LARGE-SCALE TRIALS OF VITAMIN C *

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Among the many claims made about the value of large doses of vitamin C, those relating to the prevention and treatment of "colds" have aroused most interest, and the first question to be answered is whether there is any real evidence that such an effect exists, or whether the claims are based entirely on wishful thinking. If there is no good evidence of an effect, then there is little point in pursuing the matter. If, on the other hand, the evidence suggests that there is *some* sort of effect, a host of secondary questions present themselves:

(1) Is the effect specific for the common-cold group of viruses, or is it a more general anti-infective (or even antistress) effect?

(2) Is it a reflection of an increased metabolic need in certain individuals or at certain times, or is it a pharmacological action unrelated to the normal metabolic function of ascorbic acid?

(3) Is the beneficial effect related to a regular daily intake ("prophylactic") or to extra intake during the course of an illness ("therapeutic") or to a com bination of both?

(4) Are large doses really necessary, or could equally good results be ob tained with a more moderate supplementation of normal dietary intake?

(5) If large doses *are* necessary, does the risk of side effects outweigh the possible benefits?

From a practical point of view it is this last question that most urgently needs to be answered. Further, since it seems reasonable to suppose that side effects are more likely to appear with higher doses and with prolonged intake, the first point to establish is whether there is any value to the regular "prophylactic" use of large doses of vitamin C, and whether in fact the size of the daily dose is as important as has been claimed.

In passing, it may be noted that although we have seen no symptomatic evidence of toxicity resulting from doses of up to 2000 mg daily over three or four months in healthy persons, this does not mean that this dose level is necessarily safe for longer periods, particularly in individuals with preexisting disease, or that the occasional individual might not show some unusual and undesirable reaction. Furthermore, while perhaps not a side effect in the ordinary sense of the word, the depression in blood ascorbate levels that occurs on sudden withdrawal of a chronic high intake should be recognized as a potentially harmful reaction. For example, an individual admitted to the hospital with an acute medical or surgical condition might be at a physiological disadvantage if this period of unusual stress coincided with an acute hypoascorbemia due to sudden withdrawal of a regular high intake.

What then, is the evidence regarding the prophylactic use of large doses of vitamin C? There is, of course, a great deal of anecdotal evidence, but this is of dubious value because of the well-recognized interaction between mental state

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and physical symptoms. Hence the importance of trials that are truly double-blind, and in this paper I will restrict myself to the three double-blind trials in which I have personally been involved. It should be clearly understood that in the double-blind method psychological factors are still present, but their effects tend to cancel out provided that subjects are randomly allocated to treatment and control groups and provided that the nature of the treatment (active or placebo) is truly indistinguishable to both subjects and investigators. If the initial allocation is not random, or if the active tablets can easily be distinguished from the placebo, then psychological factors will not be equally distributed and the fundamental logic of the experiment is destroyed. Under these circumstances no amount of statistical manipulation can undo the damage.

The other feature of these "free-living" trials that is often ill-understood is that a very large number of subjects may be required to achieve statistically significant results. This is due in part to the wide variation in individual sickness patterns and in part to the fact that, despite its name, even the common cold is a relatively uncommon event, with few individuals experiencing more than one or two episodes of illness in a three- or four-month period. The problem is, of course, intensified if relatively small differences in effect are being sought.

My colleagues and I have now completed three relatively large-scale trials of the effect of supplementary vitamin C on colds and other forms of spontaneously occurring winter illness. The first[1] was carried out during the winter of 1971-1972 to test the widely publicized claims of Professor Linus Pauling that the regular intake of large doses of vitamin C could reduce both the frequency and severity of the common cold.[2] Specifically, we set out to test his claim (made in a letter to the *Canadian Medical Association Journal* in September, 1971 [3]) that the regular intake of 1 gram of vitamin C per day would lead to 45% fewer colds and 60% fewer days of sickness. Since we were skeptical of the evidence on which Professor Pauling based his claim, we anticipated a negative result and therefore enrolled a large number of subjects (1,000) in the hope of avoiding an indecisive answer that would only prolong the controversy. For the same reason we added a therapeutic feature—an increase in the daily dose to 4 grams during the first three days of any illness—to give the regime every possible chance of success.

Subjects were randomly assigned to vitamin or placebo tablets and the design was strictly double-blind, with special care being taken to ensure that the two types of tablets were truly indistinguishable in color, texture and taste. The detailed results of this study have been published elsewhere [1] but, briefly, we found that among the 818 subjects who completed at least eight weeks in the study (average 14 weeks) those receiving the vitamin experienced 30% fewer days indoors or off work, differences that were statistically highly significant. On the other hand, although the mean number of episodes per subject was 7% less in the vitamin group, this difference was not statistically significant.

Detailed examination of the data failed to reveal any bias in the make-up of the two groups that could account for the observed difference in sickness experience, and we therefore organized a second experiment during the following winter in which we could study the prophylactic and therapeutic features separately, and the effect of different dosage levels.[4] This study ran for three months (Dec. 1, 1972, to Feb. 28, 1973), with a fourth month of record-keeping only to see if there was any rebound increase in sickness after stopping the vitamin tablets. (None was detected.)

Initially there were 3520 subjects, of whom 2349 completed the first three

months, giving a dropout rate of 33%. This was considerably higher than the 18% dropout rate experienced in the first study and appeared to be due largely to the use of bigger tablets, which many subjects found difficult to swallow. Eight different dosage schedules were studied, and, as in the first study, subjects were assigned "blindly" to each of the 8 groups. Each subject received two bottles of tablets, one marked "Daily" and the other "Extra." Depending on the dosage schedule of the group to which they had been allocated, subjects were instructed to take either 1 or 4 tablets daily, and 12 or 16 of the extra tablets on the first day of any illness. This resulted in the following dosage schedules: three prophylactic only (0.25, 1, and 2 g daily), two therapeutic only (4 and 8 g on the first day of illness), one combination (1 g daily and 4 g on the first day of illness), and two all-placebo. It should be noted that the increased dosage was taken on the first day of illness only, rather than on the first three days as in the first study. This was done to ensure that each subject had enough "extra" tablets for at least six episodes of illness.

Several problems were encountered during the trial and during the analysis of the results. Space limitations preclude a full discussion of these problems, but details may be found elsewhere.[4] Suffice it to say that they were due partly to the large number of groups and partly to the size of the tablets. The problems included: (1) A labeling error involving two batches of bottles, resulting in one group's receiving 40 more subjects than it should, and one group's receiving 40 less than it should. (2) Although the initial groups were well matched for various characteristics, the high dropout rate led to an imbalance between the groups, the most seriously affected being the second (1:16 tablets) all-placebo group. (3) There were a few very prolonged illnesses, and although these were distributed in an apparently random fashion among the 8 groups, they seriously inflated the overall sickness rates in one or two of the groups.[4] At the other extreme, about 40% of the reported episodes were very brief (one day or less) and are probably best ignored when comparing the incidence of significant illness in each group.

The results presented in TABLE 1 are therefore in the form of a "best estimate" of the sickness experience of the vitamin groups relative to the placebo groups, based on those episodes lasting between 2 and 14 days, and using a weighted all-placebo mean, in which the more typical all-placebo (4:12 tablets) group has been given twice the weight of the other. For comparison, the figures based on the unweighted placebo means are also given in TABLE 1.

All types of illness have been included since respiratory symptoms were present in over 90% of the episodes, and separation into various symptom complexes had little effect on the overall pattern.

Although none of the differences between the means of the vitamin and placebo groups in this study were of statistical significance, the results were compatible with the belief that the effect of the combined regimens used in both studies was probably due to the combination of a small effect from each of the prophylactic and therapeutic components. Possibly the most noteworthy aspect of these results was the absence of any dose-response effect in the prophylactic-only regimes in spite of an 8-fold range (0.25 to 2 g) in daily intake. No firm conclusions can be drawn about the presence of a dose-related gradient in the therapeutic-only regimes, since only two levels were used and the differences in sickness experience between them was within the limits of statistical variation. However, it may be noted that the differences were consistent with a dose-related response.

TABLE 1

SUMMARY OF THE RESULTS OF THE THREE DOUBLE-BLIND TRIALS OF VITAMIN C CONDUCTED IN TORONTO, 1971-1974 *

	Combined			Prophylactic			Therapeutic	
	1971–72	1972–73	1973–74	1972–73			1972–73	
Daily dose (well/sick) †	1/4	1/4	0.5/1	0.25/0	1/0	2/0	0/4	0/8
Episodes per subject	90	95	94	92	98	96	96	89
		99		*95*	*101*	*99*	*99*	*92*
Days of symptoms	86	98	90	96	99	97	97	86
		103		*100*	*104*	*101*	*101*	*91*
Indoors	70	85	79	98	92	96	95	92
		88		*102*	*96*	*99*	*98*	*95*
Off work	70	80	88	95	89	100	94	87
		83		*99*	*93*	*104*	*98*	*91*
Symptoms								
Nose	89	100	94	103	106	98	95	86
		106		*109*	*112*	*103*	*100*	*91*
Throat	87	98	83	94	94	89	95	88
		102		*99*	*98*	*93*	*99*	*92*
Chest	92	75	66	96	82	91	91	78
		81		*104*	*88*	*99*	*98*	*84*
Feverish	48	96	70	92	104	107	105	91
		101		*96*	*109*	*112*	*110*	*95*
Shivering	80	92	69	92	94	91	107	80
		94		*95*	*97*	*93*	*109*	*82*
"Malaise"	81	—	—	—	—	—	—	—
Aching limbs	—	83	76	98	114	83	101	81
		88		*103*	*119*	*87*	*106*	*85*
Depressed	—	85	92	98	94	90	103	81
		88		*102*	*98*	*94*	*107*	*85*

* In each case the mean number of days (or episodes) per subject in the group receiving vitamin C has been expressed as a percentage of the figure for the corresponding placebo group. Values for 1972-73 study are based on weighted means of the two placebo groups. Corresponding values based on the unweighted means are given in italics.

† In the 1973-74 study the 0.5-g dose was taken once weekly (not daily). Daily dose was increased to 4 g for first days of sickness (1972-73), or for first three days of sickness (1971-72). In the 1973-74 study 1.5 g was taken on the first day (0.5 g every 4 hr three times), and 1 g (0.5 g every 12 h) on the second through fifth days of illness. Brief episodes (one day or less) and prolonged episodes (15 days or more) have been excluded.

In comparing these results with those obtained by Coulehan et al. in their study of Arizona schoolchildren [5] it appeared that tissue saturation might be the limiting factor in the prophylactic use of vitamin C, and possibly even in its therapeutic use.[6] We therefore organized a third trial in which both the prophylactic and therapeutic doses were much smaller than we had used previously but the duration of the therapeutic supplement was extended to 5 days.

We also wished to see whether a sustained-release form of ascorbic acid would produce a greater clinical response than the ordinary tablet. The rationale of this was that the sustained-release capsule produced a prolonged elevation of blood ascorbate level, and if blood level was a crucial factor, this mode of delivery might possibly be as effective as several times the same dose of the regular quickly absorbed, quickly excreted form. It was also hoped that blood ascorbate levels could be monitored during episodes of illness, to see whether in fact the sustained release form was better able to maintain normal levels, but unfortunately, because of technical problems, this part of the experiment was not completed.

Six hundred volunteers were allocated blindly to three groups, and 448 completed the study. Two groups received a 500-mg dose of vitamin C once weekly, and three doses (at 4-hour intervals) on the first day of illness, continued if necessary at 12-hourly intervals for the next four days.

The preliminary results of this study are summarized in TABLE 1, using the combined exerience of the two vitamin groups, since although there was some evidence that the sustained release form was more effective than the tablets, most of the differences were neither consistent nor very large. For consistency, all of the figures given in TABLE 1 are based on episodes lasting 2 to 14 days, and although there are some individual differences in the results of the three combination trials, there are also a number of similarities. Thus, all three have shown a small vitamin "effect" on the number of episodes per subject but a more substantial effect on the days indoors or off work. Similarly, all have shown consistently little or no effect on days of nasal symptoms (thus casting some doubt on the antihistamine theory of vitamin C action), while there have been some large but inconsistent effects on days of chest symptoms, fever, and malaise. (The latter term was subdivided into "limbs ache, feel heavy," and "mentally depressed, no ambition" in the second and third studies).

By conventional 2-tailed t-tests the only differences that reached the 0.05 level of statistical significance in the third study were days of chest symptoms ($t = 1.97$), days of feeling feverish ($t = 2.14$), and days of shivering ($t — 2.23$). There was a significant difference ($t = 1.99$, $p = 0.05$) for days indoors using total episodes, but this disappeared ($t = 1.56$, $p = 0.12$) when the 2-14 day limitation was imposed.

Considering the relatively small number of subjects in the third trial, it is clear that these results are compatible with the belief that a relatively modest degree of supplementation (both prophylactic and therapeutic) may be sufficient to produce a useful reduction in overall morbidity and that the dosages used in our first trial were probably unnecessarily high. Incidentally, in none of the trials was there any evidence that sex, age, or smoking habit was related to the outcome, or that different types of illness were affected more than others.

In conclusion, I would suggest that unless and until firm evidence is forthcoming that higher doses of vitamin C are more effective, we should adhere to the principle of "primum non nocere," and advise the public to limit their daily intake to 100 or 200 mg, except possibly for brief periods during acute infection when gram doses *may* be beneficial.

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DISCUSSION

Ms. E. BARRETT: You very carefully explained the dosage and timing of your first three studies except for the sustained release preparation. You did not tell us the size of the dose, how often you gave it, and what kind of sustained preparation it was.

DR. ANDERSON: There were three groups in our third trial. One group received placebo, one group received the 0.5-gm vitamin C tablets, and the third group received the 0.5-gm sustained release capsules. They all followed the same schedule—one pill a week, three on the first day of illness, and one every 12 hours for the next four days.

Ms. BARRETT: What control did you have over supplemental treatment that the individuals in your study might have administered to themselves? Also, what evidence do you have that exposure to the infectious agent is uniform among the entire population?

DR. ANDERSON: We told the subjects that apart from taking their vitamin (experimental) tablets, to treat themselves in the way they usually would for a cold, go to bed or not go to bed, take aspirin and so on, and we asked them to make a note of what other treatment they used, as far as vitamin supplementation was concerned. We asked them not to take anything that contained more than 100 mg. We wanted to interfere as little as possible with their normal routine. As to the second question, uniformity of exposure is a basic variable of epidemiologic studies. You cannot insure that exposure is the same, but if you have a large enough group, which is randomly allocated, it is expected that these factors will tend to cancel each other out, particularly if you repeat the trial for another winter.

DR. MCKNIGHT: Have you attempted to analyze your data for interaction between the vitamin C and the other supplementary cold medicine the subjects might be taking?

DR. ANDERSON: We tried to in the first trial, but it was very involved and I do not think we got a very accurate record. These "big and dirty" trials are of limited value; they simply indicate direction.

DR. W. J. DARBY: What was the intake of vitamin C in the placebo group? Also, you indicated that you kept a daily record of the supplements taken by the individuals. However, you did not indicate whether these records were comparable between the placebo and the nonplacebo groups. Were these groups comparable in the supplements they took outside of the experimental design?

DR. ANDERSON: We did not attempt to get a proper dietary assessment of their vitamin C intake. As you saw yesterday, there were about 25 subjects that had their blood ascorbate levels studied for a few weeks. Those were not a random sample; they were not taken as typical of the entire group of 3,500 people. It was not technically feasible to determine blood ascorbate levels on all those people, scattered over the entire city, and we did not have a laboratory to do so. So, we know very little about their intake. My guess is that this was a very highly motivated group of people who knew they might be taking placebo, and they were very nutrition-conscious. Just from the fruit and vegetable juice intake, they were probably getting about 100 mg per day.

DR. G. H. BEATON: The other question Dr. Darby asked on the self-administered supplements that you did record—were the two groups the same?

DR. ANDERSON: Yes, within reason. The percentage of subjects taking extra vitamin C tablets was about 18% in both groups. I refer you to the published figures in the first study.

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* This series of papers is the result of the Second Conference on Vitamin C, sponsored by The New York Academy of Sciences and the Institute of Human Nutrition, College of Physicians and Surgeons, Columbia University, and held on October 9-12, 1974 in New York, New York.

Part VI. Ascorbic Acid and Respiratory Illness