

maternal folate status and these fetal abnormalities, although overall, the lower the maternal folate, the greater is the risk to the fetus. NTDs also can be caused by antifolate and antiepileptic drugs.

An underlying maternal folate metabolic abnormality has also been postulated. One abnormality has been identified: reduced activity of the enzyme 5,10-methylene-THF reductase (MTHFR) (Fig. 99-1) caused by a common C677T polymorphism in the *MTHFR* gene. In one study, the prevalence of this polymorphism was found to be higher than in controls in the parents of NTD fetuses and in the fetuses themselves: homozygosity for the TT mutation was found in 13% of cases compared with 5% of control subjects. The polymorphism codes for a thermolabile form of MTHFR. The homozygous state results in a lower mean serum and red cell folate level compared with control subjects, as well as significantly higher serum homocysteine levels. Tests for mutations in other enzymes possibly associated with NTDs, for example, methionine synthase and serine–glycine hydroxymethylase, have been negative. Serum vitamin B₁₂ levels are also lower in the sera of mothers of NTD infants than in controls. In addition, maternal TC II receptor polymorphisms are associated with increased risk of NTD births. However, no studies show that dietary fortification with vitamin B₁₂ reduces the incidence of NTDs.

Cardiovascular Disease Children with severe homocystinuria (blood levels ≥ 100 $\mu\text{mol/L}$) due to deficiency of one of three enzymes (methionine synthase, MTHFR, or cystathionine synthase; Fig. 99-1) have vascular disease, for example, ischemic heart disease, cerebrovascular disease, or pulmonary embolus, as teenagers or in young adulthood. Lesser degrees of raised serum homocysteine and low levels of serum folate and homozygous inherited mutations of *MTHFR* have been found to be associated with cerebrovascular, peripheral vascular, and coronary heart disease and with deep vein thrombosis. Prospective randomized trials of lowering homocysteine levels with supplements of folic acid, vitamin B₁₂, and vitamin B₆ against placebo over a 5-year period in patients with vascular disease or diabetes have not, however, shown a reduction of first event fatal or nonfatal myocardial infarction, nor have these