CORRESPONDENCE

To the Editor: Will Increasing Folic Acid in Fortified Grain Products Further Reduce Neural Tube Defects without Causing Harm? Consideration of the Evidence. In the January issue of this journal, Johnston (1) includes our group's recent analysis of data from 1999 to 2002 National Health and Nutrition Examination Survey (2) among studies providing data inconsistent with those linking higher folate status to protection from cognitive dysfunction. Our work is also cited as evidence against the idea that the anemia of vitamin B12 deficiency is cured by high folic acid intake. In fact, our study showed that high folate status was associated with good cognition in seniors with normal vitamin B12 status. However, approximately 4% of seniors who had high folate status combined with low vitamin B12 status, which represented $\frac{3}{4}$ to one million Americans, experienced significantly more anemia and cognitive dysfunction than other seniors, including seniors with low vitamin B12 status alone. Furthermore, although Johnston cites reduction of hyperhomocysteinemia and associated health outcomes as a potential benefit of fortification, a more recent analysis of data collected on vitamin B12-deficient adult participants in the same survey revealed positive associations between serum folate concentrations and circulating levels of homocysteine and methylmalonic acid (2). Although emphasizing the evidence against masking, the importance of which is questionable given the infrequency of anemia in clinically significant vitamin B12 deficiency (3) and the availability of biochemical assays, Johnston ignores a potential adverse effect of high folic acid intake that our data seem to support; namely, exacerbation of the consequences of vitamin B12 deficiency. Serum folate concentrations ≥ 45.4 nmol/L were observed in 43% of survey participants, compared with only 7% of participants in the prefortification National Health and Nutrition Examination Survey III (4). It is thus reasonable to conclude that fortification contributed to the relations we reported.

As noted in our 2005 editorial (5), an evidence-based answer to the question posed in the title to Johnston's paper will require a balance of risks and benefits based on a fair representation of all the evidence.

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Response

To the Editor: Dr. Morris and coworkers have made significant contributions to clinical nutrition, and I am grateful for their endorsement of the importance of scientific evidence in addressing the question posed in my title. The need for balanced, open-minded scientific analysis was the central point of my review. In regard to their specific comments, their reference 2 was not published by the time of submission of the review and was not cited. I did reference an earlier paper (1), which, indeed, showed an association between high blood folate and protection against cognitive decline in those with normal B-12 status, in agreement with a recent randomized controlled trial. However, a subgroup (3.2%) of those with cognitive impairment had high blood folate but low B-12 levels. The authors did not conclude that high folate exacerbated the consequences of B-12 deficiency, and I did not choose to further discuss the folic acid (FA)-cognition relationship beyond citing the references that I could find on both sides of the issue.

I reviewed the evidence against masking the anemia of B-12 deficiency by FA because this led to the Institute of Medicine's setting the tolerable upper level of synthetic FA intake at 1000 $\mu\text{g/d}$ for adults, and at proportionally lower levels for children based on weight. The Morris *et al.* article (1) cited evidence from four recent publications and their own data that favored the conclusion that FA in doses currently consumed does not mask the anemia of B-12 deficiency.

Blood folate levels have risen since the advent of fortification. However, analysis of data from the source used by the authors (1) indicates that almost all of the participants in the "high folate" group took supplements (2). In this subpopula-