The effect on winter illness of large doses of vitamin C

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Summary: Between December 1972 and February 1973, 2349 volunteers participated in a double-blind trial to assess the effect of large doses of vitamin C on the incidence and severity of winter illness. In addition, records were kept but no tablets taken during March. Subjects were randomly allocated to eight treatment regimens: three prophylactic-only (daily dose 0.25, 1 or 2 g), two therapeutic-only (4 or 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. None of the groups receiving vitamin C showed a difference in sickness experience that was statistically significant from that of the placebo groups, but the results obtained were compatible with an effect of small magnitude from both the prophylactic and therapeutic regimens, and an effect of somewhat greater magnitude from the combination regimen. The combination regimen was associated more with a reduction in severity than frequency of illness, although the extra dosage was limited to the first day of illness. In spite of the eightfold range in daily dose, the three prophylactic-only regimens showed no evidence of a dose-related effect, but the 8 g therapeutic dose was associated with less illness than the 4 g therapeutic dose. There was no evidence of side effects from the 1 and 2 g prophylactic closes of vitamin C, and no evidence of a rebound increase in illness during the month following withdrawal of the daily vitamin supplements. On the basis of this and other studies it is suggested that the optimum daily dose of vitamin C is less than 250 mg, except possibly at the time of acute illness, when a larger daily intake may be beneficial.

Resumed *Leffet de fortes doses de vitamine C sur les maladies hivernales*

De decembre 1972 a fevrier 1973, 2349 volontaires ont participe a des essais a double insu qui avaient pour but d'evaluer l'effet de fortes doses de vitamine C sur l'incidence et la severite des maladies hivernales. Outre ces essais, durant le mois de mars, on continua d'enregistrer des donnees mais sans dormer de medicament. Les sujets ont ete repartis au hasard entre huit types de traitement: trois de ceux-ci etaient exclusivement de nature prophylactique (doses quotidiennes de 0.25, de 1 ou de 2 g), deux autres etaient exclusivement therapeutiques (4 ou 8 g le premier jour de la maladie), un sixieme associait 1 g par jour et 4 g le premier jour de la maladie et les deux derniers n'utilisaient que les placebos. Chez aucun des groupes recevant de la vitamine C, on n'a note de difference statistique notable avec ceux des groupes-placebo, quant a l'experience morbide. Cependant les resultats obtenus pouvaient expliquer un certain effet provenant des essais prophylactique et therapeutique et un effet un peu plus important provenant du sixieme type de traitement utilisant la dose d'attaque et la dose d'entretien. Avec ce dernier type, on notait une diminution de la severite de la pathologic plus qu'une veritable reduction de sa frequence et ce, en depft du fait que la dose d'attaque ait ete administree le premier jour seulement. Bien que la dose quotidienne ait passe du simple a l'octuple dans les trois types prophylactiques, on n'a pu cone lure a une relation entre l'effet et la dose, mais avec la dose therapeutique de 8 g, on constatait une morbidite moindre qu'avec la dose therapeutique de 4 g. On n'a enregistre aucun effet secondaire resultant des doses prophylactiques de 1 et de 2 g, pas plus qu'une recrudescence de la maladie pendant le mois de la suspension des supplements vitaminiques. Cette etude et d'autres similaires permettent de croire que la dose quotidienne optima le de vitamine C est inferieure a 250 mg, sauf peut-etre lors de la phase aigue, periode ou il est possible qu'une dose plus elevee sort benefique.

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In a previously reported double-blind study (conducted during the winter of 1971-72) it was found that persons receiving large doses of vitamin C had significantly less disability from "colds" and other illness than a well-matched placebo group.[1] However, it was uncertain whether the apparent beneficial effect of the vitamin C might have been due to the regular "prophylactic" dose (1 g daily), or to the "therapeutic" dose (4 g daily for the first three days of any illness), or to the combination. Furthermore, since only one dosage schedule was used, there was no way of knowing whether similar results could have been

obtained with smaller doses, or, conversely, whether larger doses would have had an even greater effect.

A second trial was therefore undertaken during the winter of 1972-73 in which 3520 volunteers were allocated randomly to eight treatment groups. Three of these groups received a prophylactic-only regimen consisting of 0.25, 1 or 2 g of vitamin C daily, with extra placebo tablets to be taken on the first day of illness; two groups received a therapeutic-only regimen consisting of placebo daily, with either 4 or 8 g of vitamin C on the first day of illness; and one group received a combination regimen (1 g daily and 4 g at the onset of illness) similar to that used in the previous trial except that the extra dosage was taken on the first day of illness only, rather than on the first three days.

Finally, there were two control groups, each of which received placebo tablets throughout. The reasons for having two control groups were: first, to see if there was any evidence of a greater placebo effect in subjects receiving four placebo tablets daily than in those receiving one placebo tablet daily; and second, in the event that there was no evidence of such a difference, to be able to combine the two groups, and thus obtain a more reliable estimate of the placebo "baseline" sickness experience.

The main part of the trial ran for 90 days (from December 1, 1972 to February 28, 1973) after which subjects were asked to keep illness records, but take no tablets, for one more month to see if there was any "rebound" increase in illness following withdrawal of the regular high daily dosage of vitamin C.

Subjects were also asked to make a note of all symptoms experienced to ensure that any side effects did not pass unnoticed.

Method and material

Subjects

Most of the participants in this trial were recruited from the staffs of large hospitals and business organizations that had medical or personnel departments willing to undertake the recruitment of volunteers, the distribution of bottles of tablets and information sheets, and the subsequent monthly collection of completed record sheets.

Although subjects were recruited from a variety of occupations, it should be stressed that they were not a representative sample of the general population, since only those persons who usually suffered at least one episode of illness between December and March (but were otherwise in good general health) were accepted. Furthermore, as a general rule it was found that, as in the 1971-72 study, only about 10% of those persons canvassed actually enrolled in the study. The possible significance of this self-selection will be discussed later.

Each potential volunteer received a description of the purpose and method of the study, including the fact that some of the bottles would contain placebo tablets. Consumption of other vitamin supplements was permitted, provided that the daily intake of vitamin C from this source did not exceed 100 mg.

Tablets

Three strengths of tablets were used — 500, 250 and 0 (placebo) mg ascorbic acid equivalent. The active tablets contained no free ascorbic acid, but a mixture of sodium and calcium ascorbate in a ratio of approximately 2:1. The placebo tablets contained lactose and a small quantity of citric acid. Unlike the chewable tablets used in the previous trial, neither the vitamin nor the placebo tablets used in this trial had any additional flavouring or colouring. Bioavailability studies carried out by Dr. L. Spero (Department of Pharmacology, University of Toronto) demonstrated that blood levels of ascorbic acid after ingestion of the vitamin tablets were similar to those obtained by ingestion of an equivalent dose of pure ascorbic acid or an equivalent dose of the tablets used in the 1971-72 trial.

All three tablets were of a similar size and shape, and an initial "taste test" carried out with the help of a number of colleagues demonstrated that they were reasonably well matched in flavour, texture and appearance. This was confirmed at the end of the trial by asking the participants whether they thought their daily tablets had contained vitamin or placebo. Approximately half of each group answered "don't know", and of the remainder, approximately two thirds answered "vitamin" and one third "placebo", irrespective of the actual nature of their tablets.

Each subject received two bottles of tablets, one marked "Daily" (containing either 360 or 100 tablets), the other marked "Extra" (containing 100 tablets). Groups 1 to 4 were instructed to take four of their "Daily" tablets each day (one *qid* or two *bid)* plus 12 of their "Extra" tablets (two every hour) on the first day of any illness. Groups 5 to 8 were instructed to take one "Daily" tablet each day, plus 16 tablets (two every hour) on the first day of any illness.

Table I—Treatment schedule, number of subjects and recorded characteristics of experimental groups (means or %) based on the 2349 subjects and 1171 dropouts on February 28, 1973

Group	Total	1	2	3	4	5	6	7	8	Dropouts
Tablets (Daily/Extra)	—	4/12	4/12	4/12	4/12	1/16	1/16	1/16	1/16	—
Vitamin C (g) (Daily/1st day sick)	—	1/4	1/0	2/0	0/0	0.25/0	0/0	0/4	0/8	—
Number of subjects										
Dec. 1, 1972	*3520*	*440*	*440*	*440*	*440*	*480*	*440*	*400*	*440*	—
Feb. 28, 1973	2349	277	275	308	285	331	293	275	305	1171
Mar. 31, 1973	*2159*	*253*	*253*	*280*	*269*	*300*	*271*	*256*	*277*	*1361*
Characteristics (as of Feb. 28)										
Age	34.4	34.5	34.5	34.4	33.7	34.3	33.9	34.3	35.3	28.5
Sex (% male)	47	48	52	46	48	45	47	46	44	37
Nonsmokers (%)	57	57	59	56	58	54	59	57	58	47
*Usual episodes	1.91	1.90	1.88	1.92	1.92	1.88	1.88	1.90	1.99	2.04
*Usual days indoors	2.37	2.46	2.23	2.33	2.57	2.46	1.97	2.46	2.46	2.68
*Usual days off work	1.92	2.07	1.72	1.79	2.07	2.12	1.56	1.95	2.01	2.12
Contact with children (%)	40	35	43	42	38	38	46	37	41	41
Frequently in crowds (%)	76	74	79	73	81	76	80	73	74	82
Daily juice (oz)	3.86	3.91	3.64	3.45	4.04	4.14	3.87	3.87	3.93	3.79
Other vitamin C (%)	16	16	15	13	14	19	16	15	16	14

*Based on subjects' own estimates of their usual experience between December 1 and March 31 of each year.

The dosage schedules resulting from the different numbers and strengths of the tablets taken are indicated at the top of Table I.

The decision to restrict the extra intake of vitamin C to the first day of any illness (compared with the first three days of illness in the first study) was made to ensure that each subject had enough "Extra" tablets for at least six episodes of illness.

Adherence to the daily treatment schedule appeared to be reasonably good. Subjects were asked to count the number of tablets left in their bottles at the end of February, and the recorded figures indicated that in groups 1 to 4 (four tablets daily) 72% of the subjects had taken at least 90% of their daily tablets, while in groups 5 to 8 (one tablet daily) 80% of the subjects had taken at least 90% of their daily tablets.

Randomization

The allocation of subjects to the various treatment regimens was carried out in essentially the same manner as in the 1971-72 trial.[1] Bottler were numbered in accordance with a computer-generated list of numbers randomized in groups of eight, then given out in consecutive order as subjects registered. To facilitate distribution each major employee-group was put in alphabetical order before being assigned a block of numbers, and the consecutive numbering ensured that approximately the same number of employees were allocated to each of the eight experimental groups.

Because of the large number of bottles (over 7000), labelling was carried out in 11 stages, each stage involving 16 batches of bottles (eight groups, two bottles per subject) with each batch containing 40 bottles. At the end of the experiment one or more bottles were recalled from each batch and the contents checked. This revealed that a labelling error had occurred in two of the 176 batches, with the result that instead of each regimen receiving the intended number of 440 subjects, the group 5 regimen (0.25/0 g vitamin C) had received 480 subjects and the group 7 regimen (0/4 g vitamin C) 400 subjects. Fortunately, this had caused virtually no alteration in the overall characteristics of the affected groups.

Sickness records

As in the 1971-72 study subjects were asked to complete a checklist of the symptoms present on each day of illness. Where two episodes of recorded symptoms were separated by only one or two symptom-free days, they were considered together as a single episode. If the interval was three to six days the episodes were counted separately unless the symptom patterns were essentially the same on the two occasions. Where the interval was seven days or more, the episodes were counted separately, however similar the symptoms.

The symptoms to be recorded were essentially the same as those used in the 1971-72 study except that "malaise" was subdivided into "feverish", "limbs ache, feel heavy" and "mentally depressed, no ambition". In addition, space was provided for recording stomach cramps, vomiting and diarrhea.

Results

Of the 3520 subjects enrolled at the beginning of the

Table II—Overall sickness experience and means per subject during tablet-taking period (December 1, 1972 to February 28, 1973), subdivided according to the duration of episodes

		Group								1971-72*	
	Total	1	2	3	4	5	6	7	8	V	P
Vitamin C (g) (Daily/1st day sick)	—	1/4	1/0	2/0	0/0	0.25/0	0/0	0/4	0/8	1/4(x3)	0/0
Subjects	2349	277	275	308	285	331	293	275	305	407	411
Free of sickness	536	65	65	65	52	74	75	66	74	105	76
%	*22.8*	*23.5*	*23.6*	*21.1*	*18.2*	*22.4*	*25.6*	*24.0*	*24.3*	*25.8*	*18.5*
Episodes											
Total	3590	436	414	465	437	508	430	417	483	561	609
Mean	*1.53*	*1.57*	*1.51*	*1.51*	*1.53*	*1.53*	*1.47*	*1.52*	*1.58*	*1.38*	*1.48*
S.E.M.	*0.028*	*0.091*	*0.083*	*0.071*	*0.071*	*0.072*	*0.082*	*0.081*	*0.083*	*0.061*	*0.056*
a.	1451	178	158	181	143	217	188	164	222	112	104
b.	2087	248	252	277	285	285	238	247	255	439	493
c.	52	10	4	7	9	6	4	6	6	10	12
Days of symptoms											
Total	11,419	1489	1386	1501	1539	1580	1219	1325	1380	2138	2474
Mean	*4.86*	*5.38*	*5.04*	*4.87*	*5.40*	*4.77*	*4.16*	*4.82*	*4.52*	*5.25*	*6.02*
S.E.M.	*0.117*	*0.393*	*0.419*	*0.311*	*0.355*	*0.290*	*0.265*	*0.322*	*0.299*	*0.297*	*0.284*
a.	1451	178	158	181	143	217	188	164	222	112	104
b.	8916	1084	1082	1187	1232	1259	964	1059	1049	1824	2155
c.	1052	227	146	133	164	104	67	102	109	202	215
Days indoors											
Total	3989	471	476	554	502	570	452	458	506	531	769
Mean	*1.70*	*1.70*	*1.73*	*1.80*	*1.76*	*1.72*	*1.54*	*1.67*	*1.66*	*1.30*	*1.87*
S.E.M.	*0.059*	*0.190*	*0.181*	*0.182*	*0.159*	*0.151*	*0.138*	*0.161*	*0.163*	*0.101*	*0.138*
a.	386	48	47	52	27	60	56	41	55	21	26
b.	3259	348	375	436	450	480	373	384	413	482	693
c.	344	75	54	66	25	30	23	33	38	28	50
Days off work											
Total	2578	314	299	397	336	368	275	268	321	360	539
Mean	*1.10*	*1.13*	*1.09*	*1.29*	*1.18*	*1.11*	*0.94*	*0.97*	*1.05*	*0.88*	*1.31*
S.E.M.	*0.049*	*0.165*	*0.143*	*0.170*	*0.130*	*0.129*	*0.107*	*0.123*	*0.120*	*0.084*	*0.118*
a.	172	13	25	33	10	29	23	9	30	14	20
b.	2151	219	243	306	307	311	243	257	265	333	472
c.	255	82	31	58	19	28	9	2	26	13	47

*Results of the 1971-72 study are included for comparison. V = vitamin, P = placebo
a. = 1 day of symptoms
b. = 2 to 14 days of symptoms
c. = 15 or more days of symptoms

trial 2349 completed the first three (tablet-taking) months and 2159 also completed the fourth (records-only) month.

The higher proportion of dropouts in the tablet-taking part of this trial — 33% compared with the 18% in the 1971 study — appeared to be due mainly to the large tablets used (500 mg size compared with 250 mg previously), since difficulty in swallowing the tablets was one of the commonest reasons given for dropping out. In 74 cases a suspected side effect was given as the reason for dropping out. These cases will be examined later in more detail.

The proportion of subjects who dropped out was approximately the same in each of the eight groups, and on the whole their recorded characteristics (age, sex, etc.) were not greatly different from those of subjects who stayed in the trial (Table I). However, not only did the large number of dropouts substantially reduce the number of subjects available for analysis in each group, but some of the differences in the characteristics of the dropouts from each group accentuated the intergroup differences in recorded characteristics. Thus, while the initial randomization procedure had been successful in producing groups that were reasonably well matched (i.e. no statistically significant differences in the mean values of the recorded characteristics), the groups that were ultimately available for analysis showed larger differences, particularly group 6, which had mean values for usual days indoors and off work that were significantly different from some of the other groups. It is possible, therefore, that some of the differences seen in the sickness experience of this (and other) groups were the result of differences in their inherent characteristics, rather than in the treatment they received.

Symptoms involving the respiratory tract occurred at some stage in over 90% of the episodes, and in view of the difficulty in arriving at a generally acceptable definition of a "cold", most of the subsequent analysis has been based on all types of illness.

Approximately 23% of the subjects recorded no episodes of illness throughout the tablet-taking period, but there was no indication that the proportion free of illness in each group was related to the daily intake of vitamin C (Table II). Similarly, the total sickness experience per subject in each group showed little evidence of being related to the doses of vitamin C employed. There was also no evidence that the placebo effect of four placebo tablets daily (group 4) was any greater than that of one placebo tablet daily (group 6). On the contrary, the sickness experience of group 6 was less than that of all the other groups, including group 4.

Individual episodes varied greatly in length. Over 40% were very brief, with symptoms recorded on only one day. Since, by definition, any period of illness had to be preceded and followed by at least two symptom-free days in order to be counted as a separate episode, many of these one-day episodes were probably "false alarms", or were illnesses that were aborted by treatment. At the other extreme, although less than 2% of the recorded episodes lasted more than 14 days, these prolonged episodes accounted for approximately 10% of total days of symptoms, days indoors and days off work. Within the eight groups, this proportion varied considerably, from 26% of days off work in group 1 to less than 1% in group 7 (Table II).

To reduce the variability resulting from these unusually short and unusually long episodes and thus, it was hoped, to increase the sensitivity of the comparisons, the data were reanalysed on the basis of the 2087 episodes of intermediate duration (2 to 14 days of symptoms) that accounted for approximately 80% of the total days of sickness and disability (Figs. 1 and 2).

Apart from some of the comparisons involving group 6, none of the differences between the means (either overall or intermediate duration) was statistically significant by standard two-tailed t-tests, although it should be noted that the interpretation of the standard errors of the means must be cautious, in view of the asymmetry of the initial distributions and the truncation resulting from exclusion of the episodes lasting one day and 15 or more days.

The very low mean values in group 6 may well be related to the atypical composition of this group in terms of "usual" days indoors and off work since, of all the recorded characteristics, these showed the highest correlations (r approximately 0.1, P <0.01) with the observed sickness experience of the total group of 3249 subjects. Other recorded characteristics such as sex, age, cigarette consumption, etc. correlated even more weakly or not at all with the observed experience. Various methods of adjusting for "usual" experience were examined (regression, standardization, etc.) but they did not greatly reduce the differences in sickness experience between the two all-placebo groups (4 and 6).

Since in terms of group characteristics group 4 was the least atypical of the two placebo groups, two placebo "baselines" have been used to construct Figs. 1 and 2, one involving the experience of group 4 alone, the other the combined experience of groups 4 and 6. This serves two purposes: first, it indicates a range within which the true relative values may lie; and second, it serves to emphasize the uncertainty surrounding the estimate of any individual treatment "effect". For convenience, the corresponding values obtained in the 1971-72 trial (recalculated on the 2- to 14-day-episode basis) are also plotted in Figs. 1 and 2.

Considering the uncertainty surrounding the placebo baselines and the shorter duration of the extra dosage (one day v. three) the results in the combined-treatment group

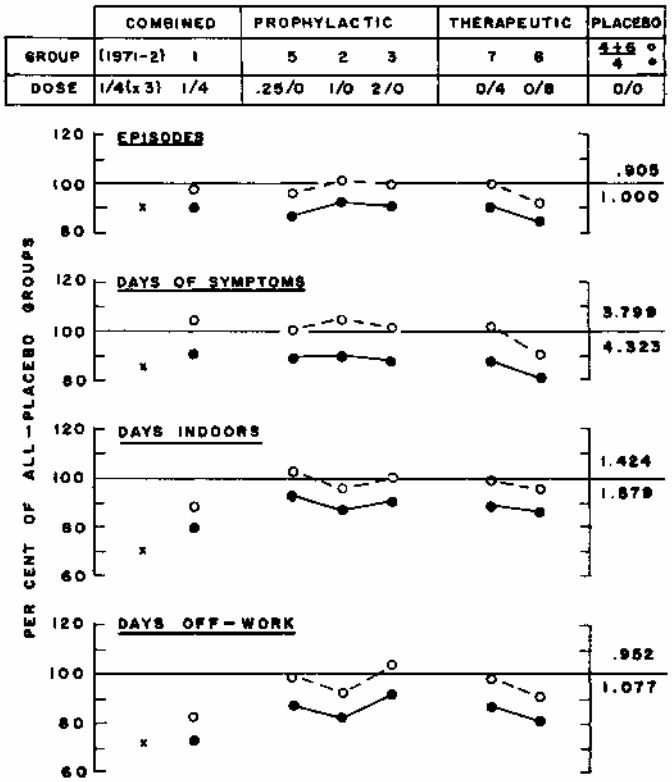

FIG. 1—The mean sickness experience per subject in the groups receiving vitamin C, based on episodes lasting 2 to 14 days from December to February, expressed as a percentage of the group 4 means (solid circles) and the combined means of groups 4 and 6 (open circles). The actual mean values for group 4 alone and for groups 4 and 6 combined are shown in the right-hand column. Corresponding values for the 1971-72 study are indicated by x's.

were not greatly dissimilar to those seen in the 1971-72 study, with some of the largest differences appearing in days indoors and off work (Fig. 1), and in constitutional rather than local symptoms (Fig. 2).

Some of the prophylactic-only means (groups 5, 2, 3) were below the placebo baselines, but in spite of an eightfold range in the daily dose (0.25 to 2 g) there was little evidence of a corresponding gradient in sickness experience. On the other hand, the twofold range in dose of the therapeutic-only regimens (groups 7 and 8; 4 and 8 g on the first day of illness) was associated with a consistent dose-related gradient in sickness experience (Figs.

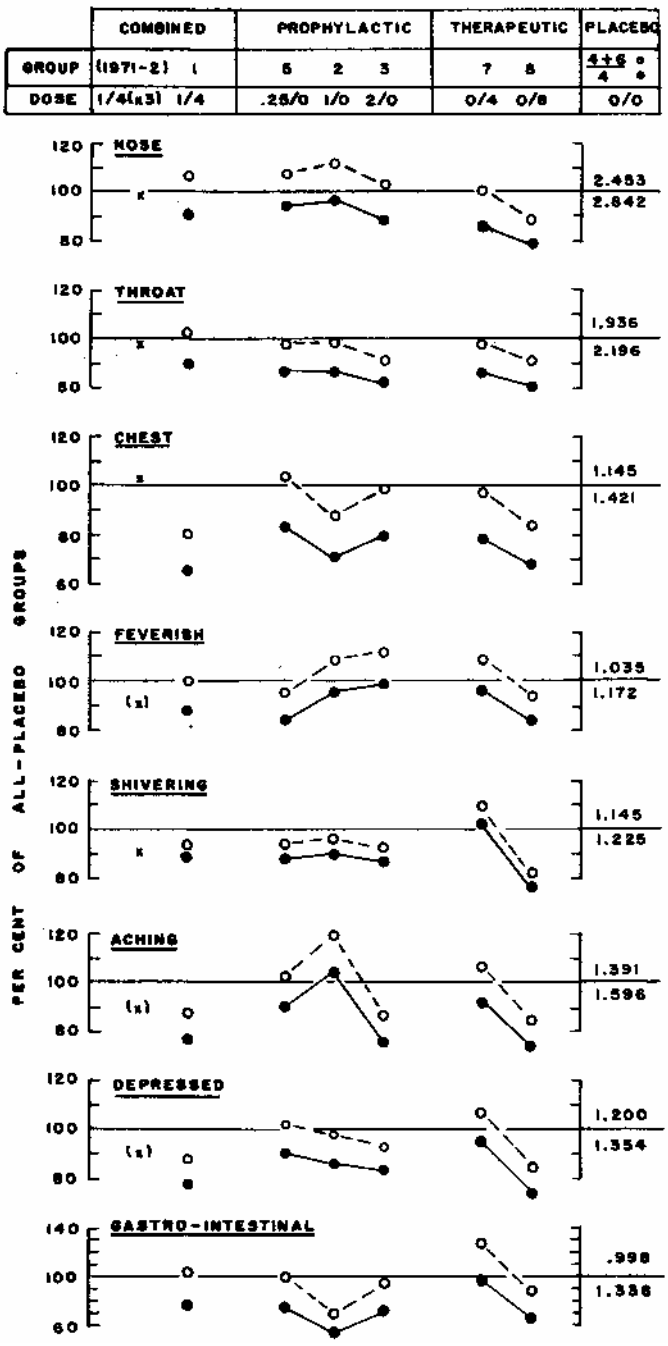

FIG. 2—The mean number of days per subject on which individual symptoms were recorded, expressed as a percentage of the all-placebo means (see explanatory notes for Fig. 1). Corresponding values for the 1971-72 study are indicated by x's, with those for malaise shown in parentheses under the headings of feverish, aching and depressed. Values for gastrointestinal symptoms are based on the sum of days of vomiting, stomach cramps and diarrhea, and are plotted on a different vertical scale.

1 and 2). This may, of course, have been largely because the various measurements of sickness were not independent of each other, but the consistent relationship of these two groups is in contrast to the apparently random relationship of the prophylactic-only values.

Two recently published studies have indicated that females may be more responsive than males to large doses of vitamin C.[2,3] The present data were therefore reanalysed separately for each sex, and although there was some evidence of a greater effect in females, this was inconsistent and not of great magnitude. Similarly, restricting the analysis to those illnesses affecting the nose, throat or chest did not substantially affect the comparisons.

March experience

Subjects were Instructed to stop taking their tablets on the last day of February but to continue keeping a sickness record for one more month. The 2159 subjects who completed and returned sickness records for March recorded a total of 869 episodes of illness during this month and a total of 4040 days of symptoms, 1043 days indoors and 670 days off work.

To compensate for the shorter duration and thus the relatively small number of episodes and days of illness in individual groups, the experience of the groups previously receiving at least 1 g daily (groups 1, 2, 3) was combined and compared with the combined experience of the groups that had previously received placebo daily (groups 4, 6, 7, 8). In terms of episodes per subject these combined means were almost identical (0.304 and 0.309 respectively), and in terms of disability there was also no evidence of a "rebound" effect in the groups that had been on a high daily dose of vitamin C. Mean values per subject for days indoors were 0.384 and 0.409 respectively in the combined vitamin and placebo groups, and for days off work 0.221 and 0.268.

Since blood levels of vitamins C have been found[2] to fall below normal values for about two weeks in persons who have previously been on a large daily dose of vitamin C it is possible that a rebound effect would only be apparent during these first two weeks. The distribution of sickness within the month of March was therefore examined, but there was no evidence that groups 1, 2 or 3 had experienced proportionally more illness in the first half of the month than had the other groups.

Side effects

Of the 1171 subjects who dropped out of the study 74 gave side effects from the "Daily" tablets as the reason for doing so. Few side effects were reported from the "Extra" tablets, and no one dropped out of the study on this account.

Seven of the 74 subjects were in group 3, receiving the highest dose (2 g) of vitamin C daily, compared with 14 and 9 in groups 1 and 2 (1 g daily) and 10 in group 5 (0.25 g daily). Groups 4, 6, 7 and 8 (placebo daily) accounted for 8, 9, 6 and 11 subjects respectively. It would therefore appear that the majority of these "side effects" were either coincidental illness unrelated to the experimental tablets, or were due to the fillers, binders, etc. used in the tablets rather than to the content of vitamin C.

The findings were similar for the specific symptoms reported. While diarrhea was reported by one patient in group 3 (2 g vitamin C daily), two patients in group 5 (0.25 g daily) and one in group 8 (placebo) also reported this symptom. Urinary symptoms were reported by two patients in group 5 (0.25 g daily), by one patient in group 1 (1 g daily) and by one in group 8 (placebo). Other symptoms such as headache, upset stomach and skin rash were reported by a number of patients, but appeared to

be randomly distributed through the eight groups, with no evidence of a frequency gradient associated with the dose of vitamin C.

Discussion

These results must clearly be interpreted with caution since, in spite of the large number of subjects within each group, most of the differences between the groups were statistically nonsignificant. Furthermore, in spite of the random distribution of subjects, the divergent experience of the two placebo groups indicates that not all of the groups were well matched in their susceptibility to illness.

None the less, some tentative conclusions are possible. First, the effects of the prophylactic-only regimens were of small magnitude, and showed no evidence of being dose-related.

This finding provides no support for the views of Pauling, Stone and others who have suggested on theoretical grounds that the beneficial effects of regular vitamin C supplementation should be proportional to the size of the daily dose.[5,6] While it would be premature to dismiss these theoretical arguments on the basis of a single experiment, it would seem that if such a dose-response gradient exists it is likely to be of small magnitude since it failed to manifest itself in the present study despite an eightfold range in daily dose.

The small size of the prophylactic-only effect also appears to be in conflict with the experience of Wilson, Loh and Foster[3] and Coulehan *et al*,[4] who have recently reported some rather substantial benefits from prophylactic-only regimens of vitamin C. However, it is possible that these differences may be related to differences in the experimental populations. Both of these studies were restricted to schoolchildren and had almost 100% participation by the available population,[7,8] while in the present study subjects were predominantly adult and consisted of an approximately 10% self-selected sample of the available population. This 10% sample is likely to have been heavily weighted with persons with an above-average interest in good nutrition, who were probably already receiving a generous intake of vitamin C (indeed, over two thirds reported a consumption of at least four ounces of fruit or vegetable juice each day). It is possible, therefore, that the discrepant results of this study may be related to the age of the participants and/or their concurrent dietary intake of vitamin C.

The second very tentative conclusion from these results is that even in a well nourished population it is possible that a large therapeutic dose may help to reduce disability from acute infections. The finding of a consistent dose-related effect associated with the 4 and 8 g therapeutic-only regimens may, of course, have been a statistical artefact or the result of poor initial matching of the groups. However, not only did the March experience show a slight gradient in the opposite direction, but group 8 (8 g on the first day of illness) experienced a larger number of one-day "false-alarm" or "aborted" episodes than any other group (Table II). This interpretation is consistent with the report by Hume and Weyers[9] that a very high daily dose of vitamin C may be required to maintain tissue saturation during an acute upper respiratory tract infection.

The experience of persons on the combined regimen (group 1) was broadly similar to that of the vitamin subjects in the 1971 study, although the extra dosage was received on only the first day, instead of on the first three days as in the earlier study. The similarity in the results of the two studies lends weight to the belief that the "effect" previously observed was a real one rather than a statistical artefact even though the present results were not themselves statistically significant.

Understandably, some fears have been expressed that very large daily doses of vitamin C may give rise to undesirable or dangerous side effects in some individuals.[10,11] While the present study provides some reassurance on this score, since no obvious side effects were detected on doses of 1 or 2 g daily, this does not rule out the possibility that the occasional individual might suffer ill effects, especially if the ingestion were to be continued for years rather than months. It should also be noted that the vitamin C used in this experiment was in the form of ascorbate rather than the free acid. Another possible cause for concern is the rapidity with which abnormally low blood levels of ascorbic acid develop following the abrupt withdrawal of a high daily dose.[2] If low blood levels have any physiological significance, this could conceivably have detrimental effects in certain situations, for example in patients admitted to hospital with acute medical or surgical problems in whom, unless the high intake was maintained, a period of severe physiological stress might coincide with a period of relative vitamin C deficiency.

In view of these potential hazards, and in the absence of any evidence that the higher intakes are associated with any additional benefits, it would seem prudent to advise the public against the regular daily ingestion of doses of vitamin C of 1 g or more. However, the possibility remains that a modest supplementation of some diets may be desirable, and that short-term heroic doses of vitamin C may prove to be justified during acute infection and possibly other forms of stress.

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