WESTERN LIFESTYLE, with its unlimited consumption of high-energy food, has resulted in a pandemic of obesity and increased prevalence of cardiovascular disease. The first observations that overeating and obesity lead to poor metabolic outcomes, including diabetes mellitus, were made in the 1920s (5). In the 1950s, Vague (13) described that abdominal obesity predisposes not only to diabetes but also to atherosclerosis. In the 1970s, Phillips (7) developed the concept of metabolic risk factors for myocardial infarction and described “a constellation of abnormalities,” encompassing glucose intolerance, hyperinsulinemia, hyperlipidemia, and hypertension. In 1988, Reaven (8) proposed insulin resistance as a cornerstone of the metabolic syndrome, which he named Syndrome X. Finally, in the 1990s, metabolic syndrome was widely recognized as a leading risk factor for cardiovascular morbidity and mortality.

There are several definitions for the metabolic syndrome, including the World Health Organization, International Diabetes Federation (www.idf.org), the European Group for the Study of Insulin Resistance, and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (2001). According to the NCEP criteria (6), the metabolic syndrome is identified by the presence of three or more of the following components: 1) abdominal obesity with waist circumference > 40 in. for men and 35 in. for women; 2) serum triglycerides > 150 mg/dl; 3) high-density lipoprotein (HDL) cholesterol < 40 mg/dl in men and < 50 mg/dl in women; 4) blood pressure > 130/85 mmHg; 5) fasting glucose > 110 mg/dl. The prevalence of the metabolic syndrome in the United States exceeds 20% (1, 6). Given a heavy burden on cardiovascular morbidity and mortality, the metabolic syndrome represents one of the most important challenges to public health and biomedical research.

Increased consumption of high-calorie food and sedentary lifestyle are major causal factors for the metabolic syndrome. Nevertheless, over the last few decades it has become evident that some racial or ethnic groups are more prone to obesity, hyperlipidemia, diabetes Type 2, and hypertension (Pima Indians, Pacific Islanders, African-Americans), whereas others demonstrate relative resistance (17). In general, obese women demonstrate a lower prevalence of metabolic abnormalities than men at the same body mass index (14). All of the above suggest that a combination of environmental and genetic factors impact on the risk of developing the metabolic syndrome and, consequently, cardiovascular morbidity and mortality.

Animal models are critical for identifying genetic risk factors for metabolic abnormalities in humans. Mouse models, in particular, are especially useful, since the entire mouse genome is now sequenced, and large numbers of transgenic animals are readily available. Transgenic mice are widely utilized in metabolic research, and a spectrum of genetically obese mice have been developed, including leptin-deficient ob/ob mice, leptin-resistant db/db mice (16), and agouti mice producing agouti-related peptide, which blocks melanocortin receptor 4 (3). Genetically obese mice commonly develop insulin resistance, glucose intolerance, and diabetes Type 2. Multiple transgenic strains have been used to study hyperlipidemia, including mice deficient in apolipoprotein E (ApoE−/−), low-density lipoprotein receptor, and scavenger receptor B1 (a HDL receptor) (4, 9, 15). Mice overexpressing sterol regulatory element binding protein 1 (SREBP-1), a master regulator of lipid metabolism in the liver, have been used as a model of fatty liver and insulin resistance (10). Transgenic mice have enabled the characterization of critical pathways of metabolism and the development of novel concepts for drug development in the treatment of obesity, diabetes Type 2, and hyperlipidemia. However, the human metabolic syndrome is seldom related to a single gene mutation but rather is a polygenic disorder associated with increased susceptibility to high caloric intake. Consequently, an alternative approach to studying transgenic animals with targeted disruption of single genes would be exploring phenotypic traits related to the metabolic syndrome in a range of inbred mouse strains.

In this issue of the Journal of Applied Physiology, Svenson et al. (12) report a comprehensive assessment of genetic susceptibility to metabolic syndrome in inbred mice after a challenge with a high-fat, high-cholesterol diet. The authors utilized the unique resources of the Jackson Laboratory and set up a high-throughput protocol to evaluate female and male mice from 43 inbred strains for 10 traits, including body composition (weight, fat, lean tissue mass, bone mineral density), plasma triglycerides, HDL and total cholesterol, glucose, insulin, and leptin, while mice consumed a high-fat, high-cholesterol diet for 18 wk. This work is a continuation of the ongoing effort of investigators from the Jackson Laboratory and elsewhere to characterize phenotypes of the most commonly used inbred mouse strains within the Mouse Phenome Project (MPP). The MPP already contains over 600 measurements for phenotypes relevant for human diseases (11).

Svenson et al. (12) described a wide range of responses to dietary fat between mouse strains with a significant degree of sexual dimorphism. All strains showed an increase in plasma total cholesterol in response to a high-fat diet in both sexes, whereas responses in HDL cholesterol, plasma triglyceride, and blood glucose varied by sex in many strains. A high-fat diet resulted in remarkable variations between the strains in body weight (3.0-fold for females, 2.8-fold for males), percentage of body fat (2.7-fold among females and 3.7-fold among males), total cholesterol, HDL cholesterol (4.9-fold in females and 14.5-fold in males), triglycerides, insulin (5.6-fold in females and 8.5-fold in males), and especially leptin (13.7-fold in females and 33.6-fold in males), whereas bone mineral density was the least variable trait. The authors identified strains that developed severe obesity on a high-fat diet (AKR/J and KK/HJ) and strains that were protected against obesity (WSB/EiJ); strains that developed severe hypercholesterolemia with a decrease in HDL cholesterol (MOLF/EiJ) and strains that were protected against hypercholesterolemia (CZECHII/EiJ for males and D2 for females); strains that developed severe insulin resistance (KK/HJ) and strains that were protected against insulin resistance (A/J). Furthermore, they identified strains that developed a phenotype with multiple metabolic abnormalities, remarkably similar to the human metabolic syndrome (strains CAST/EiJ, CBA/J, and MSM/Ms). Finally, the authors compared typical normal human reference values with their mouse data and showed that “the mouse data encompass most of the normal or desirable human values and
provided a realistic range of extreme values” (12). Thus Svenson et al. (12) assembled a unique catalogue of murine responses to a high-fat, high-cholesterol diet that will allow future investigators to select an optimal phenotype to model important characteristics of the metabolic syndrome in humans.

What is the relevance of mouse metabolic models for human disease? Indeed, despite high to very high levels of plasma cholesterol, only a handful of inbred mouse strains (C58/J, both sexes; C57BR/cdJ, females; A/J, males) develop significant atherosclerotic lesions (12), which is likely related to high levels of HDL in mice compared with humans (2). As a potential future goal of the MPP, it would be interesting to determine how a high-fat, high-cholesterol diet impacts longevity in various inbred mouse strains. Another natural progression of the work by Svenson et al. would be to identify potential gene candidates responsible for extreme metabolic phenotypes, both predisposing and protecting against metabolic syndrome. Such an approach will eventually allow a targeted search for genetic causes of metabolic syndrome in humans. In summary, the formidable body of work amassed by Svenson et al. (12) is an important advancement in the search for a mouse model of the metabolic syndrome. Svenson et al. have provided a new armamentarium for metabolic researchers, paving a road for the future developments in the prevention and treatment of the metabolic syndrome.

REFERENCES