Effects of Ascorbic Acid on the Common Cold

An Evaluation of the Evidence

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Of 14 clinical trials of ascorbic acid in the prevention and treatment of the common cold, the data from 8 were considered well enough gathered to be creditable and to warrant combining for an over-all assessment of efficacy. Differences in mean prorated numbers of colds per year and durations of illness were 0.09 ± 0.06 (± 1 standard error) and 0.11 ± 0.24, respectively, favoring ascorbic acid over the placebo. These are minor and insignificant differences, but in most studies the severity of symptoms was significantly worse in the patients who received the placebo. In one study lasting 9 months, a large number of the volunteers tasted their capsules and correctly guessed what group they were in. All differences in severity and duration were eliminated by analyzing only the data from those who did not know which drug they were taking. 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.

Widespread sales of the book "Vitamin C and the Common Cold" by Professor Linus Pauling [1] have undoubtedly resulted in even greater sales of ascorbic acid to the self-prescribing public. There has also resulted a continuing controversy over the efficacy of the drug or vitamin in the medical literature, and the addition of several more clinical trials to the many that had been carried out before publication of Dr. Pauling's book. My purpose is to review the evidence for and against the efficacy of ascorbic acid in preventing colds, shortening their duration and alleviating their symptoms. The data suggest that ascorbic acid does have some effect on the severity of cold symptoms, but the effects are quantitatively so small, and the possibility of suggestion as the primary mechanism so large, that it hardly seems worthwhile for anyone to take all those pills for such a long time. This is especially true in view of the fact that there are as yet no data on long-term toxicity.

Fourteen clinical trials carried out by 11 investigators [2–13] between 1942 and 1974 have been reviewed. Five of the studies [2–5] (Table I) have been classified as poorly controlled because

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TABLE I Ascorbic Acid and the Common Cold—Poorly Controlled Studies (neither randomized nor double blind)

Source	Ascorbic Acid			Placebo			Ascorbic Acid-Placebo Difference	
	No. of Subjects	Colds/ Person/ Year	Mean Duration (days)	No. of Subjects	Colds/ Person/ Year	Mean Duration (days)	Colds/Person/ Year	Duration (days)
Charleston, Clegg 1972 [5]	47	3.24	3.5	43	6.45	4.2	3.21	0.7
Barnes 1961 [4]	22	6.00	2.0	16	8.25	6.5	2.25	4.5
Dahlberg et al. 1944 [3]	1,259	0.40	Not reported	1,266	0.51	Not reported	0.05	Not reported
Glazebrook, Thomson 1942 [2]	335	0.43	2.5	1,100	0.52	4.9	0.09	2.5
Glazebrook, Thomson 1942 [2]	60	1.13	3.2	90	1.28	4.0	0.15	0.8
				Mean ± 1 standard error:			1.15 ± 0.66	2.12 ± 0.89

they did not employ the technics of randomization and double blinding. The data are summarized as the differences in the number of colds per year among those taking ascorbic acid and those taking a placebo, and the difference in the mean duration of colds, when available. The five studies by four groups of investigators add up to a mean difference of 1.2 ± 0.7 (±1 standard error) colds per year and a mean difference in duration of colds in days of 2.1 ± 0.9. Only the difference in mean duration is significantly different from zero ($P < 0.05$).

In the case of the randomized or double blind studies (Table II), the differences are smaller, amounting to 1/10 of a cold per year and an average difference in duration of 1/10 of a day per cold. These differences, although favoring ascorbic acid, are far from statistically significant. Two of the eight favored placebo in number of colds, and in three the duration

TABLE II Ascorbic Acid and the Common Cold—Reasonably Well Controlled Studies

Source	Ascorbic Acid			Placebo			Ascorbic Acid-Placebo Difference	
	No. of Subjects	Colds/ Person/ Year	Mean Duration (days)	No. of Subjects	Colds/ Person/ Year	Mean Duration (days)	Colds/Person Year	Duration (days)
Anderson et al. 1972 [7]	407	5.51	3.96	411	5.92	4.18	0.41	0.22
Anderson et al. 1974 [8]	583	6.03	3.28	578	6.00	3.18	−0.03	−0.10
Coulehan et al. 1974 [11]*	321	0.40	4.71	320	0.46	5.92	0.06	1.21
Wilson et al. 1973 [10]†	158	2.31	2.65	144	2.18	2.79	−0.13	0.14
Karlowski et al. 1974 [12]‡	101	1.69	6.80	89	1.81	6.30	0.12	0.50
Franz et al. 1956 [6]	44	1.27	Not reported	45	1.33	Not reported	0.06	Not reported
Cowan et al. 1942 [13]§	233	1.90	1.10	194	2.20	1.60	0.30	0.50
Cowan et al. 1942 [13]§	227	2.40	1.70	120	2.40	1.00	0	−0.70
				Mean ± 1 standard error:			0.09 ± 0.06	0.11 ± 0.24
Ritzel 1961 [9]¶	139	6.37¶	1.35	140	11.54¶	1.95	5.17¶	0.60

* Double-blind study with subjects assigned to ascorbic acid or placebo group alternately.
† Summary of several trials.
‡ Double-blind broken.
§ Blinding of subjects only, and subjects assigned to ascorbic acid or placebo group alternately.
¶ Highly inaccurate figure because the study lasted less than 2 weeks and the number of colds per person had to be multiplied by 26. Also the assurances on blinding and randomizing are taken from a review by Pauling [25] because they were not included in Ritzel's paper.

TABLE III Ascorbic Acid and the Common Cold—Challenge Experiments in Volunteers

Data	Walker et al. 1967 [14]		Schwartz et al. 1973 [15]	
	Ascorbic Acid	Placebo	Ascorbic Acid	Placebo
No. inoculated	47	44	11	10
No. colds	18	18	11	10
Mean duration of colds (days)	8	7	6	6
Mean severity score	16.5	16.5	5.2*	7.4*

* Fourth day symptoms.

was less on the placebo. In extracting the data from the nine well controlled [7–13] trials, the results in all the patients were combined in each study. Subgroup differences were thus averaged out. In the study by Wilson et al. [10] only the "whole colds" have been tabulated.

It is noteworthy that in all nine of the randomized or double blind studies, patients treated with ascorbic acid prophylactically tended to have less severe symptoms than those who received placebo. In Anderson's study [8] the subjects took increased doses of ascorbic acid with the onset of a cold, but in the study by Karlowski [12], the therapeutic increment was controlled by a placebo, and the therapeutic dose had less of an effect on the severity of symptoms than the prophylactic dose. In the studies by Wilson et al. [10] and by Coulehan et al. [11], the effects on symptoms seemed to be more striking in girls than in boys.

Two groups of investigators have tested the efficacy of ascorbic acid in preventing colds induced by experimental inoculation of viruses in normal volunteers (Table III). Walker et al. [14] gave 3 g of ascorbic acid daily for only 3 days before inoculation of a number of different viruses; they found absolutely no effect on either the number of colds, their duration or their severity. Schwartz et al. [15] gave 3 g daily for 2 weeks before inoculation of a rhinovirus and likewise found that ascorbic acid had no effect on the incidence of colds. However, in those who received the drug, symptoms were slightly less severe.

TABLE V* Results of Questionnaire on a Prophylactic Drug Ingested by Each Volunteer

Actual Drug	Suspected Drug			
	Ascorbic Acid	Placebo	Unknown	Total
Ascorbic acid	40	12	49	101
Placebo	11	39	39	89
Total	51	51	88	190

NOTE: $x^2 = 28.6$, $p < 0.001$.
* From Karlowski et al. [12].

The trial carried out by Karlowski et al. [12] among employees of the National Institutes of Health revealed data most pertinent to the discrepancy between the effects of ascorbic acid on the incidence of colds and on their severity. The quantitative data from that study are summarized in Table IV. There was a minute effect on incidence and a larger one on mean durations of colds. Analyses of the severity of symptoms revealed that volunteers who received ascorbic acid tended to have milder symptoms in 18 of 20 instances, the differences being statistically significant in 5.

However, a questionnaire at the end of the study revealed that a significant number of the volunteers had correctly guessed their medication (Table V). Many had tasted the contents of their capsules. When the severity scores were reanalyzed according to those who knew and those who apparently did not know what they were taking, the differences in symptoms between those taking the placebo and those taking ascorbic acid were lessened. In fact, the group receiving the placebo who thought they were receiving ascorbic acid had fewer colds than the group receiving ascorbic acid who thought they were receiving the placebo ($p = 0.05$). There were no differences in the durations of colds among those who did not know what they were taking; those who did

TABLE IV* Comparison of Ascorbic Acid and Placebo in Prevention and Treatment of Colds

Group		No. Persons Completing Study	Total No. of Colds	Mean† No. of Colds per Person	Mean† Duration of Colds (days)
Prophylactic	Therapeutic				
Placebo	Placebo	46	65	1.41 ± 0.19	7.14 ± 0.46
Placebo	Ascorbic acid	43	56	1.30 ± 0.18	6.46 ± 0.39
Ascorbic acid	Placebo	44	52	1.18 ± 0.16	6.71 ± 0.53
Ascorbic acid	Ascorbic acid	57	76	1.33 ± 0.15	5.92 ± 0.40

* From Karlowski et al. [12].
† ± 1 standard error.

know demonstrated an appreciable ascorbic acid "effect." Similarly the differences in severity were largely eliminated when knowledge of the pill taken was included in the analyses.

The data in this study strongly favor the possibility that the effects of ascorbic acid on symptoms are the result of the power of suggestion. However, no such effect was demonstrated in the only other study in which a questionnaire was employed to determine whether or not the blind had been broken [7].

If the minor effects of ascorbic acid are real, there are three studies of physiologic changes which might explain them. Hume and Weyers [16] found that the ascorbic acid level in leukocytes drops sharply on the first day of a cold. Zuskin et al. [17] found that ascorbic acid reduces the airway constriction induced by the inhalation of histamine in adults. Valik and Zuskin [18] also found that it diminished the airway constrictor effects of certain textile dusts.

None of the clinical trials has revealed any significant toxicity of ascorbic acid when given in doses as high as 3 to 6 g/day. It is known, however, that renal stones may complicate chronic acidification of the urine that may result from such a regimen. It has also been suggested that mobilization of calcium from bone may result from chronic ingestion of large doses of ascorbic acid [19], and this could be a very serious long-term side effect, especially in women because of their greater tendency to have osteoporosis. Late toxicity of oral hypoglycemic agents in patients with middle-age diabetes [20] and the late appearance of carcinoma of the vagina in the female offspring of women given the "harmless" stilbestrol as a means of preventing threatened abortion [21] are examples of totally unanticipated long-term toxicity. The latter is a particularly poignant one because the drug was totally ineffective in preventing abortion [22]. So the absence of any apparent short-term toxicity of ascorbic acid does not mean that there cannot be serious long-term effects, and in the case of pregnant women risks to the fetus have not been ruled out. In addition, a number of theoretic toxic effects [23] must be kept in mind. Considering the lack of efficacy in preventing colds and the very small effects on symptoms, which could be due to suggestion, it hardly seems worth the risk to encourage people to take large doses of ascorbic acid over long periods of time [24].

The conclusion drawn from this analysis of the published controlled trials is the opposite of that drawn from the analysis carried out by Pauling [25], of four trials, published before 1971. However, Pauling averaged "p" values from the different studies rather than differences in the number of colds, and he also omitted the second study by Cowan which was entirely negative.

The best way to conclude this review of the evidence for and against the efficacy of ascorbic acid in preventing the common cold and amelioration of its symptoms is to state that I, who have colds as often and as severe as those of any man, do not consider the very minor potential benefit that might result from taking ascorbic acid three times a day for life worth either the effort or the risk, no matter how slight the latter might be.

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