Vitamin/mineral supplements: of questionable benefit for the general population

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In the United States today, there is a multibillion dollar industry in dietary supplements with at least a third sold as vitamin/mineral pills and drinks. Though everyone requires small amounts of these essential micronutrients, and supplements are of benefit to some within the population, the considerable majority of people can fulfill their needs with the intake of healthy diets of mixed foods. In addition, the fortification of some processed foods adds extra amounts of several micronutrients, especially those for which there is deemed to be a need in special segments of our population. In spite of this safe and adequate level of intake, there are many who have been led to believe that the frequent ingestion of supplements will be helpful in their efforts to maintain optimal health, live longer, and even prevent or cure non-deficiency diseases. It is the intent of this article to unravel the causes and misconceptions behind this practice and to emphasize that most of the money spent on unnecessary supplementation could be better used for other purposes.

NATURE, OCCURRENCE, FUNCTION, AND NEED FOR MICRONUTRIENTS

There are 13 vitamin groups[1] and as many trace minerals[2] that are essential but cannot be made in our bodies and are therefore derived exogenously, usually from the foods we eat. The discovery, isolation, characterization, functions, and nutritional requirements for these micronutrients were detailed during the past century. Understanding at the molecular level has revealed that most vitamins and trace minerals function after metabolic conversion to cofactors within enzyme systems that catalyze reactions necessary to sustain life, or they serve in important hormonal or epigenetic roles. Because of the turnover in our body that results from catabolism, excretion, and secretion of the micronutrients and their functional forms, we need rather steady intakes of most. Without adequate and relatively frequent intakes, there is an eventual deficiency disease characteristic of each that, when protracted, can often lead to death. Also, most of such micronutrients, when chronically taken in excess, become toxic and, again, in some instances can be lethal. Hence, we need to consume those amounts, usually micro- to milligram quantities per day, that help us maintain growth, health, and normal reproductive function, but avoid such excesses as may be deleterious. Most of the peer-reviewed literature on this subject has been summarized in volumes that collate information within periodically updated chapters that are especially appropriate for nutritional professionals.[3,4] For the considerable majority of individuals, the ingestion of readily available diets that are derived from edible plant and animal tissues wherein the micronutrients also function, is sufficient to supply our needs. A healthy mix of fruits, vegetables, cereals,

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dairy products, and meats is the usual and sufficient way to obtain the recommended dietary allowances (and intakes) that are meant to cover over 97% of our population. These numbers are periodically fine-tuned as new information on requirements for different age and gender groups is obtained and published as dietary reference intakes.[5,6] Given that some processed foods are now enriched with several of the micronutrients, some of which represent special needs for certain segments of our population, it is unlikely that all but a relatively small fraction of the population, such as those suffering from abnormal absorption or metabolism that can result from single-nucleotide polymorphisms in genes, needs any further supplementation. In these cases, supplements may be recommended by health professionals trained to recognize and treat these relatively uncommon, sometimes genetic-based, causes.

MAGNITUDE AND CAUSES OF MICRONUTRIENT SUPPLEMENT USE

There are, unfortunately, extensive writings and pronouncements that go beyond evidence-based science but claim that supplements may be a benefit for all. A review of the diverse substances taken as supplements has been made available in a two-volume encyclopedia put together at the National Institutes of Health.[7] Advertisements in popular magazines and on television abound. The impact on the often-vulnerable public has been huge. The expenditures for total supplements are now estimated to run in the range of 21–25 billion dollars per year with over 8 billion dollars spent in the multivitamin/mineral category; this represents an ongoing increase from the 2000 level.[8] One-half to two-thirds of the adult population in the United States is involved in some use of such supplements. The causes behind this public consumption of vitamin/mineral supplements are several.

First, the lay public tends to trust "natural" treatments over "drug" treatments and wants to take control of their own lives.

Second, we should recognize the tendency of many to want to believe in any suggestion of how to stay young and attractive, even when no hard evidence has been presented for such an elixir. Sometimes our hopes and vanities outstrip common sense. When something has been shown helpful at one level or for one purpose, we tend to extrapolate from sense to nonsense. Apropos this foible of human nature and with specific regard to supplements, Dr Edward Rynearson, a former Director of Mayo Clinic and President of the American Medical Association, stated over a generation ago: "Americans love hogwash. They think if a little is good, more is better."

Third, we too often accept as authoritative, statements from people who are not really expert in what they claim. Misleading self-appointed "experts" have been described by Nobel Laureate Richard Feynman, first in an interview with the BBC and later, in 1999, in his posthumous book *The Pleasure of Finding Things Out* under a subdivision entitled "Science Which is Not Science."[9] Not only are there those who have little or no specific knowledge of micronutrients yet proclaim their virtue beyond fact, there are some who have a confabulation of some facts and false premises. Both types make dogmatic statements meant to convince the reader or listener and are especially convincing to those not educated in the subject. Sadly, some in our health profession, including physicians, have felt compelled to recommend the use of vitamin/mineral supplements when there was insufficient evidence of need or benefit. The American Association of Poison Control Centers reported in 2005 that there were 62,562 cases of exposure to vitamin/mineral preparations that led to 5,972 treatments at healthcare facilities; many were the result of too exuberant intake of supplements recommended by physicians; over 80% were pediatric cases.[10] It is certainly timely that Dr Paul Blumenthal, an MD who is an editor of Medscape, has made a plea that his colleagues should practice evidence-based medicine as Dan Hurley has argued should apply to supplements.[11]

Fourth, we are constantly bombarded by sales propagandists and company spokespersons who hope to garner money from a public that has sometimes opted to spend their wages entirely on themselves rather than such worthwhile matters as education and conservation.[12]

EPIDEMIOLOGICAL OBSERVATIONS VERSUS CONTROLLED CLINICAL TRIALS

A major problem with the information that has been interpreted by researchers who have meant to honestly report their conclusions on supplements has to do with methodology. There is both a conflict between how epidemiologists and biostatisticians evaluate the strength of their data and a general tendency to regard the former as having more weight than is warranted. This problem has been addressed recently by Andreas von Bubnoff in his article "Numbers Can Lie" in the 2008 volume of *The Best American Science and Nature Writing*.[13] Conflicting reports typically arise and certainly can confuse the average person who does not know that epidemiological studies are observational whether they are categorized as cohort, case-control (retrospective), or cross-sectional. They may indicate possible associations but they do not have the weight of randomized, double-blinded, placebo-controlled clinical trials that use sufficient numbers to provide clear answers about a positive or a negative effect. The randomized clinical trial is properly considered by most as the gold standard of medical research. In fairness to the continued use of epidemiological studies, however,

it is impractical (and too expensive) to evaluate the roles of nutrients in clinical trials with slow-developing chronic diseases.

UNLIKELY BENEFITS FROM MICRONUTRIENT SUPPLEMENTS FOR MOST

After a relative surge in publications concluding with claims of positive findings from the use of individual micronutrients or combinations of such nutrients in vitamin/mineral supplements to prevent and even cure diseases not known to relate to nutrient deficiencies, there has been a notable reversal in such claims. Much of this is due to larger studies in which randomized clinical trials were done and where meta-analyses of more data have been possible. An illustrative example is the meta-analysis of randomized controlled trials as related to the progression of atherosclerosis[14] and the editorial that emphasized the finding of no benefit of vitamin/mineral supplements in such cases.[15] The Annual Bibliographies of Significant Advances in Dietary Supplement Research, published by the Office of Dietary Supplements at the National Institutes of Health, are compiled with the assistance of numerous international reviewers of the general supplement literature.[16] It is instructive to see the disclaimers of any certain benefit from numerous micronutrients, toward non-deficiency diseases such as cancers, cardiovascular diseases, respiratory infections, etc. A summary of these reports from the years 2004–2008,[16] with full listings of authors and reference details, is provided in Table 1. They expand upon the conclusions from the 2006 National Institues of Health State-of-the-Science Conference on "Multivitamin/Mineral Supplements and Chronic Disease Prevention,"[17] which are summarized as follows:. "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, significant benefit of these single or paired nutrients in preventing cancer, cardiovascular disease, cataract, or age-related macular degeneration. – [There is] no short-term benefit of folic acid (with or without vitamins B_{12} and B_6) or vitamin B_6 alone in preventing cognitive decline."

In addition to these professional-level reports, it is encouraging to note the increasing numbers of statements aimed at the lay audience. An article on the "myth" of benefits from some of those vitamins and minerals often encountered in supplements was presented in *Reader's Digest* in sensible lay terms.[18] Another example is the report by Rebecca Ruiz on the Netscape "Home & Living" site that included comments solicited from nutritionists.[19] The bottom line was to declare that one could and should get one's needed vitamins and minerals from one's diet and not by taking supplements.

POTENTIAL HARM FROM MICRONUTRIENT EXCESSES

That toxicity can result from high chronic intake of several of the micronutrients has been known for some time.[1–6] With vitamins, there is generally faster clearance of the water-soluble than the fat-soluble types, the latter of which tend to be retained longer in the body. Hypervitaminoses resulting from too much vitamin A and D have been classically defined in earlier literature.[1,3–5] Reports of harm have also been noted for high intakes of some of the water-soluble vitamins, e.g., hepatotoxicity from nicotinic acid as one form of niacin. It has become apparent that more attention needs to be paid to the boundary between what is safe and needed and what becomes harmful. Fortunately, there are biological limits that disallow the attainment of cellular levels of some vitamins that are too high. For example, the solubility of riboflavin is relatively poor, such that intestinal uptake is limited for any single oral dose.[20] The same may be the case with biotin. Thiamin and pantothenic acid are quite soluble and seem relatively innocuous; however, there are reports of toxicity due to large amounts of vitamin B_6.[21]

Though a salutary effect of doubling the adult recommended dietary allowances for folate has been observed with a decrease in the number of neural tube defects in infants born to a subset of women who had a history of such births, there are questions as to the effect of too much folate consumed by others in our population. It has been reported that high folate intake, attributable to supplement use, may increase cancer risk.[22] The authors state, "The benefit of reducing a relatively small number of neural tube defects may be outweighed by the possible negative effects on tumor promotion in a substantial fraction of the population. However, even if the extent of these adverse effects was modest, a large number of individuals with cancer precursors would be affected. We currently lack good quantitative information on the effects of folic acid on the growth of preneoplastic lesions or on carcinogenic progression. Thus a precautionary approach is warranted as we consider whether to recommend an increase in folate status for all." In support of this caveat, it is known that high folate may precipitate or exacerbate the neurological damage of vitamin B_{12} deficiency, while treatment with folic acid results in improvements in the megaloblastic anemia that could be caused by deficiency of either folate or B_{12}. Recently it has been reported that high folate may suppress the two B_{12}-dependent enzymes, namely methionine synthase and methylmalonyl-CoA mutase.[23] This problem has now been found to be reflected in the elevation of homocysteine and methylma-

Table 1 **Summary of select articles reporting disclaimers of any certain benefit from numerous micronutrients, toward non-deficiency diseases such as cancers, cardiovascular diseases, and respiratory infections.**

Year of NIH Annual Bibliography reference[†]	Source publication	Title	Conclusion
2004	Bjelakovic et al., *The Lancet*	Antioxidant supplements for prevention of gastrointestinal cancers: A systematic review and meta-analysis	Antioxidant supplements (A, C, E, selenium, and ß-carotene) might not be helpful for prevention of gastrointestinal cancers and may increase overall mortality
2004	Lee et al., *Am J Clin Nutr*.	Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes?	High doses of supplemental vitamin C could be potentially harmful to older women with diabetes
2004	Meydani et al., *JAMA*	Vitamin E and respiratory tract infections in elderly nursing home residents: A randomized controlled trial	Vitamin E had no significant effect on the incidence or number of days with infection for all upper or lower respiratory tract infections or antibiotic use
2004	Lange et al., *N Engl J Med*	Folate therapy and in-stent restenosis after coronary stenting	Individuals with coronary artery stents should not use folate therapy routinely to reduce the risk of restenosis
2004	Milner et al., *Pediatrics*	Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma	Same as title
2005	Heart Outcomes and Prevention Evaluation (HOPE 1 and 2) Trials, *JAMA*	Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial	Long-term vitamin E therapy does not prevent cancer or cardiovascular events and may increase the risk of heart failure in individuals with existing disease
2005	Lee et al., *JAMA*	Vitamin E in the primary prevention of cardiovascular disease and cancer. The women's health study: A randomized controlled trial	Overall, this study with its large sample size and long duration does not support the use of vitamin E to prevent cardiovascular disease or cancer in women
2006	HOPE 2 Trial, *N Engl J Med*	Homocysteine lowering with folic acid and B vitamins in vascular disease	Findings do not support an association between B vitamin (folate, B_{12}, and B_6) supplementation, reduction in elevated homocysteine levels, and reduced risk for cardiovascular disease in individuals with existing disease
2006	Briefel et al., *J Am Diet Assoc*	Feeding Infants and Toddlers Study; do vitamin and mineral supplements contribute to nutrient adequacy or excess among US infants and toddlers?	Nutrient adequacy can be obtained from dietary intakes, and supplementation with multivitamin and/or multiminerals may not be necessary in infants and toddlers
2006	Rumbold et al., *N Engl J Med*	Vitamins C and E and the risks of preeclampsia and complications	Supplementation with the antioxidant vitamins C and E are not effective in preventing or reducing the risk of preeclampsia in women
2006	Close et al., *Br J Nutr*	Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process	Same as title

Table 1 **Continued**

Year of NIH Annual Bibliography reference[†]	Source publication	Title	Conclusion
2007	Cole et al., *JAMA*	Folic acid for the prevention of colorectal adenomas: A randomized clinical trial	This study raises the concern that folic acid supplementation may increase the risk for colorectal cancer in those with a history of adenomas
2007	Ray et al., *Ann Intern Med*	Homocysteine-lowering therapy and risk of venous thromboembolism: A randomized trial	B-vitamin supplementation is not an effective regimen for the prevention of first or recurrent episodes of venous thromboembolism
2007	Cook et al., *Arch Intern Med*	A randomized factorial trial of vitamins C and E and beta-carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study	This study does not support the regular use of antioxidants in reducing the risk of cardiovascular disease outcomes among women with risk factors for cardiovascular disease
2008	Balk et al., *Arch Intern Med*	Vitamin B_6, B_{12}, and folic acid supplementation and cognitive function	There is no adequate evidence of an effect of these vitamins alone or in combination on cognitive function testing in people with either normal or impaired cognitive function
2008	McMahon et al., *J Nutr*	Lowering homocysteine with B vitamins has no effect on blood pressure in older adults	Same as title
2008	Sawka et al., *Arch Intern Med*	Randomized clinical trial of homocysteine level-lowering therapy and fractures	Though hyperhomocysteinemia is associated with an increased risk of skeletal fractures, findings do not support the use of routine supplementation with folic acid and B vitamins for the primary prevention of fractures among middle-aged and elderly community-dwelling adults

[†] Data from the *Annual Bibliography of Significant Advances in Dietary Supplement Research* publications from the Office of Dietary Supplements at the National Institutes of Health.[16]

lonate and the lower holotranscobalamin in older adults with elevated plasma folate.[24] Further, high folate has been reported to cause a specific and significant down-regulation of its own uptake in intestinal and renal cells.[25] Also, folate must be converted in the body to its tetrahydro form before becoming coenzymatically active; the reduction requires catalysis by dihydrofolate reductase, the activity of which in the human is slow and limited by saturation at high levels of the vitamin.[26] Most recently it has been reported that supplementation with folic acid during late pregnancy and early childhood is associated with an increased risk of asthma.[27]

Arguments to avoid excess intakes of trace minerals may be even stronger because the cationic metal salts, e.g., copper (Cu^{++}), zinc (Zn^{++}), and iron (Fe^{++}), exhibit narrow ranges between benefit and toxicity. Damage from excess levels of the inorganic anions, iodide and fluoride, are also documented.[2,4,6] Selenosis from the intake of too much selenium, usually as selenite, continues to be a problem. A juice containing high levels of selenium was claimed to be a healthy vitamin/mineral supplement, but it led to toxic manifestations and death of those who drank it.[28] From all of the above, it is clear that more attention must be paid to safe upper limits, both for acute and chronic intakes of micronutrients. At least the current recommended nutrient intakes now take such upper limits, when known, into account. Different functions and the reactions that depend upon cofactors have different kinetic reflections, but the argument to have such a high intake of a cofactor so as to saturate the one with the highest Michaelis-Menten constant (Km), as implied by some,[29] ignores the many cases in which such high, saturating levels of a cofactor for a given reaction is inhibitory for another reaction dependent on the same cofactor but at lower concentrations. Certainly, more information is needed before recommending supplements to a broad population group without being certain that one is doing more good than harm.

CONCLUSION

Clinical signs of insufficiency of a micronutrient, whether vitamin or trace element, may not appear until deficiency has advanced and they may be difficult to interpret, especially where there are multiple insults. Biochemical index measurements are more specific for a particular micronutrient and they can detect mild, subclinical deficiency, which reflects suboptimal nutrition, the continuance of which leads to increased risk of future clinical deterioration. Hence, biochemical measurements can serve as early indicators of the need to increase intake of a given micronutrient, by supplementation when appropriate, and help to clarify the etiology of deficiency pathologies with multiple causation.

When there is neither biochemical nor clinical evidence for supplement need, the current US recommended dietary allowances (or reference daily intakes) suffice for almost all people. This applies not only for the avoidance of deficiency diseases but should also be considered in the, not infrequent, misuse of micronutrients to treat non-deficiency diseases where there is not secure evidence of benefit from randomized, controlled clinical trials in addition to epidemiological indications.

Sufficient regulation of the supplement industry has been difficult to achieve. The US Food and Drug Administration still operates under the Dietary Supplement and Education Act of 1994, which allows manufacturers not to register products or get approval before producing or selling them; however, they are responsible for insuring safety.[30] The problem, then, is that the FDA continues to regulate supplements as foods and not impose the more stringent laws concerning drugs. The FDA must prove harm of supplements while manufacturers must prove safety for new food additives. Thus, supplement manufacturers can market, sell, and obtain substantial profit on a supplement with efficacy and/or safety issues. This weakness in the system leads to what has been called "American Roulette."[31] It now devolves upon the Federal Trade Commission to help regulate supplement advertising. Where untruthful claims that supplements can prevent or cure non-deficiency diseases are made by manufacturers and dealers, the FTC can pursue legal action. A recent article on the US Food and Drug Administration's procedures for evaluating the scientific evidence for health claims summarizes the current situation and notes that the FDA has issued a guidance document entitled "Evidence-Based Review System for the Scientific Evaluation of Health Claims."[32]

The continued and important advice for the public is to get their essential micronutrients from foods when possible. The use of supplements should be sparing and best decided in consultation with professionals. The public may additionally benefit from a more careful examination of the excess nutrients consumed in fortified foods, cereals, and vitamin-"enhanced" products.

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