deficient in thiamine may be a major dietary component. In Western nations where the use of thiamine-enriched flour is widespread, clinical thiamine deficiency is limited primarily to alcoholics, food faddists, and patients receiving chemotherapy. Nonetheless, when thiamine stores are measured using the thiamine-pyrophosphate effect (TPPE), thiamine deficiency has been found in 20–90% of patients with chronic heart failure. This deficiency appears to result from both reduced dietary intake and a diuretic-induced increase in the urinary excretion of thiamine. The acute administration of thiamine to these patients increases the left ventricular ejection fraction and the excretion of salt and water.

Clinically, patients with thiamine deficiency usually have evidence of generalized malnutrition, peripheral neuropathy, glossitis, and anemia. The classic associated cardiovascular syndrome is characterized by high-output heart failure, tachycardia, and often elevated biventricular filling pressures. The major cause of the high-output state is vasomotor depression leading to reduced systemic vascular resistance, the precise mechanism of which is not understood. The cardiac examination may reveal a wide pulse pressure, tachycardia, a third heart sound, and an apical systolic murmur. The electrocardiogram (ECG) may reveal decreased voltage, a prolonged QT interval, and T-wave abnormalities. The chest x-ray generally reveals cardiomegaly and signs of congestive heart failure (CHF). The response to thiamine is often dramatic, with an increase in systemic vascular resistance, a decrease in cardiac output, clearing of pulmonary congestion, and a reduction in heart size often occurring in 12–48 h. Although the response to inotropes and diuretics may be poor before thiamine therapy, these agents may be important *after* thiamine repletion, since the left ventricle may not be able to handle the increased work load presented by the return of vascular tone.

Vitamin B_6, B_{12}, and Folate Deficiency (See also Chap. 96e) Vitamin B_6, vitamin B_{12}, and folate are cofactors in the metabolism of homocysteine. Their deficiency probably contributes to the majority of cases of hyperhomocysteinemia, a disorder associated with increased atherosclerotic risk. Supplementation of these vitamins has reduced the incidence of hyperhomocysteinemia in the United States; however, the clinical cardiovascular benefit of normalizing elevated homocysteine levels has not been proved.

OBESITY

(See also Chap. 415e) Obesity is associated with an increased prevalence of hypertension, glucose intolerance, atherosclerotic CAD, atrial fibrillation, obstructive sleep apnea, and pulmonary hypertension, and is associated with increased cardiovascular morbidity and mortality rates. In addition, obese patients have a distinct hemodynamic profile characterized by increased total and central blood volumes, increased cardiac output, and elevated left ventricular filling pressure. The elevated cardiac output appears to be required to support the metabolic demands of the excess adipose tissue. Left ventricular filling pressure is often at the upper limits of normal at rest and rises excessively with exercise, contributing to exertional dyspnea. In part as a result of chronic volume overload, eccentric cardiac hypertrophy with cardiac dilation and ventricular diastolic and/or systolic dysfunction may develop. In addition, altered levels of adipokines secreted by adipose tissue may contribute to adverse myocardial remodeling via direct effects on cardiac myocytes and other cells. Pathologically, there is left and, in some cases, right ventricular hypertrophy and generalized cardiac dilation. Pulmonary congestion, peripheral edema, and exercise intolerance may all ensue; however, the recognition of these findings may be difficult in massively obese patients.

Treatment with angiotensin-converting enzyme inhibitors, sodium restriction, and diuretics may be useful to control heart failure symptoms. Weight reduction, however, is the most effective therapy and results in reduction in blood volume and the return of cardiac output toward normal. However, rapid weight reduction may be dangerous, as cardiac arrhythmias and sudden death owing to electrolyte imbalance have been described.

THYROID DISEASE

(See also Chap. 405) Thyroid hormone exerts a major influence on the cardiovascular system by a number of direct and indirect mechanisms, and not surprisingly, cardiovascular effects are prominent in both hypo- and hyperthyroidism. Thyroid hormone causes increases in total-body metabolism and oxygen consumption that indirectly increase the cardiac workload. In addition, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation (e.g., tachycardia, increased cardiac output); they are mediated at least partly by both transcriptional and nontranscriptional effects of thyroid hormone on myosin, calcium-activated ATPase, Na^+-K^+-ATPase, and myocardial β-adrenergic receptors.

Hyperthyroidism Common cardiovascular manifestations of hyperthyroidism include palpitations, systolic hypertension, and fatigue. Sinus tachycardia is present in ~40% of hyperthyroid patients, and atrial fibrillation is present in ~15%. Physical examination may reveal a hyperdynamic precordium, a widened pulse pressure, increases in the intensity of the first heart sound and the pulmonic component of the second heart sound, and a third heart sound. An increased incidence of mitral valve prolapse has been described in hyperthyroid patients, in which case a midsystolic murmur may be heard at the left sternal border with or without a midsystolic click. A systolic pleuropericardial friction rub (*Means-Lerman scratch*) may be heard at the left second intercostal space during expiration and is thought to result from the hyperdynamic cardiac motion.

Elderly patients with hyperthyroidism may present with only cardiovascular manifestations of thyrotoxicosis such as sinus tachycardia, atrial fibrillation, and hypertension, all of which may be resistant to therapy until the hyperthyroidism is controlled. Angina pectoris and CHF are unusual with hyperthyroidism unless there is coexistent heart disease; in such cases, symptoms often resolve with treatment of the hyperthyroidism.

Hypothyroidism Cardiac manifestations of hypothyroidism include a reduction in cardiac output, stroke volume, heart rate, systolic blood pressure, and pulse pressure. Pericardial effusions are present in about one-third of patients, rarely progress to tamponade, and probably result from increased capillary permeability. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, distant heart sounds, and pleural effusions. Although the signs and symptoms of myxedema may mimic those of CHF, in the absence of other cardiac disease, myocardial failure is uncommon. The ECG generally reveals sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T-wave abnormalities. Chest x-ray may show cardiomegaly, often with a "water bottle" configuration; pleural effusions; and, in some cases, evidence of CHF. Pathologically, the heart is pale and dilated and often demonstrates myofibrillar swelling, loss of striations, and interstitial fibrosis.

Patients with hypothyroidism frequently have elevations of cholesterol and triglycerides, resulting in premature atherosclerotic CAD. Before treatment with thyroid hormone, patients with hypothyroidism frequently do not have angina pectoris, presumably because of the low metabolic demands caused by their condition. However, angina and myocardial infarction may be precipitated during initiation of thyroid hormone replacement, especially in elderly patients with underlying heart disease. Therefore, replacement should be done with care, starting with low doses that are increased gradually.

MALIGNANT CARCINOID

(See also Chap. 113) Carcinoid tumors most often originate in the small bowel and elaborate a variety of vasoactive amines (e.g., serotonin), kinins, indoles, and prostaglandins that are believed to be responsible for the diarrhea, flushing, and labile blood pressure that characterize the carcinoid syndrome. Some 50% of patients with carcinoid syndrome have cardiac involvement, usually manifesting as abnormalities of the tricuspid or pulmonic valves. These patients