Therapeutic Effect of Vitamin C

A Co-Twin Control Study

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• **Three different dosages of vitamin C, dependent on body weight, were administered to 44 school-aged monozygotic twins for five months using a double-blind, co-twin control study design. The mothers recorded daily observations of cold symptoms, and multiple biochemical, anthropometric, and psychological measurements were made at the beginning and end of the study. Paired comparisons showed no significant overall treatment effect on cold symptoms, but the response was not uniform in all subgroups. Treated girls in the youngest two groups had significantly shorter and less severe illness episodes, and an effect on severity was also observed in the youngest group of boys. The seven treated twins in the latter group also grew an average of 1.3 cm more than their untreated co-twins during the five-month period of the study.**

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THE PUBLICATION in 1970 of Linus Pauling's controversial book *Vitamin C and the Common Cold*[1] greatly renewed interest in the effects of pharmacologic doses of vitamin C. Pauling recommended a prophylactic daily intake of 1 to 3 gm ascorbic acid to reduce the incidence and severity of upper respiratory infections, and he attributed the inconclusive results of previous studies to inadequate dose levels. However, studies conducted since that time have still not revealed a consistent overall effect. Anderson et al[2] showed a significant reduction in morbidity in 407 adult volunteers receiving 1 gm ascorbic acid per day, in comparison with a placebo group of 411 adults, but they were unable to replicate the finding in a larger series.[3] Wilson and Loh,[4] in a nine-month study of boarding school children in Ireland, found an apparent reduction of catarrhal symptoms in girls but not in boys. A 14-week study of 641 Navajo boarding school children by Coulehan et al[5] revealed 26% fewer symptomatic days in treated younger children and 33% fewer in older girls but no effect in older boys. However, these results could not be confirmed in a subsequent trial.[6] In a study by Karlowski et al[7] that was complicated by a high attrition rate, the observed treatment effects on severity and duration were thought possibly to have resulted from departures from the double-blind protocol.

The present study was designed to assess the effect of supplemental vitamin C on the incidence and morbidity of the common cold by monitoring the occurrence and severity of its most common symptoms. School-aged, monozygotic twin pairs were enrolled in a five-month, double-blind, co-twin control study in which one member of each twin pair received twice daily doses of supplemental ascorbic acid, while the co-twin received a placebo. Numerous clinical and metabolic variables were also monitored to search for other possible treatment effects.

MATERIALS AND METHODS

Eighteen male and 26 female pairs of school-aged monozygotic twins (Table 1), ranging in age from 6 to 15 years, were recruited for the study, and only three pairs who were asked declined to participate. Zygosity was determined by dermatoglyphic analysis and extensive blood typing, and there was no conscious selection for susceptibility to colds. Informed parental consent was obtained, and the rationale for conducting a double-blind, co-twin control study was explained in detail. Within a twin pair, the assignment to the treatment group was random. The capsules contained 250 mg vitamin C or starch and were coded accordingly. The code was not broken until after the analysis of symptom data had been completed. The twin pairs were separated by body weight into three dosage groups, receiving 500 mg, 750 mg, or 1,000 mg ascorbic acid daily, administered in two doses. This effort to equalize dosage on the basis of body weight also partitioned the sample by age, with the younger twins receiving the lower dosage.

Compliance was monitored by monthly collection of casual urine samples for measurement of vitamin C excretion. Daily observations of the presence of 14 cold symptoms were recorded by the mothers using a five-point severity scale. The symptoms recorded were sore throat, cough, laryngitis, headache, nasal discharge, nasal congestion, fever, diarrhea, aching limbs, aching back, earache, cold sores, restlessness, and feeling out-of-sorts. For purposes of analysis, a cold was defined as a respiratory illness episode of two or more days' duration, with at least two different symptoms, separated by at least two days from a previous episode. A single day was counted as an episode if there was more than one symptom of moderate (3+) or greater severity.

Multiple blood studies, including 12-factor automated chemical analysis (SMA 12) and blood counts, and 24-hour urine collections were obtained prior to both the initiation and the conclusion of the study to detect other possible treatment effects. Anthropometric measurements including height, weight, and blood pressure, and clinical observations of tonsil and cervical node size were also made. At the conclusion of the study, a battery of psychological tests was administered to measure cognitive alertness, accuracy and speed, fine muscle control, reaction time, and subjective time sense. Diet histories were obtained to estimate the approximate daily vitamin C intake prior to both the initiation and the conclusion of the study. All twins received a multiple vitamin preparation that contained 50 mg of vitamin C in order to ensure that any observed treatment effect could reasonably be attributed

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to pharmacologic doses of the vitamin rather than to dietary deficiency.

The study began in November 1974 and lasted for five months. The twins were visited each month, and the mothers were contacted by phone at least once between visits to encourage interest and strict compliance with the protocol.

Vitamin C was assayed in the casual and 24-hour urine samples and in fasting plasmas by the method of Aeschbacher and Brown adapted for an automated analyzer.[8]

RESULTS

All 44 twin pairs completed the five-month study; however, two male pairs were omitted from the analysis of cold symptoms because of incomplete questionnaire data.

As shown in Table 2, an overall analysis of treated and untreated twins showed no significant difference in vitamin C excretion prior to initiation of the study, and the initial correlation between twin pairs was 0.7, doubtless reflecting similarities in diet and genetic background as well as age. In the sample obtained just before the end of the study, the paired comparison test showed a highly significant difference between treated and untreated twins ($P < 0.0001$), as expected. Although there were no impressive differences in vitamin C excretion between the sexes in untreated twins, treated boys had higher excretion levels of vitamin C than did girls in all three dosage groups. It is noteworthy that the pretreatment excretion levels were rather high, probably reflecting the generally high socioeconomic background of the families.

Table 1.—Distribution of Twin Pairs by Sex and Dosage

Dosage of Vitamin C (mg/day)	No. of Pairs		
	Boys	Girls	Total
1,000	5*	7	12
750	6*	6	12
500	7	13	20
Total	**18**	**26**	**44**

*One pair from each of these groups was omitted from the analysis of cold symptoms because of incomplete data.

For each subject the following variables were derived from the data on cold symptoms: (1) incidence of illness episodes, (2) total duration of episodes (ie, total symptom days during the study), (3) average duration (days) of episodes, (4) average total severity per episode (sum of severity ratings divided by number of episodes), and (5) total days in bed. Table 3 shows mean values for these variables. The overall average number of respiratory illnesses during the study was 4.9 per twin, with an average duration of 7.2 days per episode, and an average severity index of 26.9 per episode, which represents the average sum of the severity ratings for all the symptoms present per episode of illness. Inspection of the data presented in Table 3 shows that on the average boys had fewer colds than did girls and that the number of episodes was greater in the younger twins. Analysis of the paired comparisons showed no significant overall treatment effect on the mean differences between treated and control twins in any of the variables examined. However, a statistical analysis showed that the treatment effect on average severity and total duration was not uniform among subgroups. In particular, the combined two lower-dosage groups of girls showed significant treatment effects ($P < 0.05$) on total duration, average duration, and severity, and boys in the lowest age group also demonstrated a significant treatment effect on severity ($P < 0.05$). Failure to take into account the group and sex differences would have led to acceptance of the null hypothesis of no treatment effect; however, inspection of subgroups reveals a trend toward beneficial effects in younger girls receiving either 750 mg or 500 mg daily.

The diet histories showed no significant intrapair differences in the dietary intake of vitamin C either before or after the study. The range of estimated intakes was decreased at the conclusion of the study, attributable to the addition of the multiple vitamin with 50 mg of vitamin C for those with initially low intakes and to the replacement of high potency multiple vitamins taken by some twin pairs prior to the study.

Analysis of anthropometric measurements by means of paired comparisons also showed no overall treatment effect on blood pressure, height, weight, or tonsil and cervical node size, or on the changes in these variables during the course of the study. However, the statistical analysis did reveal an unexpected variation among groups on change in height ($P < 0.05$), resulting from an apparent treatment effect on linear growth in the lowest dosage group of male twins ($P < 0.01$); the effect was not significant in the other data subsets (Table 4). The seven pairs of young male twins in this group ranged from 6 to 11 years of age, and in all but one pair the treated twin grew from 0.64 to 2.54 cm more than did the untreated co-twin during the five-month study period. In the seventh pair there was no difference in growth.

Table 2.—Vitamin C Excretion in 24-Hour Urine Mean ± Standard Deviation (mg/day)

Dosage Level	Male Twins			Female Twins			Totals		
	Vitamin C	No.	Placebo	Vitamin C	No.	Placebo	Vitamin C	No.	Placebo
1,000 mg/day									
Before treatment	387±178	5	319±145	274±96	7	311±109	321±141	**12**	314±119
During treatment	633±169	5	430±232	546±300	7	350±145	582±248	**12**	383±181
750 mg/day									
Before treatment	310±95	6	153±98	196±111	6	243±129	253±115	**12**	198±115
During treatment	588±289	5	309±172	362±158	6	246±143	465±244	**11**	275±152
500 mg/day									
Before treatment	208±102	7	187±99	190±106	13	189±164	196±102	**20**	188±142
During treatment	397±138	6	299±258	349±107	13	217±103	365±135	**19**	245±168
Total									
Before treatment	292±139	**18**	212±124	214±106	**26**	234±148	246±126	**44**	225±138
During treatment	530±231	**16**	343±219	407±201	**26**	261±133	455±219	**42**	293±174

Table 3.—Summary of Cold Symptoms Data*

	Male Twins			Female Twins			Totals		
	Mean Value			Mean Value			Mean Value		
	Vitamin C	Placebo	$\bar{D}\pm$SEM†	Vitamin C	Placebo	$\bar{D}\pm$SEM†	Vitamin C	Placebo	$\bar{D}\pm$SEM†
1,000 mg/day									
No. of illness episodes	4.0	2.5	1.5±1.7	5.3	4.6	0.7±1.3	4.8	3.8	1.0±1.0
Total sick days	35.3	33.8	1.5±7.5	41.4	30.9	10.5±6.5	39.2	31.9	7.3±4.7
Av duration of episodes	6.7	10.8	−4.1±3.8	8.2	6.9	1.3±2.0	7.7	8.3	−0.6±1.8
Av total severity	21.4	45.8	−24.4±20.6	23.1	16.7	6.4±10.4	22.5	27.3	−4.8±9.4
Days in bed	0.5	1.0	−0.5±0.6	1.0	1.0	0.0±0.6	0.8	1.0	−0.2±0.4
750 mg/day									
No. of illness episodes	4.4	3.4	1.0±0.6	3.3	3.8	0.5±0.6	3.8	3.6	0.2±0.4
Total sick days	34.6	16.0	18.6±9.9	24.0	36.2	−12.2±5.5	28.8	27.0	1.8±5.1
Av duration of episodes	8.3	5.0	3.3±1.5	9.1	12.4	−3.3±1.4	8.7	9.0	−0.3±1.0
Av total severity	34.4	17.2	17.2±10.1	60.5	70.3	−9.8±5.0	48.6	46.2	2.4±5.0
Days in bed	2.2	1.0	1.2±0.6	3.0	4.3	−0.7±2.3	2.6	2.8	−0.2±1.2
500 mg/day									
No. of illness episodes	5.1	5.0	0.1±0.5	6.1	6.6	0.5±0.6	5.8	6.1	−0.3±0.4
Total sick days	21.4	23.0	−1.6±2.3	39.9	46.5	−6.6±3.8	33.5	38.3	−4.8±2.5
Av duration of episodes	3.9	4.7	−0.8±0.6	6.4	7.2	−0.8±0.8	5.5	6.3	−0.8±0.6
Av total severity	13.0	15.5	−2.5±2.0	15.5	20.8	−5.3±3.9	14.6	19.0	−4.4±2.6
Days in bed	0.9	0.7	0.2±0.7	1.3	1.8	−0.5±0.7	1.2	1.4	−0.2±0.5
Overall									
No. of illness episodes	4.6	3.9	0.7±0.5	5.2	5.4	−0.2±0.5	5.0	4.8	0.2±0.3
Total sick days	29.0	23.5	5.5±3.5	36.7	39.9	−3.2±2.7	33.7	33.6	0.1±2.1
Av duration of episodes	6.0	6.3	−0.3±1.0	7.5	8.3	−0.8±0.7	6.9	7.5	−0.6±0.6
Av total of severity	21.8	23.6	−1.8±5.5	27.9	31.1	−3.2±3.5	25.6	28.3	−2.7±3.0
Days in bed	1.2	0.9	0.3±0.4	1.6	2.2	−0.4±0.6	1.5	1.7	−0.2±0.4

*For number of individuals in each group, refer to Table 1.
†Vitamin C — Placebo.

Overall analysis of the blood chemistries and hematologic data showed no consistently significant treatment effect on white blood cell or red blood cell count, liver function tests, or levels of uric acid, cholesterol, electrolytes, total protein, or albumin.

Mental alertness and cognitive processing were assessed with four timed, psychometric measures that were developed as performance tasks sensitive to transient effects of psychoactive compounds.[9] The coding subtest from the Wechsler Intelligence Scale for Children–Revised,[10] a speed measure of new learning, was also administered, as was a version of the Stroop color-word interference task. No treatment effects were found for any of these tasks. Reaction time, fine motor control, tapping speed, and subjective time sense were evaluated with a series of brief, standardized tests designed by R. Shipley and R. J. Harley of Eli Lilly and Company for measuring psychomotor effects of drugs. Although no overall treatment effects were noted, there was a sex difference ($P < 0.01$) in the most sensitive tremor measure: treated boys had less tremor than their co-twins, whereas the opposite was generally true in girls. Tremor was measured by the frequency with which a probe affixed to the index finger touched the sides of a ring 1.3 cm in inner diameter during a fixed time span after a standardized period of practice.

Table 4.—Effect of Vitamin C on Growth

Dosage Level	Male Twins: Mean Growth cm	No.	$\bar{D}\pm$SEM*	Female Twins: Mean Growth cm	No.	$\bar{D}\pm$SEM*
1,000 mg/day						
Vitamin C	3.12	5	−1.07±0.89	1.91	7	−0.43±0.64
Placebo	4.19			2.34		
750 mg/day						
Vitamin C	3.56	6	+0.33±0.56	3.84	5	+0.21±0.74
Placebo	3.23			3.63		
500 mg/day						
Vitamin C	4.09	7	+1.32±0.33	2.62	12	+0.51±0.23
Placebo	2.77			3.12		

*Vitamin C — Placebo.

As a final approach to the detection of subtle treatment effects on general well-being that might not have been measured by any of our tests, each mother was asked to guess, while she and the investigator were still blinded, which twin had received the vitamin. Twenty-three of the 44 mothers could not tell any difference between the treated and control twins. However, among the 21 mothers who felt there was a detectable effect of treatment, 17 correctly identified the twin who had received the vitamin ($P < 0.05$). Among the mothers of the young twins in whom the objective evidence for a treatment effect was the greatest, eight of nine guessed correctly ($P < 0.02$).[11]

COMMENT

The use of young identical twins in the present study not only permitted perfect matching with respect to possible genetic variation in cold susceptibility and metabolic response, but also provided close matching for viral exposure and other environmental factors as well as for subjective variation in the maternal reporting

of cold symptoms. The efficiency of the co-twin control model was 2 to 14 times greater than that of an unpaired study design.[12] Thus, for some variables, if unrelated children and controls had been used, more than 14 times as many subjects would have been required to demonstrate the same effect.

The most striking overall finding was the heterogeneity of treatment effects in different age and sex groups with respect to cold symptoms, linear growth, and fine motor control. The observed effects of vitamin C on cold symptoms are consistent with several previous studies. Coulehan et al[5] studied children of a similar age range and also found a reduction in symptom days in younger children of both sexes and in older girls. Wilson and Loh[4] reported a reduction in the severity of symptoms in girls receiving 500 mg per day. It seems likely that the reduction in severity and duration of upper respiratory symptoms observed in this and previous studies represents a real effect in younger boys and girls, with girls continuing to benefit until an older age. However, estimates of the magnitude of the treatment effects revealed that even in the two younger female groups where the benefit was most pronounced, the treatment accounted for only 17% of the variation in total severity, 28% of the variation in incidence, and 21% of the variation in total duration. Thus, even though pharmacologic doses of vitamin C may have a detectable prophylactic effect in some age and sex groups, the genetic, environmental, or subjective factors would appear to account for a substantially greater fraction of the total morbidity. No evidence was found for any harmful treatment effects, as detected by the changes in the blood chemistries or hematologic indices and as revealed in a detailed, side-effects questionnaire that was administered to the mothers each month.

The effect of vitamin C on growth in young male twins was entirely unexpected. The paired comparison *t*-test for this group was significant at the 1% level. A retrospective literature review showed, however, that Lewin previously predicted that pharmacologic doses of vitamin C might influence growth either by altering the equilibrium between ascorbic acid levels in blood and bone or by stimulating collagen synthesis.[13] It is possible that there is a stage in the development of young boys at which they are unusually sensitive to increased ascorbic acid intake; however, the effect on growth observed in this study must be confirmed before it can be accepted as an established fact.

Our attempt to detect an effect of vitamin C on mental alertness and motor performance was prompted by the review of Pauling,[14] in which he reported an association between vitamin C intake and increased mental alertness and feelings of well-being. While there was no evidence of a treatment effect on distractibility, learning efficiency, reaction time, accuracy, time sense, or tapping speed, the male twins who received vitamin C showed better performance than the co-twin controls in a test of fine muscle control, and in all but five of the 16 tested male pairs, the treated twin showed less tremor. In contrast, girls in the two higher dosage groups showed the opposite effect, with the treated twin generally performing more poorly. It is possible that all genetic constitutions do not benefit equally from pharmacologic doses of vitamin C. The opinions of the mothers tend to support this view: only 21 felt there was a therapeutic effect, but of these, most were able to identify the treated twin correctly.

Although the investigators remained blinded throughout the study and the parents were not informed of the identity of the treated twin until after completion of the data analysis, four mothers acknowledged tasting the contents of the capsules. We cannot exclude the possibility that these and possibly other mothers recognized the vitamin C by taste and that this knowledge may have influenced their subjective symptom ratings.

Our results and those of previous investigators indicate that the effects of pharmacologic doses of vitamin C depend upon the age, sex, and possibly the genetic constitution of the subject, with young children being most receptive to benefit from the vitamin. However, a large number of variables have been analyzed in this study, and the majority showed no significant treatment effects. The reader should be aware that, as the number of tests performed increases, the possibility of obtaining a "significant" result by chance alone is also increased.

This investigation was supported in part by Public Health Service grants GM-21045 and HD-10291 and a grant from the Hartford Foundation.

The vitamin C capsules and multiple vitamin preparation (Novacebrin Chewable) used in this investigation were supplied by Eli Lilly and Company, Indianapolis.

Joann Campbell, Emily Harris, and Phyllis Winter assisted in this study, as well as Karyl Rickard and Deborah Repasky of the Riley Children's Hospital Dietetic Service.

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Lead in Newsprint Attractive to Children, ppm				
	Red	Blue	Yellow	Black
Sunday comics, NJ	21	16	21	30
Sunday comics, Fla	700	65	12	688
Big Little Book	0	14	267	8
Children's book	441	4	428	2
Children's magazine	47	4	5	34
Children's magazine	0	0	1	0
Comic book	19	3	0	15
Christmas catalog	1,285	1,200	1,771	657
Activity book	1	1	1	1
Newspaper magazine section	995	2	880	868
Sports magazine	136	0	2	1
Children's book	0	0	0	0

atmosphere. Paper may also be recycled, resulting in a product that may have a high lead content.

Our findings are in agreement with an earlier study[5] on the amount of lead in printed matter. The investigators found leaded inks being used to a considerable extent in comics and in national magazines. Eaton et al[6] have reported on the lead content of a number of European children's magazines. They found that 20 of 48 United Kingdom comics had lead levels above 500 ppm with a maximum in the range of 6,000 ppm. These investigators also found leaded inks being used in Spanish publications. The problem, therefore, does not appear to be confined to the United States.

We feel that the hazards of lead in printed matter should be brought to the attention of the medical profession in general since it undoubtedly contributes to the lead burden of children with pica. From our study it appears that national magazines, magazine sections of newspapers, and catalogs that may or may not be directed at children may be using leaded inks. Since many publications do not use leaded inks, one wonders why they need to be used at all since even in publications not directed at children, availability in the home may prove a hazard.

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Gastrointestinal Blood Loss

To the Editor.—It has been repeatedly demonstrated that antirheumatic doses of aspirin, especially when given unbuffered and without food, result in the daily loss of 3 to 5 ml of blood into the gastrointestinal tract. The phenylalkanoic acids appear to be less culpable with regard to minor daily blood loss, as redemonstrated by Loebl et al (237:976, 1977). It is less clear whether major gastrointestinal bleeding, which occurs in one in 6,700 heavy aspirin users annually, is any less common with the phenylalkanoic acids.[1] *The Medical Letter on Drugs and Therapy* recently reviewed reported bleeding and fatal hemorrhage in patients receiving phenylalkanoic acids.[2]

Loebl concludes that "nonsteroidal, anti-inflammatory drugs have relatively similar degrees of efficacy," citing a recent review.[3]

The Mills[3] article does not mention fenoprofen calcium or other phenylalkanoic acids specifically but does state that "none [of the nonsteroidal drugs] has any advantage over salicylate except that most are claimed to be less ulcerogenic. In terms of potency . . . they do not compare with either phenylbutazone or indomethacin." Mills notes some gastric intolerance to aspirin but concludes, "It is possible in most cases to find a regimen that will allow full therapeutic doses of salicylate to be taken without substantial risk."

Four grams of buffered aspirin cost the patient about ten cents per day. Fenoprofen, 2.4 g daily, will cost about a dollar per day, a premium of over $300 per year with no therapeutic advantage. In my opinion, aspirin remains the drug of choice unless clearly not tolerated.

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In Reply.—We find no fault with the conclusions reached by Dr Hanauer and, in fact, fully support his closing statement that "aspirin remains the drug of choice unless clearly not tolerated."

However, we feel that Dr Hanauer missed the major point of our paper, namely, that a scientific methodology is available that can be employed in a feasible manner to test the "short-term risk of erosive gastritis" in patients who receive drugs that contribute to this risk. No data were presented on long-term risks of these drugs. As indicated by Dr Hanauer, the true frequency of a major gastrointestinal bleeding episode, in contrast to the smaller amounts of bleeding usually seen in erosive gastritis, remains to be determined by clinical experience. For the short term, we suggest that objective data as illustrated by our report best assess this facet of drug action.

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Vitamin C and Growth

To the Editor.—Miller and co-workers (237:248, 1977) claim to have observed an "effect of vitamin C on growth in young male twins." Inspection of their data (Table 1) indicates that such a conclusion is unjustified.

Their conclusion was drawn solely from the comparison with placebo for 500 mg/day. An opposite conclusion could just as easily (and equally erroneously) be drawn from the figures for 1,000 mg/day for male twins. Actually, three sets grew more rapidly with vitamin C, and three more rapidly with placebo. Finally, when the total growths for both sexes are summarized, 42 vitamin C twins grew a total of 129.60 cm for an average of 3.09 cm, and 42 placebo twins grew 131.69 cm for an average of 3.14 cm. In short, growth on vitamin C was slightly, but obviously insignificantly, less than growth on placebo. In any experiment on growth rates conducted with experimental animals, such agreement between duplicate groups on the same treatment would be considered unusually good.

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In Reply.—We agree with Jukes that

Table 1.—Effect of Vitamin C on Growth

Dosage Level	Male Twins: Mean Growth, cm	Male Twins: No.	Male Twins: $\bar{D}$±SEM*	Female Twins: Mean Growth, cm	Female Twins: No.	Female Twins: $\bar{D}$±SEM*
1,000 mg/day						
Vitamin C	3.12	5	−1.07±0.89	1.91	7	−0.43±0.64
Placebo	4.19			2.34		
750 mg/day						
Vitamin C	3.56	6	+0.33±0.56	3.84	5	+0.21±0.74
Placebo	3.23			3.63		
500 mg/day						
Vitamin C	4.09	7	+1.32±0.33	2.62	12	+0.51±0.23
Placebo	2.77			3.12		

*Vitamin C − Placebo.

Table 2.—Growth of Male Twins in Group Receiving 500 mg Vitamin C Per Day

	Age, yr*	Height, cm: Before	Height, cm: After	Growth, cm	Intrapair Difference, cm (Vitamin C − Placebo)
Pair 1					
Vitamin C	7	116.84	120.02	+3.18	+0.89
Placebo		118.36	120.65	+2.29	
Pair 2					
Vitamin C	11	144.78	148.59	+3.81	+1.27
Placebo		145.42	147.96	+2.54	
Pair 3					
Vitamin C	10	129.54	134.62	+5.08	0
Placebo		129.54	134.62	+5.08	
Pair 4					
Vitamin C	9	133.35	136.53	+3.18	+0.64
Placebo		135.26	137.80	+2.54	
Pair 5					
Vitamin C	7	119.38	126.37	+6.99	+2.54
Placebo		118.11	122.56	+4.45	
Pair 6					
Vitamin C	6	104.14	108.59	+4.45	+1.91
Placebo		105.41	107.95	+2.54	
Pair 7					
Vitamin C	11	136.53	138.43	+1.90	+1.90
Placebo		135.89	135.89	0	

*Age at the conclusion of the capsule-taking period.

our data provide no overall evidence for a treatment effect of pharmacologic doses of vitamin C on growth and clearly stated this in our article. However, we did observe significant heterogeneity by analysis of variance in the response to vitamin C among treatment groups ($P<.05$) and, as reported, found an apparent effect on growth in the male twins receiving 500 mg per day ($P<.01$) when individual group means were compared. The actual measurements are given in Table 2, where it can be seen that six of the seven treated male twins grew more than their co-twins, while in the seventh pair there was no difference in growth.

We disagree with Jukes' statement that "an opposite conclusion could just as easily . . . be drawn from the 1,000 mg/day figures for male twins," since the mean difference for this group was less than twice its standard error, while the mean difference was more than four times the standard error in the group of male twins who received 500 mg/day. When the null hypothesis is rejected, as in the case of the male twins on 500 mg/day, the risk of the claim being false is known (it is the significance level of the test), while the same is not true when the null hypothesis is accepted.

Finally, it should be noted that since the twin pairs were assigned to dosage groups by body weight, they were also partitioned approximately by age. Consequently, the dosage groups cannot be considered to be replicate experiments with respect to growth potential.

As we noted in the conclusion of our article, a large number of variables were investigated, and the majority showed no significant treatment effects. As the number of comparisons increases, so does the possibility of obtaining a statistically significant result by chance. For this reason, we stated that the reported effect of vitamin C on the growth of the young male twins in the lowest dosage group must be confirmed before it is accepted as fact.

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Naproxen Overdose

To the Editor.—We have recently seen a patient who was reported to have ingested 25 g of naproxen (Naprosyn) as a single dose. This is 50 times the recommended daily therapeutic dose of naproxen in rheumatoid arthritis.

In a report on the pharmacokinetics of naproxen overdoses, Runkel and colleagues (*Clin Pharmacol Ther* 20:269, 1976) reported that, in contrast to the kinetics of salicylate elimination, high doses of naproxen of 1 to 4 g resulted in a disproportionate increase in renal excretion without evidence of saturation of the excretory mechanism.

Our clinical experience with the patient reported here appears to confirm their experimental findings. The patient's complete blood cell count, electrolytes, blood chemistries, and urinalysis were within normal limits. His symptoms were limited to mild transient gastrointestinal distress (nausea and indigestion). The serum naproxen concentration approximately 15 hours after ingestion was 414 μg/ml, a high level but one consistent with the previously reported disproportionately accelerated excretion with increasing doses.

This case report provides additional information on the safety of naproxen, particularly in comparison with the known acute toxicity of aspirin.

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Cardiac Arrest

To the Editor.—The publication of retrospective studies of causes of anesthetic contributory death, "Unexpected Cardiac Arrest During Anesthesia and Surgery," by Taylor, Larson, and Prestwich (236:2758, 1976) draws attention once again to the paucity of sound statistical mortality studies in this field.[1]

In supporting the authors' plea for a cardiac arrest registry, I would make a plea that provision be made for assessing the background population of anesthetics from which the data come. Whatever advances are claimed for