The T<sup>677</sup> polymorphism in methylenetetrahydrofolate reductase (MTHFR) affects a large percentage of the population. Depending on the group, anywhere from 2 to 15 percent are homozygous and up to 50 percent are heterozygous for this polymorphism, which affects about one-third of alleles (Frosst et al., 1995; Goyette et al., 1994; Jacques et al., 1996). Subjects homozygous for the polymorphism have lower lymphocyte MTHFR levels, higher plasma homocysteine levels, and a higher risk for vascular disease (Bousney et al., 1995; Clarke et al., 1991; Jacques et al., 1996; Kang et al., 1991; Selhub et al., 1993, 1995). Most of the adverse effects associated with this polymorphism affect the homozygote and heterozygotes behave in most regards similarly to the wild type. Because of this, most studies of this polymorphism have compared the effect of homozygosity with a control group composed of C<sup>677</sup> subjects plus heterozygotes.

The T<sup>677</sup> polymorphism in MTHFR results in a less stable enzyme but does not affect the affinity of substrates for the enzyme (R. M. Matthews, personal communication). Consequently, the metabolic effects of this polymorphism are lower amounts of enzyme activity rather than abnormal enzyme activity. In subjects with poor folate status, the homozygote would be expected to display lower MTHFR activity. However, for subjects with good folate status, the higher folate levels would stabilize the protein and reduce the difference in available enzyme compared with control subjects. It is expected that metabolic and adverse effects of this polymorphism would primarily affect people with poorer folate status. The level of folate
that is sufficient to stabilize the mutant enzyme to the extent that homozygotes would behave identically to controls is not known.

Theoretically, a decreased activity of MTHFR would decrease the rate of formation of methyltetrahydrofolate and consequently homocysteine remethylation. However, this might also be expected to redirect some of the one-carbon flux into other pathways of folate metabolism such as nucleotide metabolism, which could have a positive effect on nucleotide synthesis. Decreased MTHFR activity may explain a recent epidemiological study that reported that homozygotes of poor folate status had a reduced cancer risk compared to control subjects with poor folate status (Ma et al., 1997).

Folate deficiency per se would be expected to adversely affect all metabolic cycles of one-carbon metabolism. However, a metabolic defect in one enzyme may adversely affect one metabolic cycle but may promote another metabolic cycle. Metabolic defects in a single enzyme also greatly complicate the interpretation of normal measures of status. Methyltetrahydrofolate is a very poor substrate for folylpolyglutamate synthetase and has to be demethylated via the methionine synthase reaction before it can be converted to polyglutamates and retained by tissues (Cichowicz and Shane, 1987; Shane, 1989). If folate status is such that MTHFR levels decrease, the rate of formation of methyltetrahydrofolate should be reduced; this would promote folate accumulation by tissues and consequently decrease plasma folate concentrations. A lower plasma folate concentration in such a case would not represent poorer folate status, merely more effective folate accumulation by tissues. Some studies have shown lower plasma folate and increased erythrocyte folate in subjects homozygous for the T677 mutation (van der Put et al., 1996). Folate accumulation by fibroblasts from patients with severe defects in MTHFR is normal or increased above normal (Foo et al., 1982). Other studies, however, have reported low plasma and erythrocyte folate in homozygous subjects (Molloy et al., 1997), which is more difficult to explain in terms of our current understanding of folate metabolism. It is possible that the turnover and catabolism of folate is more rapid with nonmethylfolate. Although this could explain this last observation, there is only very limited data to support such a mechanism.

Currently, there is quite good evidence suggesting that the polymorphism has an adverse effect on homocysteine concentrations in subjects with relatively poor folate status (Selhub et al., 1993). However, there is no substantial evidence suggesting that this effect is not corrected by consuming the Recommended Dietary Allowance for folate that is presented in this report.
REFERENCES


