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Vitamin C Supplementation and the Common Cold Was Linus Pauling Right or Wrong?

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Summary: In 1970 Linus Pauling claimed that vitamin C prevents and alleviates the episodes of the common cold. Pauling was correct in concluding from trials published up till then, that in general vitamin C does have biological effects on the common cold, but he was rather over-optimistic as regards the size of benefit. His quantitative conclusions were based on a single placebo-controlled trial on schoolchildren in a skiing camp in the Swiss Alps, in which a significant decrease in common cold incidence and duration in the group administered 1 g/day of vitamin C was found. As children in a skiing camp are not a representative sample of the general population, Pauling's extrapolation to the population at large was too bold, erring as to the magnitude of the effect. Nevertheless, Pauling's general conclusion that vitamin C has physiological effects on the common cold is of major importance as it conflicts with the prevailing consensus that the only physiological effect of vitamin C on human beings is to prevent scurvy.

Introduction

Between 1930 and 1960 various authors suggested that vitamin C has beneficial effects on the common cold [1-7]. However, these suggestions had no effect on the general attitude towards vitamin C, the physiological role of which was considered to be the prevention of scurvy alone. The issue became more popular after

1970 when Linus Pauling, a dual Nobel laureate (chemistry in 1954 and peace in 1962), wrote a book in which he claimed that this vitamin both prevents and alleviates common cold episodes [8]. In 1971 Pauling carried out a meta-analysis of four placebo-controlled trials and concluded that it was highly unlikely that all the reported benefits in the vitamin C groups could be ascribed to chance alone ($p < 0.000022$) [9].

After the publication of the 1970 book [8], a number of trials were carried out to test Pauling's hypotheses [7, 10, 11]. However, the interest in the issue declined abruptly after the middle of the 1970s (Fig. 1). In 1975, two highly influential reviews [12, 13] and one particularly influential trial [14] were published; all three papers concluded that there is no evidence that vitamin C has effects on the common cold. Apparently these three papers gave a strong impression that vitamin C has no effects on the common cold and caused the subsequent decrease in the number of studies on the issue (Fig. 1).

In his reminiscences Pauling described the psychological background to his common cold book. After an acrimonious exchange of views concerning the effects of vitamin C supplementation, Pauling became "sufficiently irritated" to sit down and write a synthesis of the evidence indicating that vitamin C is beneficial against the common cold [15]. After his 1970 book was published, Pauling complained that many of his critics had not read either his texts or the original papers, giving several examples in support of his accusation [16-18].

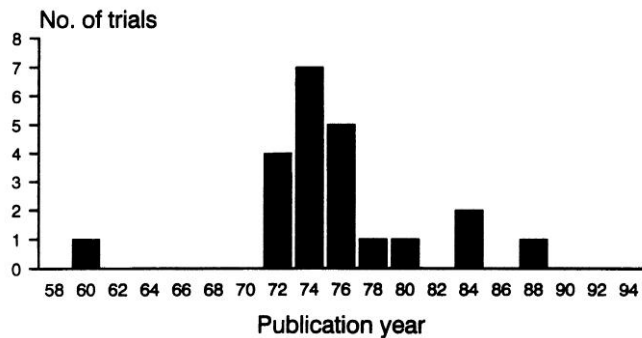


Figure 1: Placebo-controlled studies in which > 1 g/day of vitamin C was regularly administered to the subjects. Regular supplementation refers here to initiating supplementation with healthy people and continuing over the occurring common cold episodes. The number of studies published during two consecutive years is combined and plotted for the first of the two years. For the list of references to the trials, see [10, 11].

Three highly important reviews stated that there was no valid evidence to conclude that vitamin C has effects on colds [12,13,19]. These reviews were recently shown to be flawed however [20, 21]. Furthermore, the particularly influential trial carried out at the National Institutes of Health in the USA found a statistically significant difference between vitamin C and placebo groups in favour of the vitamin, but the difference was paradoxically ascribed to a break in the double-blind [14]. Recently, it was shown that such an interpretation is not valid, indicating that the differences between the study groups were caused by the physiological effects of the vitamin [22].

The results of the controlled trials are briefly described in this paper and they are compared with Pauling's conclusions.

The Effect on Common Cold Symptoms

Pauling suggested that 1 g/day or more would be useful for treating colds [8,9]. The incidence of the common cold is greater in children than in adults and hence placebo-controlled trials with children administered > 1 g/day of vitamin C are particularly interesting in seeking the effects of this vitamin. There are 10 study groups satisfying these criteria, whose results show that vitamin C alleviates common cold symptoms (Table I). For the outcomes listed in Table I the median decrease is 22%.

Evidently the main question should not be to decide whether a decrease of 22% is clinically important, but to identify the characteristics of the groups of children in which the benefit is great or small. Furthermore, as the original results are mean-values for a group of children, it is also obvious that vitamin C is much more, and much less, beneficial for some individual children than suggested by the result of a single trial or by the median of several trials.

Carr *et al* [29] found that vitamin C had a considerable effect on twins living apart, but no ef-

Table I: The effect of regular vitamin C supplementation (≥ 1 g/day) on the severity of common cold episodes in children¹

Study [ref.]	Dose (g/day)	No. of episodes	Effect on the outcome ² (%)	Outcome
Carr <i>et al</i> 1981 ³ [29]	1	164	+ 1	Duration of symptoms
Coulehan <i>et al</i> 1976 [26]	1	196	- 5	Duration of symptoms
Coulehan <i>et al</i> 1974 [25]	1	42	- 12*	Duration of symptoms
Ludvigsson <i>et al</i> 1977 [28]	1	449	- 14*	Absence from school
Miller <i>et al</i> 1977 [27]	1	95	- 20	Days in bed
Bancalari <i>et al</i> 1984 [30]	2	84	- 24*	Duration of symptoms
Coulehan <i>et al</i> 1974 [25]	2	33	- 29*	Duration of symptoms
Ritzel 1961 [9, 17, 23, 24]	1	48	- 29*	Duration of symptoms
Ludvigsson <i>et al</i> 1977 [28]	1	49	- 31	Absence from school
Carr <i>et al</i> 1981 ⁴ [29]	1	128	- 35*	Duration of symptoms
Total no. of episodes:		1288	- 20	Mean outcome
			- 22	Median outcome

¹ All trials in the table were double-blind placebo-controlled studies. In all studies children were randomly allocated to study groups, except for the Coulehan 1974 study [25], in which children were allocated to study groups alternately by alphabetical order.

² Relative effect: the difference between the outcomes in vitamin C and placebo groups divided by the outcome in the placebo group. Statistical significance: *, $p < 0.05$.

³ Twins living together.

⁴ Twins living apart.

feet on twins living together (Table I). An obvious interpretation of such a difference is that twins living together exchanged their tablets to a great extent, while twins living apart could not. Moreover, it is noteworthy in Carr's study [29] that the average duration of colds in both vitamin C and placebo groups of twins living together (5.4 days), was intermediate between the vitamin C (4.9 days) and placebo (7.5 days) groups of twins living apart, which also is consistent with the notion that tablets were exchanged by twins living together. Two other trials with children found an increase in plasma [25] and urine [27] vitamin C levels in the placebo (*sic!*) groups even more directly indicating that tablet exchange may have taken place among playful children under study conditions. Carr's subgroup analysis (Table I) is particularly important in suggesting that in some studies with children the mischief of the subjects may have caused underestimation of the true physiological effect.

A further important question in the trials is the baseline dietary vitamin C intake. Miller *et al* [27] found that at the start of the study their subjects excreted 0.2-0.3 g/day of vitamin C in urine and the intake must have been even higher. The recommended intake for 7-14 year old children is considerably lower at 45-50 mg/day [31]. Ludvigsson *et al* [28] found no difference in leukocyte vitamin C concentrations between the vitamin and placebo groups, also indicating that the dietary vitamin C intake was high. Consequently, in some studies high dietary vitamin C intake may have decreased the difference between the study groups, and the effect thus could be greater if the control group received only the recommended amount of the vitamin.

Table I consists of trials in which vitamin C was administered regularly and it is important to consider to what extent the results can be extrapolated to therapeutic supplementation initiated after the onset of symptoms. Some studies with adults have reported benefit from therapeutic supplementation [14, 22, 32, 33]. Nevertheless, in therapeutic trials there are additional sources of variation in the results since a delay in the initiation of the treatment and a short treatment period not covering the entire episode can both decrease the effect.

In a study with adult subjects, Asfora [33] found that therapeutic supplementation of 6 g/day for 5 days decreased the average duration of the colds by 48% when the treatment was initiated within 24 h of the onset of symptoms. However, if supplementation was commenced 24-48 h after the onset of the cold, the decrease was only 29%, and when the treatment was commenced still later there was no benefit. These data thus suggest that therapeutic vitamin C supplementation should be initiated as soon as possible after the first symptoms are observed.

Some of the therapeutic trials with adults [34-36] found no consistent benefit from vitamin C supplementation, but this might be attributed to a brief period of supplementation (2-3 days), which was considerably shorter than the duration of cold episodes in the same studies (5-8 days).

Even though it is clear that vitamin C has physiological effects on common cold symptoms, the clinical significance of therapeutic supplementation during cold episodes is still an open question.

The Effect on Common Cold Incidence

Most of the controlled trials have found no significant effect on the incidence of colds [10,11]. In the six largest trials there was no decrease in common cold incidence in the vitamin C groups: pooled rate ratio (RR) = 0.99 (95% CI 0.93-1.04) [37]. Large doses of vitamin C thus have no meaningful effect on the number of common cold episodes in the general population of Western countries.

Nevertheless, it is possible that vitamin C intake has some effect on cold incidence in limited groups of people or in people under specific conditions. It recently was shown that in three studies with subjects under heavy acute physical stress [38] there was a significant decrease in cold incidence in groups supplemented with vitamin C: RR = 0.50 (95% CI 0.35-0.69). In four studies with British men [37] there was also a significant decrease in cold incidence in the vitamin C groups: RR = 0.70 (95% CI 0.60-0.81). In addition to the studies falling into these two groups some other studies have found sta-

tistically significant preventive effects with vitamin C supplementation (1-tailed p).

In their 1942 study with schoolchildren Cowan *et al* [39] found a 15% lower incidence of colds in the group supplemented with 0.1-0.2 g/day of vitamin C ($p < 0.02$ [9]). In a study carried out in 1971 with miners in Czechoslovakia, Masek *et al* [40] found a 22% lower incidence of colds in a group supplemented with 0.1 g/day of vitamin C ($p < 0.02$); however, the control group was not administered placebo. In their 1972 study Anderson *et al* [41, 42] found a 21% lower incidence of "throat colds" ($p < 0.01$ [37]) in the vitamin C group (1 g/day), but there was no difference in the incidence of "nose colds". Bancalari *et al* [30] reported a significantly smaller number of "recurrent colds" in schoolchildren administered 2 g/day of vitamin C.

Another outcome reflecting the preventive effects of vitamin C supplementation is the proportion of subjects remaining free of illness during the study. In their study in 1972 [41] Anderson *et al* found that 26% of subjects remained free of illness in the 1 g/day vitamin C group, whereas in the placebo group 18% remained free of illness ($p = 0.006$ [37]). Coulehan [25] found that among schoolchildren of lower grades 32% remained free of illness in the 1 g/day vitamin C group, whereas in the placebo group only 16% did so ($p = 0.0001$ [21]). Also a significant preventive benefit from the vitamin C in children of the upper grades was found [25], but this was smaller, 63% as against 49% remaining free of illness ($p = 0.02$) [21].

The strongest evidence indicating that vitamin C intake has a physiological effect on susceptibility to colds comes from the studies with subjects under acute heavy physical stress [38] and with British men [37]. While a few other studies are compatible with the notion that regular vitamin C supplementation may be beneficial for certain people, it seems clear that in the general population large doses have no substantial effect on the number of cold episodes [37].

Was Linus Pauling Right or Wrong?

As regards the effects of vitamin C on the common cold, Pauling drew conclusions at various different levels. At the general level he claimed

that vitamin C has biological effects on the incidence and severity of the common cold [8,9]. The results published so far indicate that these general conclusions were correct. They do however conflict markedly with the prevailing consensus that the only physiological effect of vitamin C in human beings is to prevent scurvy. For example, the nutritional recommendations are concerned with the prevention of scurvy alone and the recommended intake levels are not based on controlled trials or epidemiological studies indicating that such levels are optimum amounts in the long term [18,31,43-50]. In this respect Pauling's general conclusions were of major importance in challenging the nutritional paradigm focused on scurvy alone.

Nevertheless, with respect to specific conclusions as to the size of the effect, Pauling was grossly over-enthusiastic. Pauling [9] based his estimates of the benefit on a trial published in 1961, carried out by Ritzel [23] with schoolboys in a skiing camp in the Swiss Alps. When Pauling [9] considered the topic, this particular trial was the only placebo-controlled study in which 1 g/day of vitamin C had regularly been given to subjects. Technically it was a well designed study as it was randomized, double-blind and placebo-controlled [23, 24]. Pauling put great weight on it and extrapolated the findings to the general population. He modeled the dose-dependency of the effects of vitamin C supplementation with exponential formulas in which constants were based on Ritzel's data. Pauling assumed that the main problem in his estimates was the inaccuracy caused by the "experimental error," although he also noted that "the values are, of course, expected to depend somewhat on the nature of the population and environment" [9]. However, even with these prudent reservations Pauling's conclusions were all too optimistic. He could not imagine how great the variations in the results would be in the forthcoming trials. Neither did Pauling consider the possibility that the effects observed by Ritzel [23] were caused, at least in part, by low dietary vitamin C intake, in which case a smaller dose could have produced a similar benefit. Pauling attributed the difference between the study groups solely to the large dose given to the treatment group [9].

Ritzel found that cold symptoms in the vitamin C group were 29% shorter [9, 17, 23]. This is quite comparable with the results found in other trials with children (Table I), so that the decrease observed by Ritzel [23] seems to be biologically meaningful. However, in adults the benefit has usually been much smaller. In a large-scale study recording 1317 cold episodes among 688 adult women, Elwood *et al* [51] found only a 6% decrease in the duration of colds with 1 g/day of the vitamin. Furthermore, Karlowski *et al* [14, 22] administered 3 g/day regularly to adults, but the duration of colds was reduced by just 6%. It thus seems that the extrapolation of Ritzel's finding to the general population was a major reason for the great discrepancy between Pauling's quantitative predictions [9] and the effects seen in later trials carried out largely with adults [10].

Ritzel found a 45% lower incidence of colds in the vitamin C group [9, 17, 23]. This study belongs to the group of four that used subjects under acute heavy physical stress, and in each of these studies a substantial decrease in common cold incidence was reported with vitamin C supplementation [38]. Consequently, Ritzel's finding seems biologically meaningful also in this case. However, Pauling's [9] extrapolation of this finding to the general population led him into error [37]. It is not clear to what extent Ritzel's results are attributable to the heavy stress and to what extent to relatively poor nutrition in the skiing camp, but Ritzel's result on incidence was positive because of the particular experimental conditions and therefore the finding cannot be extrapolated to the general population.

As regards the errors in Pauling's quantitative conclusions, it should obviously be taken into account that most of the trials available today were carried out after Pauling worked on the topic, and even more importantly, they were carried out precisely because Pauling made the issue popular. Without bold intellectual leaps and provocative hypotheses progress in science is slow or non-existent. In this respect the accuracy of Pauling's extrapolation from the single placebo-controlled trial using regular 1 g/day supplementation available in the early 1970s is not particularly relevant.

Pauling was highly energetic and he was also interested in the role of vitamins in treating mental disorders [44] and in the role of vitamin C in treating cancer [52-55], as well as in problems of structural chemistry. It seems that because of his numerous other activities Pauling left the common cold issue largely unfinished and was not confronted with the fact that in the later trials the observed benefits were considerably smaller than he predicted. Pauling also adhered strongly to the idea of regular supplementation which led him to analyze the results by calculating the "integrated morbidity," which is the product of the incidence and duration of colds [9, 17, 18]. However, the effects of vitamin C supplementation on incidence and duration show very different patterns and it seems to be much more fruitful to analyze these effects separately.

Retrospectively it seems surprising that Pauling did not point out the shortcomings in Chalmers' review [12, 20] or the flaws in the interpretation of Karlowski's trial [14,22]. Pauling did write two papers [56, 57] in which he pointed out certain shortcomings of the Dykes and Meier review [13]. However, there are important flaws in Dykes and Meier's review that were not pointed out by Pauling [21].

The trials carried out after Pauling wrote his 1970 book "Vitamin C and the common cold" have consistently found that vitamin C alleviates common cold symptoms (Table I; [10, 11, 21]). In this respect Pauling's opponents were not flexible enough in maintaining that vitamin C has no effect on colds. It seems that the opposition to Pauling's conclusions was not so much caused by the inaccuracy of his estimates, but rather because of disagreements at the "paradigm" level [21, 46, 47]. There are several examples of efficacious therapies being rejected because they did not "make sense" in the light of accepted theories of disease mechanism and drug action, the phenomenon being designated the "tomato effect" [58]. Such a strong adherence to the scurvy paradigm may explain the bias in several reviews [20,21] and the flawed interpretation of the Karlowski study results as well [22]. Nevertheless, the suggestions that vitamin C may have effects on the immune system go back to the 1930s [59-64], and in this respect

the question of whether it "makes sense" that vitamin C has effects on the common cold may largely depend the degree of familiarity with the immunological literature. None of the three major reviews [12, 13, 19] cited original papers or reviews dealing with the possible effects of vitamin C on the immune system.

Conclusion

Although controlled trials have shown that vitamin C does have physiological effects on the common cold, there are a number of open questions still awaiting answers: what is the best method of supplementation, what are the maximum treatment effects, how does the benefit vary in different groups of subjects, etc? Obviously, answering such questions demands further controlled trials.

It seems reasonable to assume that the effects of vitamin C on the common cold are caused by nonspecific effects on the immune system. There seems to be no reason to think that vitamin C has effects specific to the common cold, which in fact is caused by half a dozen unrelated viruses with some 200 serotypes. Consequently, it is not surprising that a few reports indicate that vitamin C intake may have effects on the prevention and treatment of other infections [65]. Finally, there is evidence that in humans vitamin C has physiological effect unrelated to both scurvy as well as infections [18,43-45,49,50,52-54,66-70]. Even though such effects are presumably modest in size, it would seem worthwhile to examine such effects in more detail since vitamin C is a cheap substance and safe even in large doses [18, 68-72], so that a cost benefit ratio may be meaningful even with modest effects.

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