COMMENTARY

Battling Quackery

Attitudes About Micronutrient Supplements in American Academic Medicine

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THROUGHOUT THE 20th century American academic medicine has resisted the concept that supplementation with micronutrients might have health benefits. This resistance is evident in several ways: (1) by the uncritical acceptance of news of toxicity, such as the belief that vitamin C supplements cause kidney stones; (2) by the angry, scornful tone used in discussions of micronutrient supplementation in the leading textbooks of medicine; and (3) by ignoring evidence for possible efficacy of a micronutrient supplement, such as the use of vitamin E for intermittent claudication.

Part of the resistance stems from the fact that the potential benefits of micronutrients were advanced by outsiders, who took their message directly to the public, and part from the fact that the concept of a deficiency disease did not fit in well with prevailing biomedical paradigms, particularly the germ theory. Similar factors might be expected to color the response of academic medicine to any alternative treatment.

In *The Crime of Galileo*, historian Giorgio de Santillana[1] presents a revisionist view of the great scientist's struggle with the Catholic church. According to de Santillana, Galileo's crime was not his propounding a heliocentric universe; it was that he wrote in Italian; he communicated his revolutionary ideas about astronomy directly to the public. Previous scientists wrote in Latin, limiting their audience to other scholars. Within this small community, controversial ideas could be entertained. Copernicus' proposal of a heliocentric universe 70 years before Galileo's treatises had elicited no attempts at suppression by the church. The 17th-century church represented the intellectual establishment, and Galileo's persecutors included some of the finest minds of his time. Galileo was punished not for writing heresy, not for threatening paradigms, but for bypassing the intellectual establishment and taking his exciting ideas directly to the people. The establishment, threatened not so much by his ideas as by his methods, did what it could to destroy his credibility.

In addition, Galileo did not respect professional boundaries. He was a mathematician, and yet his writings dealt with phenomena considered within the purview of philosophers, a profession of considerably higher status than mathematics.[2] Thus, he was considered a usurper as well as a popularizer. In what follows we argue that the reaction of academic medicine to the concept of micronutrient supplementation can best be understood in light of the foregoing description of Galileo. Our thesis is that throughout much of the 20th century, American academic medicine was resistant to the concept that micronutrient supplementation might prove beneficial, and that the cause of this resistance was similar to that which faced Galileo. This resistance is evident in several ways: (1) by uncritical acceptance of bad news about micronutrient supplements; reports of toxic effects were rarely questioned and widely quoted; (2) by the scornful, dismissive tone of the discussions about micronutrient supplementation in textbooks of medicine, a tone avoided in most medical controversies; and (3) by the skeptical reaction greeting any claim of efficacy of a micronutrient, relative to other therapies; indeed, most claims were simply ignored.

Note that in each of the areas mentioned above we examine the reaction to micronutrients relative to other therapies. It is not proof of bias to be concerned about toxicity or to be skeptical of claims of efficacy. Bias occurs when concern and skepticism are applied selectively. Also note that we are not proposing to prove that any particular micronutrient supplement is indeed efficacious. Some readers of earlier drafts of this article have concluded that we are apologists for megavitamins. We are not. Rather, the vitamin controversy is one of a series of examples we have used to discuss the forces that influence medical practice other than those stemming directly from scientific discovery.[3-7]

Herein we rely on the multiple editions of 2 major American medical textbooks: *A Textbook of Medicine*[8] and *Principles of Internal Medicine*.[9] Each has been published in 12 different editions between 1950 and 1992. They can be presumed to represent established opinions and can be used to sample how medical opinion changes over time.[3]

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UNCRITICAL ACCEPTANCE OF NEWS OF TOXICITY: THE EXAMPLE OF HIGH-DOSE VITAMIN C

To illustrate the uncritical acceptance of bad news, we focus on the discussion of one particular toxic effect—kidney stones resulting from megadose vitamin C.

It is well known that high-dose ascorbate ingestion can cause kidney stones.[10-13] In a casual survey of 20 of our physician colleagues, all were aware of the association. But where does this common knowledge come from? A search of the medical literature found no articles in refereed journals reporting instances of high-dose vitamin C causing kidney stones. Instead, review articles cite book chapters that in turn cite abstracts, letters, and other review articles. Take, for example, a 1984 article entitled "Toxic Effects of Water-Soluble Vitamins"[13] that noted that excessive intake of vitamin C may cause kidney stones and cited 7 references to buttress that statement.[14-20] Of these 7 citations, 5 were textbooks or monographs,[14,15,17-19] 1 was a letter to the *Lancet*,[20] and 1 was a case report not related to either ascorbate or kidney stones.[16] Of the 5 books, 2[15,18] cite a total of 2 additional references to substantiate the claim that high-dose vitamin C causes kidney stones; one was a letter[21] and another a chapter.[22] This chapter in turn cites the same *Lancet* letter[20] and an article in the *Medical Letter*,[23] which is without citations. Nowhere in the trail of citations is there related any fundamental information on whether or how frequently high-dose vitamin C leads to kidney stones. Instead, authors simply make the statement that vitamin C may cause kidney stones and as proof cite other authors who have said the same thing.

What is the actual evidence about vitamin C intake and kidney stones? In 3 case-control studies[24-26] there was no clear association between ascorbate intake or excretion and stone formation. In a prospective observational study[27] of 45 000 men with no history of kidney stones, those men consuming 1500 mg or more of ascorbate daily from diet and supplements had 78% the rate of kidney stone formation of those consuming less than 250 mg daily. This reduction was not statistically significant, but certainly does not support the idea that high-dose ascorbate increases the risk of kidney stones.

The story of vitamin C and kidney stones is not unique. A major component of medical writing on vitamin supplements focused on toxic effects,[10-13] under such titles as "The Vitamin Craze"[10] and "Toxic Effects of Vitamin Overdosage."[11] The 1987 and 1991 editions of Harrison's[9] contain the statement that " . . . disorders of vitamin excess may now be more common than vitamin deficiency." Once again, no evidence is cited to support this statement.

SCORNFUL, DISMISSIVE TONE: THE EXAMPLE OF DAILY MULTIPLE VITAMIN SUPPLEMENTATION

In Harrison's the practice of routine use of multiple vitamins was condemned in the 1950s, 1960s, and 1970s. The following are a few representative quotations:

> The [recommended daily] allowances can be met by ingestion of a variety of readily available foods without supplementation emphasis in original . . . the present custom of massive vitamin supplementation on the part of the American public . . . may lead to carelessness in the selection of foods, with resultant amino acid or mineral deficiencies . . . Failure to understand these principles has resulted in much useless supplementation of patients with a great variety of preparations containing vitamins" (1950, 1954, 1958, and 1962 editions).

> . . . the indiscriminate use or "routine" prescription of vitamin preparations is indefensible, it is poor medical practice . . . " (1962 edition).

> This practice [prescription of multiple vitamins] is undesirable in three counts. It is wasteful; the use of unnecessary medication is to be deplored; and such use of vitamins lulls many patients and a few doctors into neglecting needed diagnostic studies. . . . well people do not need supplemental vitamins in their diets. . . . There is no justification for the widespread marketing of multivitamins to families for their purported value in preventing colds or infections. This effect cannot be documented. The tendency among food merchants to increase the vitamin content of breakfast cereals to therapeutic levels is an insidious marketing device that cannot be justified (1970 edition).

The attitude toward supplementation with multiple vitamins in Cecil's[8] was more complex, evolving over time. The editions published prior to 1960 contained positive statements, for example: "even a liberal well-balanced diet should be supplemented with all the vitamins known to be essential to human nutrition" (1944, 1947, 1951, 1955, and 1959 editions).

In 1963 the positive comments were eliminated, and the treatment of multiple vitamin supplements became similar to that in Harrison's. For example: "For normal persons consuming foods of a normal diet, multivitamins are not necessary . . . the use of preparations containing not only a number of vitamins but also several minerals is poor medical practice" (1963 edition).

Once again, let us review some of the words: "massive, carelessness, useless, indiscriminate, false, indefensible, wasteful, insidious, unnecessary, deplored, and poor medical practice." Over the last several decades there have been many areas of medical practice about which uncertainty and controversy exist, and these are well covered in the various editions of these 2 textbooks; they include the drug treatment of hyperlipidemia and hyperglycemia, surgical vs medical treatment of angina, and indications for tonsillectomy or hysterectomy. But in none of these discussions does one encounter the contemptuous descriptions found in the discussions of multiple vitamins.

IGNORING CLAIMS OF EFFICACY: THE EXAMPLE OF VITAMIN E FOR INTERMITTENT CLAUDICATION

The proposal that vitamin E functioned as an antioxidant in vivo was first raised by several groups of investigators in the early 1940s, and this hypothesis received considerable support from experimental evi-

dence.[28] The easy availability of vitamin E formulations led to considerable human experimentation, much of it self-experimentation, looking for beneficial effects in a wide variety of diseases. A prime example is the use of vitamin E for intermittent claudication.

Exercise-induced claudication of the legs was first described by Erasistratus in the fourth century BC.[29] In modern literature Charcot[30] clearly defined the syndrome and named it intermittent claudication. Medical textbooks throughout the 20th century describe its clinical presentation, course, etiology, and treatment. During the 1940s and 1950s, several clinicians published reports that high-dose vitamin E supplementation was beneficial in intermittent claudication. These reports followed the usual progression from case reports to quasi-experimental design trials, to controlled prospective trials with controls either matched or randomized and with varying degrees of blinding.[31]

Several themes were apparent from these reports. First, high doses of vitamin E were required; the most successful studies used 400 or 800 mg daily, or 50 to 100 times greater than the current recommended daily allowance.[11] Second, the therapeutic effect was delayed, generally becoming evident only after 3 months. This delayed effect distinguished the effect of vitamin E from a placebo effect, which typically is seen early and decays over time.[32] Third, the effect of vitamin E was marked, frequently increasing exercise tolerance several-fold.[31] Four randomized, controlled, double-blinded trials[33-36] have been published. Three[34-36] found efficacy. The fourth,[33] which was negative, was criticized for its relatively brief (12-week) duration and the low levels of bioavailable vitamin E intake.[34,37]

Once again, examining the treatment of a comparison therapy may be helpful. Vasodilating agents have also been in use for intermittent claudication since the late 1940s. There have been a large number of randomized controlled trials of various agents.[38-44] Overall, about half the trials produced a statistically significant effect with treatment, and the magnitude of the effects were similar to or smaller than those found for vitamin E.

Nevertheless, vitamin E was not mentioned in the discussions of therapies for intermittent claudication in any of the 13 editions of Cecil's or the 12 editions of Harrison's published from 1947 to 1992. Both texts in their early editions emphasized a number of specific exercises and physical manipulations; the space devoted to this decreased over time. All editions of the texts discussed surgery, and all discussed the use of vasodilators.

The lack of discussion of vitamin E for intermittent claudication in the 2 major textbooks is paralleled by the dearth of medical publications citing this treatment. A MEDLINE search from 1980 through 1994 found 173 articles referenced under intermittent claudication and vasodilators, 83 articles under intermittent claudication and pentoxifylline, and 5 articles under intermittent claudication and vitamin E.

It is instructive to read some of the early trials of vitamin E treatment for claudication. Vitamin E was associated with marked decreases in the rate of leg amputation and even overall mortality, in addition to decreasing claudication.[33,45,46] It is perfectly possible, perhaps even probable, that those dramatic results, which may have been produced by advocates, would not be reproduced in more rigorous trials. We do not know. To our knowledge, no trials of vitamin E in intermittent claudication have been published in the last 20 years. Only recently, with the growth of studies on the potential role of free radicals in atherogenesis, has vitamin E made it onto the radar screen of academic medicine.

WHY THE RESISTANCE?

Negative attitudes about micronutrients did not evolve recently; they have deep roots. The resistance of the medical community to the concept that scurvy, beri-beri, and rickets were caused by vitamin deficiencies has been well documented.[47-51] Consider this statement from a 1919 report of the British Medical Research Committee:

> It is difficult to implant the idea of disease as due to deficiency. Disease is so generally associated with positive agents—the parasite, the toxin, the *materies morbi*—that the thought of the pathologist turns naturally to such positive associations and seems to believe with difficulty in causation prefixed by a minus sign.[51]

The pathologists who dominated academic medicine in the late 19th and early 20th centuries lacked the vocabulary to integrate the public health observations of vitamin deficiency into a pathophysiology dominated by the germ theory.[49,50] A popular term used to describe vitamin deficiency disease, *negative causality*, evidenced the pathologists' awkwardness in grappling with the idea.[47,49,50]

This awkwardness is reminiscent of the concept of incommensurability put forth by Feyerabend[52] and Kuhn.[53] We have previously discussed how treatments that do not make sense can be rejected in favor of less effective or more toxic therapies that better fit in with the current understanding of pathophysiology.[3,4]

There are many factors that influence the adoption of new medical treatments other than strict consideration of efficacy, toxic effects, and cost.[5,6,54-57] For example, the financial incentives conferred by patent protection that stimulate the aggressive marketing of new pharmaceuticals were lacking in the case of micronutrients.[55] However, these factors do not explain the anger and scorn illustrated in the quotations from medical textbooks given earlier. Where did the emotion come from? Why did academic medicine deploy the language of denunciation against proponents of vitamin supplements?

For answers we return to the idea with which we introduced this discussion. Galileo is one of the heroes of present day science. We see him as a role model, the man of science battling the forces of unreason. It is therefore extremely ironic, and not a little unsettling, to consider the possibility that, in the fight between academic medicine and the various proponents of micronutrient supplements, the role of academic medicine was more analo-

gous to the 17th-century curia than it was to Galileo. But one senses some of the same vehemence, the same anger directed against "popularizers" of the benefits of micronutrients that must have greeted Galileo. He was not persecuted by an ignorant mob of religious zealots; his enemies were the intellectual and scholarly elite, whom he had bypassed, usurped, and rendered irrelevant.

Of course, this was precisely the course followed by many of the proponents of the benefits of micronutrients, the most famous of whom was Linus Pauling, the chemist who intruded into clinical matters. It is instructive to reread the review articles and editorials published in the 1970s ridiculing and condemning the ideas of Pauling. He was treated as a dangerous enemy, although a few years before his death, like Galileo, he was rehabilitated to the status of a genius with controversial ideas.

Many readers might object at this point, arguing that Pauling was wrong in his advocacy of megadose vitamin C to prevent upper respiratory tract infections. That issue is unresolved,[58-60] and misses the point. Defenders of the 17th-century curia could argue that Galileo was wrong too. He thought the planetary orbits were circular. Pauling's conceptual breakthrough was to postulate that micronutrients might be beneficial in levels higher than the minimum required to avoid classic deficiency syndromes. This idea is now a respectable hypothesis, but 20 years ago it was quackery.

CONCLUSIONS

Why is it important or necessary to determine if there has been bias against micronutrient supplements? First, it is always important to talk about bias in science, whether such discussions are couched in the terminology of paradigms and paradigm shifts or whether more earthy language is used. The practice of medicine, and to a lesser extent the practice of science, takes place in and is strongly influenced by social context.[7,61] This context influences everything we do as physicians—which diseases we recognize and which we ignore, which treatments we use, and which we reject.[4] The more we learn about why we do what we do, the more likely we are to avoid errors in the future.

In most areas of investigative medicine, investigators are either right or wrong, or correct or incorrect in their scientific observation and conclusions. But in an area subject to bias the investigator is given no leeway. One error, or perhaps one poorly documented truth, and he/she is at risk of being stigmatized as a quack. Positive results are viewed with suspicion, and are usually accompanied by editorials urging caution; negative results are published in the best journals, with a celebratory tone to the accompanying editorials. What if high-dose vitamin E reduces cardiovascular disease; what if supplemental antioxidants lower the risk of cataracts; what if supplemental folate reduces atherosclerosis and birth defects? For that matter, what if spinal manipulation works better than medications for low back pain or if yoga and relaxation exercises can prevent headache? What is wrong about medical investigators getting excited about these possibilities, just as we get excited about the potential for cytokine antagonists in the therapy of acquired immunodeficiency syndrome or Alzheimer disease?

There are only 3 important questions when evaluating a potential treatment.[5] Does it work? What are the adverse effects? How much does it cost? Ideally, issues such as the theory underlying the treatment or the guild to which the proponents of the treatment belong should be irrelevant to the fundamental questions of efficacy, toxicity, and cost. The history of the response of academic medicine to micronutrient supplementation suggests that we have not attained that ideal.

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