conditions in premenopausal women—are associated with a significantly increased risk for type 2 DM. Premenopausal women with DM lose the cardioprotective effect of female sex and have rates of CHD identical to those in males. These women have impaired endothelial function and reduced coronary vasodilatory responses, which may predispose to cardiovascular complications. Among individuals with DM, women have a greater risk for MI than do men. Women with DM are more likely to have left ventricular hypertrophy. Women with DM receive less aggressive treatment for modifiable CHD risk factors than men with DM. In the WHI, CEE plus MPA significantly reduced the incidence of DM, whereas with CEE alone, there was only a trend toward decreased DM incidence.

HYPERTENSION

(See also Chap. 298) After age 60, hypertension is more common in U.S. women than in men, largely because of the high prevalence of hypertension in older age groups and the longer survival of women. Isolated systolic hypertension is present in 30% of women >60 years old. Sex hormones affect blood pressure. Both normotensive and hypertensive women have higher blood pressure levels during the follicular phase than during the luteal phase. In the Nurses' Health Study, the relative risk of hypertension was 1.8 in current users of oral contraceptives, but this risk is lower with the newer low-dose contraceptive preparations. HT is not associated with hypertension. Among secondary causes of hypertension, there is a female preponderance of renal artery fibromuscular dysplasia.

The benefits of treatment for hypertension have been dramatic in both women and men. A meta-analysis of the effects of hypertension treatment, the Individual Data Analysis of Antihypertensive Intervention Trial, found a reduction of risk for stroke and for major cardiovascular events in women. The effectiveness of various antihypertensive drugs appears to be comparable in women and men; however, women may experience more side effects. For example, women are more likely to develop cough with angiotensin-converting enzyme inhibitors.

AUTOIMMUNE DISORDERS

(See also Chap. 377e) Most autoimmune disorders occur more commonly in women than in men; they include autoimmune thyroid and liver diseases, lupus, rheumatoid arthritis (RA), scleroderma, multiple sclerosis (MS), and idiopathic thrombocytopenic purpura. However, there is no sex difference in the incidence of type 1 DM, and ankylosing spondylitis occurs more commonly in men. Women may be more resistant to bacterial infections than men. Sex differences in both immune responses and adverse reactions to vaccines have been reported. For example, there is a female preponderance of postvaccination arthritis.

Adaptive immune responses are more robust in women than in men; this may be explained by the stimulatory actions of estrogens and the inhibitory actions of androgens on the cellular mediators of immunity. Consistent with an important role for sex hormones, there is variation in immune responses during the menstrual cycle, and the activity of certain autoimmune disorders is altered by castration or pregnancy (e.g., RA and MS may remit during pregnancy). Nevertheless, the majority of studies show that exogenous estrogens and progestins in the form of HT or oral contraceptives do not alter autoimmune disease incidence or activity. Exposure to fetal antigens, including circulating fetal cells that persist in certain tissues, has been speculated to increase the risk of autoimmune responses. There is clearly an important genetic component to autoimmunity, as indicated by the familial clustering and HLA association of many such disorders. X chromosome genes also contribute to sex differences in immunity. Indeed, nonrandom X chromosome inactivation may be a risk factor for autoimmune diseases.

HIV INFECTION

(See also Chap. 226) Women account for almost 50% of the 34 million persons infected with HIV-1 worldwide. AIDS is an important cause of death in younger women (Fig. 6e-1). Heterosexual contact with an at-risk partner is the fastest-growing transmission category, and women are more susceptible to HIV infection than are men. This increased susceptibility is accounted for in part by an increased prevalence of sexually transmitted diseases in women. Some studies have suggested that hormonal contraceptives may increase the risk of HIV transmission. Progesterone has been shown to increase susceptibility to infection in nonhuman primate models of HIV. Women are also more likely to be infected by multiple variants of the virus than are men. Women with HIV have more rapid decreases in their CD4 cell counts than do men. Compared with men, HIV-infected women more frequently develop candidiasis, but Kaposi's sarcoma is less common than it is in men. Women have more adverse reactions, such as lipodystrophy, dyslipidemia, and rash, with antiretroviral therapy than do men. This observation is explained in part by sex differences in the pharmacokinetics of certain antiretroviral drugs, resulting in higher plasma concentrations in women.

OBESITY

(See also Chap. 416) The prevalence of both obesity (body mass index ≥30 kg/m^2) and abdominal obesity (waist circumference ≥88 cm in women) is higher in U.S. women than in men. However, between 1999 and 2008, the prevalence of obesity increased significantly in men but not in women. The prevalence of abdominal obesity increased over this time period in both sexes. More than 80% of patients who undergo bariatric surgery are women. Pregnancy and menopause are risk factors for obesity.

There are major sex differences in body fat distribution. Women characteristically have gluteal and femoral or gynoid pattern of fat distribution, whereas men typically have a central or android pattern. Women have more subcutaneous fat than men. In women, endogenous androgen levels are positively associated with abdominal obesity, and androgen administration increases visceral fat. In contrast, there is an inverse relationship between endogenous androgen levels and abdominal obesity in men. Further, androgen administration decreases visceral fat in these obese men. The reasons for these sex differences in the relationship between visceral fat and androgens are unknown. Studies in humans also suggest that sex steroids play a role in modulating food intake and energy expenditure.

In men and women, abdominal obesity characterized by increased visceral fat is associated with an increased risk for CVD and DM. Obesity increases a woman's risk for certain cancers, in particular postmenopausal breast and endometrial cancer, in part because adipose tissue provides an extragonadal source of estrogen through aromatization of circulating adrenal and ovarian androgens, especially the conversion of androstenedione to estrone. Obesity increases the risk of infertility, miscarriage, and complications of pregnancy.

OSTEOPOROSIS

(See also Chap. 425) Osteoporosis is about five times more common in postmenopausal women than in age-matched men, and osteoporotic hip fractures are a major cause of morbidity in elderly women. Men accumulate more bone mass and lose bone more slowly than do women. Sex differences in bone mass are found as early as infancy. Calcium intake, vitamin D, and estrogen all play important roles in bone formation and bone loss. Particularly during adolescence, calcium intake is an important determinant of peak bone mass. Vitamin D deficiency is surprisingly common in elderly women, occurring in >40% of women living in northern latitudes. Receptors for estrogens and androgens have been identified in bone. Estrogen deficiency is associated with increased osteoclast activity and a decreased number of bone-forming units, leading to net bone loss. The aromatase enzyme, which converts androgens to estrogens, is also present in bone. Estrogen is an important determinant of bone mass in men (derived from the aromatization of androgens) as well as in women.

PHARMACOLOGY

On average, women have lower body weights, smaller organs, a higher percentage of body fat, and lower total-body water than men. There are also important sex differences in drug action and metabolism that are