- Obese persons generally have hypertriglyceridemia and low HDL, both of which increase the risk of *coronary artery disease*. It should be emphasized that the association between obesity and heart disease is not straightforward, and such linkage as there may be relates more to the associated diabetes and hypertension than to weight.
- Obesity is associated with *nonalcoholic fatty liver disease* (Chapter 18). This condition occurs most often in diabetic patients and can progress to fibrosis and cirrhosis.
- *Cholelithiasis (gallstones)* is six times more common in obese than in lean subjects. An increase in total body cholesterol, increased cholesterol turnover, and augmented biliary excretion of cholesterol all act to predispose to the formation of cholesterol-rich gallstones (Chapter 18).
- Obesity is associated with hypoventilation and hypersomnolence. *Hypoventilation syndrome* is a constellation of respiratory abnormalities in very obese persons. It has been called the *pickwickian syndrome*, after the fat lad who was constantly falling asleep in Charles Dickens' Pickwick Papers. *Hypersomnolence*, both at night and during the day, is often associated with apneic pauses during sleep (sleep apnea), polycythemia, and eventual right-sided heart failure (*cor pulmonale*).
- Marked adiposity predisposes to the development of degenerative joint disease *(osteoarthritis)*. This form of arthritis, which typically appears in older persons, is attributed in large part to the cumulative effects of increased load on weight-bearing joints.

Obesity and Cancer

In 2007, the National Cancer Institute estimated that 4% of cancers in men and 7% of cancers in women were attributable to obesity, numbers that can be expected to rise as obesity increases. The clearest associations with increased risk were for cancers of the esophagus, pancreas, colon and rectum, breast, endometrium, kidney, thyroid, and gallbladder. The mechanisms by which obesity promotes cancer development are unknown, but several non–mutually exclusive possibilities have been proposed:

- *Elevated insulin levels*. Insulin resistance leads to hyperinsulinemia (Fig. 9-32), which has multiple effects that may directly or indirectly contribute to cancer. For example, hyperinsulinemia inhibits the production of the IGF-binding proteins IGFBP-1 and IGFBP-2, thereby causing a rise in levels of free insulin-like growth factor-1 (IGF-1). IGF-1 is a mitogen, and its receptor, IGFR-1, is highly expressed in many human cancers. It binds with high affinity to the IGFR-1 receptor, and with low affinity to the insulin receptor, which are also expressed on many cancers. Upon stimulation by IGF-1, IGFR-1 activates the RAS and PI3K/AKT pathways, which promote the growth of both normal and neoplastic cells (Chapter 7).
- Obesity has effects on *steroid hormones* that regulate cell growth and differentiation in the breast, uterus, and other tissues. Specifically, obesity increases the synthesis of estrogen from androgen precursors through an effect of adipose tissue aromatases, increases androgen synthesis in ovaries and adrenals, and enhances estrogen availability in obese persons by inhibiting the production of sex-hormone-binding globulin (SHBG) in the liver (Fig. 9-32).
- As discussed earlier, *adiponectin*, secreted mostly from adipose tissue, is an abundant hormone that is inversely correlated with obesity and acts as an insulin-sensitizing agent. Thus, the decreased levels of adiponectin in obese persons contribute to hyperinsulinemia.
- The *proinflammatory state* that is associated with obesity may itself be carcinogenic, through mechanisms discussed in Chapter 7.

KEY CONCEPTS

Obesity

- Obesity is a disorder of energy regulation. It increases the risk for a number of important conditions such as insulin resistance, type 2 diabetes, hypertension, and hypertriglyceridemia, which are associated with the development of coronary artery disease, as well as certain cancers, nonalcoholic fatty liver disease, and gallstones.
- The regulation of energy balance is complex. It has three main components: (1) afferent signals, provided mostly by insulin, leptin, ghrelin, and peptide YY; (2) the central hypothalamic system, which integrates afferent signals and triggers the efferent signals; and (3) efferent signals, which control energy balance.
- Leptin plays a key role in energy balance. Its output from adipose tissues is regulated by the abundance of fat stores. Leptin binding to its receptors in the hypothalamus increases energy consumption by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons.

Diet, Cancer, and Atherosclerosis

Diet and Cancer

As you will recall from Chapter 7, the incidence of specific cancers varies as much as 100-fold in different geographic areas. It is well known that differences in incidence of various cancers are not fixed and can be modified by environmental factors, including changes in diet. For instance, the incidence of colon cancer in Japanese men and women 55 to 60 years of age was negligible about 50 years ago, but it is now higher than that in men of the same age in the United Kingdom. Studies have also shown a progressive increase in colon cancers in Japanese populations as they moved from Japan to Hawaii and from there to the continental United States. Nevertheless, despite extensive experimental and epidemiologic research, relatively few mechanisms that link diets and specific types of cancer have been established.

With respect to carcinogenesis, three aspects of the diet are of major concern: (1) the content of exogenous carcinogens, (2) the endogenous synthesis of carcinogens from dietary components, and (3) the lack of protective factors.

- Regarding *exogenous* substances, *aflatoxin* is involved in the development of hepatocellular carcinomas in parts of Asia and Africa, generally in cooperation with