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Vitamin C and the Common Cold: A Retrospective Analysis of Chalmers' Review

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http://www.mv.helsinki.fi/home/hemila/vitc_colds.htm (papers on vit C and colds)

The Chalmers 1975 review has been highly influential as a support to statements that vitamin C does not have any effects on the common cold.
See a list of influential monographs and journal articles that have cited the Chalmers 1975 review as evidence that vitamin C is useless for colds:
http://www.mv.helsinki.fi/home/hemila/Chalmers1975CitedBy.htm

Problems in influential reviews on vitamin C and the common cold are discussed also in:

Hemilä H.
Vitamin C supplementation and common cold symptoms: problems with inaccurate reviews.
Nutrition 1996;12:804-809
http://dx.doi.org/10.1016/S0899-9007(96)00223-7
http://hdl.handle.net/10250/7979 Manuscript version with links to references added.

In his review, Chalmers put a great weight on the Karlowski (1975) study.
However, the Karlowski study was shown to be erroneously analysed in 1996:

Hemilä H.
Vitamin C, the placebo effect, and the common cold:
a case study of how preconceptions influence the analysis of results.
J Clin Epidemiol 1996;49:1079-1084
http://dx.doi.org/10.1016/0895-4356(96)00189-8
http://hdl.handle.net/10250/8082 Manuscript version with links to references added.

For further discussions on the problems with the influential reviews and the Karlowski study, see:

Hemilä H. **Do vitamins C and E affect respiratory infections?** Thesis 2006 pp. 21-7, 35-45.
http://hdl.handle.net/10138/20335
Relevant sections are also available as **html** files:
http://www.mv.helsinki.fi/home/hemila/reviews (problems with the influential reviews)
http://www.mv.helsinki.fi/home/hemila/karlowski (problems with the Karlowski 1975 study)

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Abstract

In 1975 Thomas Chalmers analyzed the possible effect of vitamin C on the common cold by calculating the average difference in the duration of cold episodes in vitamin C and control groups in seven placebo-controlled studies. He found that episodes were 0.11 ± 0.24 (SE) days shorter in the vitamin C groups and concluded that there was no valid evidence to indicate that vitamin C is beneficial in the treatment of the common cold. Chalmers' review has been extensively cited in scientific articles and monographs. However, other reviewers have concluded that vitamin C significantly alleviates the symptoms of the common cold. A careful analysis of Chalmers' review reveals serious shortcomings. For example, Chalmers did not consider the amount of vitamin C used in the studies and included in his meta-analysis was a study in which only 0.025–0.05 g/day of vitamin C was administered to the test subjects. For some studies Chalmers used values that are inconsistent with the original published results. Using data from the same studies, we calculated that vitamin C (1–6 g/day) decreased the duration of the cold episodes by 0.93 ± 0.22 (SE) days; the relative decrease in the episode duration was 21%. The current notion that vitamin C has no effect on the common cold seems to be based in large part on a faulty review written two decades ago.

Key teaching points:

* In 1975 Thomas Chalmers published a meta-analysis of studies that have examined the role of vitamin C supplementation on common cold morbidity.
* Chalmers' paper is often cited as proof that vitamin C has no value in treating the common cold.
* The present study shows that Chalmers' analysis is fraught with errors and misleading data from the original studies.

Dedicated to the memory of Professor Linus Pauling (1901-1994)

INTRODUCTION

There exists a long-standing controversy concerning the possible efficacy of vitamin C in treating the common cold. The first reports indicating that vitamin C may be beneficial against the common cold were published in the 1930's and 40's [1-4]. The topic received wide publicity in the 1970's after Linus Pauling concluded from the published studies that vitamin C, in doses ≥1 g/day, significantly decreases both the incidence and the severity of the common cold, and wrote a popular book discussing the topic [3,4]. Pauling also carried out a meta-analysis [5], one of the very first in medicine, of the published studies in which he demonstrated a significant decrease in total morbidity in the subjects ingesting vitamin C supplements ($p < 0.00003$). The claims of Pauling were not widely accepted within the medical community but they inspired a number of intervention studies to determine whether vitamin C does indeed have any actual effect. In fact, all 21 placebo-controlled studies published since 1970 which utilize ≥1 g/day of vitamin C have reported a decrease in the severity of symptoms or in the duration of the common cold episodes [6,7].

The general belief in conventional medical circles that vitamin C has no effect on the common cold [8-10] seems surprising since essentially all of the placebo-controlled studies carried out both before and after Pauling's conclusions have shown a beneficial effect [3-7]. We believe that the current conception that vitamin C does not affect the common cold can be traced largely to the review written by Chalmers in 1975 [11]. Chalmers carried out a meta-analysis of studies performed before 1975. From the results of seven studies, he calculated that the difference in the duration of episodes between the vitamin C and placebo groups was 0.11 ± 0.24 (SE) days, a difference considered by Chalmers to be "*minor and insignificant*", even though he noted that "*in most studies the severity of symptoms was significantly worse in the patients who received the placebo.*" Based on his analysis, Chalmers stated "*since there are no data on the long-term toxicity of ascorbic acid when given in doses of 1 g or more per day, it is concluded that the minor benefits of questionable validity are not worth the potential risk, no matter how small that might be* [11]."

Chalmers' review has been cited twice as often as Pauling's meta-analysis (Table 1). Pauling's books have been extensively cited (Table 1), but this gives a highly misleading impression of their true scientific impact. In the current edition of the Recommended

Dietary Allowances (RDA), Pauling's meta-analysis is mentioned, but Chalmers' review is referred to as proof that Pauling's conclusions were incorrect [8]. In monographs on infectious diseases Pauling's books and meta-analysis are rarely mentioned; rather, Chalmers' review is referred to as evidence that vitamin C has no effect on the common cold [9,10]. Chalmers' conclusions [11] of the published studies vary from that of other reviewers [3-7]. The present work analyzes the reasons for this apparent discrepancy.

Table 1. Citations of Reviews Analyzing the Vitamin C-Common Cold Studies [12]

Years	Chalmers' review [11]	Pauling's meta-analysis [5]	Pauling's two books [3,4]
1970-75	-	7	75
1975-79	24	15	123
1980-84	18	6	69
1985-89	14	2	35
1990-92	5	1	15
Total citations:	61	31	317

ANALYSIS OF CHALMERS' REVIEW

Shortcomings in Chalmers' Table II

The argument in Chalmers' review is based primarily on his table II, which contains studies that he referred to as "*reasonably well controlled studies*." Chalmers' table II is reproduced here (Table 2) in order to show the various shortcomings in his analysis and to compare different ways of summarizing the data in order to estimate the treatment effect. A summary of the same studies by the present authors is presented as Table 3. Several of the numerical values presented by Chalmers are dubious for various reasons and these are underlined in Table 2.

Table 2. Ascorbic Acid and the Common cold:
Reasonably Well-Controlled Studies according to Chalmers [11]

Study [reference]	Ascorbic acid		Placebo		Difference in duration (days)
	No. of subjects	Mean duration (days)	No. of subjects	Mean duration (days)	
Anderson et al 1972 [13]	407	3.96	411	4.18	0.22
Anderson et al 1974 [14]	583	3.28	578	3.18	–0.10
Coulehan et al 1974 [15]	321	4.71	320	5.92	1.21
Wilson et al 1973 [16]	158	2.65	144	2.79	0.14
Karlowski et al 1974 [17]	101	6.80	89	6.30	0.50
Cowan et al 1942 [2]	233	1.10	194	1.60	0.50
Cowan et al 1942 [2]	227	1.70	120	1.00	–0.70
				Mean ± SE:	0.11 ± 0.24
Ritzel 1961 [18]	139	1.35	140	1.95	0.60

Chalmers also listed the incidences of colds but they are left out to save space.
Erroneous and misleading numerical values are indicated by yellow and underlining
(see text and compare to Table 3).

Table 3. Ascorbic Acid and the Common Cold: Results from the Original Publications

Study [reference]	Vitamin C dose (g/day)	Ascorbic acid		Placebo		Difference in days	Relative difference (%)	Probability of difference (2-tailed)
		No. of subjects	Mean duration (days)	No. of subjects	Mean duration (days)			
Dose ≥1 g/day								
Anderson et al 1972 [13,19]	1+3	407	3.96 [a]	411	4.18	–0.22	–5	
			1.04 [b]		1.32	–0.28 [c]	–21 [c]	p < .05
Charleston & Clegg 1972 [20,21]	1	47	3.5	43	4.2	–0.7 [c]	–17 [c]	p < .05
Anderson et al 1974 [14]	1–5	860	1.74 [b]	285 [e]	1.76	–0.02	–1	
	1–5	860	1.74 [b]	293 [f]	1.54	+0.20	+13	
Coulehan et al 1974 [15]	1	190 [g]	4.95	192	5.65	–0.70 [c]	–12 [c]	p < .01 [h]
	2	131 [g]	4.44	128	6.29	–1.85 [c]	–29 [c]	p < .05 [h]
Karlowski et al 1975 [17]	3 [i]	87	6.59	46	7.14	–0.55	–8	
	3+3	57	5.92	46	7.14	–1.22 [c]	–17 [c]	p < .05 [j]
Ritzel 1961 [5,18,22]	1	139	1.8	140	2.6	–0.8 [c]	–31 [c]	p < .05
					Mean ± SE:	–0.93 ± 0.22 [c]	–21 ± 3 [c]	
						p = 0.01 [c]	p = 0.001 [c]	p < 0.000004 [k]
Dose <1 g/day								
Cowan et al 1942 [2]	0.2	208 [l]	0.58 [m]	155	0.73	–0.15	–21	
Cowan et al 1942 [2]	0.025–0.05	170 [l]	0.71 [m]	94	0.42	+0.29	+69	
Wilson et al 1973 [16]	0.2	70 [n]	2.62	58	3.10	–0.48	–15	
Wilson et al 1973 [16]	0.2	88 [o]	2.68	86	2.48	+0.20	+8	

a) Duration of symptoms.

b) Days confined to house.

c) Mean ± standard error (SE) of the point estimates for studies marked with superscript c) ; the p-value was calculated from the same point estimates with the 2-tailed t-test.

d) Study groups #1, #2, and #3 combined, all with ≥ 1 g/day of vitamin C.

e) Placebo group #4.

f) Placebo group #6.

g) School children of upper classes received 2 g/day and of lower classes received 1 g/day.

h) Significance for the total decrease in days of morbidity.

i) Two 3 g/day groups are combined (cf. Table 4).

j) Calculated by these authors from Table 4 with the t-test; the significance of the difference was not calculated by Karlowski et al [17].

k) The probabilities of the studies marked with superscript c) have been combined with Fisher's method [23,24].

l) The number of subjects who completed the study; Chalmers gives the number of subjects who began the study. Two study groups are combined in the 0.025–0.05 g/day results.

m) Days lost from school per one episode; Chalmers gives the total number of days lost from school, i.e., over all episodes.

n) Schoolgirls.

o) Schoolboys.

Table 4. Results from the Common Cold Study by Karlowski et al [17]

Group	Tablets		No. of Subjects	Vitamin C during a cold (g/day)	Duration (days; mean ± SE)	Difference (%)
	Prophylactic	Therapeutic				
1	P	P	46	0	7.14 ± 0.46	
2	P	C	43	3	6.46 ± 0.39	–10
3	C	P	44	3	6.71 ± 0.53	–6
4	C	C	57	6	5.92 ± 0.40	–17

Prophylactic tablets were given each day, i.e. also during the colds,
and the therapeutic tablets were given for 5 days when the subject caught a cold.
Tablets: P = placebo (lactose); C = vitamin C (ascorbic acid, 3 g/day). The data were taken from [11,17].
Chalmers' placebo group is indicated by yellow (cf. Table 2)

The data of the Karlowski study [17] are not correctly presented by Chalmers. Karlowski et al used four study groups and only one of these was a true placebo group; three other groups received vitamin C (3–6 g/day) according to different protocols (Table 4). The true placebo group in the study by Karlowski et al contained 46 subjects and the mean duration of the common cold episodes was 7.14 days (Table 4). However, Chalmers states that the number of subjects in the placebo group was 89 and the mean duration was 6.3 days (Table 2). Apparently, Chalmers totaled the number of subjects in groups 1 and 2 (n = 89), when in fact, group 2 received 3 g/day of vitamin C for therapy and cannot be considered a placebo group. Furthermore, the average for groups 3 and 4 (i.e. not groups 1 and 2) is 6.3 days. During the common cold episode, groups 3 and 4 were administered 3–6 g/day of vitamin C, but Chalmers gives their average as the duration in the "placebo" group (Table 2). Chalmers states that the number of subjects in the vitamin C group of Karlowski et al was 101 (Table 2) which is the sum of the subjects in groups 3 and 4 (Table 4). For the duration of cold episodes in the vitamin C group, Chalmers gives the value 6.8 days (Table 2) which is the average for groups 1 and 2 (group 1 was the true placebo group). Thus, when pooling the results, Chalmers combined the placebo group with one of the vitamin groups (groups 1 and 2), and two vitamin groups receiving different doses (groups 3 and 4). Thereafter, Chalmers exchanged the duration of the cold episodes for the two pooled groups (Tables 2 and 4).

Regarding the first study by Anderson et al [13], Chalmers displays the duration of colds according to the presence of symptoms (5% decrease with vitamin C; Table 2). However, Anderson et al observed a much greater effect on the outcome parameter "days indoors"

(Table 3). This latter parameter apparently is more interesting for patients, since it is a measure of how much the common cold infections cause actual functional limitations. Accordingly, Chalmers' presentation of the duration of symptoms only, which did not reach statistical significance (Table 3), is misleading.

In case of the second study by Anderson et al [14], Chalmers gives the duration for a placebo group without indicating that there were actually two placebo groups in the study (Tables 2 and 3). There were great differences in these two placebo groups, these being a 14% difference in "days indoors" (Table 3) and a 30% difference in the duration of symptoms [14]. Furthermore, when the subjects were asked at the start of the trial for their recollection of "usual days indoors" during a typical common cold episode, placebo group #4 gave the largest value (2.57 days), and the other placebo group, #6, gave the smallest (1.97 days) among eight study groups, six of which were given vitamin C according to different protocols. The average of "usual days indoors" for three groups with regular vitamin C intake (≥1 g/day) was 2.34 days [14], which is 19% higher than the value for the placebo group #6. During the trial, the difference between the three vitamin C groups and the placebo group #6 was +13% (Table 3), which may suggest a small benefit when compared to the bias in the recollection. In any case, there seem to have been considerable biases in the allocation of subjects into the eight groups and this problem was discussed by the authors [14]. Chalmers gives just two values derived from the study (Table 2) with no comments on the complexity of the study which may give a misleading impression of the reliability of the values presented.

In some of the publications dealing with the effect of vitamin C on the common cold two independent studies are reported simultaneously. In the case of the Cowan et al publication [2], Chalmers correctly presents the two studies separately. However, Coulehan et al [15] examined independently the effect of 1 g and 2 g daily vitamin C dosages on clinical episodes of illness, but Chalmers combines the two studies together (Tables 2 and 3). This gives more implicit emphasis to the two studies by Cowan et al. More importantly, when the estimate of the effect is calculated, the work of Cowan et al is thereby given a weighting factor of two, while the work of Coulehan et al gets a weighting of one.

Wilson et al also reported the results of two independent studies, one with boys and another with girls [16], and these too are presented as a single study by Chalmers (Tables 2 and 3). For girls, Wilson et al found a 15% decrease in the duration of episodes and a 45% decrease ($p < 0.05$) in the intensity of symptoms [16]. Vitamin C did not benefit boys (Table 3). In a more recent study Miller et al also found that vitamin C decreased the duration and severity in girls ($p < 0.05$) but not in boys [25]. In the latter study, the investigators observed that in boys given placebo, the vitamin C content of urine was increased during the study period, a phenomenon not observed in girls [25]. Thus, it is possible that the boys exchanged their tablets to some degree in the studies by Miller et al and Wilson et al. By combining the two studies of Wilson et al in his table II, Chalmers masked the marked benefit observed in girls, although Chalmers did remark in the text that in the studies by Wilson et al and by Coulehan et al, "*the effects on symptoms seemed to be more striking in girls than in boys.*"

Chalmers states that the duration of episodes in the early study by Ritzel was 1.35 and 1.95 days in the vitamin and placebo groups, respectively (Table 2). In the original article, Ritzel gives values of 1.8 and 2.6 days, respectively [18]. Chalmers gives no explanation for this discrepancy [11].

In a footnote to his table II Chalmers noted that in the studies by Cowan et al there had been "*blinding of subjects only*" and that "*subjects were assigned to ascorbic acid or placebo group alternately*" [11]. However, Chalmers collected poor quality studies in his table I specifically, with a title "*neither randomized nor double blind*", and it is not clear why he did not include the Cowan et al studies in that table. In contrast, Chalmers included the study by Charleston and Clegg [20], a single blind placebo-controlled study which found a significant benefit from the vitamin, in his table I. Technically the latter study is quite similar to the studies by Cowan et al except that a much larger dose of the vitamin was used (1 g/day). Thus, Chalmers was not consistent in selecting the studies for his table II. We have included Charleston and Clegg's study in our Table 3.

In retrospect, it is also possible to ask whether Chalmers employed the most appropriate statistical methods for analyzing the data he had available to him. For example, he did not weight the individual means with the number of subjects to arrive at a mean difference in duration per individual. Also, unlike Pauling [5], Chalmers does not report or analyze the p-values found in the studies [11].

Role of Vitamin C Intake in the Treatment and Control Groups

An important variable in vitamin C studies is the amount of the vitamin administered to the subjects but this variable was not taken into account by Chalmers. In fact, Chalmers included the study by Cowan et al in which only 0.025–0.05 g/day of vitamin C was given to the test group (Tables 2 and 3). If vitamin C does have biochemical effects resulting in the alleviation of common cold symptoms, a dose-response relationship would be apparent: very small dosages may be ineffective, whereas large dosages could produce moderate benefits. In addition, the subjects in the 0.025–0.05 g/day group of Cowan et al received several other vitamins simultaneously (vitamins A and D, thiamine, riboflavin, nicotinic acid) in addition to the small dose of vitamin C [2], and therefore any observed differences cannot be attributed specifically to vitamin C. For these reasons one might argue that this 0.025–0.05 g/day study should not have been included in Chalmers' analysis.

The optimum dose of vitamin C is not obvious [4,6,26]. Pauling selected studies for his meta-analysis in which more than 0.1 g/day of vitamin C was regularly used [5]. Furthermore, Pauling pointed out that the greatest benefit was observed in Ritzel's study in which the largest dose was used (1 g/day; [18]), and this led Pauling to propose 1 g/day or more for the prevention and treatment of the common cold [3-5]. A dose-response effect is also seen in the studies Chalmers cited. Studies using at least 1 g/day of vitamin C show quite a consistent benefit, whereas studies with smaller doses show less consistent results (Table 3). Furthermore, Coulehan et al [15] and Karlowski et al [17] found a greater benefit in the study group given a larger dose of the vitamin (Table 3). Anderson et al compared the effect of 4 and 8 g/day of vitamin C when given, in several doses, only on the first day of illness [14]; the larger dose was consistently more beneficial when eight types of symptoms were measured. Thus, by including studies using small amounts of vitamin C (<1 g/day), Chalmers diluted the positive effects noted in studies using large amounts of vitamin C (≥1 g/day).

Furthermore, to test whether ≥1 g/day of vitamin C bestows benefits beyond those obtained on the RDA level of intake (0.06 g/day; [8]), the control group should not be allowed significant dietary intake of the vitamin. If the control group receives large amounts of vitamin C, a false negative result or a very small effect may result. A healthy diet containing large amounts of fruits and vegetables may provide more than 0.5 g/day of vitamin C, and in certain studies the control group apparently received large amounts of vitamin C in its diet [6,25]. Anderson et al [13] found that vitamin C supplementation was more beneficial to those who had a low intake of fruit juices compared to those with a high intake (a decrease of 48% and 22%, respectively, in total days indoors due to the common cold). The subjects of the Karlowski study [17] were employees of the NIH and therefore their dietary intake of vitamin C may have been much higher than the average in the United States; this could explain the rather small benefit observed when considering the high doses tested (Table 3). Thus, the dietary intake of vitamin C is an important modifying factor in the studies but it was not considered by Chalmers.

Calculation of an Estimate for the Benefit of Vitamin C

When Chalmers summarized the results for the effect of vitamin C on the duration of episodes, he calculated the average number of days saved by vitamin C administration per episode (Table 2). However, depending on the definition of disease (i.e. the outcome parameter) and on several other factors, the duration of the episode may be short or long, there being a ten-fold variation in the duration in different control groups in Table 3. When absolute values (days) are used in calculating the estimate of the effect, a great weight is given to studies with long duration of episodes. However, if a 3-day cold is shortened by 1 day, and a 6-day cold by 2 days, it seems inappropriate to conclude that the latter effect is twice the former. Instead, one may consider that both decreases are 33%. Thus, the absolute difference (days) used by Chalmers may not be the best parameter when comparing the various common cold studies. Calculation of the relative effect may instead be a better means of comparing equivocal outcome parameters.

Furthermore, when Chalmers calculated the average effect, he segregated Ritzel's study from the other studies, even though he listed it in his table II. Chalmers argued that the study was not reliable since it lasted for a short period (1 week). However, a short duration may be compensated with a fairly large number of subjects and a fairly high incidence of cold episodes; both of which occurred in Ritzel's study which was carried out at a ski school in the Swiss mountains [18,22]. If Chalmers included the study by Ritzel in his calculation, calculated the differences in the study by Karlowski et al correctly, omitted the low-dosage studies (<1 g/day), and chose "days indoors" as the most relevant outcome parameter from Anderson's first study, vitamin C would have appeared much more effective.

In Table 3 we briefly present our analysis of the studies reviewed by Chalmers. We calculated the relative difference in the duration of colds to normalize the episode duration among the various studies. If the second study by Anderson et al [14] is excluded because of the technical problems discussed above, the mean decrease is 21% (median 19%). There are 13 studies not discussed by Chalmers in which a regular dose of ≥1 g/day has been used [6,7]; they have mostly been published after Chalmers' review. In these studies, the mean decrease in duration or severity of symptoms was 26% (median 22% [6,7]); therefore, Chalmers could have made a good estimate of the average benefit from vitamin C supplementation (≥l g/day). However, as noted above, there is dose-dependency in the effect. The average benefit in all studies to date with 1 g/day has been 19% (median 13%) and in studies with 2–4 g/day it has been 29% (median 29%) [6,7].

Even though we consider the relative difference is a more meaningful parameter than the absolute difference (days), we also calculated the average for the absolute differences to allow explicit comparison of our Table 3 with Chalmers' table II. Vitamin C (1–6 g/day) would save 0.93 ± 0.22 (SE) days of illness per episode (Table 3). The latter value contrasts sharply with the average calculated by Chalmers, according to whom the difference between the vitamin C (0.025–6 g/day) and control groups is only 0.11 ± 0.24 (SE) days of illness per episode. Thus, from the studies that were known to Chalmers, an eight-fold higher estimate of the decrease in the duration of episode could have been obtained for vitamin C dosages suggested by Pauling [3-5]. In contrast to Chalmers' estimate, our estimate, 0.93 days saved per episode, significantly differs from zero ($p = 0.01$). It is noteworthy that the p-value for the estimate of the relative decrease in duration, –21%, is even lower ($p = 0.001$), apparently reflecting the benefits of the normalization procedure. Nevertheless, these p-values are conservative estimates of all the evidence. The individual p-values can be combined, for example, using Fisher's method [23,24], yielding a combined $p < 0.000004$.

The variability in the definition of the outcome parameter makes us cautious regarding the significance of the exact estimate of the benefit. However, the magnitude of the average decrease (21%) by 1–6 g/day of the vitamin (or 29% by 2–4 g/day; [6,7]) seems to be potentially important considering that the common cold is the most frequent cause for absenteeism from work and school and one of the most common causes of visiting the physician [9,10]. Vitamin C is a very cheap nutrient, with no known harmful effects in the general population from 1 g/day even with long-term usage [27,28]. For example, none of the common cold intervention studies using ≥1 g/day of the vitamin, which have contained over 6000 subjects in total, have reported any significant harmful effects [6,7,13-20]. Research has indicated that our ancestors ate 0.4–2 g/day of vitamin C [29,30], and the gorilla, a close biological relative of humans, eats about 4 g/day of vitamin C [31]. Therefore, these doses are not unfamiliar to human physiology (i.e. not pharmacological) even though they are much larger than the RDA (0.06 g/day; [8]).

Placebo Effect is not a Valid Explanation of the Differences

In his review, Chalmers suggested that the benefit due to vitamin C reported in several studies could result from the placebo effect [11]. He based this suggestion on the study by Karlowski et al [17], in which the subjects who could correctly identify vitamin C reported greater benefit from the vitamin than those who could not identify it. In Karlowski's study, the placebo consisted of lactose, which can easily be distinguished from ascorbic acid by taste. However, in a large number of studies it has been explicitly reported that the placebo tablets were indistinguishable from the vitamin C tablets [2,6,7,13-15,20,22]. The tablets have often contained citric acid [13-15,20]. It appears unlikely that the placebo effect would explain the benefits observed when valid placebo tablets are used.

One may question whether Chalmers' suggestion of the role of the placebo effect is valid even in the case of the Karlowski study. After the study, Karlowski et al found by questionnaire that many of the subjects guessed correctly whether they were being given lactose or ascorbic acid [17]. The investigators reanalyzed their results by forming two groups from the subjects: those who correctly guessed their treatment, and those that did not try to guess their treatment. There were large differences in the duration of episodes between the vitamin and placebo groups among subjects who guessed their treatment correctly, but no marked differences in subjects who did not make the guess [17]. This led Chalmers to conclude that the observed differences were due to the placebo effect [11].

One should be cautious when dividing subjects into subgroups according to factors that may be associated with a possible real benefit and guessing the treatment is one of such factors. If vitamin C does produce a significant benefit certain people may identify the vitamin from its physiological effects. For example, Asfora initiated a double-blind study to test the effects of 6 g/day of vitamin C on the common cold, but subjects receiving the vitamin could be identified by their clinical progress [32]. Thus, it is possible that in Karlowski's study, mild common cold symptoms led some subjects to correctly infer that they received vitamin C, and severe symptoms led to the inference that placebo was administered; whereas symptoms of medium severity led people not to make any guess of the treatment. In any case, the validity of the placebo should be examined before the study [13-15] rather than after its completion, as was the case in this poorly conducted study [17].

CONCLUSIONS

Chalmers' review of vitamin C and the common cold has been a cornerstone for the belief that the vitamin has no significant effects in reducing the severity of the common cold. The review has been used in several monographs as a basis for the conclusion that vitamin C is worthless for the treatment of the common cold [8-10]. We have shown that Chalmers' review contains serious and numerous errors. Therefore, the widely-accepted notion that vitamin C does not have any significant effect on the common cold is largely based on an unreliable review. After Chalmers' review was published, a large number of placebo-controlled double-blind studies have been carried out. Their results consistently and persuasively support the conclusion that vitamin C supplementation alleviates the symptoms of the common cold [6,7,33]. Moreover, the benefit due to vitamin C can now be rationalized physiologically. Vitamin C may protect against the reactive oxygen species that are produced, e.g. by phagocytes during a viral infection [6,34-37]. Also, vitamin C may enhance the proliferative responses of T-lymphocytes [37-46], and increase the production of interferon [47-51].

In this paper we show that even with the studies that were available to Chalmers, a more reasonable selection of the studies, corrections in his abstractions of the published results, and appropriate analysis would have indicated that vitamin C significantly decreases the duration of episodes of the common cold, a conclusion consistent with the studies carried out subsequent to the publication of Chalmers' review. Furthermore, in the period since the publication of Chalmers' review, the safety to the general population of long-term ingestion of large vitamin C doses has been established firmly [27,28]. Still, diarrhea and other gastrointestinal disturbances are sometimes associated with large doses (≥4 g/day) in healthy people [52]. However, people with the common cold infection can often ingest over 30 g/day of vitamin C without getting diarrhea [52], apparently due to changes in vitamin C metabolism [6,53]. Finally, there is much evidence suggesting that large therapeutic vitamin C doses which start early in the course of the common cold episode significantly decrease the severity of symptoms [1,6,17,32,33,52,54-57], but the evidence showing the benefit of regular intake is much stronger as nearly all of the trials have studied the effects of regular intake.

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