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Can Nutrient Supplements Improve Functional Outcome in the Elderly?

To the Editor: It is surprising that Roberts and Sternberg find no merit at all in our studies; they have no positive comments to make, none whatsoever. They "doubt everything in it [the *Nutrition* paper]" and extend their paint brush approach to the *Lancet* paper. The two papers were reviewed by a number of referees and statisticians before the journals accepted and published them. Their statements by themselves question the scientific objectivity of Roberts and Sternberg and point to an obvious bias on their part; there may well be a conflict of interest involved.

Aging is associated with a reduction in many physiologic functions. It is now accepted that a proportion of these changes may be the consequence of an inadequate intake of vitamins, trace elements, minerals, and other nutrients.[1,2] Even a "healthful" diet cannot provide all these elements in amounts that are necessary for health promotion and prevention of acute and chronic diseases. Roberts and Sternberg[3] fault our studies[4,5] and cannot believe that nutrition can make a significant difference to functional outcomes in the elderly, especially immune responses, incidence of infection, and some aspects of cognitive function. I point out some of the inaccuracies in their very selective and biased commentary in which they cite only those references that suit their views but ignore others that go against their views. Therefore, I question the scientific basis of their comments and why the positive commendation of my work by other readers and reviewers of our studies were omitted by them.[1,6–9]

The design of our studies and methods of analysis have been commended by many individuals. The first study[4] was stated to have provided "hard evidence" based on a "well-designed prospective trial … whose results, when considered in the context of the basic and intermediate endpoint clinical data now available, are biologically credible. More prospective trials are needed, and they must be as meticulously conducted as the first one."[1] Simin Meydani, a leader in this field, has referred to this paper as "a landmark study."[6] The study plans were discussed with *The Lancet* office and many of the changes in final analyses and presentation were made as a direct result of the suggestions of the three expert referees and two statisticians of the journal who also saw the raw data that they had asked for. An author cannot ignore such recommendations and our publication resulted after the final approval of the journal's referees, statisticians, and the editorial staff. Were all of them wrong and incompetent? If so, then an author would generally be quite happy to be a part of that group.

Several studies have confirmed the beneficial effects of nutrient supplementation on immune responses in the elderly.[10–12] Not all the results can be expected to be identical to those of our trial. The strength of the evidence presented in these papers by other authors varies, dependent in part on the variety and amounts of nutrients provided, duration of the trial, outcome variables assessed, sample size, the place of residence of the subjects whether living at home or in institutions, and the baseline status of the subjects. In several studies, single nutrients were used. Zinc supplements corrected the changes in immune system resulting from induced zinc deficiency such as CD4:CD8 ratio and thymulin activity.[13] Vitamin E improved delayed hypersensitivity response and antibody level after immunization.[14] Two different commercial combinations of vitamins and trace minerals increased delayed cutaneous hypersensitivity response and other selected parameters of immunity in old subjects.[15,16] Few studies have looked at incidence of infection. Zinc and selenium supplements reduced the occurrence of infectious illness in aged adults.[17] Two clinical studies in which treated subjects received the multinutrient supplement used in our trials showed beneficial effects in terms of infection rate.[18,19] In particular, one was a very large study of 763 nursing home patients in Canada who received the multinutrient or a placebo for 19 mo. The average age of the subjects was 85 y. The mean number of episodes of infection was 1.94 in the treated group compared with 2.26 in the placebo group ($P < 0.001$); the results were considered of great significance for medical management and health care costs in long-term facilities for older individuals. A recent study reported benefits from multivitamin and mineral supplementation, most especially in older diabetic patients.[9]

Thus, it is no longer disputed that the weight of evidence, reported first by us[4] and now by others,[9,13–20] supports the concept that modest amounts, not mega doses, of vitamins and trace elements enhance immune responses, and where examined and depending upon the nutrients being supplemented and their amounts, decrease the incidence of infection.

A causal connection between nutrient deficiencies and impaired cognitive function particularly in the elderly has been postulated by many authors and is supported by considerable data.[21] In particular, attention has been given to vitamin C and B vitamins. Changes in homocysteine levels brought about by vitamin deficiencies may play an important pathogenetic role. Older subjects without clinical dementia as well as those with Alzheimer disease had higher plasma homocysteine concentrations and lower serum folate and vitamin B12 levels than did age-matched controls.[22,23] Vitamin E supplements improved clinical endpoints in patients with Alzheimer disease[24] even though there was no difference in the treated and placebo groups on the Cognitive subscale of the Alzheimer Disease Assessment Scale or any other cognitive test score. Surprisingly, Roberts and Sternberg deny what this author stated. Why? In the Nun Study, low serum folate level was strongly associated with atrophy of the cerebral cortex.[25] Multiple deficiencies are common in the elderly and can be expected to produce widespread cerebral damage, both structural and functional.

There can be differences in methods used to describe results of any study; as a reviewer of articles for some of the most prestigious medical journals, as a member of some editorial boards, and as the Editor-in-Chief of *Nutrition Research*, I have encountered many instances of a totally different approach and conclusion by two referees and by statisticians invited by a journal. We could take published papers, including those by Drs. Roberts and Sternberg, and by the editors of *Nutrition*, and ask new reviewers to evaluate them. Such an exercise will invariably result in different results, statistical numbers, and conclusions. Such an exercise for several papers in the field of nutritional immunology is being prepared for publication. Reanalysis of published psychiatry papers in a British journal has sometime led to different results.[26] Differences in statistical approaches and methods of analyses that result in different results and conclusions are common knowledge to authors and editors and have been the subject of less than generous sarcasm. The readers would be surprised to see opinions that would make one wonder why reputed journals could have accepted and published such manuscripts. In many instances, two reviewers for the same journal provide diametrically opposite recommendations for analysis, description, and discussion. In

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terms of clinical conclusions and public health application, differences in two treatment groups expressed as less than 0.001 or less than 0.00000001 are of no practical consequence.[27] For practicing clinicians, such hair-splitting is no value and a waste of everyone's time. Most editors have learnt to ignore such biased diatribe.

I and my colleagues in psychiatry, psychology, nutrition, immunology, and statistics do not agree with the comments of Roberts and Sternberg about the range of numerical scores to be expected in modified Mini-Mental State Examination and other tests of cognitive function employed by us. Restrictions on premium journal space does not always allow authors to describe these. Many editors accept this with or without the additional wording of "data not shown." Our statistical consultants also have different views about the methods of analysis that do not, in any case, alter the broad conclusions of our studies. "A difference, to be a difference, must make a difference."[28] "We think of tests of significance more as methods of reporting than for making decisions because much more must go into making medical policy than the results of a significance test."[29]

It is not clear why Drs. Roberts and Sternberg bring in the question of the patent rights of the micronutrient supplement that we used in the trial. As opposed to many studies that employed commercially available preparations and therefore the authors would have obvious or perceived financial associations with companies,[30] our studies were not funded by any industry. Moreover, we first determined the optimum amounts of each micronutrient for enhancing immunity in older subjects. This was followed by the double-blind, randomized, prospective trial.[4] There was no commercial benefit nor any conflict of interest involved, as per guidelines outlined by various editors.[31,32] Almost 10 y after the *Lancet* paper was published, the combination of nutrients used in the trial was now made available to the public on a limited scale in one province of Canada through the generosity of a small not-for-profit foundation on the stipulation that all proceeds would be given toward research in the province by third-party investigators.

Parenthetically, it remains to be explored whether Drs. Roberts and Sternberg have any conflicts of interest and bias, real or perceived, in terms of financial grants from companies that have products for the treatment of dementia or altered cognitive functions, honoraria, consulting fees, service on advisory boards, ownership of equity or options thereon, fees for expert testimony, and others.[30] No disclosure statement has been provided. My attempts to obtain this information directly from Drs Roberts and Sternberg have elicited no clear response so far.

The improvement in functional outcome reported by us has the support of many studies. It is also biologically highly plausible. Many vitamins and trace elements play an essential role as cofactors in hundred of enzymes involved in synthesis of proteins, polypeptides, DNA, and cytokines. For instance, zinc facilitates the action of more than 200 enzymes including some that promote cell replication and protein synthesis; it is also an integral component of thymulin, a T-cell maturational hormone produced by thymic epithelial cells. In their commentary, Roberts and Sternberg completely ignore these evidences. Also, they provide two versions of how others, for example, Dr. Carpenter, got to read our papers.

Shenkin et al.[33] made useful comments to which we responded.[34] To date, we have not heard from them; thus, we assume that they are satisfied with our explanations. On what basis do Roberts and Sternberg believe that our reply to Shenkin et al. was "misleading"? It is most unethical for them to attribute such a statement to others. Are Roberts and Sternerg the spokespersons and interpreters for Shenkin et al.?

It is not appropriate for Roberts and Sternberg to ask me to respond to their comments on a paper by another author, Jain, published in another journal, *Nutrition Research.*[18] I encourage them to write a formal letter to the journal about this paper and I expect that such a letter, together with the author's reply if Jain wishes to respond, will be considered by the journal for possible publication. Their comments about the *Lancet* paper has already been responded to.[35] The statement that there have been any problems with replication of the results of our study on immune responses and infection is false and totally unsubstantiated, as discussed extensively above. In fact, the contrary is true.[18,19] The paper they refer to does not appear in their bibliography, so no response from me for their unsupported and biased statement, nor a failure for letters from and to them to reach the addressee, can be expected.

Only time and other trials will attest to the strength of our conclusions. This has already happened with the immune response data. A balanced interpretation of the clinical experience and published evidence to date would indicate that supplementation with a combination of vitamins and trace elements in optimum amounts that are based on dose-response curves and tested subsequently in a well-designed, randomized, double-blind, placebo-controlled prospective trial can be expected to improve immunity, reduce infection, and improve selected cognitive functions.

Can a nutrient supplement improve functional outcome in the elderly? The answer based on the objective evidence so far is an unequivocal *yes*. I invite Drs. Roberts and Sternberg to try such a supplement for a personal confirmation of our findings.

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