To the Editor:

The critical review of cobalamin-folate interrelations by Chanarin et al.1 provided an excellent guide through the intricacies of the “methyl trap” hypothesis. However, our interest in inborn defects in the metabolism of sulfur-containing amino acids prompts us to challenge the phrase “the maintenance of near-normal serum methionine levels in children with hereditary MTHFR deficiency” (page 486). The authors are perpetuating an error that crept into the literature and has been repeated by a widely respected reference.2 The truth is that most patients with MTHFR deficiency have significant hypomethioninemia and the two references cited by Chanarin et al are probably unusual cases. Erbe,3 to our knowledge, was the first to emphasize hypomethioninemia in his review of 1979, which pointed out its significance in the causation of the CNS manifestations of MTHFR deficiency. Since then other patients4,5 with the infantile form of the disease have been described as having low blood methionine levels, although it now appears that older children and patients with a milder form of MTHFR deficiency can present with “near normal” values. We have cared for 2 infants with the disease,6 and both had hypomethioninemia. One also had low CSF methionine levels. The other infant worsened after four and one half hours of N20 anesthesia—before the diagnosis was made. In both, the major neuropathology was marked demyelination, which included the spinal cord. Smith et al.7 have recently described subacute combined degeneration in MTHFR deficiency. Despite the fact that infants with the disease also have homocystinemia, low 5 methyl THF, and low neurotransmitter metabolites in the CSF, we suspect that it is the CNS hypomethioninemia that is most devastating. And it is this biochemical parameter that requires early identification and energetic treatment if our dismal record in the therapy of this disorder is to improve.

Incidentally, it should be pointed out that megaloblastic anemia has not been reported in MTHFR deficiency, although the search for it has not always been rigorous.

STANLEY BERLOW

Waisman Center On Mental Retardation and Human Development
University of Wisconsin
1500 Highland Ave
Madison, WI 53706

REFERENCES

Critical review of cobalamin-folate interrelations [letter]

S Berlow