serum albumin. It is caused by diets severely lacking in calories—both protein and nonprotein.

- Anorexia nervosa is self-induced starvation; it is characterized by amenorrhea and multiple manifestations of low thyroid hormone levels. Bulimia is a condition in which food binges alternate with induced vomiting.
- Vitamins A and D are fat-soluble vitamins with a wide range of activities. Vitamin A is required for vision, epithelial differentiation, and immune function. Vitamin D is a key regulator of calcium and phosphate homeostasis.
- Vitamin C and members of the vitamin B family are water-soluble. Vitamin C is needed for collagen synthesis and collagen cross-linking and tensile strength. B vitamins have diverse roles in cellular metabolism.

Obesity

Excess adiposity (obesity) and excess body weight are associated with increased incidence of several of the most important diseases of humans, including type 2 diabetes, dyslipidemias, cardiovascular disease, hypertension, and cancer. Obesity is defined as an accumulation of adipose tissue that is of sufficient magnitude to impair health. As with weight loss, excess weight is best assessed by *the body mass index,* or BMI. For practical reasons, *body weight*, which generally correlates well with BMI, is often used as a surrogate for BMI measurements. The normal BMI range is 18.5 to 25 kg/m^2, although the range may differ for different countries. Individuals with BMI greater than 30 kg/m^2 are classified as obese; those with BMI between 25 kg/m^2 and 30 kg/m^2 are considered overweight. Unless otherwise noted, the term *obesity* herein applies to both the truly obese and the overweight.

Not only the total body weight but also the distribution of the stored fat is of importance in obesity. *Central, or visceral, obesity*, in which fat accumulates in the trunk and in the abdominal cavity (in the mesentery and around viscera), is associated with a much higher risk for several diseases than is excess accumulation of fat diffusely in subcutaneous tissue.

Obesity is a major public health problem in developed countries and an emerging health problem in developing nations, such as India. Globally, the World Health Organization estimates that by 2015, 700 million adults will be obese. In certain countries, obesity coexists with malnutrition in individual families. In the United States obesity has reached epidemic proportions. The prevalence of obesity increased from 13% to 32% between 1960 and 2004, and by 2010, 35.7% of adult in the United States were obese, as were 16.9% of children. Indeed, in 2009, it was estimated that the health care cost of obesity and related diseases had risen to $147 billion annually in the United States, a price tag that appears bound to rise further as the nation's collective waistline expands. The increase in obesity in the United States has been associated with the higher caloric content of the diet, mostly caused by increased consumption of refined sugars, sweetened beverages, and vegetable oils.

At its simplest level, obesity is a disease of caloric imbalance that results from an excess intake of calories that exceeds their consumption by the body. However, the pathogenesis of obesity is complex and incompletely understood. Ongoing research has identified intricate humoral and neural mechanisms that control appetite and satiety. These neurohumoral mechanisms respond to genetic, nutritional, environmental, and psychologic signals, and trigger a metabolic response through the stimulation of centers located in the hypothalamus. There is little doubt that genetic influences play an important role in weight control, but obesity is a disease that depends on the interaction between multiple factors. After all, regardless of genetic makeup, obesity would not occur without intake of food.

In a simplified way the neurohumoral mechanisms that regulate energy balance can be subdivided into three components (Figs. 9-30 and 9-31):

- The *peripheral or afferent system* generates signals from various sites. Its main components are *leptin* and *adiponectin* produced by fat cells, *ghrelin* from the stomach, *peptide YY* (*PYY*) from the ileum and colon, and *insulin* from the pancreas.
- The *arcuate nucleus in the hypothalamus* processes and integrates neurohumoral peripheral signals and generates efferent signals. It contains two subsets of first-order neurons: (1) *POMC* (pro-opiomelanocortin) and *CART* (cocaine and amphetamine-regulated transcripts) neurons, and (2) neurons containing *NPY* (neuropeptide Y) and *AgRP* (agouti-related peptide). These first-order neurons communicate with second-order neurons in the hypothalmus.
- The *efferent system* is organized along two pathways, anabolic and catabolic, that control food intake and energy expenditure, respectively. The hypothalamic system also communicates with forebrain and midbrain centers that control the autonomic nervous system.
- POMC/CART neurons enhance energy expenditure and weight loss through the production of the anorexigenic α-melanocyte-stimulating hormone (MSH), and the activation of the melanocortin receptors 3 and 4 (MC3/4R) in second-order neurons. These second order neurons are in turn responsible for producing factors such as thyroid releasing hormone (TSH) and corticotropin releasing hormone (CRH) that increase the basal metabolic rate and anabolic metabolism, thus favoring weight loss. By contrast, the NPY/AgRP neurons promote food intake (orexigenic effect) and weight gain, through the activation of Y1/5 receptors in secondary neurons. These secondary neurons then release factors such as melanin-concentrating hormone (MCH) and orexin, which stimulate appetite.

Three important components of the afferent system, which regulates appetite and satiety, are leptin, adiponectin, and gut hormones.

Leptin. The name *leptin* is derived from the Greek term *leptos*, meaning "thin." Leptin, a 16-kD hormone synthesized by fat cells, is the product of the *ob* gene. The leptin receptor (OB-R) belongs to the type I cytokine receptor superfamily, which includes the gp130, granulocyte-colony-stimulating factor, IL-2, and IL-6 receptors. Mice genetically deficient in leptin (*ob/ob mice*) or leptin receptors (*db/db mice*) fail to sense the adequacy of fat stores, overeat, and gain weight, behaving as if they are undernourished. Thus, the obesity of these animals is a consequence of the