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Vitamin B-12 and folic acid supplementation

Dear Sir:

In his editorial in the June 1997 issue of the *AJCN*, Oakley (1) dismisses as mere "speculation" all of the published proof (2-4) that folate supplementation masks pernicious anemia. In addition to those references, we also call his (and the reader's) attention to the just-published paper by Flynn et al (5), delineating that high homocysteine concentrations in elderly whites are due to vitamin B-12 deficiency.

Flynn et al's study (5) of 171 healthy, elderly (mean age 65 y), white volunteers (139 men and 32 women) enrolled in an ongoing longitudinal aging study showed that all had normal serum and red cell folate concentrations, but that the 52 subjects with high homocysteine concentrations had low vitamin B-12 or serum transcobalamin II concentrations (ie, low holotranscobalamin II) (3, 5). Serum transcobalamin II is a surrogate Schilling test for diagnosing inadequate absorption of food vitamin B-12 within a week of the start of subnormal absorption (3). This study (5) provided the final icing on the cake, showing that vitamin B-12 must always be added to any folate fortification or supplement (5, 6).

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Reply to V Herbert

Dear Sir:

I agree with Dr Herbert that it is time to add vitamin B-12 (and more folic acid, too) to enriched grains; however, we differ on the reasons for such enrichment.

There is strong evidence from the Framingham study of widespread cellular deficiency of both folate and vitamin B-12 in the elderly, resulting in elevated homocysteine concentrations, but not usually in anemia or neuropathy. Those in the cohort who consume vitamin supplements with a median of 0.4 mg folic acid and 0.006 mg vitamin B-12 have the lowest plasma homocysteine concentrations and the lowest proportion of occluded extracranial carotid arteries. They also have plasma vitamin B-12 concentrations similar to those of a younger control group. We need vitamin B-12 fortification and more folic acid fortification because this is the most cost-effective means of reducing the incidence of these two cellular deficiencies and markedly reducing homocysteine concentrations in the elderly.

The evidence that homocysteine is harmful continues to mount. The authors of a recently published paper giving results from a large case-control study concluded that an "elevated plasma" total homocysteine concentration "is now established as a strong and independent factor associated with all categories of atherosclerotic disease in both men and women" (1). They noted that folic acid supplementation with a vitamin pill reduces "homocysteine levels in both the fasting state and after methionine loading. . ." They also reported that "Users of supplements containing folic acid, cobalamin or pyridoxine had a relative risk of 0.38 (95% CI, 0.2-0.72) compared with non-users (adjusted for conventional risk factors)."

Nygard et al (2) have added strong new evidence of harm from homocysteine in a prospective study of a large sample of patients with angiographically confirmed coronary artery disease. When they used as the reference group those with a homocysteine concentration $< 9.0 \mu\text{mol/L}$ ($\sim 25\%$ of the sample) they found increasing cardiovascular mortality with increasing homocysteine. Those with a homocysteine concentration $> 20 \mu\text{mol/L}$ had a cardiovascular mortality 9.9 times that of the reference group.

Dr Herbert raises the potential risk from increased consumption of folic acid. It is well documented that patients who have the classic clinical manifestations (anemia, neuropathy, or both) of vitamin B-12 deficiency should be treated with appropriate amounts of vitamin B-12 because if they are not, they may develop neuropathy or have a "pernicious" progression of their neurologic disease. However, there are no controlled studies, including those referenced in Dr Herbert's letter that provide sufficient evidence for me to conclude that folic acid, rather than the absence of proper treatment with vitamin B-12, is harmful to patients with vitamin B-12 deficiency. Similarly, there is insufficient evidence to conclude whether or not patients who consume 0.4 mg folic acid/d are more or less likely to have a timely diagnosis of vitamin B-12 deficiency than are a group of like patients who do not consume supplemental folic acid. Whereas patients with pernicious anemia who consume 0.4 mg folic acid/d may be less likely to develop anemia, I have not seen data that would permit me to conclude that the

presence of anemia leads to a less timely diagnosis of vitamin B-12 deficiency than does the absence of anemia.

Speculation about harm to the elderly from a small increase in consumption of folic acid persuaded the US Food and Drug Administration to limit fortification of "enriched" cereal grain products with folic acid to an amount too low to prevent all folic acid-preventable birth defects. I conclude from the available data that hundreds of the elderly are likely to have unnecessary cardiovascular mortality because their folic acid concentration is not high enough. It is time to move as quickly as possible to add vitamin B-12 to grains and to increase the concentration of folic acid for the benefit of the young and the elderly. In the interim, we should encourage a healthy diet and the consumption of supplemental folic acid and vitamin B-12.

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The views expressed are the author's and do not necessarily represent the policies of the Centers for Disease Control and Prevention.

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Unmetabolized folic acid and masking of cobalamin deficiency

Dear Sir:

Kelly et al (1) raised the possibility that exposure to unmetabolized folic acid could be associated with safety risks. Their suggestion should not be dismissed without further research. However, I suggest that future discussions must include consideration of soluble (plasma) and membrane-bound folate-binding proteins (FBPs) (2), which were neither examined nor discussed in the paper by Kelly et al. Their analysis of oxidized folic acid in serum was performed subsequent to deproteinization and the values presumably represent total unmetabolized folic acid. These data are important as first estimates of exposure to this compound but the concentration of free compared with bound folic acid, folic acid's affinity for FBP, and rate of delivery of free or bound folic acid to membrane-bound FBPs are valid pharmacologic and toxicologic considerations for future clarification. When all aspects of folic acid absorption, transport, and delivery are considered, it is probable that even marginal safety concerns regarding folic acid will be dispelled. Despite their concerns regarding unmetabolized folic acid, Kelly et al clearly support the current fortification program of the US government. I hope that more detailed work can be performed quickly so that more aggressive fortification, as

suggested by some, or use of bolus folic acid can be either avoided or used without concern.

One of Kelly et al's safety concerns, which they describe as "Chief among the risks of exposure to folic acid" is the so-called masking of cobalamin deficiency. This concept of masking the neurologic aspects of cobalamin deficiency has been raised frequently in the folate fortification debate and demands critical reconsideration (3). Is there really evidence that the neurologic signs and symptoms of cobalamin deficiency, which would otherwise be present, are actually caused to be absent or even rendered less severe by use of folic acid or, rather, as I suspect, is it that in a system of number-oriented diagnosis, the probability of picking-up an increased mean corpuscular volume is reduced? We must critically differentiate masking of disease from failure to ascertain, recognize, or associate existing neurologic symptoms. We must also remember that the increased mean corpuscular volume, which has for so long been used as an important diagnostic flag for possible cobalamin deficiency, can also be delayed or prevented by concomitant iron deficiency found frequently in patients with pernicious anemia (4-6). It seems reasonable to suggest that iron deficiency in these patients may then also mask neurologic symptoms. It has been clear for some time that reliance on hematologic indexes as pivotal criteria for identification of possible cobalamin deficiency or its absence is seriously flawed and must be abandoned (7, 8). Cobalamin status cannot be inferred reliably from hematologic data, nor does it need to be. Analysis for total serum cobalamin is readily available and must be used whenever history, symptoms, or increased risk (ie, in the elderly) warrant its frequent and very cost-effective use. I would ask, which is the greatest mask of undiagnosed cobalamin deficiency: use of folic acid or lack of insight into and appreciation of its variable presentation and high prevalence, and respectfully suggest that if the latter situation were addressed aggressively, the former would cease to be an issue. I do concede that some difficulty might continue to exist among those who lack access to or choose not to use health care services. This, however, is a different problem that requires other solutions. Perhaps the suggestion of cobalamin supplementation as presented by Oakley (9) could alleviate deficiency in some of these individuals, with the exception of those having complete loss of intrinsic factor.

In conclusion, I express the opinion that authors, editors, and readers need to critically and carefully use and understand the terms *pernicious anemia* and *cobalamin* (or *vitamin B-12*) *deficiency*. I suggest that the former be used only for autoimmune loss of intrinsic factor or Addisonian pernicious anemia and the latter as a general term that covers other causes such as poor dietary intake or malabsorption for reasons other than pernicious anemia. Although Kelly et al (1) frequently used the term *pernicious anemia*, this is probably, as mentioned in the editorial by Oakley (9), a less common cause of cobalamin deficiency. If masking of cobalamin deficiency by folic acid use is a problem, it surely is a problem regardless of etiology. Nonspecific use of the term *pernicious anemia* has, in my opinion, the risk of drawing attention only to this less frequent cause of deficiency while minimizing the importance of more prevalent nonautoimmune causes of cobalamin deficiency. Inexact terminology will continue to hamper improved under-

standing, identification, and treatment of cobalamin deficiency, regardless of cause.

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Reply to HV Markle

Dear Sir:

Markle raises several interesting suggestions arising from our recent publication on unmetabolized folic acid in serum (1).

1) As he suggests, we regarded our data as a "first estimate" of exposure to unaltered folic acid. It is possible that if it is considered necessary in the future to give folic acid in doses known to produce unaltered folic acid in the serum, the toxicity of folic acid could be further addressed along the lines Markle suggests. We were simply concerned with whether there was an oral dosage below which no unaltered folic acid would ever get into the serum.

2) Markle asks for clarity of definitions, in particular, the idea of masking the neurologic symptoms of cobalamin deficiency. We never suggested that folic acid renders the signs and symptoms of neurologic disease in cobalamin deficiency "either absent or less severe." On the contrary, our group suggested in a previous publication (2) that folic acid may exacerbate the neurologic aspects of cobalamin deficiency. The problem is that the anemia would be cured by folic acid,

leaving the neurologic symptoms to progress unchecked and diagnosed.

3) We agree that mean corpuscular volume should never be used as the main or sole criterion for diagnosing cobalamin deficiency. In this regard we would always advocate the use of the microbiological assay for serum cobalamin (3) preferably with the assay of plasma homocysteine.

4) We agree that pernicious anemia and cobalamin deficiency should not be considered to be synonymous. We consider that pernicious anemia is one example of the various causes of cobalamin deficiency that can occur in the elderly. It is this population whose neurologic system would be most likely at risk when the megaloblastic anemia is masked by folic acid therapy.

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Race, ethnicity, and health: how can greater understanding be attained?

Dear Sir:

The contribution by Himes et al (1) and the editorial by Solomons (2) on the significance of the lesser red cell mass in black West Indians are part of a huge and controversial subject