The explosion of research and educational material on the "Metabolic Syndrome" attests to the recognition of its importance by clinicians. The American Association of Clinical Endocrinologists (AACE) championed the creation of the new ICD-9 Code 277.7 for the "Dysmetabolic Syndrome" and, with other groups, is leading efforts to enable clinicians to screen and treat individuals at risk. For reasons outlined below, we will use the term Insulin Resistance Syndrome to describe the consequences of insulin resistance and compensatory hyperinsulinemia, thereby focusing on the underlying pathophysiology that unites the cluster of related abnormalities.

In the absence of a straightforward diagnostic test or definitive clinical trials, identification and treatment of a syndrome as complex as this one is require thoughtful evaluation of the best available evidence and consensus among researchers and clinicians. Our task force was created by AACE and the American College of Endocrinology (ACE) to work toward this consensus and so to provide guidance to clinicians and the many others involved in and affected by the Insulin Resistance Syndrome. This is an area in rapid evolution, so progress will consist of many small incremental steps, of which the efforts of our task force are but one.

1. Differentiation between the Insulin Resistance Syndrome and type 2 diabetes

Sensitivity to insulin-mediated glucose disposal varies widely in the population at large (1). When insulin resistant individuals cannot maintain the degree of hyperinsulinemia needed to overcome the resistance, type 2 diabetes develops (Fig. 1). However, even when insulin resistant individuals secrete enough insulin to remain nondiabetic, they remain at increased risk to develop a cluster of abnormalities that have been given many names, but which we suggest is best described as the Insulin Resistance Syndrome. The primary reason for selecting this name is to focus explicitly on the central role of insulin resistance with compensatory hyperinsulinemia in the pathogenesis of the associated cluster of abnormalities. Use of alternative labels such as "the metabolic

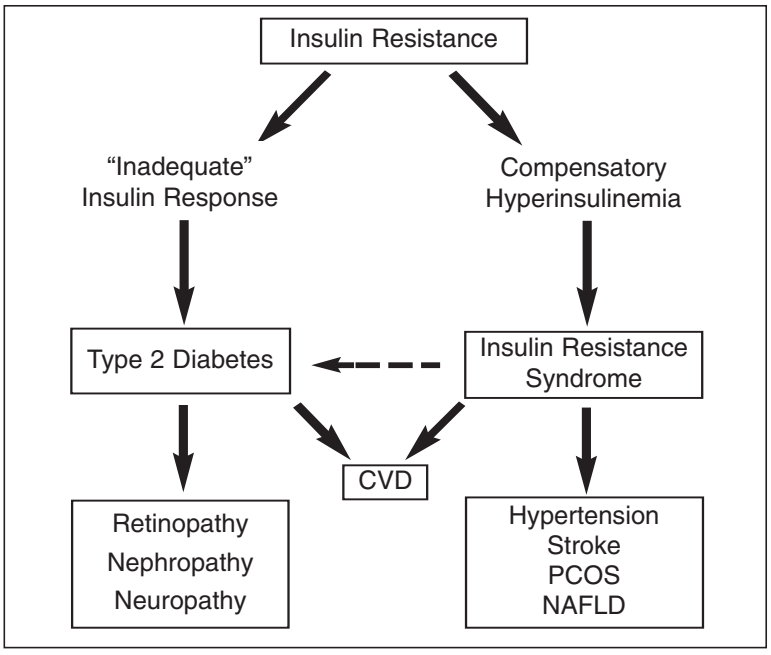

Fig. 1. Differentiation between the Insulin Resistance Syndrome and type 2 diabetes.

syndrome" or the "dysmetabolic syndrome" relies on an unclear definition of "metabolic," and these terms are likely to become even less appropriate as the abnormalities associated with insulin resistance and compensatory hyperinsulinemia continue to expand. Furthermore, use of these labels usually leads to a descriptive compilation of clinical findings that tend to cluster within an individual, without implying any mechanistic explanation for why this happens. In contrast, the Insulin Resistance Syndrome offers a clear statement of the presumed pathogenesis of the syndrome, is based on evidence that insulin resistance and compensatory hyperinsulinemia significantly increase the likelihood of an individual developing a cluster of related abnormalities, and provides a broad umbrella under which all of the abnormalities related to insulin resistance with compensatory hyperinsulinemia can be gathered.

As depicted in Fig. 1, some individuals with the Insulin Resistance Syndrome will eventually develop diabetes because they lose the ability to secrete the large amount of insulin needed to overcome the insulin resistance (2). However, while the majority of insulin resistant individuals do not become frankly diabetic, they remain at increased risk (2) to develop CVD and all of the other clinical consequences of insulin resistance/compensatory hyperinsulinemia. Since CVD is also the major cause of morbidity and mortality in patients with type 2 diabetes (3), and because the vast majority of individuals with CVD and/or type 2 diabetes are also insulin resistant (2), it could be argued that the differentiation between the two clinical syndromes outlined in Fig. 1 is inappropriate. However, the diagnosis of type 2 diabetes is relatively straightforward and based primarily upon the degree of hyperglycemia that increases risk of diabetic microangiopathy (4). An approach to identifying those individuals who do not have diabetes, but who do have the Insulin Resistance Syndrome, is not so simple and is the primary goal of this report. This decision is not meant to deny the many similarities between the Insulin Resistance Syndrome and type 2 diabetes, but only to develop a construct that recognizes the clinical importance of insulin resistance and compensatory hyperinsulinemia in the absence of frank hyperglycemia.

A secondary goal is to outline briefly the therapeutic approaches to prevent, or attenuate, the pathophysiological consequences of the Insulin Resistance Syndrome.

2. What are the disease-related consequences of insulin resistance/compensatory hyperinsulinemia (the Insulin Resistance Syndrome)?

Insulin-mediated glucose disposal by muscle varies approximately 10-fold in healthy, nondiabetic, normotensive individuals (1). The more insulin resistant the muscle, the more insulin needs to be secreted in order to maintain normal glucose homeostasis. Table 1 presents a list of the changes that are more likely to occur in insulin resistant individuals who are able to maintain the degree of compensatory hyperinsulinemia needed to prevent the onset of type 2 diabetes. In addition to representing the abnormalities generally accepted as belonging to the Insulin Resistance Syndrome, the changes listed in Table I have also been shown to increase the likelihood of an individual developing type 2 diabetes and/or CVD (5-26). It should be noted that the conditions associated with insulin resistance/compensatory hyperinsulinemia continue to expand, and there is increasing evidence that nonalcoholic steatohepatitis (NASH), and perhaps even several forms of cancer, are more likely to occur in individuals with the Insulin Resistance Syndrome (27,28).

Not all insulin resistant/hyperinsulinemic individuals will develop the entire cluster of abnormalities that currently make up the Insulin Resistance Syndrome (Table 1). At the simplest level, the number of manifestations present in an insulin resistant individual will vary with the criteria used to separate normal from abnormal. In addition, neither insulin resistance nor the plasma insulin concentration is the sole regulator of the abnormalities listed in Table 1. For example, two individuals can be equally insulin resistant or hyperinsulinemic, with a comparable increase in hepatic triglyceride (TG) secretion, but differ in terms of their ability to remove TG-rich lipoproteins from plasma. As a consequence, one subject will have a TG concentration of 140 mg/dL, while the other will have a concentration of 180 mg/dL.

The situation is even more complicated in the case of essential hypertension. Even though insulin resistance/hyperinsulinemia is likely to be responsible for increased blood pressure in no more than 50% of patients with essential hypertension (17), the fact remains that the elevation of blood pressure in a substantial proportion of patients with essential hypertension is one of the manifestations of the Insulin Resistance Syndrome.

Insulin resistance is not a disease in and of itself, but rather a physiological abnormality that increases the risk of developing one or more of the abnormalities listed in Table 1. Not all insulin resistant individuals develop these abnormalities, nor is their appearance confined to insulin resistant individuals. On the other hand, the presence of any one of them indicates that the individual may be insulin resistant and increases the possibility that the other abnormalities will be present. The more insulin resistant an individual, and the greater the degree of compensatory hyperinsulinemia, the more likely the person is to have the Insulin Resistance Syndrome. However, in order to emphasize that the abnormalities listed in Table 1 can also occur independently of insulin resistance and compensatory hyperinsulinemia, they are listed separately.

In the remainder of this section we will explore the relationships between insulin resistance/hyperinsulinemia and currently recognized components of the Insulin Resistance Syndrome listed in Table 1.

1) Glucose tolerance—The majority of persons with the Insulin Resistance Syndrome will have a "normal" fasting plasma glucose (FPG) concentration (<110 mg/dL). However, the likelihood that insulin resistance is present is increased in

Table 1
Components of the Insulin Resistance Syndrome

1. Some degree of glucose intolerance
   - Impaired fasting glucose
   - Impaired glucose tolerance
2. Abnormal uric acid metabolism
   - Plasma uric acid concentration
   - Renal uric acid clearance
3. Dyslipidemia
   - Triglycerides
   - HDL-C
   - LDL-particle diameter (small, dense LDL-particles)
   - Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
   - Sympathetic nervous system activity
   - Renal sodium retention
   - Blood pressure (~50% of patients with hypertension are insulin resistant)
5. Prothrombotic factors
   - Plasminogen activator inhibitor-1
   - Fibrinogen
6. Markers of inflammation
   - C-reactive protein, WBC, etc.
7. Endothelial dysfunction
   - Mononuclear cell adhesion
   - Plasma concentration of cellular adhesion molecules
   - Plasma concentration of asymmetric dimethylarginine
   - Endothelial-dependent vasodilatation

individuals with either "impaired fasting glucose" (FPG concentration >110 and <126 mg/dL) or "impaired glucose tolerance" (FPG concentration <126 mg/dL, and a plasma glucose concentration >140 and <200 mg/dL 120 min after a 75-g oral glucose challenge). Procedures for performing and interpreting oral glucose challenges have been published (18).

2) Uric acid metabolism—Plasma uric acid concentrations are higher in insulin resistant individuals, associated with a decrease in the renal clearance of uric acid, which almost certainly account for the results of population-based studies demonstrating an association between CVD and plasma uric acid concentration. However, plasma uric acid concentration is not a very sensitive predictor of insulin resistance. Thus, an elevated plasma uric acid concentration increases the likelihood that an individual is insulin resistant, but a normal concentration does not mean that an individual is insulin sensitive.
3) Dyslipidemia—A high plasma TG and low plasma concentration of high-density lipoprotein cholesterol (HDL-C) concentration are common findings in insulin resistant/hyperinsulinemic persons. This characteristic dyslipidemia is accompanied by a smaller and denser low-density lipoprotein (LDL) particle and an increase in the postprandial accumulation of TG-rich remnant lipoproteins. These 4 changes result in a highly atherogenic lipoprotein profile that is the most well-established mechanistic link between the Insulin Resistance Syndrome and CVD, and one that must be aggressively treated.
4) Hemodynamic—The increase in sympathetic nervous system activity and renal sodium retention seen in the Insulin Resistance Syndrome provide causal links that help explain why approximately 50% of patients with essential hypertension are insulin resistant/hyperinsulinemic. The insulin resistant/hyperinsulinemic subset of patients with essential hypertension also often share the characteristic dyslipidemia of the Insulin Resistance Syndrome, and it is these individuals who have the greatest CVD risk (19,29).

5) Hemostasis and 6) Inflammation—Plasma concentrations of plasminogen activator inhibitor-1 are frequently increased in insulin resistant/hyperinsulinemic individuals. The presence of increased fibrinogen levels has been a less consistent finding and may be more likely a manifestation of an acute-phase reaction associated with inflammation of the vascular wall in patients with the Insulin Resistance Syndrome. In this context, there is evidence that other markers of inflammation are present in the Insulin Resistance Syndrome, e.g. C-reactive protein and higher white blood cell counts. Whether these latter changes are simply an epiphenomenon, increased because of the enhanced atherogenesis in insulin resistant individuals, or play a causal role in the development of CVD, remains to be determined.
7) Endothelial dysfunction—Mononuclear cells isolated from insulin resistant/hyperinsulinemic individuals bind with greater adherence to cultured endothelium, associated with increases in plasma concentrations of cellular adhesion molecules and asymmetric dimethylarginine (an endogenous inhibitor of nitric oxide synthase). Functionally, endothelium-dependent vasodilatation is decreased in insulin resistant/hyperinsulinemic individuals.

3. Identification of individuals at risk for the Insulin Resistance Syndrome

The prevalence of insulin resistance is increased in nondiabetic individuals with diagnosed CVD, essential hypertension, or acanthosis nigricans as shown in Table 2. Women with PCOS (26), or a history of gestational diabetes (30), are likely to be insulin resistant, and at increased risk to develop one or more of the clinical components of the Insulin Resistance Syndrome. Insulin resistance has been shown to be a familial characteristic (31-33), and a family history of type 2 diabetes, hypertension, or CVD increases the likelihood of an individual being insulin resistant. In contrast to the CVD risk associated with a high LDL-C concentration, there is no evidence that the earlier the history of CVD in the family, the more likely the individual is to be insulin resistant/hyperinsulinemic. Finally, a prior diagnosis of glucose intolerance suggests that insulin resistance may be present.

Ethnicity is also a powerful predictor of insulin resistance/hyperinsulinemia (34), and manifestations of the Insulin Resistance Syndrome are increased in essentially every group of non-Caucasian ancestry in which comparisons have been made. Furthermore, these differences persist when adjustments are made for the impact of lifestyle variables known to lead to insulin resistance.

The most powerful modulators of insulin action are differences in degree of obesity and physical activity, and there is evidence in both Pima Indians and Caucasians that approximately 50% of the variability in insulin-mediated glucose disposal can be attributed to variations in degree of obesity and physical fitness (35). The two variables were approximately equally powerful, and it is quite likely that at least a portion of the untoward effect of obesity on insulin resistance is due to the fact that overweight individuals are often physically inactive. Degree of physical fitness is not routinely quantified, but body weight is. We suggest that body mass index (BMI, weight in kg/height in meters squared) be used as the criterion for defining a person as being overweight/obese, and that a BMI >25.0 kg/m^2 identifies individuals at increased risk to have the Insulin Resistance Syndrome. It is recognized that using a BMI value of 25 or more to identify individuals at increased risk to have the Insulin Resistance Syndrome may be too high for ethnic groups in whom the prevalence of insulin resistance/hyperinsulinemia is more common. On the other hand, inclusion of ethnicity as a risk factor minimizes the lack of definitive ethnic-specific data concerning the relationship between adiposity and insulin resistance.

Age, per se, has relatively little effect on insulin resistance (35), but body weight tends to increase, and physical activity decrease, as persons get older. Thus, although somewhat arbitrary, it seems reasonable to evaluate all individuals >40 years of age for manifestations of the Insulin Resistance Syndrome. On the other hand, it must be emphasized that manifestations of the Insulin Resistance Syndrome can occur at any age.

Finally, it should be emphasized that obesity and physical inactivity are variables that not only significantly increase the likelihood of an individual being insulin resistant, but also represent predictors of the Insulin

Table 2
Factors That Increase the Likelihood of the Insulin Resistance Syndrome

• Diagnosis of CVD, hypertension, PCOS, NAFLD, or acanthosis nigricans
• Family history of type 2 diabetes, hypertension, or CVD
• History of gestational diabetes or glucose intolerance
• Non-Caucasian ethnicity
• Sedentary lifestyle
• BMI >25.0 kg/m^2 (or waist circumference >40 inches in men, >35 inches in women)
• Age >40 years

Resistance Syndrome that can be modified by changes in lifestyle. The importance of weight loss and increased physical activity in treatment of the insulin resistance syndrome will be discussed subsequently.

4. Obesity and the Insulin Resistance Syndrome

The relationship between obesity and the Insulin Resistance Syndrome outlined in this document differs in two respects from many other published considerations of this topic. In the first place, descriptions of the Insulin Resistance Syndrome often include obesity, usually abdominal obesity, as one of the features of the syndrome, rather than as a lifestyle factor that, because of its adverse effect on insulin-mediated glucose disposal, increases the risk of the Insulin Resistance Syndrome. The decision to view obesity in this latter manner was based upon the following considerations. Obesity is not a consequence of insulin resistance/hyperinsulinemia, but a physiological variable that decreases insulin-mediated glucose disposal. Furthermore, not all insulin resistant individuals are overweight/obese, nor are all overweight/obese individuals insulin resistant. For clarity of the physiological construct of the Insulin Resistance Syndrome, it is important that obesity be viewed as contributing to the insulin resistance/hyperinsulinemia, rather than being a consequence of the abnormal insulin metabolism. This view of the relationship between obesity and insulin resistance/hyperinsulinemia should not be construed as minimizing the important role that the current epidemic of obesity plays in increasing the incidence of both type 2 diabetes and the Insulin Resistance Syndrome.

Secondly, it is proposed that BMI, rather than abdominal circumference, be used to identify individuals at increased risk to have the Insulin Resistance Syndrome. This decision was based on the following considerations. Height and weight are simple and routine measurements that are easily quantified, in contrast to estimates of abdominal circumference, which are neither routinely performed nor is its quantification as well standardized. In addition, BMI has been widely used to define obesity status in the U.S. and Europe, and the classification of normal weight, overweight, and obesity is based on use of BMI, as are current guidelines for the appropriate use of pharmacological treatment of obesity. Furthermore, available evidence does not demonstrate that measurements of abdominal circumference provide a superior estimate of insulin resistance than does BMI. For example, the relationship between insulin-mediated glucose disposal as measured by the euglycemic clamp technique and obesity based on the results of >1100 subjects studied by the European Group for the Study of Insulin Resistance was not increased when abdominal circumference replaced BMI as the marker of obesity (36). Additional support for this decision came from the observation that the relationship between obesity and plasma glucose and insulin concentrations, before and 120 min after a standard oral glucose load, was identical when either BMI or abdominal circumference was used as the estimate of obesity in the 3300 individuals in the NHANES III database in whom these measurements were made (37). Finally, BMI and abdominal circumference were closely related, with correlation coefficients of approximately r=0.9 in the 15,271 participants in the NHANES III study, irrespective of gender or ethnicity. For all of these reasons, it has been suggested that BMI be used as the marker to identify individuals that should be evaluated for the Insulin Resistance Syndrome. On the other hand, there would not be a great deal to lose if an increase in abdominal circumference (>40 inches for men and >35 inches for women) was used instead of (or in addition to) BMI as a way to identify individuals at increased risk to have the Insulin Resistance Syndrome.

5. "Diagnosing" the Insulin Resistance Syndrome

Recognition of the importance of insulin resistance/hyperinsulinemia as increasing risk of CVD has led to the publication of criteria for diagnosing what was referred to as the "Metabolic Syndrome (38)" and the creation of an ICD-9 code 277.7 for the "Dysmetabolic Syndrome X." Unfortunately, the experimental evidence available does not exist that can be translated into simple criteria for diagnosing the Insulin Resistance Syndrome. The Insulin Resistance Syndrome is not a specific disease, any more than insulin resistance is, but rather a group of abnormalities that tend to cluster together, occur with greater prevalence in insulin resistant/hyperinsulinemic persons, and identify individuals at increased risk to develop type 2 diabetes and CVD. Consequently, it seems useful to provide the means, using the relatively simple tests described in the next section, to identify individuals who are likely to be insulin resistant/hyperinsulinemic because they display at least one of the components of the Insulin Resistance Syndrome as summarized in Table 1. The more the number of components an individual has, and the more severe the magnitude of the abnormality, the more likely that individual is to have the Insulin Resistance Syndrome, and also to be at increased risk to develop type 2 diabetes and/or CVD.

6. Criteria for predicting the Insulin Resistance Syndrome

The abnormalities listed in Table 3 are increased in prevalence in insulin resistant/hyperinsulinemic individuals and predict the development of type 2 diabetes and/or CVD. However, the relationship is far from perfect, and each of these changes can occur independently of insulin resistance. Furthermore, the actual numerical values are, at best, approximations. For example, defining a plasma TG concentration >150 mg/dL as evidence of the Insulin Resistance Syndrome may be reasonable, but there is no evidence that using a TG concentration of 175 mg/dL as a cut point would be any less useful. In the absence of rigorous criteria, we propose, for the sake of consistency

Table 3
Identifying Abnormalities of the Insulin Resistance Syndrome

1.	Triglycerides	>150 mg/dL
2.	HDL cholesterol	
	Men	< 40 mg/dL
	Women	< 50 mg/dL
3.	Blood pressure	>130/85 mm Hg
4.	Glucose	
	Fasting	110-125 mg/dL
	120 min post-glucose challenge	140-200 mg/dL

and in recognition of the important contribution made by the National Cholesterol Education Program, to use the values suggested by the Adult Treatment Panel III (ATP III) for identifying the dyslipidemic and blood pressure characteristics of the Insulin Resistance Syndrome (38). However, the plasma glucose concentration criterion has been modified to focus on the response to a 75-g oral glucose challenge, with a plasma glucose concentration 120 min after the glucose load >140 mg/dL (and < 200 mg/dL) replacing a fasting plasma glucose concentration of >110 mg/dL. It should be emphasized again that the Insulin Resistance Syndrome, as defined, excludes patients whose degree of hyperglycemia fulfills the diagnostic criteria for type 2 diabetes.

The decision to use a post-glucose challenge measurement to identify insulin resistant individuals is not in conflict with the recommendation of the American Diabetes Association that determination of FPG be used to diagnose diabetes (18). The use of FPG to identify patients with type 2 diabetes is an effort to provide a practical approach to identify individuals who are sufficiently hyperglycemic to be at risk for the microvascular complications of diabetes. If the focus is shifted to provide a more sensitive screen to identify individuals at increased risk to have the Insulin Resistance Syndrome, and develop CVD, there is evidence showing the superiority of determining the post-oral glucose challenge plasma glucose concentration in contrast to the fasting plasma glucose concentration (39). In support of this proposition are the results of the analysis of 3280 individuals in the NHANES III database, aged 40-74 years, without self-reported diabetes or a fasting plasma glucose concentration >126 mg/dL, in whom there were values for plasma glucose concentrations before and 120 min after a 75-g oral glucose challenge. In this population, approximately 10% had fasting glucose concentrations 110-126 mg/dL, whereas about 25% had a glucose concentration >140 and <200 mg/dL 120 min after a 75-g oral glucose challenge (37).

The results in Table 4 provide additional evidence of the clinical utility of using post-glucose plasma glucose concentrations to differentiate insulin resistant from insulin sensitive individuals. This information is based on analysis of the results in a large population of apparently healthy, nondiabetic individuals, in whom specific measurements of insulin action were available (1,40). Measurements of insulin-mediated glucose disposal in these 490 individuals demonstrated that this variable was distributed continuously throughout the population, making it impossible to create rigid criteria for identifying an individual as being either insulin resistant or insulin sensitive. However, there are prospective data available demonstrating that in a population without obvious disease at baseline that CVD and type 2 diabetes developed to a significant degree in the most insulin resistant tertile, and did not occur in the most insulin sensitive tertile (41,42). Thus, for the analysis in Table 4, we divided the 490 volunteers in whom specific measurements of insulin action were available into tertiles, and calculated the ability of several plasma glucose concentrations to identify individuals as being in the third of the population that was either the most insulin sensitive or the most insulin resistant. The fasting plasma glucose criterion recommended by the ATP III (FPG >110 and <126 mg/dL) identified only 30 individuals, 19 of whom were in the insulin resistant tertile. In contrast, 71 individuals had an elevated plasma glucose concentration two hours after a glucose challenge, and 54 of them were in the insulin resistant tertile. Thus, there was an approximate 3-fold increase in identifying insulin resistant individuals by determining the plasma glucose concentration 2 hours after a standard oral glucose challenge. Table 4 also indicates that lower fasting plasma glucose concentrations are even less helpful than the cut point suggested by the ATP III in distinguishing between insulin resistant and insulin sensitive individuals.

Based upon the NHANES results discussed above, and the data in Table 4, it appears that the extra effort involved in measuring plasma glucose concentration 120 min after oral glucose results in a more sensitive means of identifying individuals at risk to have the Insulin Resistance Syndrome. Alternatively, measurement of

Table 4
Number of 490 Nondiabetic Volunteers Identified as Being Insulin Resistant or Insulin Sensitive on the Basis of Plasma Glucose Measurements

Variable	Total number	Insulin sensitive	Insulin resistant
FPG >90 mg/dL	277	63	112
FPG >100 mg/dL	100	14	61
FPG >110<126 mg/dL	30	3	19
2 hr >140 mg/dL	71	4	54

plasma glucose concentration 120 min after the oral glucose challenge could be limited to those individuals who had a fasting plasma glucose concentration <110 mg/dL.

It is tempting to use the criteria outlined in Table 3 as the basis for making a diagnosis of the Insulin Resistance Syndrome, but the goal of this exercise is not to provide a rigid recipe for classifying an individual as being insulin resistant or insulin sensitive. Indeed, it could be argued that such an effort at the present time would do more harm than good. Rather, the goal has been to emphasize the fact that defects in insulin-mediated glucose disposal, and the manner in which the body responds to this abnormality, greatly increase the risk of an individual developing a variety of adverse outcomes. Having said that, it also seems reasonable to suggest that an individual at increased risk to have the Insulin Resistance Syndrome as outlined in Table 2, and with values that exceed the cut points for 2 of the 4 variables listed in Table 3, is both insulin resistant and at increased CVD risk. That conclusion is not meant to imply that an individual with only one of the abnormalities listed in Table 3 is insulin sensitive and not at risk to develop CVD. Indeed, there are outcome studies indicating that all of the variables in Table 3 have been identified as increasing CVD risk. Furthermore, it must be emphasized that the cut points in Table 3 are arbitrary, selected to be highly sensitive to the presence of insulin resistance, and represent an effort to avoid the false-negative identification of an individual as being insulin sensitive. Consequently, it seems prudent that appropriate lifestyle and/or pharmacological interventions be initiated in individuals identified in Table 2 to be at high risk for the Insulin Resistance Syndrome and whose values exceed any one of the cut points outlined in Table 3.

7. Plasma insulin concentrations and the Insulin Resistance Syndrome

Since hyperinsulinemia plays such a central role in the pathogenesis of the Insulin Resistance Syndrome, why is measurement of plasma insulin concentration not included as one of the approaches to identifying insulin resistant individuals? Plasma insulin concentrations are a useful surrogate marker of insulin resistance, with highly statistically significant correlations between measures of insulin-mediated glucose disposal and both fasting (r=~0.6) and post-glucose challenge (r=~0.8) plasma insulin concentrations (1). However, they have not been suggested as a means of identifying the Insulin Resistance Syndrome for the following reasons. Methods to quantify plasma insulin concentrations are not standardized, and it is difficult to compare values measured in different clinical laboratories. The lack of standardized methodology is particularly important when evaluating fasting plasma insulin concentrations, where the absolute difference between an insulin resistant and insulin sensitive person is not very great. Furthermore, there are not reliable data permitting an individual to be defined as being insulin resistant, and at increased risk of developing any of the components of the Insulin Resistance Syndrome, on the basis of a specific value of plasma insulin concentration alone. Finally, it has not been established that an increase in plasma insulin concentration, by itself, in the absence of any of the changes listed in Table 3, can predict the development of CVD. Although this situation could change in the future as the result of more standardized methods to measure insulin concentrations, and with population-based studies showing that hyperinsulinemia predicts either type 2 diabetes or CVD more accurately than the components listed in Table 3, it currently seems necessary to consider measurement of plasma insulin concentrations a research, not a clinical, tool.

8. Evaluation of the criteria in Table 3

In order to evaluate the potential utility of the criteria outlined in Table 3 in an objective manner, the prevalence of these 4 abnormalities in the 40-74 year-old age group in the NHANES III database was determined (37). The results of this analysis appear in Table 5, and emphasize how often the four individual components of the Insulin Resistance Syndrome listed in Table 3 appear in the U.S. population. Although hypertension was somewhat more common than the other 3 abnormalities, the prevalence of all 4 was reasonably similar. Indeed, the least common abnormality, an elevated post-glucose challenge plasma glucose concentration, was present in approximately 1/4 of the individuals surveyed.

To further pursue this issue, the number of abnormalities present in the 40-74 year-old age group as a whole was determined, as well as when they were divided as a

Table 5
Prevalence of the 4 Abnormalities of the Insulin Resistance Syndrome in NHANES III*

Variable	Prevalence (%)
TG> 150 mg/dL	35
Low HDL-C	36
Hypertension	44
120 min glucose >140 mg/dL	26

*The population includes 3280 individuals, aged 40-74, without diabetes by history or a fasting plasma glucose concentration >126 mg/dL.

function of BMI. The results of this analysis are seen in Table 6, and demonstrate that being classified as of normal weight (BMI<25.0 kg/m^2) did not protect 26% of the population from having 2 of the 4 abnormalities of the Insulin Resistance Syndrome. These data also demonstrate that the prevalence of the 4 abnormalities increases in parallel with BMI, with 62% of the individuals with BMI >30.0 kg/m^2 having 2 abnormalities, and 3 components being present in 30% of this subgroup.

Table 7 presents the prevalence of the individual abnormalities by themselves, and their appearance in combination with the other 3 abnormalities. It can be seen from these data that all theoretical combinations occur to some extent, although some more often than others. Whether or not some of these will be more useful than others in predicting clinical outcome is an issue worth pursuing.

9. Clinical utility of recognizing the Insulin Resistance Syndrome

The purpose of this position paper is, in part, to acquaint heath-care professionals with the major role that the Insulin Resistance Syndrome plays in what are often referred to as "diseases of Western civilization." Although the prevalence of these diseases is increasing in association with the epidemic of obesity in developed countries, it is also clear that the incidence is not lagging that far behind as the benefits of a "Westernized" lifestyle reach previously undeveloped areas. The information in Tables 1-3 is presented to increase understanding of the role of insulin resistance/hyperinsulinemia in the etiology and pathogenesis of the manifestations currently associated with the components of the Insulin Resistance Syndrome, as well as a relatively simple approach to identify persons with the Insulin Resistance Syndrome. This information should not serve as the sole means to "rule out" the Insulin Resistance Syndrome. Indeed, at this time, that "either/or" decision has the potential to do more harm than good. However, the information presented provides evidence-based criteria to identify individuals most likely to have the Insulin Resistance Syndrome, and those so identified can then be considered for the most appropriate therapeutic intervention. As described above, our purpose is to provide information that is both simple, so it will be used, and sensitive, so that individuals at risk can be confidently screened.

10. Treatment of the Insulin Resistance Syndrome

A discussion of treatment considerations for patients with the Insulin Resistance Syndrome must begin by

Table 6
Age-Adjusted Prevalence of the 4 Abnormalities of the Insulin Resistance Syndrome as a Function of BMI*

	Abnormalities			
	1	2	3	4
Total population (n=3280)	71%	42%	17%	4.5%
BMI				
<25 kg/m^2 (n=1113)	59%	26%	8%	1.3%
25-27 kg/m^2 (n=560)	70%	39%	15%	4.7%
27-30 kg/m^2 (n=690)	78%	51%	21%	4.9%
>30 kg/m^2 (n=917)	86%	62%	30%	9.1%

*The population includes 3280 individuals, aged 40-74, without diabetes by history or a fasting plasma glucose concentration >126 mg/dL.

differentiating between efforts focused on improving insulin sensitivity itself and those aimed at treatment of any of the specific manifestations of the insulin resistant syndrome.

A. Efforts to improve insulin sensitivity

1) Lifestyle—As discussed previously, both adiposity and level of physical activity are powerful modulators of insulin-mediated glucose disposal. More importantly, in contrast to the other factors that affect insulin action, they are modifiable by safe, straightforward lifestyle changes. Thus, weight loss of 5-10% of body weight in overweight/obese individuals, who are also insulin resistant, will significantly enhance insulin sensitivity, lower ambient plasma insulin concentrations, and improve the manifestations of the Insulin Resistance Syndrome (43).

An increase in physical activity in insulin resistant individuals is also of considerable utility, and provides two benefits. At the simplest level, any increase in energy expenditure will help insulin resistant individuals maintain or lose weight. The greater the magnitude of the increase in energy expenditure, the greater will be the benefit to the individual. It is also possible to enhance insulin sensitivity directly if an individual is able to exercise aerobically for approximately 30-40 min, 4 times/week.

Perhaps the most dramatic evidence of the beneficial effects of lifestyle intervention is the evidence from recent prospective intervention studies showing that the combination of weight loss and increased physical activity can significantly decrease the development of type 2 diabetes in high-risk individuals (44,45).

Before ending the discussion of the clinical benefits of weight loss, three additional points must be emphasized: 1) Not all overweight/obese individuals are insulin resistant, or have manifestations of the Insulin Resistance Syndrome, and weight loss does not lead to significant enhancement of insulin sensitivity in these individuals (43). 2) There is no persuasive evidence that obese, insulin resistant individuals have any more difficulty in losing weight in response to energy-restricted diets than do equally overweight persons who are not insulin resistant (43). 3) It does not appear that the ability to lose weight in response to energy-restricted diets varies as a function of the macronutrient composition of the diet (46).

2) Pharmacological—Given the difficulty in changing lifestyle, and the probable limits of its efficacy in many individuals, it could be argued that treatment of the Insulin Resistance Syndrome would be a drug(s) that could significantly enhance insulin sensitivity, as well as the other manifestations of the Insulin Resistance Syndrome. In this context, the use of thiazolidinedione (TZD) compounds, either agents currently available or future ones, is of particular interest in that they are capable of improving insulin sensitivity. However, TZD compounds are currently approved by the FDA for the treatment of hyperglycemia only in patients with type 2 diabetes, and at the present time there are no compelling experimental data that establish their clinical utility in nondiabetic individuals with the Insulin Resistance Syndrome. The potential benefits of this class of drugs are being intensively evaluated at this time, and it is highly likely that a clearer view of their role in treatment of the Insulin Resistance Syndrome will soon be apparent.

Although metformin does not seem to act by directly improving insulin sensitivity, it may also offer potential benefit for treatment of the Insulin Resistance Syndrome. It has been used worldwide for the treatment of type 2 diabetes, has an outstanding safety record, and has been shown to be effective in treatment of PCOS (47). In addition, although not as effective as weight loss and increased physical activity, metformin also decreased progression to type 2 diabetes in patients with impaired glucose tolerance (45). Finally, there is evidence that metformin administration can lower circulating insulin levels and improve glucose and lipid metabolism in patients with characteristics of the Insulin Resistance Syndrome (48).

Given the importance that obesity plays in the development of insulin resistance in susceptible individuals, pharmacological treatment of obesity may play an important role in the management of overweight individuals with the Insulin Resistance Syndrome. If overweight/obese patients with the Insulin Resistance Syndrome cannot lose weight with simple caloric restriction, both orlistat and sibutramine have been shown to be more effective than diet alone in the treatment of obesity. Furthermore, administration of both drugs to appropriately selected individuals has been shown to result in attenuation of the manifestations of the Insulin Resistance Syndrome (43,49).

B. Efforts to treat the manifestation of the Insulin Resistance Syndrome

1) Lifestyle—Although macronutrient composition of the diet, by itself, has little or no direct effect on insulin-mediated glucose disposal, a variety of studies have shown that it certainly can impact on the manifestations of the Insulin Resistance Syndrome in the absence of weight loss (50). In this context, some general principles should be kept in mind when treating insulin resistant persons with manifestations of the Insulin Resistance Syndrome. Of greatest importance is the avoidance of low fat-high carbohydrate diets unless weight loss is also occurring. The more insulin resistants individual are, the more insulin they must secrete in order to maintain normal glucose homeostasis. As a consequence, in the

absence of weight loss, manifestations of the Insulin Resistance Syndrome will be accentuated when insulin resistant persons increase the amount of carbohydrate in their diet (50). A simple alternative, and one consistent with efforts to minimize the intake of saturated fat, would be to replace saturated fat with unsaturated fat, rather than with carbohydrate, thus maintaining a moderate carbohydrate intake. Parenthetically, this dietary manipulation is as effective as low fat-high carbohydrate diets in lowering LDL-C concentrations (51,52). Although this general approach will have the greatest benefit in minimizing the untoward manifestations of the Insulin Resistance Syndrome, additional benefit may be gained by increasing intake of soluble dietary fiber, as well as by decreasing intake of highly refined carbohydrates.

2) Pharmacological intervention—In the absence of evidence that there is one drug capable of addressing the entire cluster of abnormalities associated with insulin resistance/hyperinsulinemia, pharmacological treatment at this point is by necessity directed to the individual manifestations of the Insulin Resistance Syndrome, i.e. hypertension, dyslipidemia, etc., that persist despite appropriate changes in lifestyle. It is not appropriate within the context of this document to discuss extensively the pros and cons of the various pharmacological approaches that can help to ameliorate the manifestations of the Insulin Resistance Syndrome, but it is totally relevant that a thorough search be made to both identify and initiate appropriate drug treatment for any of the manifestations of the Insulin Resistance Syndrome that have not responded to lifestyle modifications. There are no evidence-based guidelines to provide therapeutic targets for treatment of the central manifestations of the Insulin Resistance Syndrome, but efforts to obtain values for the lipid, glucose, and blood pressure cut points outlined in Table 3 seem reasonable. Finally, although a high LDL-C concentration is not part of the Insulin Resistance Syndrome, it also seems reasonable to treat hypercholesterolemia aggressively, possibly to the same degree as is recommended for patients with type 2 diabetes (53).

Table 7

Prevalence of Combinations of the 4 Metabolic Abnormalities* of the Insulin Resistance Syndrome†

	Prevalence (%)
One abnormality	
BP	11.4
HDL-C	9.1
TG	5.2
Glucose	3.0
Two abnormalities	
TG, HDL-C	7.2
BP, glucose	5.4
BP, TG	4.6
BP, HDL-C	4.1
HDL-C, glucose	2.0
TG, glucose	1.4
Three abnormalities	
TG, HDL-C, BP	5.8
TG, BP, glucose	3.1
TG, HDL-C, glucose	2.4
HDL-C, BP, glucose	1.5
Four abnormalities	
TG, HDL-C, BP, glucose	4.6

*Values defining an abnormality are shown in Table 3.
†The population includes 3280 individuals, aged 40-74, without diabetes by history or a fasting plasma glucose concentration >126 mg/dL.

CONCLUSIONS

This document has attempted to provide a means of understanding the Insulin Resistance Syndrome and a practical clinical approach to identifying and managing individuals at risk. By necessity, we had to limit discussion to outline form only, especially with regard to treatment. While we have accepted the lipid and blood pressure guidelines from ATP III, we do suggest certain differences from earlier excellent efforts to identify individuals who are insulin resistant and hyperinsulinemic, and at increased risk to develop type 2 diabetes and CVD. These differences may be summarized as follows: 1) The Insulin Resistance Syndrome is used to describe the cluster of abnormalities that are more likely to occur in insulin resistant/hyperinsulinemic individuals. 2) The Insulin Resistance Syndrome is differentiated from type 2 diabetes. 3) BMI, rather than waist circumference, is used as the index of obesity, and viewed as a physiological variable that increases insulin resistance, rather than as a criterion for diagnosis of the Insulin Resistance Syndrome. 4) Ethnicity is introduced as an important risk factor for insulin resistance, and non-Caucasian ancestry identified as increasing risk of the Insulin Resistance Syndrome. 5) Other factors have been identified that increase the risk of developing the Insulin Resistance Syndrome, including a family history of type 2 diabetes, hypertension, CVD, as well as a personal history of CVD, PCOS, gestational diabetes, and acanthosis nigricans. 6) Fasting plasma glucose concentrations are used to identify individuals with type 2 diabetes, and the plasma glucose concentration 2 hours after a 75-g oral glucose load is introduced as a more sensitive measure of risk for the Insulin Resistance Syndrome.

We are supportive of current concepts in medically supervised therapeutic lifestyle change, including concerns about high carbohydrate diets, efforts directed to the treatment of obesity, and strategies for increasing physical activity. Further research into pharmacologic interventions for the treatment of the Insulin Resistance Syndrome appears very promising. We fully concur that the emergence of the Insulin Resistance Syndrome is among the most pressing problems of public health in the developed world, and many diverse talents and resources will need to work together to meet this challenge.

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APPENDIX

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