Ascorbic Acid and the Common Cold

Analysis of controlled studies shows with statistical significance that this vitamin has protective power.

Linus Pauling

Linus Pauling is Professor of Chemistry in Stanford University, Stanford, California 94305.

For many years there has existed the popular belief that ascorbic acid has value in providing protection against the common cold, and in ameliorating the manifestations of this viral disease. This popular belief has, however, not been generally shared by physicians, authorities on nutrition, and official bodies.

I was puzzled by the contradiction between the popular belief and the official opinion, and I made a study of published reports of controlled trials of ascorbic acid in relation to the common cold. On the basis of this study and of some general arguments about orthomolecular medicine (1), (the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present in the body and are required for health), I reached the conclusion that ascorbic acid, taken in the proper amounts, decreases the incidence of colds and related infections, and also decreases the severity of individual colds. These arguments were presented in my book Vitamin C and the Common Cold, which was published in December 1970 (2).

In this book I presented a discussion of the studies that had been made, including several carefully controlled double-blind studies carried out by competent medical investigators. The evidence and arguments presented in this book apparently were not convincing to some physicians, experts in

nutrition, and health officials. Many statements contradicting my conclusions were made within a few weeks of the publication of the book. Although the analysis in my book of the published accounts of controlled studies in this field seemed to me to be clear and straightforward, I have decided that, because of the importance of the question, it is desirable for me to publish a more detailed account of the evidence, including a more thorough statistical analysis of the controlled trials that have been carried out.

The Nature of the Statistical Analysis

Most of the reports discussed in this paper describe studies of two groups of subjects selected at random from one population. The subjects in one group are administered the active substance (L-ascorbic acid, vitamin C) in certain amounts once or more every day, and those in the second group are administered an apparently identical inactive material, a placebo. Several of the studies were double-blind, with neither the subjects nor the investigators knowing which subjects received the ascorbic acid and which received the placebo, that information being kept by some other person until all of the information had been collected.

The question that I attempt to answer by analyzing the published reports is the following: To what extent, if any, does the regular administration of ascorbic acid over a period of time beginning before the subjects have contracted a cold, and with the subjects exposed to cold viruses under ordinary living conditions, have an effect greater than that of a placebo in decreasing the incidence and the severity of the common cold? A comparison with a placebo, with the subjects not knowing which group they are in, is essential because of the well-known "placebo effect" of even inactive medications.

The statistical methods used in the analysis are the conventional ones, for the most part the calculation of χ^2 and then of the probability

χ : Pfk chi

P(one-tailed) that the observed difference in effect of ascorbic acid and placebo (or a larger difference) would be obtained by chance alone in two groups taken at random from a uniform population if the null hypothesis of equal effectiveness of ascorbic acid and placebo were true. I have chosen to give P(one-tailed) rather than P(two-tailed) because no one contends that the placebo (usually citric acid) has a greater effect than ascorbic acid in preventing or ameliorating the common cold; the difference of opinion is between those people who state that ascorbic acid is no better than a placebo and those who say that it is better. Moreover, in none of the studies discussed did the investigators find a greater protective effect of the placebo than of ascorbic acid; in every study ascorbic acid is reported to provide greater protection than the placebo against the common cold, and the question to be answered is the level of confidence with which the reported results can be accepted and the null hypothesis of equal effectiveness of placebo and ascorbic acid can be rejected.

In the following analysis I discuss the reported effects in three aspects: first, the incidence of colds (number of colds per person in unit time, usually taken as the period of the study); second, the average severity of individual colds (as measured by days of illness per cold or number of days when symptoms were recorded); and third, the integrated morbidity (the product of the other two). Mention is made also of the incidence and severity of other infectious diseases, to the extent that they were reported by the investigators.

The Work of Ritzel

An important study (3) that gave results with statistical significance was reported in 1961 by Dr. G. Ritzel, who is a physician with the medical service of the School District of the City of Basel, Switzerland. The study

was carried out in a ski resort with 279 skiers during two periods of five to seven days. The conditions were such that the incidence of colds during these short periods was large enough (approximately 20 percent) to permit results with statistical significance to be obtained. The subjects were roughly of the same age and had similar nutrition during the period of study. The investigation was double-blind, with neither the participants nor the physicians having any knowledge about the distribution of the ascorbic-acid tablets and the placebo tablets. The tablets were distributed every morning and taken by the subjects under observation such that the possibility of interchange of tablets was eliminated. The subjects were examined daily as to symptoms of colds and other infections, as listed in the footnote of Table 1. The records were largely on the basis of subjective symptoms, partially supported by objective observations (measurement of body temperature, inspection of the respiratory organs, auscultation of the lungs, and so on). Persons who showed cold symptoms on the first day were excluded from the investigation.

After the completion of the investigation a completely independent group of professional people was provided with the identification numbers for the ascorbic-acid tablets and placebo tablets, and this group carried out the statistical evaluation of the observations.

The principal results of the investigation are given in Table 1. The author points out that the group receiving ascorbic acid showed only 39 percent as many days of illness, per person, as the group receiving the placebo, and that the number of individual symptoms per person was only 35 percent as great for the ascorbic-acid group as for the placebo group, and states that the statistical evaluation of these differences by two-by-two tables gives a significant difference, $0.001 < P < 0.01$. The author also points out that the average number of days per cold for the ascorbic acid group was 1.8 (more accurately 1.82), 29 percent less than the value for the placebo group, 2.6 (2.58), and that this difference is statistically significant, with $P < 0.05$ on a t-test.

In Table 2 of the paper by Ritzel the values of the number of patients showing different symptoms (the seven classes of symptoms listed in the

Table 1

The Study by G. Ritzel

	Placebo group	Ascorbic-acid group	P(1-tailed)*	Decrease
Number in group	140	139		
Number of colds	31	17		
Incidence of colds	0.221	0.122	<0.02	45%
Total days of illness	80	31		
Total individual symptoms **	119	42		
Severity of individual colds,				
from days of illness per cold	2.58	1.82	<0.05	29%
from individual symptoms per cold	3.84	2.47	<0.05	36%
Integrated morbidity				
from days of illness per person	0.571	0.223	<0.01	61%
from individual symptoms per person	0.850	0.302	<0.01	64%

* For rejection of null hypothesis of equal effect of ascorbic acid and placebo.

** Pharyngitis, laryngitis, tonsilitis, sore throat; bronchitis, coughing; fever, chills; otitis media; rhinitis; herpes labialis; other symptoms (muscle ache, headache, abdominal pain, vomiting, diarrhea, general malaise).

footnote to Table 1) are given, and the number of days of illness for each symptom. It is interesting that for each of these seven classes of symptoms the number of patients showing the symptom is less for the ascorbic-acid group than for the placebo group, and that, moreover, the number of days of illness per patient showing the symptom is also less.

Let us discuss separately the effect of ascorbic acid on the incidence of the common cold and its effect on the severity of individual colds. The number of colds was 31 for the placebo group and 17 for the ascorbic-acid group. (The number of colds was not given explicitly in the paper. However, the number of days of illness for each of the two groups was given (80, 31), and the average number of days of illness per cold (2.6, 1.8). The only integral values for the number of colds allowed by these numbers are 31 for the placebo group and 17 for the ascorbic-acid group.) The incidence of colds is accordingly 0.221 per person for the placebo group and 0.122 for the ascorbic-acid group, a decrease by 45 percent for the ascorbic-acid group. The value of χ^2 is found to be 4.81, with P(one-tailed) <0.02. This investigation accordingly shows with statistical significance that the null hypothesis that ascorbic acid has only the same effect as the placebo is to be rejected.

Two values may be calculated for the effect of ascorbic acid on the severity of individual colds. In Table 1 the number of days of illness per cold for the placebo group is given as 2.58, and for the ascorbic-acid group as 1.82, 29 percent smaller. Moreover, the average number of individual symptoms recorded per cold (they were recorded daily) is given as 3.84 for the placebo group and 2.87 for the ascorbic acid group, 36 percent smaller. Each of these differences is statistically significant, the null hypothesis that the two populations are the same with respect to the number of days of illness per cold and the individual symptoms per cold being rejected at the level P(one-tailed) <0.05.

Two values are given in Table 1 for the integrated morbidity, one as measured by the number of days of illness per person and the other as measured

by the number of symptoms (recorded daily) per person. These values are 61 percent and 64 percent less, respectively, for the ascorbic-acid subjects than for the placebo subjects, with the differences significant at the level $P < 0.01$.

This investigation seems to have been very well planned and executed. Dr. Ritzel was aware of the problem of obtaining reliable results in the study of the common cold, and he discussed the problem in some detail. His paper is provided with an English-language summary, reading as follows: "The possibility of preventing infection by administration of vitamin C was investigated in a moderately large test population during a period of increased exposure. The trial was conducted in such a way as to exclude sources of error in assessing subjective symptoms. Statistical evaluation of the results confirmed the efficacy of vitamin C in the prophylaxis and treatment of colds. Problems of therapeutic trials with pluripotential preparations which have to be judged chiefly on the basis of subjective symptoms are discussed."

It is interesting that in an often-quoted review of the evidence about ascorbic acid and the common cold, which ended with the statement that "there is no conclusive evidence that ascorbic acid has any protective effect against, or any therapeutic effect on, the course of the common cold in healthy people not depleted of ascorbic acid" (4), the work of Ritzel was covered in two sentences, stating quite erroneously that he had reported "a reduction of 39 percent in the number of days ill from upper respiratory infections and a reduction of 35 percent in the incidence of individual symptoms in the supplemented group as compared with the placebo group;" (the correct values are 61 percent and 64 percent, respectively).

The Work of Cowan, Diehl, and Baker

One of the best studies of ascorbic acid and the common cold was

reported by Cowan, Diehl, and Baker in 1942 (5). Dr. Diehl was at that time Dean of Medical Sciences in the University of Minnesota. He is now retired. Dr. Cowan is Chief of the Student Health Service in the University, and Dr. Baker is Professor of Neurology there. The principal work on ascorbic acid was done during the winter "cold season" of 1939-1940. The subjects were all students in the University of Minnesota who volunteered to participate in this study because they were particularly susceptible to colds. Persons whose difficulties seemed to be due primarily to chronic sinusitis or allergic rhinitis, as shown by examination of the nose and throat and consideration of symptoms of allergy, were excluded from the study. The subjects were assigned alternately and without selection to an experimental group and a control group. The subjects in the control group were treated exactly like those in the experimental group, except that they received a placebo instead of the ascorbic acid. The subjects were instructed to report to the Health Service whenever a cold developed, so that special report cards could be filled in by a physician. Dr. Cowan has informed me that the study was a double-blind one, with neither the subjects nor the physicians knowing which group a subject was in. Each subject was interviewed every three months in order to check the completeness of the reports.

The study was continued for 28 weeks. Of the 233 students initially in the ascorbic acid group, 183 received 200 mg per day throughout the period of 28 weeks, and 50 received 200 mg per day for two weeks, followed by 100 mg per day except on inception of a cold, when an additional 400 mg per day for two days was administered. This group numbered 208 subjects at the completion of the study, 25 having dropped out. If the composition of the group remained unchanged, the average intake of ascorbic acid was 180 mg per day. The students in the control group initially numbered 194, of whom 155 completed the study (Table 2).

The authors report the observed incidence of colds by giving the average and the probable error. The corresponding values of the standard deviation, as calculated from the probable error, are given below in paren-

Table 2

The Study by Cowan, Diehl, and Baker

	Placebo group	Ascorbic-acid group	P(one-tailed)	Decrease
Number in group	155	208		
Incidence of colds	2.2	1.9	<0.02	14%
Severity (days of illness per cold)	0.73	0.58	<0.02	21%
Integrated morbidity (days of illness per person)	1.6	1.1	<0.01	31%

theses. The average number of colds per person during the period of study was 2.2 ± 0.08 (S.D. 0.113) for the control group, and 1.9 ± 0.07 (S.D. 0.099) for the ascorbic acid group. The difference between the average number of colds in the control group and in the experimental group is given by the authors as one-third of a cold and also as 0.3 ± 0.11 (S.D. 0.156).

The authors state in their paper that "The actual difference between the two groups during the year of the study amounts to one-third of a cold per person. Statistical analysis of the data reveals that a difference as large as this would arise only three or four times in a hundred through chance alone. One may therefore consider this as probably a significant difference, and vitamin C supplements to the diet may therefore be judged to give a slight advantage in reducing the number of colds experienced."

Because the authors rounded off the numbers giving the actual numbers of colds per person, the difference is not known exactly. Dr. Cowan has informed me that the original records and the original calculations are no longer available. There is evidence, however, that the actual difference between the average number of colds in the two groups is 0.32, with uncertainty 0.01. If the difference had been less than 0.29 the authors would have said "one quarter of a cold per person", rather than "one third of a cold per person". Moreover, the value of P(two-tailed) calculated for a difference of 0.31 with standard deviation 0.156 is 0.042, and that calculated for difference 0.33 is 0.031. The statement by the authors that the difference would arise only three or four times in a hundred through chance alone accordingly restricts the difference to the range 0.31 to 0.33, with 0.32 as the likely value.

This difference represents a decrease by 14.4 percent in the incidence of colds in the ascorbic-acid group as compared with the control group.

The value of P(one-tailed) for difference 0.31 to 0.33 is 0.021 to 0.016. We can accordingly state that the observed difference is statistically

significant, with P(one-tailed) less than or equal to 0.02. The null hypothesis that ascorbic acid has the same effect as the placebo is accordingly eliminated at this level.

The average number of days lost from school per person in the placebo group was reported as 1.6, and in the ascorbic-acid group as 1.1, giving a decrease of 31 percent in integrated morbidity. The average number of days lost from school per cold was 0.73 for the placebo group and 0.58 for the ascorbic-acid group, a decrease in severity of individual colds by 21 percent. For both severity and integrated morbidity the null hypothesis of equal effectiveness of ascorbic acid and placebo is decisively rejected, with P(one-tailed) < 0.01.

The Work of Franz, Sands, and Heyl

A double-blind study of ascorbic acid and the common cold was carried out by Franz, Sands, and Heyl of Dartmouth Medical School during the three-month period from February to May 1956, with 89 volunteer medical students and student nurses (6). The subjects were divided, in a random way, into four groups, three of twenty-two subjects and one of twenty-three subjects. One group received tablets containing ascorbic acid, the second ascorbic acid and a bioflavonoid (naringin), the third a placebo, and the fourth naringin only. The daily amount of ascorbic acid was 205 mg and that of the bioflavonoid was 1000 mg. Symptoms of colds were systematically recorded. The results for the bioflavonoid groups, with or without ascorbic acid, were the same as for the corresponding groups without bioflavonoid. The authors concluded that the administration of a bioflavonoid had effect neither on the incidence or the cure of colds nor on the ascorbic acid level of the blood.

The results reported by the authors are given in Table 3.

From this table we see that the incidence of colds in the two ascorbic-acid groups is nearly the same as in the other groups (4.6 percent less).

Table 3

The Study by Franz, Sands, and Heyl

Group	Number in group	Number of colds Total	Not cured or improved in 5 da
Ascorbic acid	22	8	0
	44	14	1
Ascorbic acid plus bioflavonoid	22	6	1
Placebo	23	7	4
	45	15	8
Bioflavonoid	22	8	4

Total incidence of colds 4.6% less for ascorbic-acid groups than for other two groups, not statistically significant; incidence of severe colds (not cured or improved in 5 days) 87.5% less for ascorbic-acid groups than for other groups, statistically significant at the level P(one-tailed) < 0.01.

The difference is not statistically significant. Because of the small numbers of subjects and colds, a decreased incidence would have to be as great as 50 percent to be significant at the level P(one-tailed) <0.05.

The authors point out that the subjects receiving ascorbic acid showed more rapid improvement in their colds than those not receiving it, and that this difference is statistically significant at the 0.05 level. This statistical analysis was made by Professor J. Laurie Snell, of the Department of Mathematics, Dartmouth College.

The statistically significant observation reported by the authors is that 8 of the total of 15 colds in the placebo and bioflavonoid groups remained uncured or unimproved in five days, whereas of the 14 colds in the two groups receiving ascorbic acid only one remained unimproved or uncured in five days. The authors accordingly reported a much lower incidence of severe colds (unimproved or uncured in five days) for the two ascorbic-acid groups than for the two other groups. The observed incidence of severe colds (not improved or cured in five days; one in 44 ascorbic-acid subjects, eight in 45 other subjects) leads to $\chi^2=5.88$, and is statistically significant at the level P(one-tailed) <0.01. My conclusion is that the double-blind study carried out by Franz, Sands, and Heyl has shown with statistical significance that ascorbic acid has a greater effect than a placebo in decreasing the incidence of severe colds. A comparison with statistical information about the duration of colds leads to the conclusion that the integrated morbidity for the ascorbic-acid subjects was approximately 40 percent less than for the placebo subjects.

The Work of Wilson and Low

During the past six years Professor C. W. M. Wilson, Chairman of the Department of Pharmacology of the University of Dublin, has, together

with his coworkers, been carrying out clinical trials on the effect of ascorbic acid on school children. In this work 200-mg tablets of ascorbic and corresponding placebo tablets were administered daily to children in boarding schools during winter periods of six or seven months (7). The studies were double-blind, and the numbers of infections were large enough to give statistically significant results. Several reports of this work are now in process of publication (8). One paper, describing a study of 108 subjects in a girls' school, has been published (7). Of these subjects, 57 received ascorbic acid (200 mg per day) and 46 received placebo tablets. The authors (Wilson and Low) report that "As a result of computer analysis it was found that the symptoms in all the children could be separated into two unrelated groups, consisting of sore throat, headache, feverish and out of sorts, defined as toxic colds; and cold in the head, cough, nasal obstruction and nasal discharge, defined as catarrhal colds. Ascorbic acid reduced the incidence, duration, and severity of these symptoms in comparison with those in children receiving dummy tablets. The form of the toxic and catarrhal colds was also significantly altered, so that symptom association was reduced in the presence of ascorbic acid. Duration of the symptoms, cold in the head and nasal discharge, was reduced from 14 to 8 days in children receiving ascorbic acid... It is concluded that the prophylactic administration of ascorbic acid to young adults significantly reduces the intensity of the symptoms, and form of their association, in the common cold."

The information so far published by Wilson and Low does not permit an independent statistical analysis to be carried out. The statement about statistical significance made by Wilson and Low (and confirmed in a letter from Professor Wilson) corresponds to rejection of the null hypothesis at the level $P(\text{two-tailed}) < 0.05$, and hence to $P(\text{one-tailed}) < 0.03$. The reduction of the average period of duration of symptoms from 14 to 8 days indicates a decrease in integrated morbidity by about 40 percent.

The Work of Glazebrook and Thomson

In 1942 Glazebrook and Thomson, of the Department of Clinical Medicine and Bacteriology, University of Edinburgh, reported a study carried out with about 1500 boys 15 to 20 years old in a large training school in Scotland (9). The subjects received a normal diet rather low in ascorbic acid, the daily ration being estimated to contain only 10 to 15 mg. The principal study, carried out over a period of six months, involved 1100 control subjects and 335 ascorbic-acid subjects. The control subjects, in seven dining groups, received the ordinary diet. The ascorbic-acid subjects, in two dining groups, received the ordinary diet but with ascorbic acid administered in the milk and cocoa that was served. The average amount of ascorbic acid administered is somewhat uncertain. The authors state that vitamin C was added to the supplies of cocoa or milk serving the tables for the appropriate divisions. In their discussion of preliminary experiments carried out to determine the daily urinary excretion of ascorbic acid it is stated that initially 200 mg per day was given to each boy, 100 mg being placed in the morning cocoa and 100 mg in an evening glass of milk, the mixing being done in bulk in the kitchens. Analysis of the cocoa and milk showed an average of 63 mg per cup of cocoa and 98 mg per glass of milk, suggesting that about 160 mg per day was the average intake.

Because a number of preliminary studies had been carried out, and the ascorbic acid was added in the kitchens, it is likely that this investigation can be considered to have been a blind study. The authors mention that careful records had been kept of the incidence of all infections for 18 months before the observations described in their paper were begun, and that in the preceding year there had been an epidemic of tonsilitis that had affected all the divisions uniformly, so that they could not be regarded as separate units within the larger population. All of the divisions had a population more or less the same as regards the duration of stay in the establishment. Records were kept of the common cold (coryza), tonsilitis (hemolytic streptococcal

disease of the nose and throat, covering tonsilitis, sore throat, otitis media, pharyngitis, and cervical adenitis), and other infective conditions (conjunctivitis, boils, impetigo, etc., as well as pneumonia and acute rheumatism).

The total numbers of cases of colds during the 6-month period of the study are given in Table 4 for the control group and the ascorbic-acid group. There is a decrease in incidence in all colds by 17 percent, with P(one-tailed) < 0.05, and in colds serious enough to require hospitalization (sick quarters) by 23 percent, with P(one-tailed) < 0.02.

For other infectious diseases a decreased incidence for the ascorbic-acid group was also reported (except for tonsilitis with inclusion of the mild cases). The reported decreases of 100 percent for pneumonia and acute rheumatism are significant at the level $P < 0.02$.

Glazebrook and Thomson in their paper point out that the difference in incidence of pneumonia and acute rheumatism in the control group and the ascorbic-acid group is statistically significant, and also that the period of hospitalization for tonsilitis is statistically significant. They give the average stay in the hospital for control subjects (83) hospitalized with tonsilitis as 16.7 days, standard deviation 11.86, and for the vitamin-C subjects (18) as 10.05, standard deviation 6.96, and state that analysis shows that a difference as great as or greater than that obtained would be expected once in 50 times in a homogeneous population.

Glazebrook and Thomson give information in their paper that permits the severity of individual colds or other infectious diseases and the integrated morbidity, as measured by the number of days hospitalized, to be calculated. These values are given in Tables 5 and 6. The values of P(one-tailed) in the tables have been calculated by assuming a Poisson distribution in the days of hospitalization per period of illness.

The results described in Tables 4, 5, and 6 thus indicate that ascorbic acid has the effect of decreasing the incidence and severity of tonsilitis, pneumonia, and acute rheumatism, as well as the common cold, for the principal population studied by Glazebrook and Thomson.

Table 4

The Principal Study by Glazebrook and Thomson

Incidence of Illnesses

	Control group		Ascorbic-acid group		P(one-tailed)	Decrease
	Number	Incidence	Number	Incidence		
Number in group	1100		335			
Colds	286	0.260	72	0.215	<0.05	17%
Colds, sick quarters	253	.230	59	.176	<0.02	23%
Tonsilitis	94	.086	29	.087	~0.5	-1%
Tonsilitis, sick quarters	83	.075	18	.053	<0.08	28%
Pneumonia	17	.016	0	.000	< 0.02	100%
Acute rheumatism	16	.015	0	.000	<0.02	100%

Table 5

The Principal Study by Glazebrook and Thomson

Severity of illness, measured by average number of days hospitalized per hospitalized case

	Control group	Ascorbic-acid group	Decrease
Common Cold	1.47	1.11	24%
Tonsilitis	1.26	0.54	57%
All infective conditions*	5.0	2.5	50%

* Common cold, tonsilitis, pneumonia, acute rheumatism, conjunctivitis, boils, impetigo, etc.

Table 6

The Principal Study by Glazebrook and Thomson

Integrated morbidity, measured by average number of days hospitalized per subject*

	Control group	Ascorbic-acid group	Decrease
Common Cold	0.334	0.195	41%
Tonsilitis	.095	.029	69%

* Values for all infective conditions not available because total number of hospitalized cases not reported.

The Total Evidence for the Effectiveness of Ascorbic Acid

The foregoing careful studies of ascorbic acid have given the statistically significant result that the hypothesis that ascorbic acid administered daily to subjects who have not yet caught cold and are subjected to ordinary conditions of exposure to cold viruses show the same incidence, severity, and integrated morbidity of colds and related infections as placebo subjects is to be rejected. I now ask what the weight of the total body of evidence is.

In Table 7 the values are given of P(one-tailed) at which each of several studies rejects the null hypothesis.

The study by Ritzel gave results for the integrated morbidity (Table 1) rejecting the null hypothesis at the level P(one-tailed) < 0.01. The results for the incidence of colds and the severity of individual colds are not independent of those for the integrated morbidity, and accordingly do not change the level at which the null hypothesis is rejected. The value $P < 0.01$ is entered in Table 7 for the Ritzel study.

Similarly, the value < 0.01 of P(one=tailed) for the integrated morbidity as found by Cowan, Diehl, and Baker (Table 2) is also entered in Table 7, together with the value < 0.01 for the incidence of severe colds reported by Franz, Sands, and Heyl, the value < 0.03 for the study by Wilson and Low, and the value < 0.02 for the incidence of colds requiring hospitalization reported by Glazebrook and Thomson.

There is no doubt that the five studies listed in Table 7 are independent of one another. We may accordingly combine them to obtain a measure of their total significance in rejecting the null hypothesis. Fisher's method leads to χ^2 (10 degrees of freedom) $= -2\Sigma \ln P_i = 42.47$, and hence to $P < 0.00001$. There is some question as to whether or not the study by Glazebrook and Thomson can be considered to have been a double-blind study. If it is omitted, application of Fisher's method to the other four, which were double-blind studies involving comparison of an ascorbic-acid group and a placebo group, leads to χ^2 (8 degrees of freedom) $= 34.64$ and $P < 0.0001$.

Table 7

The Weight of Evidence for Rejecting the Null Hypothesis of Equal Effectiveness of Ascorbic Acid and Placebo

Investigators	Value of P(one-tailed) at which the null hypothesis is rejected
Ritzel	<0.01
Cowan, Diehl, and Baker	<0.01
Franz, Sands, and Heyl	<0.01
Wilson and Low	<0.03
Glazebrook and Thomson	<0.02
Combined value *	<0.00001

* X^2 (10 degrees of freedom) = $-2\Sigma \ln Pi = 42.47$

We conclude that there is overwhelming evidence requiring rejection of the null hypothesis that ascorbic acid has no more value than a placebo in decreasing the incidence, severity, or integrated morbidity of the common cold when it is regularly administered in amounts 180 mg to 1000 mg per day to subjects exposed to cold viruses in the ordinary way (contact with other persons), over a period of time beginning before colds have been contracted. The chance that, through a statistical fluctuation, the five investigations listed in Table 7 would have given the results described for two samples of a single population (in each study), with ascorbic acid having the same effect as the placebo (the null hypothesis) is only 1 in 100000 (1 in 10000 for the first four studies alone).

It is interesting that there is strong evidence in these studies that ascorbic acid in these amounts also has a protective effect against tonsilitis, pneumonia, acute rheumatism, and other diseases.

Dependence on Amount of Ascorbic Acid

An additional test of the positive results (protective effect of ascorbic acid against the common cold) reported in the five investigations described above can be made by checking their consistency with respect to the amount of protective effect. Because of the heterogeneity of the general population, it is not unreasonable that the effect of ascorbic acid taken daily in addition to the amount in the normal diet would for smaller daily added intake be proportional to this intake, and that for larger intake it would, if ascorbic acid has in fact protective effect, approach the limit of 100 percent effectiveness. Values of the incidence and also of the severity of individual colds reported in the five investigations are plotted in the upper part of Figure 1, and values of the integrated morbidity in the lower part. (The values of incidence and severity are plotted together because they are observed to be approximately equal.) Smooth curves have been drawn as indicated by the points.

It is seen that the results of the different studies are consistent with one another. None of the observed values differs from the corresponding point on the curve by an amount that is statistically significant at the level $P(\text{two-tailed}) < 0.05$.

These curves are, of course, only approximations; the protective effect of ascorbic acid, relative to that of a placebo, can be expected to depend on various factors, such as the average genetic nature of the population, the food ingested, and the nature of the cold viruses to which the subjects are exposed, in addition to the daily intake of the vitamin.

The observed decreases in incidence, severity, and integrated morbidity of the common cold for the five studies are summarized in Table 8, together with the results of some other studies, discussed in the following paragraphs.

Table 8

Summary of Observed Decreases in Incidence, Severity, and Integrated Morbidity in Controlled Studies

	Daily amount of ascorbic acid	Observed decrease in Incidence	Severity	Integrated morbidity
Ritzel	1000 mg	45%	29, 36%	61, 64%
Cowan, Diehl, and Baker	180 mg	14%	21%	31%
Franz, Sands, and Heyl	205 mg	5%	37%	40%
Wilson and Low	200 mg		43%	
Glazebrook and Thomson	160 mg	17%	24%	41%

The Smaller Study by Glazebrook and Thomson

A smaller study was also reported by Glazebrook and Thomson (9), with 150 recruits who entered the institution and were studied during the second half of the six-months period. The results of this trial, as reported by the authors, are given in Table 9. A decrease in the incidence of colds by 12 percent was noted, with, however, little statistical significance. The incidence of tonsilitis was 79 percent less for the ascorbic-acid group than for the control group, statistically significant at P(one-tailed) < 0.05. The value 12 percent for the decreased incidence of colds does not differ significantly from the corresponding value 18% given by the curve of Figure 1.

The Second Study by Cowan, Diehl, and Baker

Cowan, Diehl, and Baker (5) also reported the results of a second study, carried out with three groups of subjects (students in the University of Minnesota) in the winter of 1940-1941. The subjects in the first group (82) received 50 mg of ascorbic acid per day, plus other vitamins, those in the second group (88) received 25 mg per day (plus other vitamins), and those in the third group received a placebo. The investigators reported no differences among the groups in the number and severity of colds. The upper curve in Figure 1 leads an expected decrease in incidence and in severity by 7 percent for the first group and by 4 percent for the second group. The differences between these values and the observed values (0 percent) are not statistically significant.

The Work of Dahlberg, Engel, and Rydin

A study by Dahlberg, Engel, and Rydin (10) has been quoted as show-

Table 9

The Smaller Study by Glazebrook and Thomson

Incidence of colds and tonsilitis

	Control group		Ascorbic-acid group		P(one-tailed)	Decrease in incidence
	Number	Incidence	Number	Incidence		
Number in group	90		60			
Colds	29	0.322	17	0.283	<0.30	12%
Tonsilitis	7	.078	1	.017	<0.05	79%
Colds plus tonsilitis	36	.400	18	.300	<0.10	25%

ing that ascorbic acid has no value in preventing the common cold or affecting its duration. For example, in the book The Vitamins in Medicine by Bicknell and Prescott (11) there is the following statement: "Dahlberg, Engel, and Rydin carried out a mass experiment on 2,500 Army conscripts, one-half receiving 200 mg of ascorbic acid, the other half acting as controls. No difference was noted in the frequency or duration of colds, fever, endurance tests, or diseases of any description in the two groups."

Dahlberg, Engel, and Rydin themselves, in the summary of their paper, state that "No difference could be found as regards frequency or duration of colds, degrees of fever, etc. Military competitions, arranged to relieve the tedium, disclosed no difference between the two groups. Thus, the soldiers who only received the diet of the Swedish Army, and who showed a 'pathological deficit' [in ascorbic acid in the blood], did not differ in any respect from those who had been given ascorbic acid during the entire period of investigation. Consequently, there is no reason to assume vitamin C to be at all instrumental in preventing colds when supplementing the degree of vitamin deficiency existing among soldiers in the north of Sweden."

Examination of the paper by Dahlberg, Engel, and Rydin shows, however, that these statements are not true. The investigators in fact reported a decrease in the incidence of colds, a decrease in the incidence of other infectious diseases, a decrease in the number of subjects with fever, and a small improvement in functioning in the endurance tests. The statement by the authors is misleading; presumably they meant to say that no statistically significant differences were found.

The study was carried out with 2,525 infantry soldiers stationed in an isolated region in northern Sweden, during the 90 days from 3 March to 31 May, inclusive. It was a double-blind test, the composition of the tablets being kept secret from both the doctors and the soldiers. The subjects were

divided into two groups, the ascorbic acid group (1259) and the placebo group (1266), in a random way, by odd and even identity numbers, respectively. The placebo tablets contained a suitable amount of citric acid to disguise any difference in taste. The ascorbic-acid subjects received 200 mg per day for the first 24 days, and 50 mg per day for the remaining 66 days, an average of 90 mg per day. After 24 days and after 90 days a statistically significant difference was found between the average ascorbic-acid levels in the urine of the two groups, both during a fasting period and after ingestion of 200 mg or 300 mg of ascorbic acid, in a loading test. (The loading test results are referred to in the words "pathological deficit" in the summary of their paper.) The ascorbic-acid tablets and placebo tablets were dispensed at the first meal of the day, and special steps were taken to see that they were consumed at that time, and did not go to the wrong person. The soldiers were told what the investigation was for, and were requested not to eat any other food or other medicines during the time of observation than what was provided in camp. About half of the subjects (in certain companies of soldiers) in each group were carefully checked, and the average intake of 90 milligrams per day of ascorbic acid is reliable for them. For the other half, in other companies, there were some periods when some proportion of the subjects did not always take the tablets regularly. The authors present the results separately, but in fact they are closely similar, and in the following discussion all ascorbic-acid subjects are grouped together, and all placebo subjects. The failure to check the regular ingestion of the tablets occurred during only a part of the 50-mg-per-day period, and it seems likely that the average ingestion of ascorbic acid, taken as 90 mg per day, is not more than 10 percent high.

The observations, presented in the original paper in five tables, are summarized in Table 10. The second row gives the number of colds for the placebo group and the ascorbic-acid group. These numbers cor-

respond to a 7.4 percent smaller incidence of colds for the ascorbic-acid group than for the placebo group. The next three rows give further information about colds; namely, the numbers of subjects with colds (one or more during the period of the study), registered as ill with colds, and with colds and fever. In these three categories, too, there are reported decreases in incidence in the ascorbic-acid group, ranging from 2.5 percent to 3.7 percent. All four values may be compared with the value 12 percent given by the upper curve of Figure 1 for the average intake of 90 mg per day. The differences are not statistically significant, and the investigation does not require rejection either of the null hypothesis that ascorbic acid has no more protective effect than a placebo nor of the hypothesis that it has the amount of protective effect indicated by the curves of Figure 1.

It is interesting that the reported amount of protective effect for all infectious diseases (last four lines in Table 10) is somewhat larger than that for the common cold alone (average of four values 8.0 percent, as compared with 4.3 percent).

A field competition was held, participated in by 359 members of the placebo group and 357 members of the ascorbic-acid group. The median ranking of the ascorbic-acid participants was 2.0 percent higher than that of the control participants. Some superiority of the ascorbic-acid group over the placebo group was accordingly reported in this test (presumably the endurance test mentioned by Bicknell and Prescott), even though the superiority is small, and not statistically significant.

Dahlberg, Engel, and Rydin mentioned that they had recorded the number of days each patient was on the sick list, and how many days, if any, he had been treated in hospital. These numbers are, however, not given in the paper, and it is accordingly not possible to use them in assessing the severity of individual colds.

Table 10

The Study by Dahlberg, Engel, and Rydin

Incidence of colds and of all infectious diseases

	Number, placebo group	Number, ascorbic-acid group	Decreased incidence in ascorbic-acid group
Total number of subjects	1266	1259	
Total number of colds*	152	140	7.4%
Subjects with common cold	130	126	2.5%
Subjects registered as ill with common cold	94	90	3.7%
Subjects with common cold and fever	73	70	3.6%
Registered cases of disease	162	145	10.0%
Diseased subjects	141**	131	6.6%
Subjects registered as diseased	103	95	7.3%
Subjects diseased and with fever	80	73	8.2%

* From Table 1, corrected for other acute infections

** Average of 142 in Table 1 and 140 in Table 5

The statistical significance of the results of this large-scale study, involving 2525 subjects, is less than that of the study of Cowan, Diehl, and Baker, involving only 363 subjects, for two reasons. First, the period of time was less than half as great in the former study, and second, the incidence of colds was much less, presumably because the soldiers were in an isolated camp in northern Sweden, and not exposed to many cold viruses. The total number of colds reported by Dahlberg, Engel, and Rydin is 292, whereas the total number reported by Cowan, Diehl, and Baker is about 735. Moreover, the amount of ascorbic acid per day in the Scandinavian study was less than half as much as in the Minnesota study, so that an effect only about half as great would be anticipated.

The study by Dahlberg, Engel, and Rydin indicates that ascorbic acid in the average amount 90 mg per day has some protective effect, but that the null hypothesis of no protective effect is not eliminated with statistical significance. On the other hand, the hypothesis of the amount of protective effect indicated in Figure 1 is also not eliminated with statistical significance, and it is not justified to claim that this work has shown ascorbic acid to have no value in controlling the common cold.

So far as I am aware, there have not been published any other reports of carefully controlled studies of the protective value of ascorbic acid against the common cold when it is administered over a period of time to subjects who had not yet contracted colds and were exposed to cold viruses in the ordinary way, by contact with other people.

In the effort to make my search complete, I have written to about a score of persons who have stated that it has been shown that ascorbic acid has no protective value against the common cold, asking for reference to any controlled investigation that has given statistically significant results causing

rejection of the hypothesis that ascorbic acid has the protective effect indicated by the curves in Figure 1 when administered over a period of time to subjects exposed to cold viruses in the ordinary way. This effort was unsuccessful; most of my correspondents replied, and all who replied either stated that they did not know about any such investigation or referred me to one or another of the publications discussed in this article.

The Work of Walker, Bynoe, and Tyrrell

The study by Walker, Bynoe, and Tyrrell (12) is often mentioned as having shown that ascorbic acid has no protective value against the common cold. Of the 91 subjects, 47 received 3g of ascorbic acid per day for three days before inoculation with viruses (rhinoviruses, influenza B virus, or B814 virus) and for six days after inoculation, and 44 subjects received a placebo. The incidence of colds was only 6 percent less for the ascorbic-acid group (18/47) than for the placebo group (18/44); this difference is not statistically significant. The upper curve in Figure 1 suggests a decreased incidence of colds by about 60 percent for an intake of 3g per day. The reported result, 6-percent decrease, causes the hypothesis that the protective effect is this great to be rejected with statistical significance (P(one-tailed) < 0.01). The investigators concluded that there is no evidence that the administration of ascorbic acid has any value in the prevention or treatment of colds produced by five known viruses. In fact, their study rejects with statistical significance (P(one-tailed) < 0.05) a protective effect greater than 45 percent, but not a smaller effect.

I conclude that it is probable that under the conditions of the study

carried out by Walker, Bynoe, and Tyrrell ascorbic acid in the amount 3g per day does not have protective effect as large as 45 percent. The extrapolation of the upper curve of Figure 1 to a value of about 60 percent decrease in incidence seems to me to be reasonable. The results of this investigation accordingly disagree with those of the five investigations represented by the points in Figure 1.

A possible explanation of the disagreement is that the process of inoculation with a virus suspension introduces so many virus particles into the nose and throat as to overcome the protective effect of the ascorbic acid. This possibility could be checked by studies in which the number of virus particles used for inoculation was varied.

Other Investigations

There is some additional evidence that the protective power of ascorbic acid increases with increase in the magnitude of the viral infection. Dr. E. Regnier (13) has reported the results of a blind study of 137 colds, in 22 subjects (mostly professionals), over a five-year period. Some colds were treated by administration of 600 mg of ascorbic acid every three hours, beginning at the first sign of the cold. Of 84 incipient colds treated in this way, only 8 developed into full-blown colds, whereas of 53 treated with a placebo, 50 developed into full-blown colds. The difference has high statistical significance ($P \ll 0.001$). Other investigators have reported that a similar treatment is effective in stopping a cold. Wood (14) recommends taking 1000 mg as soon as one says to himself, "I think I am catching a cold," followed by 500 mg every two hours during waking periods for a total of 4 or 5 g per day, and Stone (15) recommends a succession of 1.5-g doses at 1-hour intervals, beginning at the first sign

of a cold. All three report that the treatment is unsuccessful if it is delayed. I surmise that ascorbic acid can control infection with a small number of virus particles, such as at the beginning of a cold, but cannot control a large number, such as when the cold has developed.

Some studies of the effect of treatment of the common cold with ascorbic acid beginning after the cold has developed have given negative results. All of these have involved smaller amounts than recommended by Regnier, Wood, and Stone, and with less effort to have the treatment begin at the first sign of a cold. An example is the work by Tebrock, Arminio, and Johnston (16), who studied about 1900 subjects, and found no difference between the colds treated with ascorbic acid and those treated with a placebo. The treatment was begun when the subject came to the dispensary. He then received one 50-mg tablet of ascorbic acid (or placebo), and was given eleven others to be taken over a three-day period. It seems likely that the negative result was caused by the small amount of ascorbic acid used and by the delay in initiating the treatment.

It is worth while to quote two sentences from a publication by Dr. Frederick R. Klenner, who for 27 years has used ascorbic acid for the treatment of all virus infections: "I have several hundred patients who have taken 10g or more of vitamin C daily for three to fifteen years. Ninety percent of these never have colds; the others need additional ascorbic acid" (17). The reported decrease in the incidence of the common cold in this uncontrolled study, 90 percent by 10g per day of ascorbic acid, is not unreasonable in comparison with the upper curve of Figure 1.

Conclusion

An analysis has been made of published results of controlled studies of the effect of ascorbic acid on the incidence, severity, and integrated morbidity of the common cold in populations receiving the ascorbic acid regularly, beginning before colds have been incurred, and with the subjects exposed to cold viruses in the ordinary way (contact with other people). The observations reject with high statistical significance the null hypothesis that under these conditions ascorbic acid has the same effect as a placebo. Ascorbic acid in the daily amount 200 mg decreases the incidence of colds and the severity of individual colds by about 20 percent and the integrated morbidity by about 35 percent. In the daily amount 1,000 milligrams it decreases the incidence and the severity by about 40 percent and the integrated morbidity by about 60 percent. No controlled study under these conditions has given results rejecting with statistical significance the hypothesis that this amount of protective effect occurs.

The effectiveness of ascorbic acid taken after a cold has been incurred seems to depend upon the amount of ascorbic acid taken and the amount of delay in beginning the treatment.

Little protective effect is reported when the colds are induced by inoculation with a virus suspension.

There is evidence that ascorbic acid has a protective effect also against infections other than the common cold.

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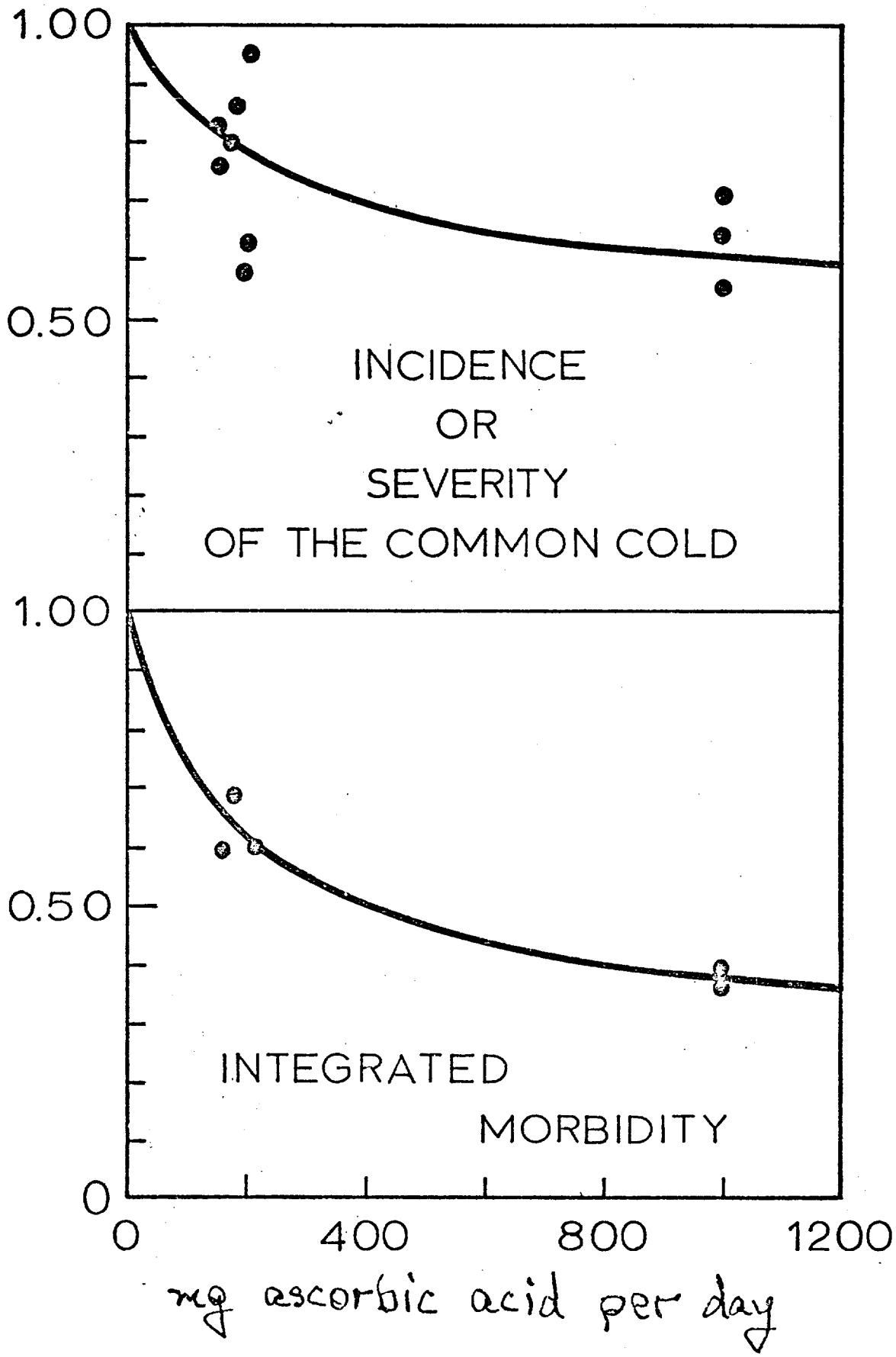

Fig. 1 Pauling

Legend for Figure

Fig. 1. Points representing observed values of the incidence of the common cold or the severity of individual colds (above) and of the integrated morbidity (below), plotted against the milligrams of ascorbic acid taken per day. All values are relative to the corresponding values of incidence, severity, or integrated morbidity for control subjects.