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VITAMIN C PROPHYLAXIS IN A BOARDING SCHOOL

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Abstract A double-blind study to evaluate vitamin C supplements for respiratory-infection prophylaxis was conducted among 641 children at a Navajo boarding school over a 14-week period. Supplements of 1 and 2 g, or placebo, were given daily. A sample of each group had serial blood ascorbic acid determinations, which showed significant rises among groups treated with vitamin C, but no difference in mean levels between those receiving 1 and those given 2 g.

Although there was no difference between treatment groups in number of respiratory episodes, those given vitamin C had fewer days of morbidity than those receiving placebo, both in older (34 per cent) and in younger (28 per cent) age groups. In active surveillance, there were 26 per cent fewer symptomatic days observed in younger vitamin C groups, and 33 per cent fewer in older girls on vitamin C. No such difference was seen in older boys. Nasal discharge and cough were the two symptoms apparently benefited. Significantly more children on vitamin C had no sick days observed in the periodic survey. In addition, treated children with higher blood ascorbic acid levels had fewer symptomatic days noted than those with lower levels. (N Engl J Med 290:6-10, 1974)

In his book, *Vitamin C and the Common Cold*,[1] Linus Pauling claimed that ascorbic acid in large daily doses could prevent upper respiratory infections. He recommended 1 to 3 g daily for prophylaxis. These speculations were based on the results of several clinical trials,[2-4] as well as personal experience and evolutionary considerations. However, the studies on which Dr. Pauling relied had defects in design or reporting[5-7] (or both) that rendered their results inconclusive. Since the appearance of Dr. Pauling's book, two clinical trials have been published that show some benefit of vitamin C. Anderson, Reid and Beaton[8] conducted a large double-blind study with adult "cold-prone" volunteers over a two-month period. They found a highly significant (30 per cent) reduction in days of disability among the group receiving 1 g of ascorbic acid daily as compared with the placebo group. Wilson and Loh,[9] who assessed the prophylactic value of placebo and 200 mg or 500 mg of ascorbic acid in school children over a nine-month period, found that catarrhal cold symptoms were reduced by over 50 per cent in girls taking 500 mg of ascorbic acid daily, but there was no consistent effect in boys.

The present investigation was designed to test the null hypothesis that daily vitamin C supplements and placebo supplements have identical effects as prophylactic agents in respiratory disease. To test this hypothesis, a double-blind study in a Navajo boarding school was conducted, daily vitamin C supplements of 1 and 2 g versus placebo being used.

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Methods and Materials

Subjects

The study population included children enrolled at Toyei Boarding School, an elementary school for Navajo children located at Steamboat, Arizona. Parental permission for inclusion in the study was sought and obtained for each child attending the school in January, 1973. Likewise, permission for this investigation was granted by appropriate Indian Health Service and Tribal authorities. There were 666 children at the outset, ranging in age from six through 15 years. The children all lived at school, although approximately one third of them returned home on any given weekend. There was an Indian Health Service clinic at the school with a nurse available at all times, and the school physician was present one day each week.

Tablets and Procedures

Tablets manufactured for this study* contained 500 mg of vitamin C, whereas placebos were formulated from citric acid to be indistinguishable in taste and appearance from the vitamin C tablets. All children were assigned alternately, from an alphabetical listing by classroom, to one of two study groups. A pharmacist, not otherwise involved in this investigation, then allocated one group vitamin C and the other placebo. Tablets were distributed to school teachers in containers labeled only by code number. The only master list was maintained by the pharmacist. Persons involved in data collection were aware neither of which group received vitamin C nor of the group to which any given child belonged.

The study period was 14 weeks from early February through mid-May. Children on vitamin C in Grades 1 through 4 (ages six to 10) received 1 g daily, whereas those in Grades 5 through 8 (ages 10 to 15) received 2 g. Children in the placebo group received two or four tablets of placebo, respectively. All supplements were given in a single daily dose observed by the teacher. The same number of tablets were given whether or not a child had symptoms of illness. On Fridays or before a holiday, each child was given a packet containing his tablets for the weekend or holiday period. Those who left school unexpectedly or did not return promptly from home had no tablets during their absence.

Blood Studies

A group of children was chosen for serial whole-blood ascorbic acid determinations. Every third child was selected from an alphabetical listing of school enrollment by classroom. The first blood drawing took place in January, before the study period, the second seven weeks after the study began, and the final drawing in late-May, two weeks after the study period ended. Vitamin C levels were determined by the 2,4-dinitrophenylhydrazine method described by Lowry, Lopez and Bessey,[10] and the microprocedure used was shown by Bradley et al.[11] to yield results equivalent to those obtained with use of venipuncture whole blood.

Data Collection

Two types of observation were made in this study. In the first, clinical episodes of illness were observed. These included all illnesses for which children sought medical care through the routine channels (e.g., self-referral to clinic or referral by dormitory aides or teachers). Secondly, active surveillance was maintained to observe those respiratory illnesses for which no medical care was sought.

To qualify as a discrete "episode," an illness had to have an onset preceded by at least seven symptom-free days. Written diagnostic criteria were established for five respiratory syndromes† (uncomplicated upper respiratory infection, pharyngitis, otitis media, bronchitis and pneumonia). Other illnesses were lumped together, with the exception of gastrointestinal complaints. Injuries were excluded entirely from consideration. Diagnosis and duration of symptoms before day of diagnosis were recorded. The nurse followed each ill child daily until all symptoms were resolved, thus allowing for computation of total duration of illness.

A medically trained clerk or the school nurse conducted active surveillance in four classrooms daily. All classrooms were seen in a regular rotation. Each child's temperature was taken, each was examined for nasal discharge, and each asked individually in the Navajo language if any of the following symptoms were present on that day: runny nose, sore throat, earache or cough. Only the presence or absence of these signs and symptoms was recorded. Temperatures of 37.5°C or over were considered elevated.

Results

Six hundred and forty-one of the 666 children (96 per cent) completed the entire 14-week study period. Of these, 321 received vitamin C supplements (C), and 320 received placebo tablets (P). The other 25 subjects (13 C and 12 P) were eliminated from the study because they dropped out of school during its course. No children were eliminated because of adverse effects.

Table 1 shows whole-blood vitamin C levels of the children who had two or three serial determinations. March blood samples were drawn 20 to 26 hours after the preceding day's supplement was given. All C groups had highly significant increases in ascorbic acid levels at that point, seven weeks after the supplementation had begun. Upper-grade children receiving 2 g daily had increases slightly smaller than those in the lower grades who were taking only 1 g daily. In addition, upper-grade P children showed significant blood vitamin C increases from January to March, although these were much smaller than those found in the C groups. Determinations were also performed on blood drawn in May, two weeks after supplementation was completed. There were no significant variations when the January and May levels of the same children were compared.

The school doctor or nurse treated 75 respiratory-illness episodes and 89 other illness episodes at the clinic during the 14-week period. None involved the lower respiratory tract. No differences in number of treated episodes were found between C and P groups. Only nine cases of gastrointestinal illness were seen (four in C and five in P groups). Table 2 shows total days of morbidity and average duration of episodes. There were significantly fewer days of morbidity from respiratory illness in C children than in P children, in both lower-grade (28 per cent) and upper-grade (34 per cent) groups. Percentage differences were similar in males and females. There were also fewer morbid days from "nonrespiratory" causes (30 per cent) among the lower-grade C children than among those in the P group. The distributions of episode duration were compared for C and P children in each grade level and sex combination with use of the Mann–Whitney U-test. This nonparametric test was used to avoid comparing

Table 1. Whole-Blood Vitamin C Levels.

Sex	Levels in January*		Levels in March†		Levels in May‡	
	Vitamin C group	Placebo group	Vitamin C group	Placebo group	Vitamin C group	Placebo group
			mg/100 ml ± SD			
Lower grades:						
Male	1.42	1.46	2.39	1.55	1.46	1.35
	±0.21	±0.24	±0.60§	±0.17	±0.17	±0.17
Female	1.44	1.47	2.29	1.56	1.51	1.40
	±0.23	±0.19	±0.58§	±0.27	±0.20	±0.15
Higher grades:						
Male	1.25	1.22	2.06	1.51	1.36	1.35
	±0.29	±0.39	±0.55§	±0.23¶	±0.36	±0.21
Female	1.33	1.31	2.08	1.47	1.56	1.31
	±0.20	±0.20	±0.43§	±0.29¶	±0.23	±0.20

*Before supplements (142 children).
†During supplements (142 children).
‡2 wk after supplements (107 children).
§Jan-Mar increases, t statistic, $p<0.001$.
¶Jan-Mar increases, t statistic, $p<0.05$.

*Kindly supplied by Hoffmann-LaRoche, Inc., Nutley, N.J.
†Available from the authors on request.

Table 2. Clinical Episodes of Illness and Days of Morbidity.

Group	No. of Children	No. of Episodes	Days of Morbidity from All Episodes	Average Duration of Episodes (Days)	Change in Days of Morbidity on Vitamin C (%)
Respiratory illness:					
Lower grades:					
Vitamin C	190	19	94	4.95	−28*
Placebo	192	23	130	5.65	
Upper grades:					
Vitamin C	131	16	71	4.44	−34†
Placebo	128	17	107	6.29	
Other illness:					
Lower grades:					
Vitamin C	190	25	108	4.32	−30*
Placebo	192	26	154	5.92	
Upper grades:					
Vitamin C	131	19	115	6.05	−8
Placebo	128	19	125	6.58	

*3x2 table comparing days of respiratory illness, days of other illness & days not known to be ill; chi-square = 13.20; 2 df, $p<0.01$.

†As above, chi-square = 8.93; 2 df, $p<0.05$.

mean durations while assuming other distribution parameters to be identical between groups. There were no significant differences in these distributions with the exception of respiratory episodes in older girls. In that case, the C distribution was different from the P distribution in favor of shorter illness duration (K = 28, U = 102, $p<0.05$).

A clerk visited each classroom regularly every 13th day, completing seven circuits of the school during the study. Of the possible 4487 child-days of observation (641 children × seven circuits), there were actually 3929 (87 per cent) child-days observed, with the remainder accounted for by days absent. The presence, on a given observation day, of any one of the five criteria (elevated temperature, cough, earache, sore throat or nasal discharge) was considered indicative of a "sick day." Table 3 lists the findings on active surveillance for symptomatic days in all groups. There were 26 per cent fewer symptomatic days in lower-grade C children than in P children, a difference highly significant for both boys and girls. Upper-grade C girls had 33 per cent fewer sick days than those on placebo, although there was no difference between the groups of upper-grade boys. When days sick with each symptom or sign were considered separately, it was clear that the better experience of those on vitamin C was related entirely to reduction in cough and nasal discharge. No consistent pattern was noted for fever, earache and sore throat. The lower-grade C group as a whole had 30 per cent fewer days of one symptom (221 vs. 156 per 1000 observations), and 16 per cent fewer days of two or more symptoms (63 vs. 53 per 1000 observations) than P children. In the upper-grade girls, 28 per cent fewer days of one symptom (122 vs. 82 per 1000) and 40 per cent fewer days of two or more symptoms (43 vs. 26 per 1000) were noted in children on vitamin C.

A separate analysis was made of the children who remained well on active surveillance throughout the study as contrasted with those who had at least one sick day observed (Table 4). Again with the exception of

Table 3. Results of Active Surveillance.

Sex	Placebo		Vitamin C		Chi-Square Value (df=2)*	Change on Vitamin C/1000 Observations (%)
	Child-Days Observed	Days Sick	Child-Days Observed	Days Sick		
Lower grades:						
Male	525	143	500	95	10.78†	−30
Female	658	191	708	158	13.04†	−23
Higher grades:						
Male	346	33	375	37	4.59	+ 4
Female	393	48	424	35	6.61‡	−33

*3×2 table, comparing days known well, days known ill & days unknown (child absent).

†$p<0.01$. ‡$p<0.05$.

higher-grade boys, significantly more children in C groups had no symptoms observed at all. Thirty-two per cent of younger C children had no sick days noted, whereas only 16 per cent of the younger P children remained well on survey days. These differences, when considered in sum for the entire school, were very highly significant. However, since observations were made only periodically of a given child, these findings do not imply that children without observed sick days actually remained well throughout the study period.

Finally, the symptomatic experience on active surveillance of the C children who had blood samples drawn in March was considered. There were 100 such children, and their whole-blood ascorbic acid levels were arrayed from highest to lowest. The active surveillance experience of children who had levels in the upper one third (34 in number) was then compared with that of those whose levels were in the lower one third (33). Only a small number of sick days was involved; yet those in the higher level group had 46 per cent fewer sick days noted than those with lower levels (30 days vs. 55 days, comparing sick days, observed well days and days of unknown status, chi-square = 12.35, 2 d.f., $p<0.01$).

Discussion

This study tested the null hypothesis that daily vita-

Table 4. Children in Vitamin C and Placebo Groups Never Ill on Active Surveillance.

Sex	Vitamin C		Placebo		Chi-Square
	No. of Days without Sickness Observed/Total in Group	% Days without Sickness Observed	No. of Days without Sickness Observed/Total in Group	% Days without Sickness Observed	
Lower grades:					
Male	31/81	38	18/87	21	6.28*
Female	30/109	28	12/105	11	8.78†
Both	61/190	32	30/192	16	14.29‡
Higher grades:					
Male	40/62	64	34/61	56	0.98
Female	42/69	61	29/67	43	4.21*
Both	82/131	63	63/128	49	4.70*
All grades	143/321	44	92/320	29	16.52‡

*$p<0.05$. †$p<0.01$. ‡$p<0.001$.

min C supplements and placebo supplements have identical effects as prophylactic agents in respiratory disease. Although this null hypothesis was supported regarding the incidence of illness episodes, there were statistically significant differences between treatment groups in the duration of morbidity. Children taking 1 and 2 g of vitamin C supplements daily were ill fewer days than those taking placebo, although the prophylactic benefits were modest and not entirely consistent.

Clinical episodes represented the more severe illness that occurred during the study period. In retrospect, children were usually not referred to the clinic for upper respiratory symptoms, unless they were obviously febrile or toxic. Nevertheless, there were, on the average, 30 per cent fewer days of morbidity from respiratory episodes among C children than among those in P groups. This finding, however, must be interpreted with caution. There were relatively few episodes included in the study, and, when the actual distributions of duration were compared between groups by means of a nonparametric statistical test, the differences were not significant, except for older girls. Active surveillance findings represent milder forms of the "common cold," not requiring medical intervention or absence from school. Similar decreases in sick days were seen in all C groups, with the exception of older boys. These findings are consistent with a decrease in duration of morbidity and do not imply fewer illness episodes. Because of the methodology, however, it is not certain that each unit of observation (child-day) was independent, and, therefore, the results of these chi-square analyses must also be interpreted with caution.

Our results do correlate with those of recent studies on the prophylactic value of vitamin C. Anderson et al.[8] found 30 per cent fewer days of disability among volunteers taking 1 g daily of vitamin C supplements, and also noted that significantly more of this group remained well throughout the study as compared with those on placebo. Our surveillance data indicate that more C children had no sick days observed, as opposed to one or more sick days, than P children. Likewise, Anderson noted that the apparent benefit of vitamin C in reducing morbidity includes "other, nonrespiratory" episodes. Our findings suggest a similar pattern in that days of morbidity from nonrespiratory causes were 30 per cent fewer in younger C children. This category, however, may contain acute illnesses that involved respiratory symptoms at some time in their course but did not qualify as "respiratory" on the day of diagnosis by our criteria.

Wilson and Loh[9] differentiated "toxic colds" (sore throat, headache and fever) from "catarrhal colds" (cough, nasal obstruction and nasal discharge) in a double-blind study involving Dublin school children. The severity and intensity of symptoms were reduced over 50 per cent in girls receiving 500 mg of vitamin C supplements, predominantly in catarrhal syndromes. This caused the authors to suggest that vitamin C may have a local effect in reducing mucosal inflammation, rather than altering more systemic symptoms. Our findings on active surveillance concur with this selectivity since days with cough or nasal discharge were fewer, but days with other symptoms unchanged, in those on vitamin C.

The blood ascorbic acid levels in this study indicate that there was no evidence of deficiency in this population at the outset.[12] Moreover, children on vitamin C had highly significant rises in ascorbic acid levels even at a "steady state" 20 to 26 hours after their last dose, although there was no real difference in levels between those given 1-g and those given 2-g supplements. The latter finding may be due to greater body volume in the older children, a change in metabolism with age or a difference in compliance between the younger and older age groups. Thirdly, older P children of both sexes had significantly higher blood ascorbic acid levels in March than in January, suggesting that some P children may have been switching tablets at times with C children or getting excess ascorbic acid in some other way. Such switching could not have taken place on a large scale since each teacher observed ingestion of tablets on school days. Finally, paired comparison of baseline and post-study blood levels of the same children showed essentially no difference over time. There was no evidence to support a rebound lowering of ascorbic acid levels to "pre-scorbutic" values[13] at a point two weeks after large daily supplements were terminated.

The actual clinical meaning of these findings remains unclear. If we assume for the sake of argument that vitamin C does have prophylactic value, it is unlikely that such massive supplements are correcting nutritional deficiencies. On the contrary, the evidence suggests some pharmacologic effect of vitamin C. We recommend that further clinical trials be performed to confirm these associations — in particular, the suggestion that higher blood ascorbic acid levels correlate with fewer symptomatic days. The most convincing evidence, in this case, would involve concomitant variation of illness experience with blood levels in given subjects. A more fundamental area of investigation would be the specific pharmacologic action, if any, of ascorbic acid. Our data are consistent with local mucosal effects, whereas those of Anderson[8] suggest a more generalized benefit. Massive doses of vitamin C may increase resistance to certain infections, may mask symptoms through local or systemic actions or may indeed be virocidal in some way. There is no substantial evidence for a specific mode of action at present, but there are enough data suggesting a beneficial influence of vitamin C on respiratory infections to warrant further investigation.

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BACKGROUND READING

References 1, 6 and 7

ISOLATED GONADOTROPIN DEFICIENCY

A Heterogenous Syndrome

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Abstract Seven female patients with primary amenorrhea were shown to have isolated gonadotropin deficiency. Thyroid and adrenal function and growth hormone secretion were normal. Basal levels of follicle-stimulating hormone, luteinizing hormone and estradiol 17β were below the limit of sensitivity of our assays, and there was no change after intravenous estrogen or oral clomiphene citrate. With luteinizing-hormone-releasing hormone, levels of both follicle-stimulating and luteinizing hormones rose in five subjects, of luteinizing hormone only increased in one subject, and in the remaining patient there was no change in either hormone. In all three patients to whom urinary gonadotropins (menotropins) were administered serum estradiol 17β was elevated. Subsequent therapy with human chorionic gonadotropin led to ovulation, with an increase in serum progesterone, and two patients became pregnant.

The syndrome of isolated gonadotropin deficiency thus appears to be heterogenous although in most patients the pituitary gonadotrope is intact and the defect resides in the hypothalamus. Ovarian responsiveness is retained. (N Engl J Med 290:10-15, 1974)

ISOLATED deficiency of pituitary secretion of the gonadotropins human follicle-stimulating hormone (hFSH) and human luteinizing hormone (hLH) has long been recognized.[1-6] The advent of radioimmunoassay has permitted documentation of subnormal or absent peripheral levels of both hormones in this syndrome ("hypogonadotropic hypogonadism").[7,8] The low circulating hFSH and hLH levels could be consequent upon failure of the gonadotrope or failure of the appropriate signal to reach the gonadotrope via the pituitary portal circulation. Thus, the defect could be in the hypothalamus or at an even higher central level.

The identification of the thyrotropin-releasing hormone (TRH) has helped to pinpoint the nature of the defect in states of thyroid-stimulating hormone (TSH) deficiency. Many patients with idiopathic hypopituitarism, including secondary hypothyroidism, respond with a rise of TSH after TRH, indicating that the thyrotrope is intact.[9,10] Fleischer et al. have reported a positive response to TRH in one patient with isolated TSH deficiency.[10] Kaplan et al.[9] have suggested that most states of idiopathic pituitary deficiency are in fact due to hypothalamic rather than pituitary disease.

Availability of luteinizing-hormone-releasing hormone (LHRH)[11] has allowed similar examination of the site of the lesion in isolated gonadotropin deficiency, and there have already been some reports of its administration in this condition.[12-16] In our study of seven female patients with this syndrome we sought answers to two questions: whether the site of the lesion in the hypothalamic-pituitary unit could be identified; and what was the responsiveness of the ovary, deprived of endogenous gonadotropin, to therapy with human menopausal gonadotropins (hMG) and human chorionic gonadotropin (hCG).

Our results show that the syndrome of isolated gonadotropin deficiency is heterogenous. Whereas none of the patients responded to clomiphene citrate or to conjugated estrogens, responses to LHRH were varied.

Abbreviations Used

hCG:	human chorionic gonadotropin
hFSH:	human follicle-stimulating hormone
hGH:	human growth hormone
hMG:	human menopausal gonadotropins
LHRH:	luteinizing-hormone-releasing hormone
TRH:	thyrotropin-releasing hormone
TSH:	thyroid-stimulating hormone

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