

Ascorbic Acid and the Common Cold

Evaluation of Its Efficacy and Toxicity

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• We reviewed the clinical data relating to the efficacy and safety of pharmacologic doses of ascorbic acid in the prevention and treatment of the common cold. Although one study tentatively supports the hypothesis that such doses of ascorbic acid may be efficacious, a second study by the same group did not confirm the significant findings, and no clear, reproducible pattern of efficacy has emerged from the review of all the evidence. Similarly, there is currently little adequate evidence on either the presence or the absence of serious adverse reactions to such doses of ascorbic acid, although many such reactions have been hypothesized. The unrestricted use of ascorbic acid for these purposes cannot be advocated on the basis of the evidence currently available.

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IN 1938, THE JOURNAL published a review of the current scientific knowledge relating to the therapeutic usefulness of ascorbic acid.¹ In relation to the infectious diseases, the authors noted that favorable reports of its usefulness in pneumonia, pertussis, and rheumatic fever had appeared,

See also p 1038.

but they concluded, "It is evident that vitamin C is not a specific therapeutic agent in the treatment of any of these diseases." Apparently, its usefulness as a prophylactic or therapeutic

agent for the common cold had not been studied at that time.

This monograph will discuss the clinical data published since 1938 on the efficacy of pharmacologic doses of ascorbic acid in the prevention and treatment of the common cold. It will also discuss both the clinical data and some data obtained from intact animals that relate to the possible toxicity of high doses of ascorbic acid. Material will only be considered that was published in the scientific literature and was, therefore, subjected to both the careful editorial peer review and the critical scrutiny of the general scientific community that are inherent in that process.

PROPHYLACTIC AND THERAPEUTIC EFFICACY

It is well recognized that the use of double-blind randomized trials is es-

sential for a great many therapeutic evaluations.² This is especially true in those situations where evaluation depends substantially on a subjective report by the patient or where there is a substantial element of judgment required of the investigator. The evaluation of symptoms of the common cold involves both of these elements, and it has been generally recognized that only carefully controlled studies can provide useful evidence on the prophylaxis and therapy of this condition.

Controlled studies of ascorbic acid have been carried out, the first as long ago as 1942,¹ with varying doses, outcomes, and interpretations. On the whole, until recently, the evidence has been judged unfavorable to ascorbic acid, on grounds that there were defects in the favorable studies or that the effect seemed to be too small to merit attention. However, between 1970 and 1973, Prof Linus Pauling⁴⁻⁷ produced a number of reviews of the data and argued that (1) previous studies used too small a dose, and (2) nonetheless, they showed results that, if properly analyzed, indicated a substantial beneficial effect. Pauling's arguments have been influential in reopening serious consideration of the possible merits of ascorbic acid for prevention and treatment of the common cold.

In view of the fact that many con-

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trolled studies of ascorbic acid and the common cold have now been completed, it might be hoped that the matter of efficacy could be clearly settled one way or the other. In fact, because of the great variability in experience with colds from one subject to another, and because of the considerable subjectivity inherent in the evaluation of a cold, even a slight fault¹ in experimental design or procedure may open the way to a bias of substantial magnitude. For most of the studies on which the arguments supporting efficacy are based, the measures taken to protect against such bias fall short of a satisfactory level, and the conclusions must therefore be assessed with great caution. It has been claimed that daily ascorbic acid doses ranging from a few hundred milligrams up to several grams show beneficial results in diminishing the incidence and severity of colds. Most of the controlled studies have been reviewed by Pauling,⁵⁻⁷ but four have been reported recently,⁸⁻¹⁰ one in this issue (p 1038). We review those that meet some reasonable criteria of design, in that attempts were made to achieve unbiased allocation and "blind" conditions. The studies that have been advanced in support of efficacy will be presented individually; several negative studies will be presented as a group.

Cowan et al

This early (1939-1940) study, using 200 mg of ascorbic acid per day, was carried out among student volunteers at the University of Minnesota, and lasted 28 weeks. It used placebos said to be indistinguishable from the ascorbic acid tablets, and assignment to ascorbic acid or placebo was described as follows: "The students were assigned alternately and without selection to an experimental and a control group." The reporting system consisted of instruction to visit the clinic "whenever a cold developed" so that a report card could be filled out, supplemented by interviews at three-month intervals. The investigators were clearly not "blind" at the time of assignment. Pauling^{5,6} states that a personal communication from Diehl said that evaluation of cold episodes

	Treatment	
	Ascorbic Acid	Placebo
Subjects who began study	233	194
Subjects who completed study	208	155
Dropouts	25	39
Dropout rate, %	10.1	20.1
Reported colds per person during previous year	5.5±0.12	5.9±0.11
Colds per person during study	1.9±0.07	2.2±0.08
Percent of subjects with no colds during study	11.5±2.2	8.1±2.2

Group	No. of Subjects	No. of Colds Reported	No. of Colds			
			Cured	Improved	Not Changed	Worse
Placebo	23	7	1	2	3	1
Bioflavonoid*	22	8	1	4	0	3
Ascorbic acid	22	8	5	3	0	0
Ascorbic acid and bioflavonoid	22	6	3	2	0	1

*Table 5 in the original publication, reporting "improved or cured," erroneously records 4 in place of 5=1+4 for the bioflavonoid group.

	Treatment	
	Ascorbic Acid	Placebo
Subjects who completed study	407	411
Total days confined to house per subject*	1.30±0.101	1.87±0.138
Total days off work per subject†	0.88	1.31
No. (%) of subjects who remained free of illness‡	105 (26)	76 (18)

*t test, $P < .001$.
 †t test, $P < .01$.
 ‡ $\chi^2 = 5.92$; $P < .05$.

was done "blindly." No details of control to assure this are described.

Certain quantitative aspects of this study (Table 1) throw doubt on the presumptions of unbiased allocation and of "blindness." First, the reported incidence of colds during the previous season was significantly higher ($P < .05$) for those assigned to placebo than for those assigned to ascorbic acid. (A P value of .05 is the highest value generally accepted as statistically significant; it indicates that a deviation as large as was observed would not occur more than five times in 100 if there were no differences due to the treatment.) If allocation had been effectively unbiased and random, this would have been a most unlikely occurrence regardless

of the quality of student memories about prior colds.

Second, allocation by alternation as described should have resulted in initial group sizes far more nearly equal than 233 vs 194. Third, the dropout rate among the placebo group (20%) was twice that among the ascorbic acid group (10%). As asserted by Pauling (*Vitamin C and the Common Cold*, San Francisco, W. H. Freeman & Co., Publishers, 1970), this may be because the fraction of students who believed themselves to have benefited was smaller in the former than in the latter group. Against that suggestion lies the enthusiasm reported among placebo takers by the authors of this study, and the absence of any such difference in the far-better-controlled

study of Anderson et al.¹¹

A second placebo-controlled part of this study failed to reveal any reduction in the incidence, severity, and duration of colds reported by two groups of 88 and 82 students who, respectively, took one or two multiple vitamin capsules (each contained 25 mg of ascorbic acid) daily.

Franz et al¹

This 1956 study was carried out over three months with medical and nursing student volunteers. Ascorbic acid, 195 mg, and bioflavonoid, 1,000 mg, were administered daily in a factorial arrangement (placebo, ascorbic acid only, bioflavonoid only, ascorbic acid and bioflavonoid) to a total of 89 subjects. Subjects were assigned "in rotation" to the four treatments, in order of their appearance. The reporting system called for the subject to report in each time he had a symptom of a cold, at which time a physical examination and blood sample for ascorbic acid determination were obtained.

The description in the text of the article suggests that the observers were "blind" only with respect to the medication given to each group, but that they may well have known which group the subjects were in. Each reported cold was scored, after five days, as cured, improved, not changed, or worse, and the results in the four groups are shown in Table 2.

The four groups were remarkably homogeneous in total number of colds reported, but there appears to be some tendency in the groups receiving ascorbic acid for their colds to be classed as cured or improved. Pauling⁵ makes a calculation of statistical significance based on apparently erroneous summary results. Calculation with the corrected table gives a one-sided Fisher exact test probability of 0.0283 corresponding to a two-sided significance level of $P=0.0566$.

Ritzel¹

Pauling⁷ gives great weight to a 1961 study by Ritzel carried out among skiers on each of two week-long ski trips. The study is described as double-blind, with placebo and ascorbic acid (1 gm) tablets administered each morning. The method of

allocation—eg, random, alternation—is not specified. The placebo is not described, nor is any attention given to its effectiveness in maintaining "blindness."

Evaluation of symptoms was largely subjective, but supplemented (to an extent not stated) by objective measures, such as body temperature. Unfortunately, the number of subjects experiencing colds is not specified, and the presentation of the data is confused and unclear in a number of respects. It is, therefore, not possible to determine whether the calculations of significance were appropriate. Pauling¹ infers the number of subjects by dividing "illness days" by "mean illness days" and concludes that there is a significant difference in proportions of subjects experiencing colds. If his interpretation is correct, the difference is indeed significant. If one uses the continuity correction and the familiar two-sided test, however, it is only marginally so at the 5% level ($P=0.04$).

Anderson et al¹¹

This 1971-1972 study was carried out in Toronto over several weeks in the winter. A total of 1,000 volunteers, representing "a reasonable cross-section of the general population," were allocated randomly to receive either ascorbic acid or placebo. The subjects took 1 gm of ascorbic acid or comparable placebo daily during the study period (minimum of two months) and increased the dose to 4 gm daily during the first three days of any illness. The study was double-blind and appears to have been well controlled and not subject to many of the criticisms applicable to the others discussed here. The placebo used was tested, and fairly convincing evidence given that it successfully imitated the taste of the ascorbic acid tablets. The proportion of dropouts was moderate (18%) and although such dropouts are always a potential source of bias, it is reassuring that the dropouts in both groups were very nearly the same in number and characteristics.

Of the 818 volunteers who completed the trial, 407 had received ascorbic acid, and 411 had received placebo. A number of sickness indices were compared, and those for total

days of disability (confined to house and off work) and number of individuals free of illness during the test period are shown in Table 3. The estimated effect is considerably less than that predicted by Pauling¹ for the dose level.

Anderson et al

This double-blind randomized study was carried out the year following the earlier (positive) study by the same group.¹¹ In an attempt to acquire clear quantitative measures of both prophylactic and therapeutic effects, eight different treatment regimens were established, with approximately 300 subjects in each group. Some evidence is given to indicate that the subjects remained "blind" concerning their treatment regimens. However, in this study the dropout rate was 33%, compared to 18% in the earlier study, an effect the authors attribute to the larger tablet size used. (A question is raised whether one of two control groups may have been biased as a result of dropouts, but the data given are not sufficient to evaluate this point.) In this study, all the differences between measures of illness were small compared to the standard errors, and none approached statistical significance.

Wilson et al¹⁴⁻¹⁶

This 1967-1968 study was conducted in four Dublin boarding schools, using placebo vs either 200 or 500 mg of ascorbic acid per day. In one girls' school, placebo and 200 mg of ascorbic acid were compared, and in another, 200 and 500 mg of ascorbic acid were compared. The same design was used in two boys' schools.

The study was planned to be double-blind, and evidence is given of effective randomization within each school. Various reasons for withdrawing subjects (eg, failure to take pills) are listed, but no data on withdrawal are given. The analysis of prophylactic benefit is much complicated by the subdivision of colds into catarrhal, toxic, or whole, as the definitions permit some episodes to be counted separately as both catarrhal and toxic. Each of nine symptoms was graded each day by the student on a scale of 0 to 4, and tablets were self-adminis-

tered from a two-week supply. No comment on the makeup of the placebo is given, nor is any evidence provided on maintenance of blind conditions. Of the four indices chosen for analysis—incidence, duration, severity, and intensity—the last, which appears to be the average of the daily total of the severity scores for all symptoms, seems most apt for measurement of overall experience.

Despite the authors' analysis of benefits and losses for different subgroups, the overall findings appear not to demonstrate benefit from the use of ascorbic acid. In both boys' schools, almost every index appeared to show a disadvantage for ascorbic acid. For catarrhal colds, 200 mg of ascorbic acid per day was associated with an intensity that was more than twice that associated with placebo, and the difference was significant. (The *t* value given in the article, 0.96, appears to be incorrect.¹⁵ The value calculated from the means and standard errors given in the article is 2.33; a *t* value greater than 2.0 indicates significance at the 0.05 level.)

In the girls' schools, the indices tended to be positive, with significant reductions in intensities for catarrhal and for whole colds in those who received ascorbic acid. The summary indices that would reflect total experience for all colds of all types cannot be reconstructed from the data given, and it is not very surprising to find several *t* values in the significant range among the 48 *t* values calculated.

Coulehan et al

This 1973 study was carried out over 14 weeks in a boarding school for Navaho children. Two levels of ascorbic acid (1 gm for lower-grade and 2 gm for upper-grade children) and placebo were employed. Of an initial 666 children allocated by alternation to the treatment groups, 25 dropped out (ie, left the school); these were equally divided between the ascorbic acid and the placebo groups. Although the coding scheme is only partly described, it appears that placebo-treated subjects received medication in bottles with a common number, and ascorbic acid-treated subjects also received bottles with a different common number.

Thus, independence of judgments about symptoms in different subjects may have been hard to maintain.

The appraisal of illness included both voluntary reporting (by pupil or teacher) and "active surveillance" of several classrooms each day. Days of morbidity from respiratory illnesses were found to be about 30% lower in the ascorbic acid groups than in the placebo groups. Similar differences were found in numbers of subjects who experienced no illness while on active surveillance. However, details of statistical analysis are not presented and the authors correctly doubt the validity of the χ^2 test as applied. Because the data required for an appropriate analysis are not presented, the statistical significance of the differences reported cannot be considered to have been established.

Karlowski et al

In this randomized study (p 1038), there were approximately 80 subjects in each of four groups (0 or 3 gm/day of prophylactic ascorbic acid, and 0 to 3 gm of additional ascorbic acid during each day of a cold) in a factorial design. Although planned as a double-blind study, with all medication in capsule form, the contents of the placebo capsule were noticeably different in taste from the contents of the ascorbic acid capsule, and clear evidence was obtained of deliberate breaking of the "blind" conditions by many of the subjects. The dropout rate, more than 40%, was extremely high. (This may in part have been due to the intensive study of reported colds, which included throat cultures and encouragement to have nasal washings and blood titers performed.)

The analysis of subjects completing the study revealed effects favoring ascorbic acid for average duration of reported colds and for average severity of the symptoms of the colds, but not for number of colds reported per subject. However, subjects taking placebo who broke the code reported increased severity of symptoms compared with their companions, whereas subjects taking ascorbic acid who broke the code reported reduced severity of symptoms. When the analysis is restricted to those subjects who

did not know their treatment, no appreciable differences were found in any of the reported indices.

Additional Studies

Dahlberg et al¹⁷ studied the prophylactic effect of ascorbic acid (200 mg/day for 24 days, then 50 mg/day for 54 days, then 300 mg/day for several days of loading tests) vs similar-tasting placebos in a group of Swedish soldiers in 1941. The tablets were dispersed according to identity numbers (odd or even) in a double-blind manner. No differences were found in either the incidence or duration of colds in the 2,525 soldiers studied (1,259 received ascorbic acid).

Three studies¹⁸⁻²⁰ of the use of ascorbic acid for the treatment of the common cold all failed to demonstrate efficacy. The two older studies utilized 667 mg of ascorbic acid (or placebo) every four hours for up to ten doses in 153 students,¹⁸ and 200 mg of ascorbic acid (or flavonoid or placebo) four times daily for three days in 1,923 patients.¹⁹ The more recent study was conducted by the General Practitioner Research Group on 270 members of their families.²⁰ The study included random allocation to, and double-blind evaluation of, the efficacy of 3 gm of ascorbic acid (or placebo) per day for up to 14 days.

Two placebo-controlled studies^{8,21} have been conducted in which volunteers received 3 gm of ascorbic acid for three days and for two weeks, respectively, before being challenged by intranasal instillation of rhinovirus 44⁸ and a group of respiratory viruses,²¹ respectively. In both studies, the ascorbic acid was continued for one week after the challenge. In neither instance was it clear how the tablets were allocated, but both studies were double-blind. Apart from a significant ($P < .01$) reduction in the incidence of nasal discharge, nasal stuffiness, and rhinitis on the fourth day after the challenge in the smaller of the two studies,⁸ there was no evidence supporting the efficacy of ascorbic acid. It is important to note, however, that a cold contracted by artificial means may differ from one contracted naturally. Despite this limitation, such studies provide evidence from carefully controlled cir-

cumstances (eg, known dose and nature of virus) that cannot be reproduced in the usual clinical setting. Indeed, such studies must eventually be successfully prosecuted if a beneficial effect of ascorbic acid on the common cold is to be accepted. Although these two studies do not demonstrate any appreciable benefit, they are numerically too small to be counted as substantial negative evidence.

ADVERSE REACTIONS AND PRECAUTIONS

It has been generally accepted that ascorbic acid is nontoxic²² and that even the administration of large amounts produces no demonstrable effects,²³ as the excess is eliminated harmlessly in the urine.²⁴ However, some evidence has accumulated²² that may require modification of this position, particularly with regard to the use of large quantities of ascorbic acid over long periods of time by large numbers of people to prevent or ameliorate the common cold. It must be emphasized that neither the experience gained in the clinical trials that have been conducted, nor scattered observations to the effect that some humans appear to be able to tolerate a sustained high intake of ascorbic acid without obvious harm,⁴ are adequate to establish the safety of ascorbic acid for this use. Although the common cold is undoubtedly an uncomfortable and inconvenient disease, it is rarely anything but a benign and short-lived one. Thus, even a prophylactic agent of obvious and substantial value would have to be shown to be safe in a large, varied population before its unrestricted use could be unconditionally advocated.

Formation of Urinary Tract Calculi

Measurements in man have demonstrated that the daily urinary excretion of oxalic acid rises significantly ($P < 0.01$) by an average of 45 mg after the ingestion of 8 gm of ascorbic acid daily for a week.²⁵ Similar measurements on patients without gout have suggested that the intravenous injection of 500 mg of ascorbic acid on two consecutive days raises the urinary excretion of uric acid.²⁶ Despite re-

ports that individuals have ingested as much as 4 gm of ascorbic acid daily for 13 years without developing urinary calculi,²⁷ the previous evidence, and the report that one of a group of volunteers demonstrated an increase in daily urinary oxalate excretion from 58 to 622 mg after the ingestion of 4 gm of ascorbic acid daily for a week,²⁸ suggest that some individuals may be particularly prone to develop calculi²⁹ when receiving large daily doses of ascorbic acid. Additional human studies are required to clarify this relationship and determine its clinical importance.

Effect on Fertility and the Fetus

A controlled study has demonstrated that the oral administration of 500 mg of ascorbic acid daily to ten guinea pigs after mating resulted in three abortions, four stillbirths, six neonatal deaths, and only two living offspring; 25 animals given only the solvent suffered no abortions, stillbirths, or neonatal deaths.³⁰ A later study by the same author not only provided some evidence that daily subcutaneous injections of 150 mg of ascorbic acid may induce rats (average weight, 180 gm) to abort, but also demonstrated that 16 of 20 pregnant women developed menstrual-type bleeding one to three days after a three-day course of 6 gm of ascorbic acid per day given in an attempt to induce abortion.⁵¹ On the basis of purely anecdotal evidence, it has been suggested that doses of ascorbic acid above 2 gm daily may reduce fertility in some women.³² Despite the existence of additional animal evidence supporting the concept that doses of ascorbic acid that produce no evidence of general toxicity may adversely affect both fertility and the fetus,^{33,34} additional human studies are required to clarify this relationship and determine its clinical importance.

Effect on Carbohydrate Metabolism

A study in rats (weight range, 112 to 149 gm) has demonstrated that 80 mg of dehydroascorbic acid, given in three daily intravenous injections, could result in the development of a hyperglycemia that responded to insulin therapy but was still present

three weeks later.³⁵ However, a study in humans demonstrated that the daily ingestion of 1.5 gm of ascorbic acid for five days did not affect the blood glucose levels or cause glycosuria in 80 diabetics, and that the ingestion of the same amount for six weeks did not affect glucose tolerance or cause glycosuria in 12 normal men.³⁶ An early study had demonstrated that ascorbic acid saturation reduced the insulin requirements of stable insulin-dependent diabetics, but did not affect glucose metabolism in diabetics who were not receiving insulin or in normal subjects.³⁷ Whether or not massive doses of ascorbic acid can produce diabetes mellitus in man, and the extent to which moderate doses of the substance can affect the clinical management of insulin-dependent diabetes mellitus do not appear to be known. Additional human studies are required to clarify this relationship and determine its clinical importance.

Effect on Gastrointestinal Tract

It appears to be accepted that an intake of 1 gm of ascorbic acid daily may produce diarrhea.³⁸ Early reports suggested that supplemental ascorbic acid might cause increased intestinal peristalsis,^{39,40} and the following data from a recent study of the changes in levels of ascorbic acid in leukocytes during the common cold support this view.⁴¹ Seven subjects suffering from the common cold ingested ascorbic acid daily: 200 mg for one week; 1 gm for the second week; 3 gm for the third week; 6 gm for the fourth week; and in four subjects, 10 gm for a fifth week. It was observed that although most of the subjects experienced abdominal colic and some diarrhea when they began the third week, these adverse effects did not persist. No other adverse effects of the ascorbic acid were observed.

It is interesting that of the 28 patients who left one of the clinical trials because of suspected side effects, nine suffered gastrointestinal symptoms such as nausea, abdominal cramps, or diarrhea.¹¹ However, four of the nine had been receiving the placebo. In general, the subjects who participated in the clinical trials of ascorbic acid either as a prophylactic

or as a therapeutic agent for the common cold have apparently remained essentially free of any side effects.

Withdrawal Reactions

Studies in guinea pigs have demonstrated that when placed on a diet deficient in ascorbic acid, those animals that had been receiving large doses of ascorbic acid developed and died of scurvy before those animals that had been on a normal diet.^{42,43} One hospital's experience during the siege of Leningrad (1941-1943) suggests that malnutrition may have led to a higher incidence of scurvy (81% vs 67%) in humans who had previously been receiving large quantities of supplementary ascorbic acid.⁴⁴ Although some of the cases that have been presented in support of this concept are purely anecdotal and unconvincing,⁴⁵ a report of two cases of infantile scurvy⁴⁶ and another of a self-experiment⁴⁷ are of interest. The two infants were the only ones of a group of 42 consecutive cases of infantile scurvy in whom an adequate post-natal intake of ascorbic acid could be clearly established. In both instances, the mother had been ingesting approximately 400 mg of ascorbic acid daily during pregnancy. In a small confirmatory study in guinea pigs, the two offspring who demonstrated evidence of ascorbic acid deficiency, despite daily intraperitoneal injections of 1.5 mg of ascorbic acid, were born of the parents who had received the largest amount (1 gm) of ascorbic acid daily during pregnancy. In the self-experiment, a male scientist developed symptoms of early scurvy, including swelling and bleeding of the gums and loosening of all teeth, four weeks after completing a two-week-long course of 10 to 15 gm of ascorbic acid daily. The symptoms, after persisting for ten days, were treated with ascorbic acid and did not reappear. Additional human studies are required to clarify this relationship and determine its clinical importance.

Drug Interactions

It has been reported that ascorbic acid has been shown to be capable of interfering with the anticoagulation produced by both heparin and dicumarol in animals.²² One patient has

been reported who was receiving warfarin and in whom it appeared that the ingestion of ascorbic acid may have caused a reduction in the desired prolongation of prothrombin time.⁴⁸ Although an additional report of ascorbic acid administration, 1 gm daily for 14 days, to five patients receiving long-term warfarin therapy did not confirm this finding,⁴⁹ it also did not necessarily invalidate it. In general, the effect of drugs on the response to warfarin is difficult to evaluate because of the great fluctuations that occur in any one individual's responsiveness to the anticoagulant. Additional human studies are required to clarify this relationship and determine its clinical importance.

Miscellaneous Reports and Theories

A temporal relationship between several exacerbations of sickle cell-thalassemia,⁵⁰ and another between one episode of deep-vein thrombosis,⁵¹ and the ingestion of high doses of ascorbic acid have been reported. These reports are purely anecdotal and require confirmation before the relationships can be accepted as anything other than coincidental. It has also been hypothesized, on the basis of animal work, that the administration of large doses of ascorbic acid to growing children might predispose the children to some type of bone disorder in later life.⁵² This hypothesis also requires confirmation before it can be accepted. Finally, it has recently been suggested, on the basis of in vitro studies⁵³ and some partially controlled clinical observations,⁵⁴ that pharmacologic doses of ascorbic acid might destroy substantial amounts of vitamin B₁₂ when they are ingested within an hour of each other. Further clinical studies of this phenomenon are also warranted.

COMMENT

A review of the controlled studies of the efficacy of ascorbic acid in the prophylaxis and therapy of the common cold that meet some reasonable criteria of design reveals *little convincing evidence to support claims of clinically important efficacy*. Most of the studies that have been used to support such claims suffer from one or more important defects; these defects

are particularly serious because in this case the evaluation of efficacy either depends largely on subjective reports by the patients or requires a substantial element of judgment on the part of the investigator.

The most compelling evidence is that of Anderson et al.¹¹ This study suggests that 1 gm of ascorbic acid daily may increase the proportion of individuals who remain free of illness from 18% to 26%, and that 4 gm of ascorbic acid daily taken during a cold may reduce the number of days confined to the house per individual by approximately half a day during the three winter months. However, in their second study¹⁰ this group was unable to confirm the significant findings of their first study, and it is obvious from review of all the evidence that no clear, reproducible pattern of efficacy has emerged, and that these hypotheses are most tentative and require confirmation. Even if it ultimately transpires that ascorbic acid does reduce the incidence or severity of the common cold to a statistically significant but clinically unimportant degree, such a finding would demand additional study into mechanism of action, including additional challenge (nasal instillation) studies with the hope that clinically important efficacy might eventually prove to be feasible.

The acceptability of clinically important efficacy will depend, of course, on availability of adequate evidence of lack of serious adverse reactions. There is little such evidence currently available, although many hypothetical adverse reactions have been proposed. Indeed, it may be necessary first to agree on acceptable standards for establishing the safety of large quantities of substances such as ascorbic acid used over long periods of time by large numbers of people to prevent or ameliorate the common cold or other essentially benign and short-lived diseases.

Until such time as pharmacologic doses of ascorbic acid have been shown to have obvious, important clinical value in the prevention and treatment of the common cold, and to be safe in a large varied population, *we cannot advocate its unrestricted use for such purposes*.

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