Do Nutritional Supplements Improve Cognitive Function in the Elderly?

To the Editor: In 2001 in this journal, R. K. Chandra reported that a vitamin and trace-element supplement taken for a year greatly improved the performance of elderly subjects on tests of memory and other cognitive functions.[1] Because the subjects were drawn from the general population, the results seemed to imply that millions of people would benefit from such supplements, as the *New York Times* report on this paper would imply.[2] Chandra holds a patent on the particular formula used,[3] which is now being marketed.

We began to question the results, as did Shenkin et al.,[4] because the effect of supplementation seemed too large—for example, improvement of the average score on the Mini-Mental State Examination (MMSE) from 18 to 28 (perfect score is 30). The MMSE consists of very easy questions, such as "What month of the year is this?" and, being shown a pencil, "What is this called?"[5] (The improvement cannot be due to practice because the placebo group did not improve.) Then we noticed that some results were impossible. Three of the standard errors in Table II of the paper are more than the maximum possible standard error, which occurs when a distribution with the specified mean is as variable as possible. For example, 28 ± 4 ($n = 45$), one of the MMSE averages, is impossible because all individual scores on the MMSE are between 0 and 30. With a mean of 28 and a sample size of 45, the maximum possible standard error is 1. In August 2001, we notified Chandra of this problem. Two months later, we were told of the "typographical error" mentioned in Chandra's reply to Shenkin et al.[6]: What the paper described as "standard errors" were actually standard deviations.

Standard deviations and standard errors are quite different, of course—with a sample size of 45, they differ by a factor of about 7. The change from one to the other solved one problem but created several more:

1. The 96 subjects are described as having been randomly assigned to the placebo and supplement groups. In Table II of the paper, however, the placebo and supplement groups differed significantly on all seven measures when the experiment began. Comparing the two groups at the start of the experiment, the two-tailed *P* values for the seven tests (Wechsler, Halstead-Reitan, etc.) are 0.0007, 0.0003, 0.02, 0.0004, 0.0000000000004, 0.01, and 0.0000000000009 (assuming 48 subjects per group). If assignment was random, this outcome is essentially impossible.
2. In Table II of the paper, the significance levels associated with the effects of supplementation are highly inaccurate. The seven stated *P* values (one per test) are < 0.01, < 0.05, < 0.001, <0.01, <0.01, <0.01, not significant, and <0.01. The correct *P* values are all <0.0000000000001. (We assume that the correlation of before and after scores over subjects is non-negative, as is surely the case.)
3. According to Table III, the scores of "deficient" and "adequate" subjects overlapped remarkably little. Figure 1 shows this problem for three of the tests (the most extreme examples). The normal distributions shown in Figure 1 are based on the means and standard deviations. For each test, the scores of "deficient" and "adequate" subjects were linearly transformed so that the scores of the "adequate" subjects had a mean of 0 and a standard deviation of 1, and the "deficient" scores were less than the "adequate" ones. This degree of separation is highly implausible because the definition of "deficient" was arbitrary (the lowest 5%) and general (a deficiency in any of 14 nutrients would cause a subject to be classified "deficient").

Moreover, at least some of the results bore little resemblance to other uses of the same tests with persons the same age. According to norms for the MMSE, Chandra's subjects should have had an average score between about 26 and 28.[7] Their average score was about 20. The paper refers to a 1983 paper that used the Halstead-Reitan Categories test with elderly subjects.[8] The nutritionally adequate subjects in that study had a mean of about 80 errors and a standard deviation of about 30 errors. Chandra's nutritionally adequate subjects had a mean of 60 errors and a standard deviation of 7 errors. These differences are too large to be due to chance.

We pointed out these or similar problems to Chandra in letters sent September 2001 (to which we received a short reply on his behalf) and November 2001 to which so far (July 2003) we have received no reply.

While preparing this letter, we noticed more problems. One of the memory tests, which Chandra calls the "Wechsler Memory Test," resembles the Semantic Memory subtest of the Wechsler Memory Scale, which involves reading a story and asking for recall immediately and a half-hour later. In the reference that Chandra gives for this test, the mean scores for normals are 23 (immediate) and 21 (delayed).[9] However, Chandra reports only one score for this test, with mean values near 5. Another test used by Chandra is called "long-term memory recall." No reference is given. The entire description is: "This test assesses memory of events that happened a long time ago, e.g., high school graduation, first job, etc." What such a test measures is normally called *autobiographical memory*, not *long-term memory*. Moreover, lack of a specific identifier (as in *Wechsler* Memory Test or *Salthouse* Listening Span Test) is odd because creation of a widely usable test of autobiographical memory is difficult (determining the accuracy of the answers is not easy, for instance) and would be a considerable accomplishment. We have found only one test of autobiographical memory, the Kopelman Autobiographical Memory Test.[10] However, in one use of this test,[11] the mean scores for the control subjects averaged 21, whereas Chandra's mean scores range from 78 to 91.

Learning of our concerns about the 2001 paper in *Nutrition*, Professor Kenneth Carpenter, in the Department of Nutritional Sciences and Toxicology at the University of California at Berkeley, reexamined a 1992 paper by Chandra published in *Lancet* based on the same experiment.[12] The earlier paper (*Lancet*) reported measures of immune function, such as days of sickness due to infection. The effects of supplementation were, to Carpenter, surprisingly large. He and the department's statistical consultant noticed two inconsistencies in the statistical analyses. One is that the results shown in the paper's figure (two histograms) do not agree with the text. The text states that "mean [SD]" days of infection was 23[5] for the supplement group. The corresponding histogram, however, shows a sample with a standard deviation between 14 and 21 (the standard error of the mean is between 2.2

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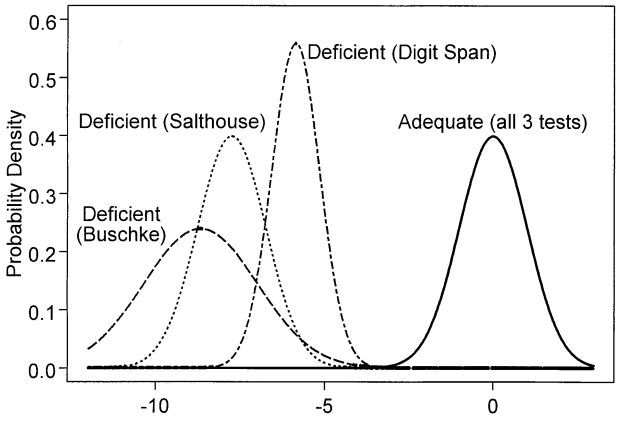

FIG. 1. Insufficient overlap of test scores of "deficient" and "adequate" subjects. Table III of the paper provides means and standard deviations for two groups of subjects, "deficient" and "adequate," on each of eight tests. For example, on the Buschke test, the scores of the "adequate" subjects were 15 ± 3, and those of the "deficient" subjects were 41 ± 5. The figure shows results for three of the tests, assuming normal distributions. The distributions have been scaled so that the "adequate" distribution has a mean of 0 and a standard deviation of 1 and so that lower scores correspond to worse performance.

and 3.3). The same discrepancy also occurred with the placebo results. According to the text, "mean [SD]" days was 48[7]; according to the figure, the standard deviation was between 13 and 21 (the standard error was between 1.9 and 3.0). The other problem is in Table III of the paper, which includes 1) *P* values derived from comparison of the supplement group's scores at the start and end of the experiment ("S_0 and S_{12}") and 2) *P* values derived from comparison of the supplement group's and placebo group's difference scores ($P_{12} - P_0$ and $S_{12} - S_0$). When the placebo group changed in the same direction as the supplement group, the second *P* value must be larger than the first because the difference (the numerator of the *t* ratio) is smaller and the estimated variability of that difference (the denominator) is greater. However, in all of the five cases in which the two groups changed in the same direction and *P* values were given, the impossible occurred: The second *P* value was smaller than the first. Carpenter wrote to Chandra in November 2001, pointing out these problems and asking for the raw data. He has received no reply.

The January–February 2002 issue of *Nutrition Research* (which Chandra edits) contains two reports of replications of the *Lancet* study, one by Chandra[13] and the other by Amrit Jain,[14] whose institutional affiliation is "the Medical Clinic and Nursing Home, Jaipur, India" but whose mailing address is a rented mailbox in Canada. In both reports, there is once again the problem that the reported *P* values (Table 4 in Chandra and Table 1 in Jain) are far from what the associated means and standard deviations imply. Jain did not reply to a letter about this. Given that successful replications, especially by independent investigators, are among the best defenses of a study against criticism, we find it noteworthy that in his reply[15] to our critical comments[16] about his 1992 paper in *Lancet*, Chandra mentioned neither Jain's replication study[14] nor his own.[13]

The earlier letter by Shenkin et al. concerning the 2001 *Nutrition* article noted that the MMSE scores at the start of the experiment seemed too low to be consistent with Chandra's statement in the article that, at the beginning of the experiment, "none [of the subjects] suffered from … dementia" (p. 709). In his reply,[6] Chandra stated that "a dichotomy between Mini-Mental State Examination scores and clinical assessment and cognitive test scores is recognized." However, Chandra's reference for this statement,[17] a study of Alzheimer patients, does not support it. For this population, mean MMSE scores agreed with the means of other measures (the Clinical Dementia Rating and the Blessed Dementia Scale): all indicated dementia. Furthermore, his reference says nothing about the MMSE scores of persons without dementia. All of its subjects, at the beginning of their involvement, had a Clinical Dementia Rating of 2, which indicates moderate dementia.[18] Such a study does not provide information about the MMSE scores of persons without dementia. More specifically, it does not show that persons without dementia may get a low score on the MMSE, which is what Chandra appeared to claim in his reply. Chandra also stated in his reply that "the subjective experiences of thousands of individuals who have used the vitamin and trace element supplements assessed in our studies support the results of the objective controlled trials by others and us." Again, Chandra's reference for this statement[19] does not support it. The reference says nothing about "subjective experiences," nor does it refer to or describe "controlled trials by others." Because Chandra's reference is a leading editorial, perhaps he meant to refer to all of the articles in that issue of the journal. However, none of them is about cognitive function.

The large number of serious problems with the 2001 paper in *Nutrition*[1] make us doubt the data and their implications. Similar problems, as described above, about the 1992 *Lancet* study and its replications, Chandra's failure to reply to letters about these issues, and his reply to Shenkin et al. reduce its credibility even more.

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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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