A health care crisis of epidemic proportion faces western industrialized societies. From Reaven’s early description of “syndrome X,” both the prevalence and general awareness of what is now known as the metabolic syndrome have risen rapidly. The importance and complexity of the metabolic syndrome as one of the major health care issues currently facing society are eloquently discussed in the present issue of Circulation by Drs Haffner and Taegtmeyer and Reilly and Rader. The consensus opinion expressed by these thought leaders is startling in both magnitude and implication.

Magnitude of the Problem
Although estimates of prevalence are critically dependent on the exact definition used, the metabolic syndrome has reached epidemic proportion. Using the 5 clinically evident diagnostic criteria (abdominal adiposity, hypertriglyceridemia, low HDL, hypertension, and fasting hyperglycemia) set forth by the National Cholesterol Education Program (NCEP), prevalence of the metabolic syndrome currently exceeds 20% of individuals who are at least 20 years of age, and 40% of the population/40 years of age. The NCEP requires that at least 3 of 5 clinical criteria be present for the diagnosis of metabolic syndrome to be made. Furthermore, these clinically evident manifestations most likely reflect only the proverbial “tip of the iceberg.” For example, the authors agree that insulin resistance likely plays a central pathophysiological role in the metabolic syndrome. The clinical prognostic criterion of a fasting blood glucose >110 mg/dL is insensitive as a surrogate measure for underlying insulin resistance as compared with other clinically applicable measures of insulin sensitivity. In addition, the NCEP clinical definition of metabolic syndrome does not incorporate inflammatory or hemostatic variables. Indeed, the incremental adverse prognostic value provided by elevated levels of C-reactive protein in patients with the NCEP diagnosis of metabolic syndrome has been demonstrated and could be explained by proximate pathogenetic roles of innate immunity and inflammation that are common to the cluster of cardiovascular risk factors characteristic of this syndrome. The predictive power of the metabolic syndrome for both coronary heart disease events and the occurrence of new-onset diabetes is enhanced by the presence of an elevated C-reactive protein level. Furthermore, fibrinolytic dysfunction (elevated levels of plasminogen activator inhibitor-1) appears central to the pathogenesis of cardiovascular events for individuals with the metabolic syndrome.

Common Pathogenesis
Drs Haffner, Taegtmeyer, Reilly, and Rader are consistent in identifying insulin resistance as being a central pathophysiological process behind the metabolic syndrome. In addition, they identify innate immunity and inflammation possibly secondary to genetic predisposition, further modified by environmental stimuli, as likely proximate causes for the development of insulin resistance. The implications of this theory for pathogenesis as outlined in the Figure provided by Drs Reilly and Rader is that, in the absence of a shift in the genetic pool, the present spiraling “epidemic” of metabolic syndrome has most likely been triggered by environmental factors, immunity and inflammation. The potential utility of inflammatory measures for contributing to the diagnosis or response to treatment of the metabolic syndrome is evident. Indeed, the limitations of the current clinically based diag-

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From the Carl and Edyth Lindner Center for Research and Education (D.J.K.), Ohio Heart Health Center, Cincinnati, Ohio, and St Luke’s Episcopal Hospital/Texas Heart Institute (J.T.W.), Houston, Tex.
Correspondence to Dean J. Kereiakes, MD, The Lindner Center for Research and Education, 2123 Auburn Ave, Suite 424, Cincinnati, OH 45219.
E-mail lindner@fuse.net

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nostic algorithm for accurately establishing prevalence or prognosis in this syndrome are obvious and should prompt revision.

**A Call for Aggressive Treatment**

Our experts agree that early and aggressive therapy directed at dyslipidemia and insulin resistance, although at present unproven, is an attractive treatment strategy for the metabolic syndrome. In addition to behavioral intervention (weight loss, diet, and exercise), therapy with fibrates, metformin thiazolidinediones, and possibly dual peroxisome proliferator-activated receptor (α and γ) agents may be useful in addressing the central physiological disturbances. Treatment of clinical risk factors (dyslipidemia, hyperglycemia, and hypertension) should be even more intensive than called for by current guidelines based on the additive “global” risk posed for the syndrome itself. At present, no consensus optimal “targets” for LDL, blood pressure, etc, in the treatment of metabolic syndrome have been determined.

**The Future**

The current trends are disturbing. The prevalence of obesity is rising dramatically in an aging population. In the foreseeable future, one half or more persons over 60 years of age will satisfy the current diagnostic criteria for the metabolic syndrome. If markers of inflammation and more exacting measures of insulin resistance are incorporated into the diagnostic algorithm for this syndrome, the scope of the epidemic extends further. Only a concerted effort with focus on dietary patterns and increased physical activity among the young and elderly alike is likely to achieve any modicum of success in countering this burgeoning societal problem. The ramifications with respect to morbidity and mortality associated with the metabolic syndrome and its individual components are clear. The recommendations put forth by Drs Reilly and Rader should be addressed swiftly and effectively. Refine the definition, define distinct pathophysiological components, determine the degree of incremental risk conferred, and identify specific life-style and pharmacological interventions that can be directed toward the primary pathogenetic abnormalities. However daunting these tasks may appear, the dire societal consequences of this syndrome mandate action at government, corporate, and professional society levels to allocate the resources necessary to achieve these goals.

**References**
