Reply to J Hathcock

Donald B McCormick

Dear Sir:

The letter by Hathcock, an advocate of the dietary supplement industry, attempts to question the accuracy of the assumptions in my editorial (1) and their relevance to the meta-analysis by Bleys et al (2). In the first place, I made no assumptions but simply related the essence and background of that report. Careful perusal of both my editorial and the report show that Bleys et al extensively reviewed the literature to identify those studies that were randomized controlled clinical trials of vitamin and mineral use in the prevention or treatment of atherosclerosis. Moreover, they provided an appendix of online supplemental data and their search strategy. It was obvious from a review of these data that many of the reports identified had design flaws. No doubt, some of these studies proposed benefits of multivitamin-mineral use, whereas others did not.

The conclusion that Bleys et al reached, based on an analysis of those studies that were screened and deemed properly controlled, provided, according to the authors, "no evidence for a protective effect of antioxidant or B-vitamin supplements on the progression of atherosclerosis, thus providing a mechanistic explanation for their lack of effect on clinical cardiovascular events." Hathcock's claim that the report by Bleys et al "is not an accurate reflection of the literature" because their analysis failed to include findings from the Women's Health Study (3) is clearly off the mark given the conclusions of that study. As noted in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2005* (4), "Overall, this study with its large sample size and long duration does not support the use of vitamin E to prevent CV [cardiovascular] disease or cancer in women." The findings of the HOPE and HOPE TOO trial investigators, which were also summarized in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2005*, were similar: "The investigators concluded that long-term vitamin E therapy does not prevent cancer or cardiovascular events and may even increase the risk of heart failure in individuals with existing disease."

Despite Hathcock's assertions, the meta-analysis remains a useful tool, although certain conclusions are best secured, as in any analysis, when the data set is large. It is additionally informative to consider the results of testing of single micronutrients and combinations of micronutrients, as were summarized in the reports by Alberg et al and by Huang et al in the Conference on Multivitamin/Mineral Supplements, which was held in May of 2006 (5). Alberg et al stated, "With few exceptions, the available evidence from RCTs (randomized clinical trials) of β-carotene, vitamin E, vitamin A (in combination with zinc or β-carotene), or combined riboflavin and niacin indicates no consistent benefit of these single or paired nutrients in preventing cancer, cardiovascular disease, cataract or age-related macular degeneration." Huang et al stated, "The overall strength of evidence on the efficacy of multivitamin/minerals for the prevention of chronic disease is rated as very low."

Certainly, there has been no attempt to misconstrue or prejudge present reports insofar as they represent carefully controlled studies. The number of reports currently available in the literature that disavow the previously hyperbolic claims of benefits from supplements in preventing and treating nondeficiency diseases is growing and should receive careful consideration. Additional studies that provide unbiased interpretations are needed. What is not needed is the disservice of those who, for misguided intentions, mislead the public into practices not based on facts.

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Reply to J Hathcock

Dear Sir:

We thank Hathcock for his interest in our analysis of the currently available literature on vitamin-mineral supplementation and the progression of atherosclerosis (1). After a systematic review of all available randomized controlled trials, we concluded that there is no clear evidence to support the use of antioxidant vitamin and B vitamin supplements to reduce the progression of atherosclerosis.

Hathcock argues that, because of the small number of trials, the statistical power to detect intervention effects was small. For antioxidant vitamins, several trials were of high quality and of sufficient size to identify clinically relevant effects. For instance, the HDL-Atherosclerosis Treatment Study (HATS) tested both simvastatin plus niacin and vitamin E, vitamin C, selenium, and β-carotene in a 2-by-2 factorial design. Simvastatin plus niacin provided a marked angiographic benefit in terms of the progression of atherosclerosis, but antioxidant vitamins did not (2). Likewise, the Study to Evaluate Carotid Ultrasound changes in patients treated with ramipril and vitamin E (SECURE) tested ramipril and vitamin E in a 2-by-2 factorial design. Again, ramipril showed a beneficial effect, but vitamin E did not (3). The overall lack of effect of antioxidants on the progression of atherosclerosis in subjects who did not undergo percutaneous transluminal coronary angioplasty likely did not result from a lack of power.

Although there is less scientific evidence available on the effects of B vitamins on the progression of atherosclerosis and on the effects of vitamin-mineral supplements in patients undergoing percutaneous transluminal coronary angioplasty, our meta-analysis provided a transparent and systematic appraisal of the current evidence. Overall, there is no convincing evidence that vitamin-mineral supplements reduce the progression of atherosclerosis.

Hathcock also cites the results of the Women's Health Study to support a beneficial effect of vitamin E supplements on cardiovascular disease mortality. The conclusions of this study, based on all cardiovascular events, however, were sobering: "These data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women" (4).

Antioxidant vitamin and B vitamin supplements have been extensively studied for a presumed beneficial effect in the prevention of clinical cardiovascular events in large, high-quality, randomized controlled trials, with disappointing results. In view of the randomized evidence, the epidemiologic evidence discussed by Hathcock cannot be used as grounds for supporting the use of these vitamin supplements to prevent cardiovascular disease. Therefore, there is currently no sound evidence to support the use of antioxidant vitamin and B vitamin supplements to prevent clinical cardiovascular events or the progression of atherosclerosis.

None of the authors had a conflict of interest.

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Breastfeeding prevents type 2 diabetes mellitus: but, how and why?

Dear Sir:

The conclusion of the recent systemic review of the published studies that breastfeeding in infancy is associated with a reduced risk of type 2 diabetes, with marginally lower insulin concentrations in later life, and with lower blood glucose and serum insulin concentrations in infancy (1) is interesting.

Human milk contains tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, transforming growth factor β1 and β2 (TGF-β1 and TGF-β2), chemokine growth-related oncogene protein α, monocyte chemoattractant protein-1, IL-8, IL-1 receptor antagonist, soluble forms of the receptors for TNF-α, the antiinflammatory cytokine IL-10, and RANTES (regulated upon activation, normal T cell expressed, and secreted) (2–5). Lysozyme present in human milk suppresses chemotaxis and respiratory burst activity in human polymorphonuclear leukocytes (6). The presence of an ascorbate-like material, uric acid, α-tocopherol, and β-carotene in human milk ensures that phagocyte-produced oxidant molecules cannot persist, and this contributes to the antiinflammatory effects of milk. Thus, human milk exerts antiinflammatory effects and still exerts significant protective action against infections in breastfed infants. In addition, human breast milk is a good source of polyunsaturated fatty acids (PUFAs), especially of γ-linolenic acid (GLA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (7).

Breastfed infants have a significantly higher percentage of DHA and other PUFAs in muscle phospholipids than do nonbreastfed infants. Higher PUFA concentrations in the skeletal muscle membrane are associated with lower fasting plasma glucose concentrations (8), whereas low concentrations of DHA and other PUFAs can result in insulin resistance. We showed that prior oral administration of pure GLA, AA, EPA, and DHA (which are present in human breast milk) prevents alloxan-induced diabetes mellitus by protecting pancreatic β cells from the apoptotic actions of alloxan (9, 10) supports the conclusions made by Owen et al (1).

Early nutrition is an important environmental signal that can induce lifetime effects on metabolism, growth, and neurodevelopment and on major disease processes, such as diabetes mellitus (11). It is likely that breastfeeding ensures adequate nutrition and PUFAs that are essential for brain growth and development (7, 12). Recent studies indicate a significant role for brain insulin receptors in the control of insulin secretion and carbohydrate metabolism (12). It is likely that breastfeeding ensures an adequate supply of PUFAs, which, in turn, will lead not only to the growth and development of brain but also to adequate numbers of insulin receptors in the brain to maintain normal glucose metabolism (13). In view of this evidence, it will be interesting to study whether perinatal supplementation of PUFAs could prevent or postpone the development of diabetes mellitus in high-risk subjects (14, 15).

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