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Dissent

To the Preceding Article by H. Hemilä

It is a pleasure, albeit a somewhat painful one, to respond to the article by Hemilä criticizing our clinical trial of the prophylactic and therapeutic use of ascorbic acid in the common cold. I am pleased to have attention paid to the trial, 20 years after its publication, because I am more proud of it than almost any other that I have published. I am proud of it for essentially four reasons:

1. When I assumed directorship of the Clinical Center of the National Institutes of Health (NIH) in 1970 I was anxious to establish my firm belief that all physicians engaged in practice and administration should conduct research relatedjo their clinical responsibilities. The Employee Health Department of the whole NIH was under my jurisdiction, and the appearance of the late Linus Pauling's book on vitamin C and the common cold (Ref. 9 in Hemilä's article) suggested a strong need for a well-designed and conducted clinical trial, a nice challenge to an employee health department. Dr. Thomas R. Karlowski was a Clinical Associate in the Department who enthusiastically accepted the challenge.
2. At the time where there was too little biostatistical input into clinical trials in the design stage and we were fortunate to enlist the collaboration of an experienced statistician in one of the Institutes. When the breaking of the blind described below was discovered, he withdrew and requested an anonymity that I have respected because he considered that it was too flawed a study to be published. I disagreed and felt strongly that we had a unique opportunity to publicize a defect that probably occurs quite commonly, but had never been documented in the past. His important contribution is illustrated by the unique stopping rules, a most important part of clinical trials that is seldom acknowledged. The protocol called for the study to be stopped before the estimated necessary sample size was achieved if "(1) the dropout rates from the group treated with ascorbic acid and the placebo groups . . . were . . . significantly different (the level of significance was to be taken at 0.15); (2) the number of persons under study fell below 200; and (3) at six months from the beginning of study the number of colds in the ascorbic acid treated group was significantly greater than the number in the placebo group (level of significance, 0.05)." The study was stopped 9 months after the last subjects had entered, when both the number remaining dropped below the estimated minimal number of 200, and it was apparent that more of the dropouts were in the placebo group ($p = 0.10$). The wisdom of this move is obvious, and the lesson for other studies is that there is a real advantage, one that overwhelms any mythical disadvantage of multiple looks, of monitoring trial results closely, with emphasis on the direction of the trends as well as how they fit with other related studies.
3. The third aspect of the trial of which I am proud is the very one that Hemilä attempts to criticize: that we did a routine check on the blinding by obtaining answers to a questionnaire, and that we recorded after interviews how many volunteers confessed to cheating by opening the capsules and tasting the contents. In any event Hemilä accuses us of assuming that if the volunteers guessed correctly which group they were in that means that they knew, which is obviously not the case. Hemilä repeatedly ignores our stated caveat that the numbers were too small for reliable retrospective analyses and we are castigated for attempting them in an effort to shed some light on the fact that our study did not confirm what seemed to be the popular conception. He is infuriated by our conclusion that it might well be a popular misconception.
4. As far as I know this was the first use of a 2-by-2 factorial design to investigate prophylaxis and treatment in the same patients. Since there was no suggestion of interaction we combined the two prophylaxis and the two treatment groups to successfully answer both questions with the same patients. Hemilä criticizes us for combining groups without saying why. He apparently does not understand what a 2-by-2 factorial design is.

There are many other improper "straw men" in this review and a previous one he has published of our meta-analysis of the published randomized control trials. For one we used capsules and not tablets to reduce the likelihood of an unintentional breaking of the blind. For another he writes as though we established a dose-response relationship by our 2-by-2 design, and no such conclusion can be drawn from the data. It was not concluded by us that the apparent slight and clinically minimal effect on severity of symptoms was "entirely due to the placebo effect." When he quotes opposing views of the efficacy of ascorbic acid as demonstrated by randomized controlled trials (RCTs), the majority of reference numbers refer to his published reviews and two editions of Pauling's book.

In summary, I resent the time that I have had to devote to this author's biased defense of his late mentor's infatuation with ascorbic acid. It may be that a properly done, unbiased, and updated meta-analysis of the RCTs should be carried out, but I think it would be a waste of time.

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Response

To the Dissent by Thomas Chalmers

Chalmers comments that "Hemilä accuses us of assuming that if the volunteers guessed correctly which group they were in that means that they knew, which is obviously not the case." In the Methods section of Karlowski's *Journal of the American Medical Association* (JAMA) paper [1] it is stated that "a questionnaire was submitted to each of the participants *asking them to guess which substance they had been taking*. The results of the questionnaire (Table 2) made it mandatory to perform the analyses both in toto as well as according to the *participants' impression* as to what they were taking" (italics mine). In Table 2 of the Karlowski paper there are 40 and 39 subjects who correctly "suspected" their drug was ascorbic acid or placebo, respectively [1]. Table 4 of the same article is titled "Distribution of colds according to *knowledge of capsule contents*" (italics mine) and in this table it is stated that the same 40 and 39 subjects "knew" whether they were being administered ascorbic acid or placebo [1]. However, the authors did not say how they became convinced in between Tables 2 and 4 that a subject actually knew the treatment instead of merely suspecting. Table 6 lists the results for the subgroup of "unblinded" subjects [1]. The term "unblinded" indicates that the subjects genuinely knew their treatment, whereas the Methods section implies that these are actually subjects that gave a correct answer when asked to "guess" which capsules they had been taking. In their conclusion the authors stated that [1]: "an association between severity and duration of symptoms and *knowledge of the medication taken* seems to have been clearly established" (italics mine). Thus the JAMA paper itself suggests that the correct answers on the questionnaire were interpreted by the authors as actual knowledge of the treatment, although a great proportion of the correct answers could have been due to correct guesses, as pointed out in my paper.

Chalmers claims that no conclusions on the dose-response relationship can be drawn from their study. This statement seems inconsistent with the JAMA paper [1], in which the authors commented that "volunteers taking placebo had colds of a mean duration of 7.14 days, while those taking 3 gm of ascorbic acid had colds of a mean duration of 6.59 days and those taking 6 gm had colds of a mean duration of 5.92 days. Thus, each 3-gm increment of ascorbic acid would appear to shorten the mean duration of a cold by approximately half a day." The authors thus explicitly paid attention to the apparent dose dependence, and it seems that they implicitly considered the possibility that larger doses might have produced still greater effects. They nonetheless discarded the notion of dose dependence since they concluded from their subgroup analysis that the observed differences were due to the placebo effect. If the placebo effect interpretation is to be rejected, as I suggest in my paper, the apparent dose dependence becomes a relevant issue again.

There are numerous popular misconceptions about vitamins and about nutrition in general. Nevertheless, the effect of vitamin C on colds has been of great interest in the academic community also. Kleijnen *et al.* [2,3] carried out a thorough literature search and found 61 controlled trials related to the question of whether vitamin C has effects on the common cold. In the early 1970s Pauling concluded that ≥1 g/day prevents and alleviates colds [4], and since then 21 placebo-controlled studies using regular high-dose vitamin C supplementation (≥1 g/day) have been published [5]. These studies may be considered as tests of Pauling's hypothesis. It is clear that Pauling overestimated the effects of vitamin C supplementation. The incidence of the common cold has not been markedly reduced in subjects administered vitamin C [5]. The effect on symptoms has been less than Pauling supposed, even though consistent benefit has been observed [5]. Still, vitamin C is safe even at high levels of intake [6] and costs few cents per gram, so that even a modest effect may be of practical importance. It would seem worthwhile to investigate in detail what the quantitative effects on colds are, and which groups of people would benefit most. The clinical significance can then be estimated more accurately. I do not think that either popular misconceptions or Pauling's overoptimism should hamper such investigation.

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