



**FIGURE 128-1** The role of folates in DNA synthesis and in formation of S-adenosylmethionine (SAM), which is involved in numerous methylation reactions. DHF, dihydrofolate; GSH, glutathione. (Reprinted from AV Hoffbrand et al [eds]: Postgraduate Haematology, 5th ed. Oxford, UK, Blackwell Publishing, 2005; with permission.)

usually marked, and there may be weight loss, diarrhea, or constipation. Glossitis, angular cheilosis, a mild fever in more severely anemic patients, jaundice (unconjugated), and reversible melanin skin hyperpigmentation also may occur with a deficiency of either folate or cobalamin. Thrombocytopenia sometimes leads to bruising, and this may be aggravated by vitamin C deficiency or alcohol in malnourished patients. The anemia and low leukocyte count may predispose to infections, particularly of the respiratory and urinary tracts. Cobalamin deficiency has also been associated with impaired bactericidal function of phagocytes.

#### GENERAL TISSUE EFFECTS OF COBALAMIN AND FOLATE DEFICIENCIES

**Epithelial Surfaces** After the marrow, the next most frequently affected tissues are the epithelial cell surfaces of the mouth, stomach, and small intestine and the respiratory, urinary, and female genital tracts. The cells show macrocytosis, with increased numbers of multinucleate and dying cells. The deficiencies may cause cervical smear abnormalities.

**Complications of Pregnancy** The gonads are also affected, and infertility is common in both men and women with either deficiency. Maternal folate deficiency has been implicated as a cause of prematurity, and both folate deficiency and cobalamin deficiency have been implicated in recurrent fetal loss and neural tube defects, as discussed below.

**Neural Tube Defects** Folic acid supplements at the time of conception and in the first 12 weeks of pregnancy reduce by ~70% the incidence of neural tube defects (NTDs) (anencephaly, meningomyelocele, encephalocele, and spina bifida) in the fetus. Most of this protective effect can be achieved by taking folic acid, 0.4 mg daily, at the time of conception.

The incidence of cleft palate and harelip also can be reduced by prophylactic folic acid. There is no clear simple relationship between maternal folate status and these fetal abnormalities, although overall the lower the maternal folate, the greater 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. 128-1) 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,