of a rare form of heritable human obesity. Affected individuals develop marked obesity in childhood as a consequence of increased food intake. Leptin secretion normally follows a circadian pattern, with higher levels during evening and night hours. Loss of leptin secretion has particularly marked effects during these hours, resulting in a phenomenon known as night-eating syndrome, in which patients tend to consume large amounts of food during the night.

Other single-gene defects identified as rare causes of human obesity include loss-of-function mutations in genes encoding carboxypeptidase E, melanocortin-4 or melanocortin-3 receptors, and serotonin-2C or serotonin-1B receptors. Obesity is also a feature of many other genetic disorders in which the specific mechanisms of the obesity are less well understood. These different syndromes may have autosomal dominant, autosomal recessive, or X-linked inheritance patterns, consistent with multiple different genetic causes. Among the best known of these disorders, the Bardet-Biedl syndrome, is an autosomal recessive disorder characterized by obesity and other abnormalities, including hypogonadism in men, mental retardation, retinal dystrophy, polydactyly, and renal malformations. In Prader-Willi syndrome, loss of portions of the long arm of chromosome 15 (q11-13) is associated with obesity, poor muscle tone in infancy, defects in cognition, behavioral abnormalities (irritability), short stature, and hypogonadotropic hypogonadism.

Although known single-gene mutations account for only a small percentage of human obesity, there is evidence for widespread heritable influences in more common forms of human obesity. For example, in twin and adoptee studies, both members of identical twin pairs tend to become obese in concordance with the same weight pattern as their biologic parents, even when raised apart. Metabolic rate, spontaneous physical activity, and thermic response to food seem to be heritable to a variable extent, but the specific genes that contribute to prevalent forms of human obesity have not yet been defined. Genomic analyses in large populations have identified multiple genes or genetic regions in which polymorphisms are associated with obesity risk. These include polymorphisms in or near genes for the melanocortin-4 receptor (a protein involved in appetite suppression pathways in the hypothalamus), brain-derived neurotrophic factor (role in energy balance); the β_3-adrenergic receptor (role in visceral fat accumulation), and peroxisome proliferator-activated receptor-γ2 (PPAR-γ2, a transcription factor involved in adipocyte differentiation. Multiple other sites of genetic variation associated with increased obesity risk have been identified for which potential mechanistic links to obesity are not yet apparent. It is hypothesized that the heritable component of common forms of human obesity derives from the effects of variations in these and many yet unidentified genes acting both additively and synergistically.

Important environmental factors driving the recent increased prevalence of obesity include increased caloric intake (reflecting greater availability of high-calorie, low-cost foods) and decreased energy expenditure (as a consequence of decreased physical activity). Lower socioeconomic status, lower education level, cessation of smoking, and consumption of carbohydrates with a high glycemic index have been identified as specific confounders of obesity. Additional factors that may influence obesity risk include intrauterine growth and nutritional history, levels of reproductive and other hormones, and factors that may alter the feedback between energy intake and expenditure. Ultimately, an increase in total body fat results from energy intake that exceeds energy expenditure. This occurs through the operation of genetic and environmental influences, together with individual behavioral characteristics.

PATHOLOGY OF OBESITY-ASSOCIATED HEALTH RISKS

Adipose tissue is not just a passive depot for lipids. Adipocytes also function as a complex and active endocrine organ with metabolic and secretory products (hormones, prohormones, cytokines, and enzymes) that play a major role in whole-body metabolism. Relationships between obesity and both insulin resistance and endothelial dysfunction (the early stage of atherosclerosis) are mediated through the release of several hormones from adipose tissue. These hormones, designated adipocytokines or adipokines, comprise a group of pharmacologically active low- and medium-molecular-weight proteins that possess autocrine and paracrine effects and are known products of the inflammatory and immune systems. They play an important role in adipose tissue physiology and in initiating metabolic and cardiovascular abnormalities, not only in overweight and obese individuals but also in lean persons with higher visceral fat mass. Adipokines include adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), resistin, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, and monocyte chemoattractant protein-1 (MCP-1). An increased amount of adipose tissue or its disproportionate distribution between central and peripheral body regions is related to altered serum levels of these factors. With the exceptions of leptin and adiponectin, the adipokines are produced both from fat cells and from adipose tissue–resident macrophages in the stromal tissues surrounding fat cells. For unknown reasons, an increase in the amount of body fat is associated with increases in the number of adipose tissue macrophages and their production of cytokines.

Human adiponectin is a relatively abundant, 244-amino-acid polypeptide in plasma, accounting for 0.01% of total plasma proteins. Adiponectin gene expression in adipose tissue is associated with obesity, insulin resistance, and type 2 diabetes (T2DM). Hypoadiponectinemia is more strongly related to the degree of insulin resistance than to the degree of adiposity or glucose intolerance. Genetic polymorphisms may influence the regulation of adiponectin and lead to variations in its levels among different individuals. Several human studies have shown that high adiponectin levels protect against development of T2DM and point to the possible future use of adiponectin as an indicator of diabetes risk. Low plasma concentrations of adiponectin are observed in patients with coronary artery disease (CAD), and lower adiponectin levels have been found in diabetic patients with CAD than in those without CAD. In obesity, a 10% reduction in body weight leads to a significant increase in adiponectin (40% to 60%) in both diabetic and nondiabetic patients. Adiponectin is also involved in the modulation of inflammatory responses through attenuation of TNF-α–mediated inflammatory effects, regulation of endothelial function, and inhibition of growth factor–induced proliferation of vascular smooth muscle cells.

Leptin is a 167-amino-acid adipocyte-derived hormone that circulates in the plasma in free and bound forms. It affects energy balance by activating specific centers in the hypothalamus to