

**To the Dissent by Thomas Chalmers [Response]**

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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  $\geq 1$  g/day prevents and alleviates colds [4], and since then 21 placebo-controlled studies using regular high-dose vitamin C supplementation ( $\geq 1$  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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