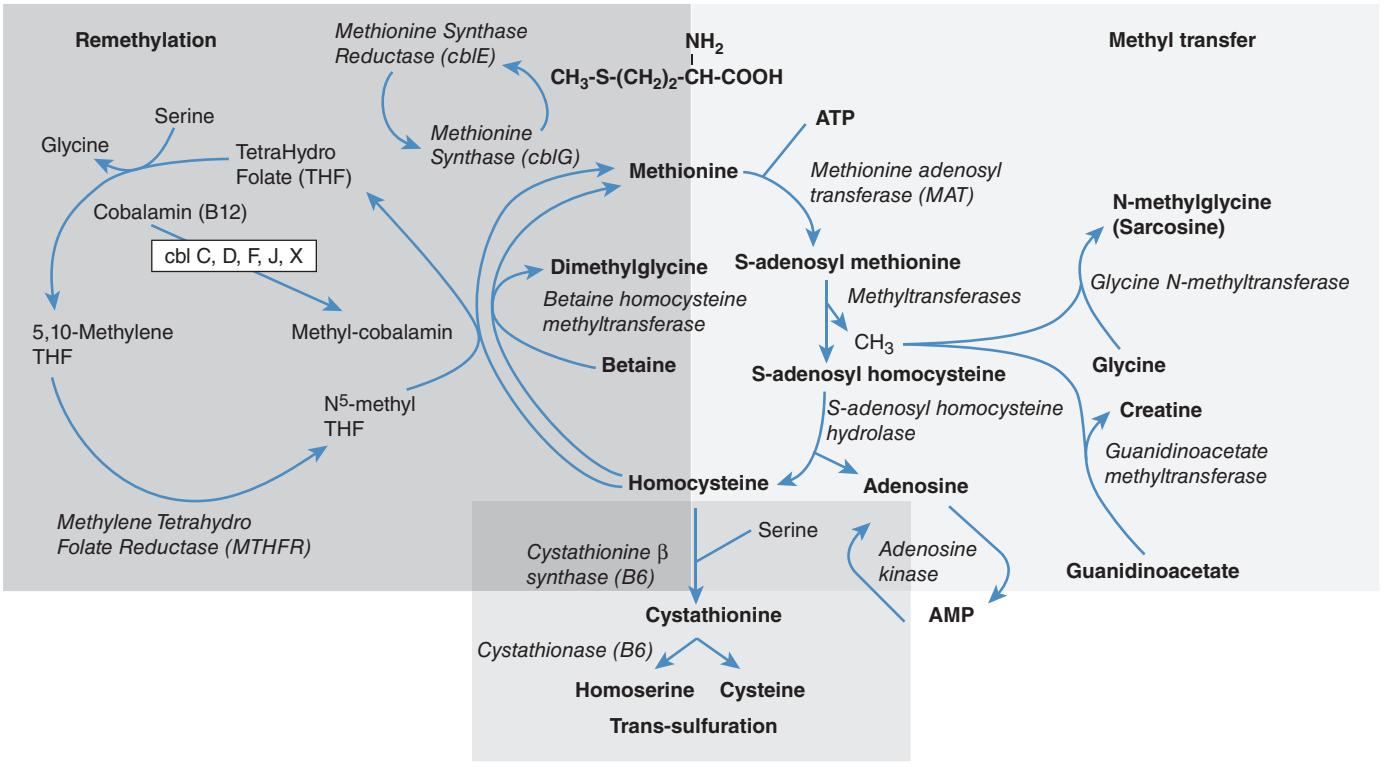

FIGURE 434e-1 Pathways, enzymes, and coenzymes involved in the homocystinurias. Methionine transfers a methyl group during its conversion to homocysteine. Defects in methyl transfer or in the subsequent metabolism of homocysteine by the pyridoxal phosphate (vitamin B_6)-dependent cystathionine β-synthase increase plasma methionine levels. Homocysteine is transformed into methionine via remethylation. This occurs through methionine synthase, a reaction requiring methylcobalamin and folic acid. Deficiencies in these enzymes or lack of cofactors is associated with decreased or normal methionine levels. In an alternative pathway, homocysteine can be remethylated by betaine:homocysteine methyl transferase.

3 and 5 years of age with dislocated optic lenses and intellectual disability (in about half of cases). Some patients develop a marfanoid habitus and radiologic evidence of osteoporosis.

Life-threatening vascular complications (affecting coronary, renal, and cerebral arteries) can occur during the first decade of life and are the major cause of morbidity and mortality. Classic homocystinuria can be diagnosed with analysis of plasma amino acids, showing elevated methionine and presence of free homocystine. Total plasma homocysteine is also extremely elevated (usually >100 μ*M*). Treatment consists of a special diet restricted in protein and methionine and supplemented with cystine. In approximately half of patients, oral pyridoxine (25–500 mg/d) produces a fall in plasma methionine and homocystine concentration in body fluids. Folate and vitamin B_{12} deficiency should be prevented by adequate supplementation. Betaine is also effective in reducing homocystine levels in pyridoxine-unresponsive patients.

The other forms of homocystinuria are the result of impaired remethylation of homocysteine to methionine. This can be caused by defective methionine synthase or reduced availability of two essential cofactors, 5-methyltetrahydrofolate and methylcobalamin (methyl-vitamin B_{12}).

Hyperhomocysteinemia refers to increased total plasma concentration of homocysteine with or without an increase in free homocystine (disulfide form). Hyperhomocysteinemia, in the absence of significant homocystinuria, is found in some heterozygotes for the genetic defects noted above or in homozygotes for milder variants. Changes of homocysteine levels are also observed with increasing age; with smoking; in postmenopausal women; in patients with renal failure, hypothyroidism, leukemias, inflammatory bowel disease, or psoriasis; and during therapy with drugs such as methotrexate, nitrous oxide, isoniazid, and some antiepileptic agents. Homocysteine acts as an atherogenic and thrombophilic agent. An increase in total plasma homocysteine is an independent risk factor for coronary, cerebrovascular, and peripheral arterial disease as well as for deep vein thrombosis (Chap. 291e). Homocysteine is synergistic with hypertension and smoking, and it is additive with other risk factors that predispose to peripheral arterial disease. In addition, hyperhomocysteinemia and folate and vitamin B_{12} deficiency have been associated with an increased risk of neural tube defects in pregnant women. Vitamin supplements are effective in reducing plasma homocysteine levels in these cases, although there are limited effects on cardiovascular disease.

ALKAPTONURIA

Alkaptonuria is a rare (frequency 1:200,000) disorder of tyrosine catabolism in which deficiency of homogentisate 1,2-dioxygenase (also known as *homogentisic acid oxidase*) leads to excretion of large amounts of homogentisic acid in urine and accumulation of oxidized homogentisic acid pigment in connective tissues (*ochronosis*). Alkaptonuria may go unrecognized until middle life, when degenerative joint disease develops. Prior to this time, about half of patients might be diagnosed for the presence of dark urine. Foci of gray-brown scleral pigment and generalized darkening of the concha, anthelix, and, finally, helix of the ear usually develop after age 30. Low back pain usually starts between 30 and 40 years of age. *Ochronotic arthritis* is heralded by pain, stiffness, and some limitation of motion of the hips, knees, and shoulders. Acute arthritis may resemble rheumatoid arthritis, but small joints are usually spared. Pigmentation of heart valves, larynx, tympanic membranes, and skin occurs, and occasional patients develop pigmented renal or prostatic calculi. Pigment deposition in the heart and blood vessels leads to aortic stenosis necessitating valve replacement, especially after 60 years of age. The diagnosis should be suspected in a patient whose urine darkens to blackness. Homogentisic acid in urine is identified by urine organic acid analysis. Ochronotic arthritis is treated symptomatically with pain medications, spinal surgery, and arthroplasty (Chap. 394). Ascorbic acid and protein