Dr. Gerald Reaven’s report (1) of the death of the metabolic syndrome may be exaggerated. Whether his obituary relates specifically to the National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) (2) definition of metabolic syndrome or to all attempts at making a clinical definition of the metabolic syndrome is unclear. Regardless, he does a thorough autopsy on the ATP III report and appears to find widespread systemic disease. After reading his postmortem examination, however, one wonders whether he is reporting on the death of the syndrome or rather is dissecting it while it is still alive. The editors of Clinical Chemistry have given me a last chance to resuscitate what appears to be a badly mangled body. In my examination of the corpus, however, I see signs of life. Thanks to advances of modern medicine, it may be possible achieve survival. This is my assigned task.

Of interest is the fact that Dr. Reaven’s sharp blade cuts only into the ATP III definition of the metabolic syndrome. Other definitions escape his knife, specifically those of the WHO (3), the European Group on Insulin Resistance (EGIR) (4), and the American Association of Clinical Endocrinologists (AACE) (5). The definitions put forward by these organizations are similar to those of ATP III, but apparently Dr. Reaven believes that the ATP III is the most flawed of the group. Because I was a member of the team that issued the ATP III criteria, perhaps I can offer a rationale for having done so. Several points can be made in their defense.

Clinical Management of Obesity and Its Metabolic Complications

In 1993, the ATP II report (6) placed increased emphasis on management of obesity to reduce risk for atherosclerotic cardiovascular disease (ASCVD). This emphasis was not widely adopted by practicing physicians, and by all accounts, the problem of obesity in the United States has become progressively worse (7). In an effort to simplify the daunting task of dealing with obese patients in clinical practice, ATP III focused on those overweight/obese persons who exhibit evidence of medical complications. Such persons deserve priority in clinical efforts to prevent the comorbidities of obesity, particularly ASCVD and type 2 diabetes. The concept of the metabolic syndrome appeared to be the best way to identify those persons in greatest need of clinical intervention. According to ATP III, the metabolic syndrome consists of a constellation of “metabolic risk factors” for ASCVD that associate with obesity, namely, atherogenic dyslipidemia, increased blood pressure, increased glucose, a prothrombotic state, and a proinflammatory state. Most individuals with this constellation will be insulin resistant and thus will be at higher risk for type 2 diabetes if they do not already manifest hyperglycemia. Because identification of all of the components of the syndrome is not available in routine clinical practice, the attempt was made to simplify clinical criteria for easy identification of persons most likely to be at risk. Five measures that are commonly present in individuals with the metabolic syndrome were listed as diagnostic criteria: increased waist circumference (abdominal obesity), increased triglycerides, decreased HDL-cholesterol, increased blood pressure, and increased plasma glucose. Available evidence indicates that most persons who have 3 of these 5 abnormalities will have most of the other components of the metabolic syndrome and thus deserve the diagnosis. Once a person is identified as having the metabolic syndrome, efforts can be made to reverse the syndrome as much as possible through lifestyle changes, particularly weight reduction and increased physical activity.

Renewed Emphasis on Long-Term (Lifetime) Risk

Most current recommendations for management of cardiovascular risk factors focus on relatively short-term risk, e.g., 10-year risk for ASCVD events. In accord, ATP III (2) categorizes persons according to 10-year risk, e.g., high risk, moderately high risk, moderate risk, and lower risk. Use of cholesterol-lowering drugs to reduce risk for ASCVD is relegated largely to persons at high risk and moderately high risk. Nonetheless, ATP III recognized that some people who are at lower to moderate short-term

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risk can still be at high long-term risk if they have categorical risk factors (e.g., hypercholesterolemia and hypertension). Such persons can be candidates for drug therapy to reduce long-term risk if their risk factors are severe enough. The primary intervention in lower-to-moderate-risk individuals, however, is through intensification of lifestyle therapies to reduce long-term risk. High on the list in this category are people with the metabolic syndrome who do not already have type 2 diabetes. Hence, lifestyle therapies represent the primary approach in these individuals.

Some investigators and clinicians have surmised that diagnosis of the metabolic syndrome carries with it a relatively high risk for ASCVD in the short term. If so, its presence would indicate the need for drug therapy to reduce risk. However, the metabolic syndrome itself is a poor indicator of absolute short-term risk because it does not contain key determinants of short-term risk, such as age, serum cholesterol, gender, and smoking status. A more accurate predictor of short-term risk is Framingham scoring, which includes all of the major risk factors (8). Attempts to use the metabolic syndrome as a risk assessment tool to estimate short-term risk thus is a clear misuse of the syndrome. Instead, its presence identifies a person with relatively high long-term risk and thus calls for intensified lifestyle therapy. At the same time, if the patient with the metabolic syndrome has a high-risk condition, such as ASCVD or diabetes, drug therapies will be required to supplement lifestyle therapies for the purpose of reducing risk. Drug therapies also may be required if persons without these conditions are found to be at higher risk by Framingham risk scoring.

**Stimulation of Epidemiologic Research**

One unintended consequence of introducing the metabolic syndrome into ATP III was to motivate epidemiologists in the fields of ASCVD and diabetes to examine the contribution of metabolic syndrome to the development of these comorbidities (9–14). Their investigations have helped to define the impact of various combinations of metabolic risk factors on development of ASCVD and diabetes. They have shown clearly that the presence of the metabolic syndrome as a whole carries a substantially higher relative risk for both ASCVD and diabetes than in its absence. Even when short-term risk for these conditions is not increased, a high relative risk translates into a higher long-term risk. These epidemiologic studies thus support the ATP III contention that identification of the metabolic syndrome in clinical practice is worthwhile to promote preventive efforts through lifestyle therapies.

**Stimulation of Basic and Clinical Research**

The metabolic syndrome is a complex disorder. The pathophysiology of the development of multiple metabolic abnormalities in one person is not well understood. Dr. Reaven (15) introduced the bold hypothesis that a state of insulin resistance simultaneously engenders multiple metabolic risk factors. Some investigators now call this constellation of abnormalities by the name “insulin resistance syndrome” (5). There seems little doubt that insulin resistance contributes considerably to development of type 2 diabetes. On the other hand, whether insulin resistance is a direct cause of atherogenic dyslipidemia, increased blood pressure, a prothrombotic state, and a proinflammatory state is less certain. Recent investigators (16, 17) point to excess adipose tissue as a source of several “adipokines” that may contribute to these several metabolic risk factors. In obese persons, adipose tissue output of cytokines, plasminogen activator inhibitor 1 (PAI-1), leptin, and resistin is increased, and adiponectin secretion is impaired. Moreover, adipose tissue in obesity is a source of excess nonesterified fatty acids (NEFAs), which some investigators (18) believe drive many of the abnormalities of the metabolic syndrome, notably insulin resistance in muscle, fatty liver, and atherogenic dyslipidemia. To say that insulin resistance is the cause of all of the metabolic risk factors one would have to expand the definition of insulin resistance to include a host of intracellular signaling abnormalities engendered by excess NEFAs and other adipokines. Thus, the term insulin resistance is a simplifying euphemism that likely fails to capture the complex origins of multiple metabolic risk factors. Some investigators appear to hold the following: whatever the metabolic syndrome is, its cause is insulin resistance. Recently, other investigators (19) have been making a different claim: whatever the metabolic syndrome is, its cause is inflammation. These beliefs in themselves do not convey much understanding of the complex pathophysiology of the metabolic syndrome, but they may nonetheless point to new areas for investigation into the biological mechanisms underlying the metabolic syndrome. Likewise, it can be said that the ATP III definition increased the concept of the metabolic syndrome to a level of clinical urgency that requires greater investment of resources into research on the pathogenesis of the syndrome.

There is no doubt that the pharmaceutical industry has recently shown greater interest in the metabolic syndrome as a target of drug therapy. Because of the complexity of the syndrome, it may not be possible to develop a single drug that will wipe out all of the metabolic risk factors at once. Nonetheless, the process of probing new and different metabolic pathways has been a boon to our understanding of the underlying metabolic pathways that contributes to the field in general.

In conclusion, the concept of the metabolic syndrome represents a powerful hypothesis that unifies the metabolic factors underlying the development of both ASCVD and diabetes. Dr. Reaven (15) played a crucial role in the development of this concept through his synthesis of multiple lines of evidence into a single entity he called “syndrome X”. After another decade of research that provided additional information on the condition, several
guideline panels have come to believe that this concept should be further simplified into a recognizable entity that will facilitate the clinical management of patients. Because of the variable clinical face of the syndrome, there will be continuing debate about the best way to bring the concept into clinical practice. The stimulus provided to the medical community by introduction of the ATP III definition of metabolic syndrome and related definitions nonetheless appears to have justified transforming a theory into a usable clinical tool. It is one of several tools that may help to reduce comorbidities that otherwise will be inevitable because of the expanding prevalence of obesity in the United States and worldwide (20).

References

Counterpoint Just Being Alive Is Not Good Enough

Gerald Reaven

Although Dr. Scott Grundy assures us that the Adult Treatment Panel III (ATP III) version of the metabolic syndrome is still alive (1), the real question is whether its continued existence provides us with any useful informa-
tion. Just being alive is not enough, for as Sportin’ Life points out in Gershwin’s Porgy and Bess, “Methuselah lived 900 years, but who calls it living, when no gal will give in, to him that’s 900 years.”

Does Diagnosing the Metabolic Syndrome Have Clinical Utility?

Before addressing the substance of Dr. Grundy’s comments, I must defend myself against his charge that I have limited my critical comments to the ATP III version of the