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Large Scale Studies with Vitamin C

T.W. ANDERSON

At the previous symposium (Pioppi 1973) I reported on our first large-scale study of vitamin C in the prophylaxis and treatment of the common cold (1, 2). Since then, my colleagues and I have carried out two more studies, so that our experience now involves over 5,000 subjects. Since these studies have been reported in detail elsewhere (3, 7) I will simply summarize our findings and then discuss some aspects of the vitamin C controversy that have perhaps not received as much attention as they deserve.

Our first study was carried out in the winter of 1971-72. It was a simple double-blind trial involving 1,000 volunteers, half of whom received 1,000 mg of vitamin C daily and the remainder identical placebo tablets. During the first three days of any illness extra tablets were taken to bring the daily dose up to 4,000 mg. We found a slight reduction in the frequency of colds and other respiratory infections, but the most striking result was a 30% reduction in days of disability. This was statistically highly significant and prompted us to carry out a more elaborate second trial. The following winter we therefore organized a trial involving over 3,500 volunteers who were allocated at random to 8 treatment groups (3). Three of these groups received vitamin C daily while at the time of illness their extra tablets contained placebo. Two other groups received placebo tablets daily and vitamin C tablets at the time of illness, and finally two groups received placebo both on a daily basis and extra at the time of illness. Our third trial, involving over 600 persons examined two hypothesis. First, that the results obtained in our first trial could have been achieved with much lower doses, and second that a sustained release form of vitamin C would be more effective than a simple tablet. Although, partly because of smaller numbers, the results were not as clear-cut as in the first trial, the first hypothesis did in fact appear to be confirmed,

Professor of Epidemiology, Department of Preventive Medicine & Biostatistics, University of Toronto, Canada

since we saw a 25% reduction in days of disability. On the other hand, there was no evidence that the sustained release form was any more effective than the simple tablet (4).

The results of these three trials are summarized in Figure 1. Note first that there is no evidence of a dose-related gradient for those persons receiving only the regular daily vitamin supplement (placebo as extra medication at time of illness). This lack of gradient is evident both in number of episodes and in days of disability. On the other hand when one looks at the combined regimen of daily supplement plus extra vitamin C at time of illness it is evident that although there is little effect on total number of episodes there is a rather consistent effect of disability (days spent indoors). It should also be noted that in these

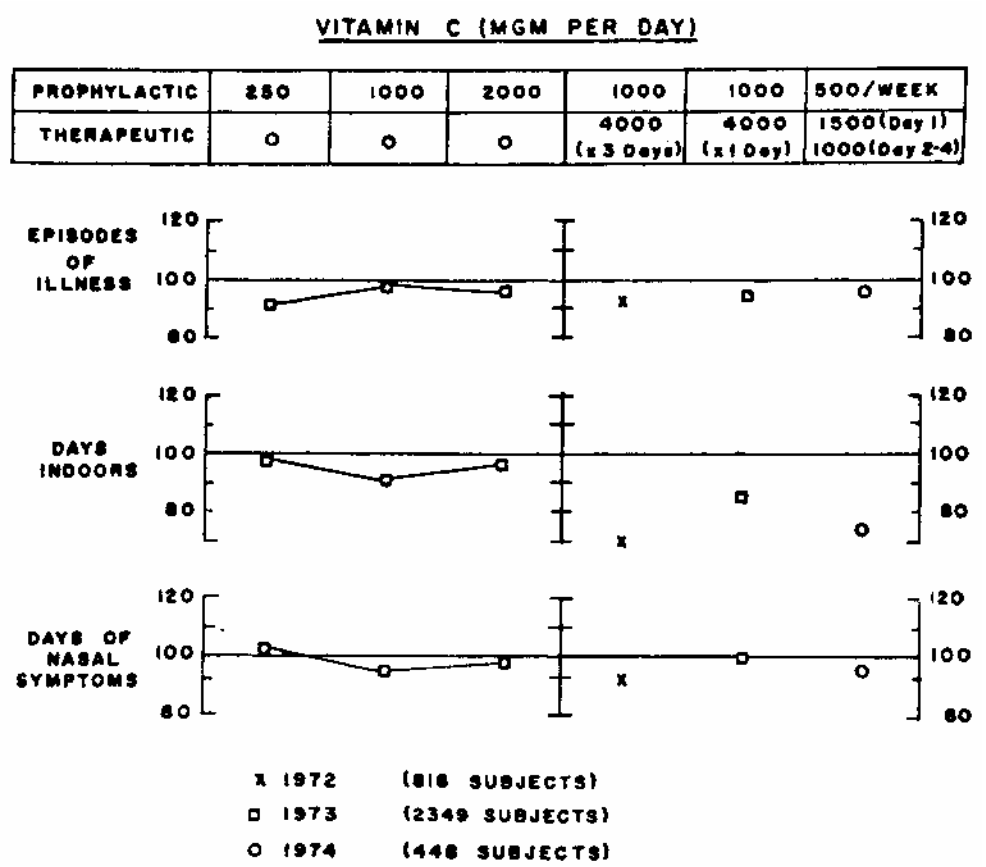

Fig. 1 • The average sickness experience of vitamin subjects (expressed as a percentage of corresponding placebo experience in three Toronto winter-illness studies).

There was little effect from the prophylactic - only regimens, and no suggestion of a dose-related gradient. The combined prophylactic and therapeutic regimens showed a consistent effect on disability, but little effect on the total number of episodes, or on the frequency of local (nasal) symptoms.

studies the actual size and duration of the « extra » dosage was somewhat variable, and this may account for some of the variation in the size of the effect that we saw. Thus in the first study subjects received 4 grams of vitamin C daily for the first three days of any illness, in the second study (because of the desire to ensure that every subject would have enough tablets for several episodes) we restricted the extra dosage to the first day of illness only, and in the third trial although the dosage was much lower it continued longer. Thus on the first day patients received 500 mg every four hours for three doses, making a total of 1,500 mg on the first day, then 1,000 mg daily for the next four days.

Also in Figure 1 is shown the effect on days of nasal symptoms, and as can be seen, there was very little effect from either the prophylactic or the combined regimen. This would seem to indicate that the effect of the vitamin C supplementation is not on a direct local basis on the respiratory organs, or indeed a direct action on the viruses responsible, but rather a more non-specific effect on host resistance, hence the reduction in disability.

This conclusion must of course be tentative until further studies are done but it is a useful working hypothesis and may help to resolve some of the conflict that has grown up about vitamin C and common colds and other illnesses.

The conflict is summarized diagrammatically in Figure 2. Traditionally the recommended daily intake of vitamin C in many countries has been around 30 mg because this is the dosage at which one can virtually guarantee that no member of the general public will ever develop scurvy (Figure 2A). The opposing view, put forward by Professor Linus Pauling and others, is that the dose-response curve continues to rise up to levels of many thousands of milligrams a day (Figure 2B). Taking our results in conjunction with those of Professor Wilson and others, I suggest that the truth may lie somewhere between these two extremes, and may involve the idea of « saturation ».

This is illustrated diagramatically in Figure 2C and involves not only the idea that the intake of vitamin C necessary to maintain saturation may be around 120 mg per day, but that at times of acute infection and perhaps other forms of stress the intake necessary to maintain saturation rises, as shown by the shift of the curve to the right. I would add however that I do not exclude the possibility that very large doses of vitamin C may also have a direct effect on viruses and other organisms.

I would now like to turn to one or two aspects of these studies that deserve more attention then they have received in the past.

First, we have frequently been asked whether we could not have carried out our experiments with much smaller numbers if we had done more precise measurements. The answer is, unfortunately, no. The large numbers are necessary because of the relatively small effect that one is seeing, and the great variation in individual experience of colds and other illnesses. The question we were trying to answer was « Does the intake of extra vitamin C in a free-living population result in a decrease in spontaneous illness? » To answer this question it is essential to have large numbers, since colds and other respiratory infections are relatively infrequent. If one rephrases the question and asks « Does vitamin C interfere with artificially induced infections in a laboratory setting? » then one can of course make do with smaller numbers but it must be clearly borne in mind that it is now a different question that one is trying to answer. (This is not to say that the laboratory question

is not worth answering, but simply that it may not be entirely synonymous with the first question).

Another commonly heard criticism of our trials is that we relied on subjective impressions, i.e. whether the subjects themselves felt ill. Now this is obviously a very « soft » form of scientific measurement, yet I submit that it can be just as valid a piece of evidence as a more precise «mathematical» measurement. The crucial point, of course, is that the trial should be carried out in a strictly double-blind fashion, since the slightest break in the blind design could introduce bias and thus drastically affect the results. Now to achieve a convincing double-blind trial it is necessary to take great care with the active and placebo preparations and we have a routine now that involves submitting various strengths of placebo and active tablets to a « taste committee » made up of colleagues and students in the department (8). Only when we are completely satisfied that the placebo and active tablets are truly indistinguishable to the five senses do we go ahead and have the tablets manufactured in large quantity. Another important aspect of this double-blind technique is to avoid providing all the active tablets in bottles marked « A » and

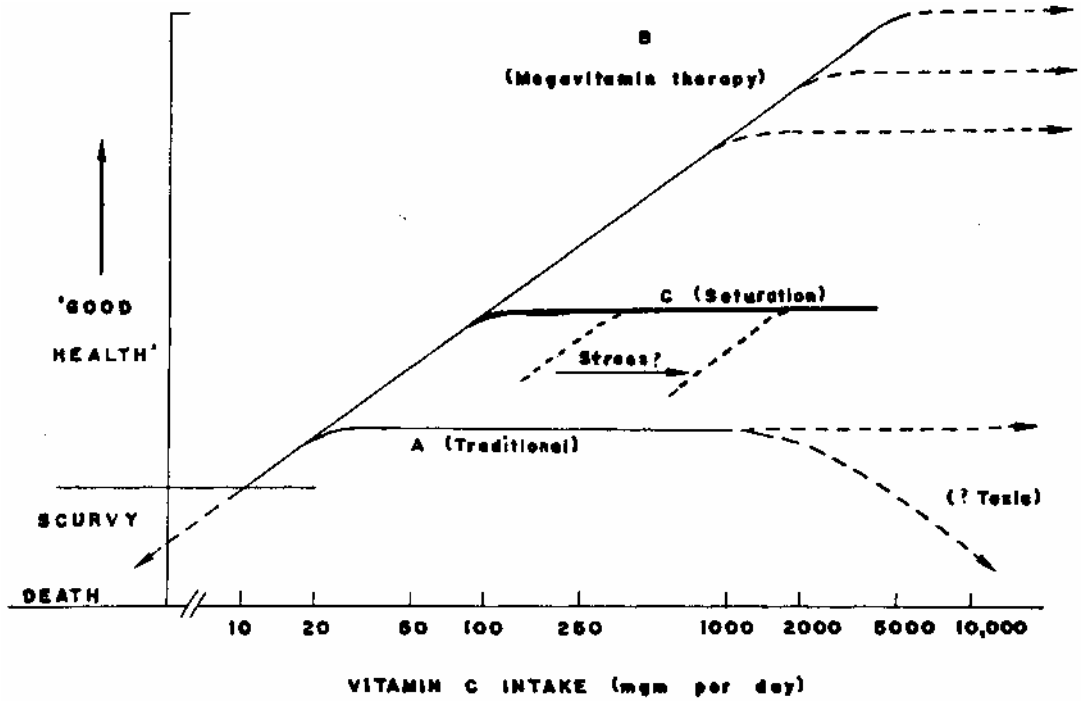

Fig. 2 - A diagrammatic comparison of the «traditional».

(A) and « megavitamin » (B) views of the relationship between daily intake of vitamin C (horizontal, logarithmic scale) and « good health ». Superimposed is a third possibility (C); namely that tissue-saturation limits maximum useful intake. Normally this requires about 120 mgm per day, but at times of stress an increased intake may be required to maintain saturation, causing the curve to shift to the right.

all the placebo tablets in bottles marked « B », or some similar simple arrangement. The danger here is that it only requires one person to break the code and the entire experimental allocation is exposed. The only satisfactory way to handle this problem is to label the bottles with code numbers, say from 1 - 1000 and use a randomized sequence to allocate numbers to the vitamin and placebo bottles. The numerical code is then kept by a colleague until all the information from the trial has been coded, put onto punch cards, and is ready for final analysis.

Another question that is sometimes raised is the extent to which the results obtained in a self-selected group of volunteers can be extrapolated to the general population. This is, of course, a very valid question and the answer is that if any extrapolation is to be done it must be done very cautiously. For one thing, the general population is probably less prepared to take pills regularly! Perhaps a more important problem associated with self-selection is the difficulty it creates in comparing studies carried out in different situations. Thus some of the differences between the results obtained by Professor Wilson and ourselves may well be related to the fact that his experiments were conducted in an institutional setting with virtually 100% involvement of the available population, whereas in our studies we were working mainly with industrial groups and never obtained much more than a 10 or 15% volunteer-rate from the available population. This small proportion of the population would almost certainly be more nutrition conscience than the majority, and thus better nourished. If saturation is indeed a critical factor then this may explain why we obtained a rather indifferent result with our prophylactic only regimens, since our group was probably already close to saturation and had less room for improvement.

Thus when comparing the results from different trials, I think it is important that in addition to asking what were the differences in the dosage of vitamin C employed one should also ask what were the differences in the initial degree of saturation in the two groups.

One last point concerning the design and execution of these double-blind trials: many people are concerned that the active and placebo groups may have been different in other respects, particularly in such things as basic susceptibility to infection and disability, and also may have been different in their use of other forms of treatment. The answer to this query is that although one routinely checks that the distribution of known characteristics (such as age and sex, usual number of colds, etc.) is even between the groups, it is always possible that other unrecognized (or unmeasurable) factors may not have been evenly balanced, and may have had a profound influence on the results. One therefore has no choice but to rely on the random allocation process to produce two well balanced groups. It is of course always possible that by some fluke one group or the other has received an excessive number of particularly susceptible individuals but this becomes less likely as numbers increase. Nonetheless, for this reason it is hazardous to draw conclusions too strongly from a single experiment, and always better to see if the same results are obtained in repeated trials.

Turning now from the methodology of the trials to some of the less well-known items of information that we obtained from them: one claim made by Professor Pauling in his book on Vitamin C and the Common Cold (9) was that persons experienced an increased sense of «well-being» from an extra intake of vitamin C. We examined this

claim in our first study by asking all participants to record at the end of the trial whether they had in fact experienced an increased sense of well-being while they had been taking the tablets. Nineteen percent of those receiving the vitamin answered «_Yes ». Standing alone this is quite an impressive piece of evidence, but when one realizes that 19% of the placebo group also answered « Yes » it becomes somewhat less impressive! However, we were working with a very self-selected group who were probably close to saturation. It is therefore possible that in a less saturated population one might obtain a more positive result to this question.

Another small study carried out during and after our first trial involved the effect of vitamin C on serum cholesterol. This was prompted by a report in the Lancet that in persons under the age of 25 the intake of 1000 mg of vitamin C daily resulted in a significant lowering of serum cholesterol (10). In view of the great importance of cholesterol levels in heart disease we decided to test this claim. Since our trial was already in progress we were unable to take blood samples from our subjects before their intake of vitamin C had gone up but as an alternative we measured serum cholesterol levels at the end of the study, then waited six weeks and measured the levels again. The results are summarized in Table I, and it can be seen that — unfortunately — the intake of 1000 mg of vitamin C a day did not apparently have any effect on the serum cholesterol of our subjects. Once again however one must remember that our subjects were well-nourished and our findings certainly do not rule out the possibility than in persons who are only partially saturated with vitamin C an increased intake may reduce serum cholesterol levels.

Finally, I would like to report briefly on the question of side-effects from large doses of vitamin C. This is an extremely important issue since there would be little advantage in cutting down disability from winter infections if we inflicted other disorders that were as bad or worse. We have therefore kept careful check on side-effects in our trials and have always asked subjects to report any unusual or suspicious symptoms.

Table I - Mean serum cholesterol.
Values (mgm %) ± tandard error mean, in 41 subjects aged 18 to 24.

Group	N	(A)	(B)
Vitamin	18	194 (±5)	193 (±5)
Placebo	23	185 (±6)	185 (±5)

(A) during 12th week on a daily intake of 1000 mgm vitamin C or placebo, and (B) 6 weeks after the end of the trial.

Table II - Suspected side-effects in 28 drop-outs from first Toronto trial of vitamin C.
(1000 mgm daily)

	Vitamin	Placebo
Urinary symptoms	0	3
Skin rash	2	3
Stomach upset	5	4
Other *	8	3
Total	15	13

* Miscellaneous, e.g. dizziness (1), headache (1), etc.

Table III • Suspected side-effects in 74 drop-outs from second Toronto trial of vitamin C.

Daily dose → (mgm)	2000	1000	1000	250	0	0	0	0
Urinary	—	1	—	2	—	—	—	1
Diarrhoea	1	—	—	2	—	—	—	1
Other *	6	13	9	6	8	9	6	9
Total	7	14	9	10	8	9	6	11

* Miscellaneous, e.g. headache (1), upset stomach (2), skin rash (2), etc.

The experience with our first trial is summarized in Table II. The percentage of persons reporting « unusual symptoms » while taking the tablets was approximately the same in the two groups (V 12%, P 11%), and of the 28 persons who actually dropped out of the study because of suspected side-effects, .15 were in the vitamin group and 13 in the placebo group. With these sort of numbers it is, of course, impossible to tell whether the two extra cases in the vitamin group were related to the vitamin intake or not, however the distribution of specific symptoms does *not* appear related to the sort of side-effects that have been suggested as theoretically possible with prolonged intake of large doses of vitamin C. Similarly, in our second trial there was no evidence of any gradient in side-effects frequency between the patients taking zero- or 250 mg daily and those taking 2000 mg daily (Table III). At the same time it must be recognized that all our subjects were in good health, that the trials ran a maximum of three months, and that a side-effect would need to be relatively common to be picked up with certainty in trials of this magnitude. The possibility that rare individuals may be intolerant of high doses can never be ruled out on the basis of studies of this type.

While most of the discussion of possible side-effects has centered on the direct toxicity of vitamin C, there is in my opinion a more worrying possibility. This is that there may be a decreased ability to deal with stress in persons who suddenly *stop* taking very large doses. This possibility is suggested by the changes in whole blood ascorbic acid

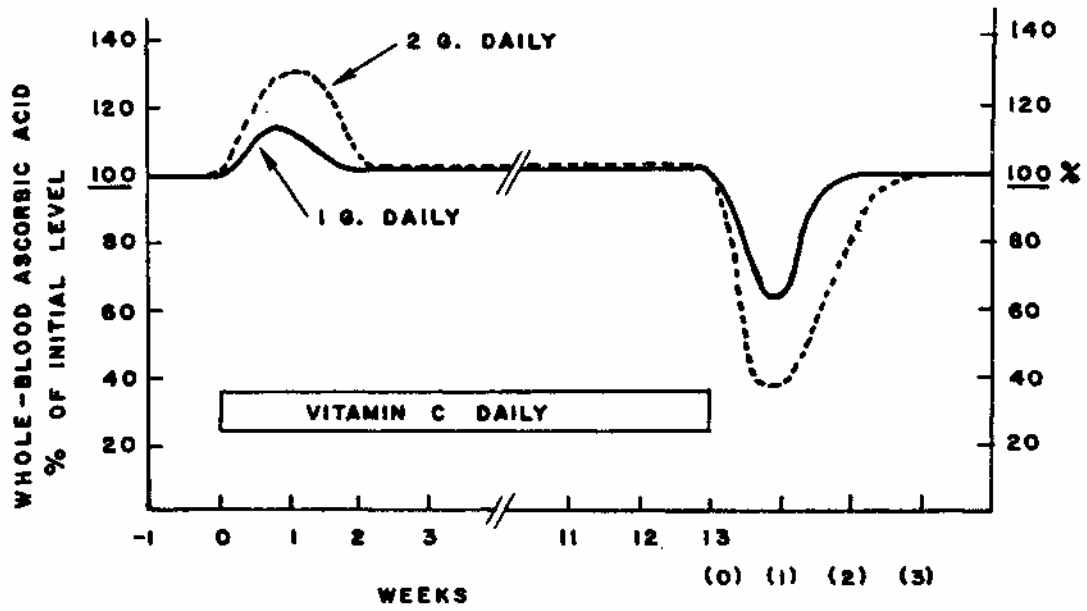

Fig. 3 - Whole-blood ascorbic acid levels during and after a 13-week trial (expressed as percentage of pre-trial levels).

In these well-nourished subjects the additional large intake of vitamin C caused only a transitory rise in blood levels. At the end of the study there was a marked decline in blood levels, but in all cases the body's readjustment to « normal » vitamin C intake appeared to be complete within 2 to 3 weeks. (Based on data of Professor L. Spero).

that were observed in a small group of volunteers during our second study. This investigation was carried out by my colleague Dr. L. Spero and its results are summarized in Figure 3. It shows that although there was an initial rise in blood ascorbic levels in these subjects, this did not persist (presumably because they were close to saturation already) but 12 weeks later when the intake was stopped there was a profound drop in blood levels which then gradually came back to normal over a two or three week period. Although we saw no evidence of an increased rate of infection or disability during these two or three weeks in the main body of our volunteers, I am concerned that patients who go off their high doses when admitted to hospital may be at a disadvantage when faced with severe surgical or medical stress. In conclusion, while there is reason to believe that an increased intake of vitamin C may be beneficial to many people, we should proceed cautiously to ensure that we achieve maximum benefit at minimum risk.

SUMMARY

The combination of a regular daily supplement of vitamin C with extra dosage at the time of illness has been shown to reduce the disability due to common colds and other winter illness, but we have seen little effect on frequency of infections, sense of « well-being », or levels of serum cholesterol. The variable results that have been obtained from some other trials of vitamin C may be due in part to variation in the initial nutritional state of the subjects, with the greatest effects to be expected where there is most room for improvement. Because of the great variation in individual susceptibility to infection large numbers of subjects are required in these trials and they must be strictly double-blind

Although we have seen no clear evidence of harmful side-effects, occasional sensitivity to large doses of vitamin C cannot be ruled out, and the withdrawal depression of blood levels could conceivably interfere with a patient's ability to handle stress.

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