VITAMINS FOR THE PREVENTION OF COLDS

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Repeated studies have shown that both animals and man have a decreased resistance to infections of various kinds when suffering from vitamin deficiencies. Apparently this may be true for each of the better known vitamins. On the other hand, it has not been shown by adequately controlled experiments that the addition of any of the vitamins to a reasonably adequate diet produces increased resistance to infections of the upper respiratory tract, the millions of dollars' worth of vitamin preparations which are sold each year for this alleged purpose notwithstanding.

Most of the studies of vitamins for the prevention of colds have been limited to vitamin A alone or to vitamins A and D as contained in cod liver oil. The experiments with vitamin A have resulted almost uniformly in negative results, while cod liver oil has been reported by a number of authors to reduce the severity and by some the frequency of colds. Most of the latter reports, however, are based on inadequately controlled studies.[1]

Investigations of the use of multiple vitamins in the prevention of colds have been very few. Stone and her co-workers [2] reported that the daily administration of concentrates of vitamins A, B_1, B_2 and D were effective in reducing the incidence of infection of the upper respiratory tract in 11 students. These few subjects however, were in poor general physical condition, in addition to being very susceptible to colds, and the observations extended only over a period of three and one-half months.

Kuttner [3] studied 108 rheumatic children in a domiciliary institution. All these children were on the regular institutional diet, but one half of them received each day, in addition to the regular diet, 15,000 U. S. P. units of vitamin A, 1,870 U. S. P. units of vitamin D, 2,000 international units of vitamin C, 1,000 international units of vitamin B_1, 480 Sherman-Bourquin units of vitamin B_2, 40 "rat day" units of vitamin B_6, approximately 40 growth units of "filtrate factor" and the equivalent of 50 Gm. of whole liver in nicotinic acid or one of its derivatives. Both groups were observed from January 1 to June 1, 1939 and from Dec. 1, 1939 to May 1, 1940. The conclusion of the author was that this study did not present any evidence that the addition of these vitamins to an ordinary, well balanced diet reduced the incidence of infections of the upper respiratory tract.

From the Students' Health Service, University of Minnesota.

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1. These include:
Hess, A. F.; Lewis, J. M., and Barenberg, L. H.: Does Our Dietary Require Vitamin A Supplement? J. A. M. A. **101**: 657 (Aug. 26) 1933.
Tress, Esther M.: Vitamin A as a Prophylactic Against the Common Cold in Groups of School Children, Am. J. Digest. Dis. & Nutrition **1**: 795 (Jan.) 1935.
Holmes, A. D.; Pigott, Madeline G.; Sawyer, W. A., and Comstock, Laura: Cod Liver Oil: A Five Year Study of Its Value for Reducing Industrial Absenteeism Caused by Colds and Respiratory Diseases, Indust. Med. **5**: 359 (July) 1936.
Sherman, J. B.: Prophylaxis of the Common Cold, Brit. M. J. **2**: 903 (Oct. 29) 1938.
Spiesman, I. G.: Massive Doses of Vitamins A and D in the Prevention of the Common Cold, Arch. Otolaryn. **34**: 787 (Oct.) 1941.

2. Stone, Florence G.; Bird, Mira S., and Field, Hazel E.: Vitamins A, B_1, B_2 and D: Effects of Daily Administration of Concentrates, California & West. Med. **50**: 125 (Feb.) 1939.

3. Kuttner, A. G.: The Effect of Large Doses of Vitamins A, B, C and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children, J. Clin. Investigation **19**: 809 (Nov.) 1940.

OUTLINE OF STUDY

The present investigation concerns the value of large doses of vitamin C alone (1939-1940 series) and of large doses of mixed vitamins (1940-1941 series) in the prevention of colds. As in our previous cold prevention studies, the subjects were all students of the University of Minnesota who volunteered to participate in the study because they were particularly susceptible to colds.

Students applied for admission to the "Cold Prevention Group" soon after school started in the fall quarter. At this time a record was made of each applicant's recent history of acute infections of the upper part of the respiratory tract with particular attention to the number and severity of colds experienced during the previous two years, the type of these colds, their duration and like information. In order to exclude from the study persons whose difficulties seemed to be due primarily to chronic sinusitis or allergic rhinitis, special attention was paid to the condition of the nose and throat and to symptoms suggestive of allergy. As in previous studies, the students were assigned alternately and without selection to an experimental and to a control group. The students in the control group were treated exactly like those in the experimental groups except that they received placebos instead of the vitamin preparations.

Name .....

Report for week beginning Sunday, ... (date)

Cold: Date of onset: .....

Continued from previous week, ☐ yes, ☐ no.

Days of cold this week: .....

Severity: ☐ mild; ☐ moderately severe; ☐ severe; ☐ very severe

Symptoms: ☐ nasal discharge ☐ sputum ☐ aching ☐ in bed
☐ nasal obstruction ☐ sore throat
☐ cough ☐ fever Other .....

Medicine: Treatment other than the vaccine taken: .....

Have you taken cold prevention medication daily? ☐ yes, ☐ no.

Reactions: .....

Comments: .....

If, during the week here reported, you have just recovered from a cold, indicate whether that cold *as compared with your colds in previous years* was AS A WHOLE

☐ very much milder ☐ somewhat milder ☐ very much more severe than average
☐ about the same ☐ more severe

☐ Check here if you have had no symptoms of a cold this week.

(This card must be returned promptly whether you have had a cold or not)

Date of report ..... Signature .....

Fig. 1.—Weekly report card. (The original cards measure 4 by 6 inches.)

THE REPORTING OF COLDS

The students in all groups were instructed to report to the Health Service whenever a cold developed so that a special report card could be filled in by a physician indicating the type of cold, the symptoms and the like. In addition, all students were interviewed every three months in order to check the completeness of the reports filled out at the time of each respiratory infection.

During the second year of the study (1940-1941) a supplementary check on the accuracy of reporting was instituted. This consisted in having each student fill out and return to the Health Service each week the special report card shown in figure 1. This card is

similar to the one used by Stafford [4] and provides an accurate check on the incidence of colds as well as some information as to the relative severity of each cold reported.

The data contained on these weekly report cards were transferred to each student's "master card," which was

(721) COLD PREVENTION, 1940-41—INDIVIDUAL MASTER SHEET

Name_____ Group_____

Address (or P. O.)_____ Age_____ Sex_____

Number of colds in previous years (average)_____

Evidence of allergy_____

USUAL SYMPTOMS: ☐ Nasal discharge ☐ Nasal obstruction ☐ Cough ☐ Sputum ☐ Sore throat ☐ Fever ☐ Aching ☐ In bed

Usual treatment_____

PREVIOUS COLD PREVENTION—FORM: Injected ☐ Oral ☐ RESULTS: Good ☐ Indifferent ☐ Bad ☐

SUMMARY OF DATA

Week	Date	Days of Cold	Severity* O.	Severity* M.	Week	Date	Days of Cold	Severity* O.	Severity* M.	Week	Date	Days of Cold	Severity* O.	Severity* M.
1					11					21				
2					12					22				
3					13					23				
4					14					24				
5					15					25				
6					16					26				
7					17					27				
8					18					28				
9					19					29				
10					20					30				

* Relative severity should be expressed as follows: +=mild; 2+=moderately severe; 3+=severe; 4+=very severe.

Fig. 2.—Master card.

kept on file in the Health Service (fig. 2). At the end of the school year these various reports were summarized according to experimental and control groups.

DAILY USE OF LARGE DOSES OF VITAMIN C

At the beginning of the school year 1939-1940, 427 were enrolled in the "cold prevention group." One hundred and eighty-three of these were supplied with 100 mg. tablets of synthetic ascorbic acid and were instructed to take 2 such tablets (200 mg.) daily throughout the "cold season," a total of twenty-eight weeks. Fifty other students, also supplied with 100 mg. tablets of ascorbic acid, were instructed to take 2 tablets (200 mg.) daily for the first two weeks, then 1 tablet (100 mg.) daily throughout the season unless and until an infection of the upper respiratory tract developed, in which case they were to take 5 tablets (500 mg.) on each of the first two days of the cold,

TABLE 1.—*Vitamin C in the Prevention of Colds*

	Vitamin C Group		Control Group
Subjects who began study	233		194
Subjects who completed study	208		155
Percentage who completed study	89.3		79.9
Number of colds per person during previous year* (average)	5.5 ± 0.12		5.9 ± 0.14
Number of colds per person during year of study (average)	1.9 ± 0.07		2.2 ± 0.08
Difference between average number of colds in experimental and control groups		0.3 ± 0.11	
Percentage of group who had no colds during year	11.5		8.4
Number of days per person lost from school (average)	1.1		1.6
Percentage of students with colds in which complications developed	26.4		22.6
Percentage of group reporting such reactions as headache, nausea, hot flashes and so on	4.8		1.3

* Reported from memory.

after which the 100 mg. daily dose was to be resumed. Since the results of these two subgroups were not significantly different, they are presented in table 1 as a single vitamin C group.

To serve as a control group 194 students were supplied with placebo tablets of the same size, shape, appearance and taste as the ascorbic acid tablets.[5] These students, of course, did not know that they were serving as controls. The instructions were to take 2 of these placebo tablets daily throughout the "cold season."

It will be noted that, while the students who took vitamin C throughout the "cold season" experienced only 1.9 colds per person annually during the study as compared with the reported 5.5 colds per person annually previous to the study, a reduction of 65.5 per cent, the controls reported an average of 2.2 colds per person a year during the study as compared with 5.9 colds per person annually in previous years, a reduction nearly as great, namely 62.7 per cent. 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 supplement to the diet may therefore be judged to give a slight advantage in reducing the number of colds experienced. However, one may well

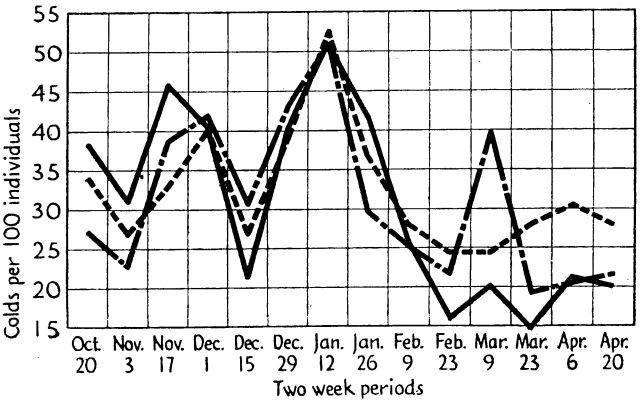

Fig. 3.—Incidence of colds in three groups of students from Oct. 20, 1940 to April 20, 1941. Broken line indicates group given 2 multiple vitamin capsules daily; dot and dash line indicates group given 1 multiple vitamin capsule plus added thiamine hydrochloride and nicotinic acid daily, and solid line indicates control group given 2 placebo capsules daily.

question the practical importance of such a difference. There are also slight differences in favor of the vitamin C group in regard to the percentage of students who had no colds of twenty-four or more hours' duration during the year of the study and in regard to the average number of days lost from school because of colds. On the other hand, those who took the vitamin C had, if anything, more complications such as bronchitis, otitis and sinusitis than did those in the control group.

MULTIPLE VITAMINS IN COLD PREVENTION

At the beginning of the school year 1940-1941 a total of 347 students were enrolled in the multiple vitamin study. Of this group only 264 cooperated throughout the year, which represents a smaller percentage than in most of our studies, possibly because of the increased demand made on the students during this year in the form of weekly report cards, special examinations of the nose and throat and the like. The results shown in figure 3 and table 2 are based only on those who cooperated throughout the "cold season."

At the beginning of the year 120 of these 347 students were instructed to take 2 capsules of multiple vitamins ("Hepicebrin") daily throughout the "cold season."

4. Stafford, C. I.: The Common Cold: An Evaluation of an Oral Vaccine Based on a Controlled Study, Journal-Lancet **60:** 319 (July) 1940.

5. Both the ascorbic acid and the placebo tablets were furnished by Hoffmann-LaRoche, Inc., Nutley, N. J.

These provided a daily supplement of 20,000 U. S. P. units of vitamin A, 1.2 mg. of thiamine hydrochloride, 200 micrograms of riboflavin, 50 mg. of ascorbic acid and 2,000 U. S. P. units of vitamin D. A second group of 107 students was given the following daily vitamin supplements: vitamin A 10,000 U. S. P. units, thiamine hydrochloride 48.6 mg. daily for the first week and 3.6 mg. daily thereafter, riboflavin 100 micrograms, ascorbic acid 25 mg., vitamin D 1,000 U. S. P. units and after January 1 nicotinic acid 50 mg. daily. This dosage was obtained by the daily administration of 1 multiple vitamin capsule together with the thiamine hydrochloride and nicotinic acid already indicated.

The control group for the experiment consisted of 120 students who were furnished placebo capsules which were indistinguishable from the multiple vitamin capsules.[6] These were prescribed at the rate of 2 daily throughout the "cold season."

TABLE 2.—*Multiple Vitamins in the Prevention of Colds*

	Two Multiple Vitamin Capsules Daily	One Multiple Vitamin Capsule + Thiamine + Nicotinic Acid Daily	Control (Two Capsules Placebo Daily)
Subjects who began study	120	107	120
Subjects who completed study	82	88	94
Percentage who completed study	68.3	82.2	78.3
Number of colds per person during previous year * (average)	4.9	5.0	5.0
Number of colds per person during year of study (average)	2.4	2.4	2.4
Percentage of group with no colds during year	4.9	8.0	5.3
Number of days per person lost from school (average)	1.8	1.6	1.0
Percentage of students with colds in which complications developed	23.5	15.2	13.5
Percentage of students hospitalized with complications	2.5	5.1	1.1
Classification of colds experienced (percentage of total colds in group):			
1. Based on symptomatology: †			
Mild	73.2	73.8	72.2
Moderately severe	14.1	14.8	16.6
Severe	9.6	8.1	7.6
Very severe	3.0	3.3	3.6
2. Based on student's opinion as to comparison with previous colds: †			
Very much milder than average previous cold	28.3	28.2	22.6
Somewhat milder than average previous cold	31.2	22.4	25.0
About the same as average previous cold	28.9	34.0	36.9
More severe than average previous cold	9.8	10.9	8.9
Very much more severe than average	1.7	4.5	6.5
3. Average duration of colds, days	8.2	8.0	8.1

* Reported from memory.
† Classifications explained in text.

RESULTS WITH MULTIPLE VITAMINS

Table 2 and figure 3 present the results of this study. From table 2 it is apparent that there is no difference in the number of colds reported by the experimental and control groups. The same is true for the weekly occurrence of colds as shown in figure 3. The total number of colds reported by students in all groups was higher in this study than in most of our other experiments. This is in keeping with the general impression that the year 1940-1941 was characterized by an exceptionally high incidence of colds in the general school population.

Table 2 also presents an attempt to evaluate the relative severity of the colds reported by the students in the various groups. Three sets of criteria were used in this analysis. The severity of colds as reported on the weekly cards was estimated in much the same manner as was utilized by Shibley and Spies [7] and by Stafford.[4] The occurrence of nasal discharge and obstruction with or without cough, sputum or sore throat lasting for more than one day but without aching, fever or confinement to bed was classified as a mild cold. The presence in addition of one of the recorded features of fever, aching or confinement to bed resulted in the classification moderately severe; if two of these features were present the cold was labeled severe, and if all three were present, that is if the student reported that he had fever, generalized aching and was confined to bed, the cold was classified as very severe.

In a further attempt to determine whether the medication modified the severity of the colds, the student was asked at the end of each cold he did experience to give an opinion as to how that particular cold compared with his previous colds (fig. 1).

An examination of table 2 does not reveal any evidence that the multiple vitamins reduced the severity of the colds. In fact, complications were more frequent among the students who got the vitamin supplements than among the control group. Furthermore, the average duration of each cold was the same for all three groups.

SUMMARY

This controlled study yields no indication that either large doses of vitamin C alone or large doses of vitamins A, B_1, B_2, C and D and nicotinic acid have any important effect on the number or severity of infections of the upper respiratory tract when administered to young adults who presumably are already on a reasonably adequate diet.

ABSTRACT OF DISCUSSION

DR. JOHN A. FERRELL, New York: May I inquire of the authors whether some of their study and control groups were known to have one or more vitamin deficiencies when the observations began? If not, what would be the rationale of administering vitamins to persons among whom no deficiencies had been determined with a view of influencing the incidence of colds due to viruses? With regard to the influenza viruses, the authorities in this field report that when resistance is built up against a specific virus the antibody titer for this virus is raised to a notable degree. Did you make any tests of your subjects relative to their antibody status for one or another of the viruses? The answers to these questions would be of real importance when testing the effectiveness of any therapeutic agent against a specific infection.

DR. JOSEPH S. LAWRENCE, Albany, N. Y.: Although the figures show practically no difference in the prevalence of colds between the two groups, if I gathered correctly from the statistics, there was, however, an appreciable diminution of colds among those examined as compared with the prevalence of colds among other students that winter. The students of both groups claimed also that they had had fewer colds than in the preceding winter. I wonder if the authors of the paper have an explanation for this apparent difference in incidence.

DR. HAVEN EMERSON, New York: This is a matter of the greatest importance to officers of the government concerned with the character of advertising claims that certain commercial preparations will stop and cure colds. The whole technic of

6. The vitamins as well as the placebo capsules were furnished by Eli Lilly & Co. Indianapolis.

7. Shibley, G. S., and Spies, T. D.: The Effect of Vitamin A on the Common Cold, J. A. M. A. **103**: 2021 (Dec. 29) 1934.

testing colds is at stake, and this is a good example of a carefully controlled study. I hope other questions as pointed as those that have been asked will be put to the authors. This is not an isolated undertaking in clinical research. Dr. Diehl and his colleagues have made many efforts to unravel the epidemiology of colds and to produce some practical proof of prevention and of successful treatment.

DR. DONALD W. COWAN, Minneapolis: In regard to the first question, we did no analyses to see whether or not the students were suffering from vitamin deficiency. We assumed that they were not, since most of them were on a reasonably adequate diet. We made no antibody studies either. We had no preconceived idea as to the value of vitamin therapy in the reduction of colds. We didn't know whether they would help or would not help. We merely used the vitamins because so many of them were being used by so many people that we thought a real controlled study was indicated to determine whether or not there might be something to the belief that persons taking large doses of expensive vitamins had fewer colds. There is, as far as I know, no rationale for it, and we certainly were not able to demonstrate that the vitamins were of any value. In regard to the question asked by Dr. Lawrence, there is a remarkable decrease in the reported number of colds on the part of both the control subjects and the experimental subjects in all of our cold prevention studies. We are at a loss to explain this 60 to 65 per cent reduction that we find in persons who are taking injections of sterile saline solution when they are controlling an experiment with injected vaccine, or starch tablets when they are controlling some oral vaccine, or capsules of liquid petrolatum when they are acting as controls for vitamin concentrates. One thing that might enter into the remarkable reduction in the number of colds among students in the control group is the fact that when one is taking two or three pills every day or is given a shot in the arm once or twice a week because he is cold susceptible he is continually being reminded that he is trying to do something about his colds; and he might consciously or unconsciously practice better general hygiene, which might decrease the number of colds which he has. For example, at Minnesota students are often observed dashing from their rooming houses to the corner drug store at 20 below zero without hats or coats. I wonder whether they aren't more likely to put on a hat and coat when they are in the cold prevention group.

DR. HAROLD S. DIEHL, Minneapolis: In further response to Dr. Ferrell's question, the reason for making this study was not that we thought these students exhibited vitamin deficiencies but that the average population is buying millions of dollars' worth of these vitamins every year, much of which is stimulated by advertising which suggests that vitamins will prevent colds. The question that we were attempting to answer was Are vitamins of any value for the prevention of colds in a cross section of the population such as we get in a university? In a group of university students one would not expect to find much vitamin deficiency, and yet in a big state university, such as Minnesota, a large portion of our students are self supporting, living in rooming houses and eating in restaurants. Observing cafeteria selections, we know their diets are not what we would recommend. Hence we can be certain that the economic level of these students and the type of diet they are getting is probably not as good as that of the average person who buys vitamin pills. Another point emphasized by this study, as well as by our previous studies on colds, is that if studies of this sort are to have any significance they must be done with a control group, and that control group must be treated in the same way as the experimental group. Results are not significant if this control group receives nothing. The control group must be given something which has the same psychologic effect as the treatment received by the experimental group. Our studies show that placebos frequently give what appear to be excellent results. It is common for the control group to report a reduction from an average of five to about two colds a year. In fact, certain results reported by many persons who received placebos would serve as splendid testimonials for anything for the prevention of colds.

CARDIAC EFFICIENCY AND PROGNOSIS FOLLOWING RECOVERY FROM ACUTE CORONARY OCCLUSION

THE RESULTS OF VARIOUS FUNCTIONAL TESTS

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In previous reports we [1] presented detailed clinical observations of 202 patients with acute coronary occlusion followed for a period of one to seven years after discharge from the hospital. Particular attention was paid to the cardiac status as determined by symptoms and physical examination. It was found that at least one third of the patients were able to lead a fairly active life with little or no restriction of ordinary activities and one half were able to return to full or part time work.

This study represents the results of objective tests of cardiac function performed serially in these 202 patients now followed two to eight years. These tests were vital capacity, the "Master two step" exercise tolerance, teleoroentgenogram for the size and configuration of the heart, fluoroscopic and roentgenkymographic study of ventricular pulsation, ordinary electrocardiogram and electrocardiogram after the standard "two step" exercise. An attempt was made to correlate the results of the tests with the clinical symptoms, physical findings and subsequent course of the patient. By repetition of the tests at intervals of three to twelve months it was possible to determine approximately when each test returned to normal.

To evaluate the various tests, the patients were grouped according to the degree of recovery. This was based on the presence and severity of angina pectoris, dyspnea and weakness and the physical findings, such as heart size, heart sounds and rate, signs of heart failure and blood pressure. Recovery of 66 patients (33 per cent) was considered good, of 57 (28 per cent) fair and of 79 (39 per cent) poor.

VITAL CAPACITY

Peabody and Wentworth,[2] Pratt [3] and subsequently other investigators [4] demonstrated a close relationship between a decreased vital capacity and pulmonary congestion due to left ventricular failure. White and

From the Mount Sinai Hospital,

Owing to lack of space, this article has been abbreviated for publication in THE JOURNAL. The complete article appears in the authors' reprints.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Experimental Medicine and Therapeutics at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1942.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

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