

products over the course of a day would ingest $> 56 \mu\text{g}$ vitamin B-12— ≈ 28 times the recommended dietary allowance (2). Yet the safety of high intakes of vitamin B-12 has been questioned by a study that found an odds ratio of coronary artery disease (CAD) of 1.5 per quartile increase in plasma vitamin B-12 concentration, even when important CAD risk factors, including high-density-lipoprotein and low-density-lipoprotein cholesterol concentrations, were controlled for in the multivariate analysis (3). Obviously, we cannot infer a cause and effect relation from this one study, but we should remain cautious about the effects of ingestion of such large quantities of vitamin B-12 until further studies are performed. As Herbert himself stated in this Journal in 1988, "It will probably turn out eventually that too much vitamin B-12, like too much of anything, is harmful" (4).

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REFERENCES

1. Herbert V, Bigaouette J. Call for endorsement of a petition to the Food and Drug Administration to always add vitamin B-12 to any folate fortification or supplement. *Am J Clin Nutr* 1997;65:572-3.
2. National Research Council. Recommended dietary allowances. 9th ed. Washington, DC: National Academy Press, 1980.
3. Pancharuniti N, Lewis CA, Sauberlich HE, et al. Plasma homocyst(e)ine, folate, and vitamin B-12 concentrations and risk for early-onset coronary artery disease. *Am J Clin Nutr* 1994;59:940-8.
4. Herbert V. Vitamin B-12: plant sources, requirements, and assay. *Am J Clin Nutr* 1988;48:852-8.

Reply to JB Lavine

Dear Sir:

Lavine's claim that the Pancharuniti et al study (1) questioned the safety of high intakes of vitamin B-12 added to grains, in relation to coronary artery disease (CAD), is incorrect. To the contrary, Pancharuniti et al (1) stated, "We found, as have others, that plasma folate and plasma vitamin B-12 concentrations were inversely associated with [plasma homocysteine] Hcy concentrations." High plasma Hcy concentrations promote CAD. They went on to note that, after adjustment for Hcy (which eliminated the Hcy as a risk factor for CAD, a risk factor lowered by vitamin B-12 supplementation), high serum vitamin B-12 in their study population (males aged 30-50 y with CAD) was a marker for CAD, which was explainable, in their words, because, "whereas vitamin B-12 is protective through its influence on Hcy concentration, because it is found in foods such as red meats, its protective influence may be offset by its association with high-risk foods."

Pancharuniti et al (1) are correct. The highly absorbable iron in red meat is an independent risk factor for CAD (2). Had Pancharuniti et al measured serum ferritin and saturation of serum iron-binding capacity, they very likely would have found iron to be the culprit (2) and serum vitamin B-12 to be merely a marker for the real culprit in vitamin B-12-rich foods.

Lavine also ignored the cautionary statement by Pancharuniti et al (1) that their study was limited to white males with early-onset (ages 30-50 y) CAD. "The generalization of these results to other races and to females, as well as to those with later-onset CAD, remains to be determined."

As we stated in our recommendation (3) to which Lavine referred, the major beneficiaries of grains fortified with vitamin B-12 as well as folate will be people who need pharmacologic amounts of vitamin B-12 because of gastric atrophy preventing absorption of physiologic amounts, namely, fertile African American females and Americans of all ethnic groups older than 50 y.

In summary, on careful reading of the papers (1, 3) cited, there is no evidence that adding $25 \mu\text{g}$ vitamin B-12/100 g grain has any downside. In fact, Brantigan (4) noted that his "wife, who had taken folate supplements, developed quite advanced neurologic findings from vitamin B-12 deficiency because of the absence of anemia as an alerting symptom" (ie, she had folate-masked pernicious anemia). In reply, Tucker et al (5) admitted that 16.2% of 694 elderly Framingham Heart Study subjects had early vitamin B-12 deficiency masked by absence of anemia at the approved folate fortification level ($140 \mu\text{g}$ pteroylglutamic acid/100 g grain-cereal product). They found low vitamin B-12 concentrations in 18.5% but low hemoglobin in only 2.3% of the population: 18.5% minus 2.3% equals 16.2% with vitamin B-12 deficiency masked by absence of anemia due to adequate folate.

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REFERENCES

1. Pancharuniti N, Lewis CA, Sauberlich HE, et al. Plasma homocyst(e)ine, folate and vitamin B-12 concentrations and risk for early-onset coronary artery disease. *Am J Clin Nutr* 1994;59:940-8.
2. Herbert V, Shaw S, Jayatilleke E. Vitamin C-driven free radical generation from iron. *J Nutr* 1996;126(suppl 4):1213S-20S.
3. Herbert V, Bigaouette J. Call for endorsement of a petition to the Food and Drug Administration to always add vitamin B-12 to any folate fortification or supplement. *Am J Clin Nutr* 1997;65:572-3.
4. Brantigan CO. Folate supplementation and the risk of masking vitamin B12 deficiency. *JAMA* 1997;277:880 (letter).
5. Tucker KLK, Jacques P, Selhub J. Folate supplementation and the risk of masking vitamin B12 deficiency. *JAMA* 1997;277:880-1 (letter).