anyone recorded a value near zero for either linoleic acid or cholesterol—one can only speculate as to how low the lowest values might be.

Given this kind of variability in diet composition it is not surprising that the CV in total serum cholesterol was also of the order of 17%, suggesting individual values as much as 34% above and below the means. Other lipid measurements show similar variability. Although the total serum cholesterol response was found to be significantly higher with the lauric acid diet than with the palmitic acid diet, an inspection of Figure 1 in the paper (2) suggests that this was the result of two or three individuals who showed unusual responses. These might represent individuals with aberrant intakes. Furthermore, although individuals do respond differently to dietary modification, it is highly unlikely that the same diet can cause an increase in serum cholesterol of \( \approx 1 \text{ mmol/L} \) (40 mg/dL) in one subject and a decrease of \( \approx 0.6 \text{ mmol/L} \) (20 mg/dL) in another when compared with a standard diet. This kind of variability in response is consistent with poor dietary control. Hence, the serum lipid responses, at least in some individuals, may have had little to do with the fatty acids under study.

It is unfortunate and misleading when poorly controlled trials are interpreted as quantitative studies.

DM Hegsted

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REFERENCES


Reply to DM Hegsted

Dear Sir:

We are familiar with the concerns inherent to various dietary assessment methods and agree with Hegsted that dietary intake data should always be treated with caution. However, the interpretation of these data by Hegsted is incorrect. Because guidelines for the use of the experimental products were given per day (margarines, bread, biscuits, cheese, and custards) and per week (pie and cake), variation of fat intake between subjects was present by definition because food intake was only recorded for 4 d. The dietary intake data, therefore, should be interpreted on a group level and should not be used to calculate extremes of individual intakes. Although not reported in the paper (1), we have also determined dietary fatty acid intakes by analyzing duplicate portions of all food and drinks consumed during one weekday and one weekend day (2). These data were in excellent agreement with the intakes as outlined. Also, compliance with the experimental diets was confirmed by fatty acid analysis of serum total fatty acids. The percentages of both lauric and myristic acids increased significantly with the lauric acid diet compared with both the palmitic acid and the oleic acid diets. Palmitic acid increased with the palmitic acid diet compared with the lauric acid and the oleic acid diets. Serum oleic acid concentrations were lower and palmitic acid concentrations were higher with the saturated fatty acid diets compared with the oleic acid diet. The three diets did not change the proportion of serum polyunsaturated fatty acid (2).

Nevertheless, between-subject variation was present in cholesterol concentrations. However, this between-subject variation is very common even under strict metabolic ward conditions (3, 4) because diet is not the only determinant of serum lipid and lipoprotein concentrations. Rotterdam et al (5) estimated that the within-person CV of subjects consuming controlled natural diets was \( \approx 5\% \). Therefore, it would not be unusual for the difference between two consecutive cholesterol measurements of one individual to be \( \approx 0.50 \text{ mmol/L} \) even if no treatment is given. Some other important factors such as differences in the subjects’ genetic background could cause the variation in diet responses (6). Consequently, it would have been more suspect if no—what Hegsted calls—“unusual” responses were present.

Thus, given the three independent measurements confirming compliance with the diets and the logical presence of variation in lipid concentrations, we feel that Hegsted’s criticism is not justified.

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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 on 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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REFERENCES


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 μmol/L (~25% of the sample), they found increasing cardiovascular mortality with increasing homocysteine. Those with a homocysteine concentration > 20 μmol/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 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