Evidence-based decision making on micronutrients and chronic disease: long-term randomized controlled trials are not enough

Dear Sir:

The State-of-the-Science Conference on Multivitamin/Mineral (MVM) Supplements and Chronic Disease of the National Institutes of Health was held in May 2006; the report of the conference was recently published as a special supplement in this Journal (1). The purpose of the conference was to evaluate the science relevant to the use of MVM supplements in chronic disease prevention. A wide range of epidemiologic, biochemical, and mechanistic evidence is relevant to these goals. However, the planning committee limited the scope of evidence to long-term randomized controlled trials (RCTs) that examined clinical endpoints such as cancer. Such RCTs, the panel said, are "generally considered the gold standard for evidence-based decision making" (2). Of course these RCTs are of major importance, but we strongly criticize the panel's decision to base policy recommendations *only* on evidence from RCTs. This does not make good scientific sense. Policy recommendations should be based on the full range of relevant scientific evidence. Very few long-term RCTs involving MVMs or individual vitamins and minerals have been conducted. In addition, as noted in the conference's summary statement (2), such RCTs are extremely difficult. They must be conducted for decades to detect effects on long-latency disease incidence, and compliance is difficult to maintain, particularly in control subjects who can readily take MVM supplements, as we discussed in reports prepared for the conference (3, 4). Such studies are not likely to yield definitive answers, as the panel itself concluded. The experience of the Women's Health Initiative trial of vitamin D and calcium (5) exemplifies many of these difficulties—choosing an adequate dose for testing, maintaining a sufficient level of adherence, and conducting the trial for a long enough period to provide an adequate test of hypotheses. Indeed, sensible public policy recommendations for not smoking, physical activity, and weight control provide examples of policy decisions that did not require RCTs. Moreover, RCTs were misleading with respect to smoking (6, 7).

Yet, there is a great deal of epidemiologic and mechanistic evidence concerning the effects of micronutrient deficiencies on cancer and other chronic disease endpoints and on biochemical endpoints relevant to chronic disease mechanisms. Instead of a reliance solely on long-term RCTs, all relevant scientific evidence should be taken into account in making supplementation recommendations (3, 8, 9). Short-term RCTs that focus on endpoints such as DNA damage (10) or markers of inflammation (11) are feasible and are more likely to yield informative results. Many other types of experiments in humans and animals, including biochemical, mechanistic, and epidemiologic studies, are also relevant.

The panel excluded this highly relevant body of evidence from consideration, and it came to the conclusion, "[T]he present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease" (2). We contend that, by conveying the impression that long-term RCTs, which are inherently limited, represent the only scientific evidence relevant to "evidence-based decision making," the panel presents a highly biased and misleading picture.

One of us (BNA), in a report originally prepared for this conference but published elsewhere (3), recently discussed the large body of evidence indicating that deficiencies in many micronutrients cause DNA damage, such as chromosome breaks. Some of these micronutrient deficiencies also cause mitochondrial decay with oxidant leakage and cellular aging and are associated with late-onset diseases such as cancer. Ames also introduced a theory that provides a rationale for why micronutrient deficiencies may lead to greater risk of chronic diseases such as cancer. He proposed that DNA damage and late-onset diseases are consequences of a "triage allocation response" to micronutrient scarcity. Episodic shortages of micronutrients were common during evolution. Because natural selection favors short-term survival at the expense of long-term health, Ames hypothesized that short-term survival was achieved by allocating scarce micronutrients by triage, in part through an adjustment of the binding affinity of proteins for required micronutrients. The hypothesis is testable, and, if correct, it predicts that micronutrient deficiencies triggering the triage allocation response would accelerate cancer, aging, and neural decay but would leave critical short-term metabolic functions, such as ATP production, intact.

In conclusion, whereas we agree that policy decisions should be evidence-based and not hasty, we do not agree that the evidence base should be constrained to one type of study—in particular, not to a study design that is inherently limited. Do we really want to wait perhaps decades for results of long-term RCTs, which almost certainly will not provide definitive evidence, while ignoring other relevant evidence involving shorter-term endpoints? An example is provided in the panel's own summary statement (2). In lauding RCTs as the "gold standard for evidence-based decision making," the panel proudly points to the fact that, even though folate was well known to decrease the risk of neural tube defects in animal studies, policy recommendations for folate supplementation to prevent neural tube defects were delayed while authorities waited some years for confirmation from RCTs. One can only wonder how many infants were born with neural tube defects while authorities waited.

Of course, everyone would agree that all persons should be encouraged to eat a good diet, but we are far from achieving this goal, especially among the poor. In most cases, a simple way to improve micronutrient status is to take an MVM. However, even if one eats an ideal diet and takes an MVM, some vitamins can remain below recommended concentrations in some subgroups. For example, the efficiency of absorption of vitamin B-12 decreases with age, and supplements containing more than the Recommended Dietary Allowance are needed to correct the deficiency (12). The ability of the skin to use ultraviolet light to synthesize vitamin D_3 also decreases with age and is inefficient in dark-skinned people. Because dietary sources of vitamin D3 are not plentiful, supplements are recommended for those groups (13).

A significant fraction of Americans have micronutrient intakes below the Estimated Average Requirement. Why establish values such as the Estimated Average Requirement and not take simple steps to eliminate deficiencies? Because MVMs are cheap, readily available, and nontoxic (3), why not recommend that people take an MVM, particularly because much epidemiologic, biochemical, and other evidence points to the need for an adequate supply of vitamins and minerals for optimum function on many levels? At a minimum, taking an MVM is good insurance.

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Reply to BN Ames et al

Dear Sir:

The above letter from Ames et al provides the opportunity for some useful clarification about National Institutes of Health (NIH) State-of-the-Science conferences and about the particular conference in which we participated as panel members. The NIH State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention was convened primarily to reflect on the strength of the available evidence, to identify gaps in the evidence, and to offer recommendations to address those gaps. Ames et al are correct that the planning committee for the conference—as distinct from the panel that authored the conference statement—did restrict the formal evidence review (1) to randomized controlled trials (RCTs). That review, prepared by an Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality, was a resource used by the panel in its preparations for the conference and in its deliberations. However, at the conference itself, several speakers—including Ames and Stampfer—presented results from important observational studies. These studies were considered in, and also were helpful to, the panel's deliberations.

We agree that there are practical challenges to the conduct of RCTs in any arena, in particular an arena as complex as diet, and we made reference to such limitations in the conference statement. Similarly, we noted both the usefulness and the limitations of observational studies (2). The panel's recommendations focused on measures that would enhance the ability to answer the key conference questions by improving the quality and the quantity of the evidence available, including observational studies, and on measures that would improve the safety and reliability of the products marketed to the American public.

It is important to note that our panel was not charged with asking whether vitamins and minerals play a role in human disease—a topic that occupies much of the letter by Ames et al, and for which observational evidence is indeed central—but, as a State-of-the Science Panel, was charged to reflect on the state of the available evidence for a treatment recommendation on the use of vitamins and minerals in the general population. For treatment decisions, the RCT is the established standard. No better proof of this principle can be found than in the RCTs reviewed in our report, which showed serious harm from vitamin ingestion in certain circumstances.

Hence, on the basis of the evidence and its charge, the panel made no recommendation regarding the use of multivitamin/mineral supplements to prevent chronic disease; it only observed that study results were insufficient to compel a recommendation either for or against their use. We were not charged with, and did not consider, other factors that may prompt such recommendations by other groups or persons.

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