in a few weeks. (2) Early-onset doxorubicin cardiotoxicity develops in about 3% of patients during or shortly after a chronic course, relating closely to total dose. It may be rapidly progressive, but may also resolve to good, but not normal, ventricular function. (3) The chronic presentation differs according to whether therapy was given before or after puberty. Patients who received doxorubicin while still growing may have impaired development of the heart, which leads to clinical heart failure by the time the patient reaches the early twenties. Late after adult exposure, patients may develop the gradual onset of symptoms or an acute onset precipitated by a reversible second insult, such as influenza or atrial fibrillation. Doxorubicin cardiotoxicity leads to a relatively nondilated ventricle, perhaps due to the accompanying fibrosis. Thus, the stroke volume may be severely reduced with an ejection fraction of 30–40%, which would be well tolerated in a patient with a larger ventricle typical of other cardiomyopathies with systolic dysfunction. Therapy includes angiotensin-converting enzyme inhibitors and β-adrenergic blocking agents used for other causes of heart failure, with careful suppression of "inappropriate" sinus tachycardia, and attention to postural hypotension that can occur in these patients. Once thought to have an inexorable downward course, some patients with doxorubicin cardiotoxicity improve under careful management to near-normal clinical function for many years.

Trastuzumab (Herceptin) is a monoclonal antibody that interferes with cell surface receptors crucial for some tumor growth and for cardiac adaptation. The incidence of cardiotoxicity is lower than for anthracyclines but enhanced by coadministration with them. Although considered to be more often reversible, trastuzumab cardiotoxicity does not always resolve, and some patients progress to clinical heart failure and death. As with anthracycline cardiotoxicity, therapy is as usual for heart failure, but it is not clear whether the spontaneous rate of improvement is enhanced by neurohormonal antagonists.

Cardiotoxicity with *cyclophosphamide and ifosfamide* generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of *interferon-α* can cause hypotension and arrhythmias. Clinical heart failure occurring during repeated chronic administration usually resolves after discontinuation.

Many small-molecule *tyrosine kinase inhibitors* are under development for different malignancies. Although these agents are "targeted" at specific tumor receptors or pathways, the biologic conservation of signaling pathways can cause these inhibitors to have "off-target" effects that include the heart and vasculature. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include withdrawal of the tyrosine kinase inhibitor (when possible) and substitution with a congener (when available), as well as conventional treatment for heart failure. Prophylactic treatment with beta blockers and angiotensin-converting enzyme inhibitors prior to and during chemotherapy is a topic of ongoing investigation.

Other therapeutic drugs that can cause cardiotoxicity during chronic use include hydroxychloroquine, chloroquine, emetine, and antiretroviral therapies.

Toxic exposures can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cardiotoxicity include hydrocarbons, fluorocarbons, arsenicals, lead, and mercury.

METABOLIC CAUSES OF CARDIOMYOPATHY

Endocrine disorders affect multiple organ systems, including the heart. *Hyperthyroidism and hypothyroidism* do not often cause clinical heart failure in an otherwise normal heart, but commonly exacerbate heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure are a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

Pheochromocytoma is rare, but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations (Chap. 407). Patients with pheochromocytoma often have postural hypotension. In addition to α-adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether *diabetes* and *obesity* are sufficient to cause cardiomyopathy. Most heart failure in diabetes results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes is a typical factor in heart failure with "preserved" ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to *obesity* is generally accepted. In addition to cardiac involvement from associated diabetes, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

Nutritional deficiencies can occasionally cause dilated cardiomyopathy but are not commonly implicated in developed Western countries. *Beri-beri heart disease* due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol, and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very high output heart failure that can later progress to a low output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in *carnitine* metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as *selenium* can cause cardiomyopathy (Keshan's disease).

Calcium is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium repletion. *Phosphate* is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. *Hypophosphatemia* can develop during starvation and early refeeding following a prolonged fast, and occasionally during hyperalimentation. *Magnesium* is a cofactor for thiamine-dependent reactions and for the sodium-potassium adenosine triphosphatase (ATPase), but