0031-3998/08/6304-0450
PEDIATRIC RESEARCH

Vol. 63, No. 4, 2008
Printed in U.S.A.

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 ¾ 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.

Martha Savaria Morris
Nutritional Epidemiology Program
martha.morris@tufts

Paul F. Jacques
Nutritional Epidemiology Program

Irwin H. Rosenberg
Nutrition and Neurocognition Laboratory

Jacob Selhub
Vitamin Metabolism Laboratory

The Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University
Boston, MA 02111

REFERENCES

1. Johnston RB Jr 2008 Will increasing folic acid in fortified grain products further reduce neural tube defects without causing harm? Consideration of the evidence. Pediatr Res 63:2–8
2. Selhub J, Morris MS, Jacques PF 2007 In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci USA 104:19995–20000
3. Carmel R 1996 Subtle cobalamin deficiency. Ann Intern Med 124:338–340
4. Pfeiffer CM, Caudill SP, Gunter EW, Osterloh J, Sampson EJ 2005 Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey1999–2000. Am J Clin Nutr 82:442–450
5. Rosenberg IH 2005 Science-based micronutrient fortificaiton: which nutrients, how much, and how to know? Am J Clin Nutr 82:279–280

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 μg/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-

tion, the contribution from fortified grain products falls well below that obtained from taking supplements (2).

An randomized controlled trial has shown that very low oral doses of B-12 can effectively increase serum B-12 in individuals with age-related B-12 malabsorption (3). It seems important to pursue the possibility that the supplement-taking subgroup with high folate-low B-12 have preclinical pernicious anemia and cannot absorb oral B-12 adequately (1,2). Regardless of folate status, they could benefit from parenteral or high-dose oral B-12. Moreover, if low B-12 status is as common as Morris *et al.* estimate, why are we not mounting a public health campaign to raise B-12 intake in older Americans? The experience and expertise of Morris and workers with B-12 nutrition suggest that they would be effective leaders of such an initiative.

No one wants to harm older Americans while protecting babies, and interested parties should work openly and collaboratively to optimize FA nutrition in individuals of all ages. Posited harms from FA intake should be investigated. But the data show clearly that FA fortification has reduced the rate of serious birth defects. The posited harms carry varying levels of biologic plausibility, but to date none is a proven risk.

Richard B. Johnston Jr
Office of the Dean, C290
University of Colorado School of Medicine
4200 East Ninth Avenue
Denver, CO 80262
richard.johnston@uchsc.edu

REFERENCES

1. Morris MS, Jacques PF, Rosenberg IH, Selhub J 2007 Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 85:193–200. (See also Morris et al. 2007 Reply to Berry RJ, et al. Am J Clin Nutr 86:267–268)
2. Berry RJ, Carter HK, Yang Q 2007 Cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 86:265–267
3. Blacher J, Czernichow S, Raphael M, Roussel C, Chadefaux-Vekemans B, Morineau G, Giraudier S, Tibi A, Henry O, Vayssiere M, Oudjhani M, Nadai S, Vincent J-P, Bodak A, Di Menza C, Menard J, Zittoun J, Ducimetiere P 2007 Very low oral doses of vitamin B-12 increase serum concentrations in elderly subjects with food-bound vitamin B-12 malabsorption. J Nutr 137:373–378