6. A gamma globulin fraction isolated from pooled "sensitized" rabbit sera caused partial inhibition of tubercle development while the remaining protein fraction did not.

7. There was a suggestion of partial tuberculostatic effect due to a gamma globulin fraction isolated from pooled sera of patients with minimal tuberculosis although the data were insufficient to be statistically significant.

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WEATHER AND SUSCEPTIBILITY IN RELATION TO THE SPREAD OF COMMON COLD; EFFECT OF ASCORBIC ACID, IN MASSIVE DOSAGE, ON DURATION

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This is a report of an analysis of the day-to-day changes in incidence of common cold during the year 1942–3 in a group of 1600 girls of college age; the season-to-season changes in average physiological fitness; and the differences in average duration of common cold as affected by the administration of ascorbic and citric acid.

The day-to-day changes in number of new colds developed were first examined for indications of possible effect from weather.

I. WEATHER AND INCIDENCE OF COMMON COLD

Teague, in 1912, presented an epochal report of his observations during an outbreak of pneumonic plague in Manchuria, during weather so cold that the exhaled breath became visible, due to the rapid condensation of its moisture content. The air-borne source of the disease was proved to become dispersed in the air surrounding the pneumonic plague patients as a result of coughing, etc., and to remain able to carry the disease to animals longer under conditions of low temperature and condensing moisture than under conditions favoring evaporation, such as are found in the warm areas of India, where the disease is rare. Dispersions, in the air, of other bacteria were found to be similarly affected. Factors coming under the heading of weather were, for the first time, conclusively shown to have a possible effect on the ability of an agent responsible for an air-borne infection to remain infective and dangerous. Teague commented that "In other pneumonias . . . it is not unlikely that the dosage and virulence of the inhaled bacilli and the susceptibility of the host are factors of far greater importance than in plague pneumonia; hence the influence of atmospheric temperature in their spread would be more or less obscured by the other factors" (1).

The host, also, is affected by the weather. Petersen has brought forward much challenging evidence of effects from the weather on circulation and other factors affecting ability to resist infection (2).

Fewer colds develop during the warm summer months than during the winter. However, comparisons of colds-incidence and average temperature on a seasonal, monthly or even weekly basis can be misleading. A cool day cannot be averaged with a warm day and the average considered to be representative of either. The periods to be compared must be so taken as to actually correspond to cool intervals, warm intervals, etc., as has been ably pointed out by Sargent (3).

[1] Deceased.

Observation and record, in a common cold study, must be kept on a day-to-day basis and not on a weekly or other basis obliterating the differences being tested for. Sargent directed primary attention to the type of change in weather which, to the meteorologist, indicates the passage of a "cold-front," and observed changes in the day-to-day incidence of common cold at Phillips Exeter Academy (N.H.) suggesting that the passage of a cold front may bring on, within 1 to 3 days, a rise in incidence of common cold extending over the period of dropping temperature following. This observation would appear to anticipate, in part, the findings reported below, as does, also, the observation by Duffield of an increased prevalence of common cold following heavy rain (4).

The group studied

The 1600 girls taking part in this study comprised all of the resident population that maintained residence for the whole of the school year 1942–3. A similar group had been studied during the year preceding and an adequate organization perfected for effective and continuous collaboration between the personnel of the division of student health, the students and those in authority over the students in dormitory and classroom, and the investigator studying the accumulating data for evidences of correlation.

The condition termed common cold

Common cold was considered, for this study, purely as a clinical entity, having a variable course and requiring study in the group rather than in the individual.

Call was made for an immediate report to the health center of each new cold developed, together with the date of probable onset. Cooperation was established, through the dormitory counselors, and the school as a whole kept alert to the necessity for prompt, complete and accurate reporting. Roughly half the reports gave sufficient information to permit precise allocation to a definite day of onset. This was, on the average, one day earlier than the day of report and was assumed so to be for the instances where day of report, only, was available.

Examination, at the time of report, usually revealed the presence of an already established reddening of the nasal mucous membranes and/or swollen turbinates; "stopped-up" head; sneezing or nasal discharge; dry and/or reddened, sore, scratchy or congested throat.

The weather changes

A record of the day-to-day changes in temperature, humidity, rainfall, wind velocity and sunshine was obtained from the Columbia, Mo., station of the Weather Bureau of the U. S. Dept. of Commerce. (The accompanying changes in barometric pressure were not given.) A detailed search of this weather record was made for associations with the changing number of new colds per day. Only one clearly defined relationship was found—the relationship indicated in table 1.

During the beginning days of the school year (Sept. 15–18), the average temperature was 80 and the rainfall not heavy. On Sept. 19, the temperature fell

TABLE 1

Increased number of new colds per day per thousand during periods of falling or subnormal temperature accompanied by an average, daily rainfall of more than 0.17 inches

PERIOD	NO. OF DAYS	MEAN TEMPERATURE, °F		AVG PER DIEM PRECIPITATION, INCHES	AVG NO. OF PERSONS REPORTING A NEW COLD PER DAY PER 1000
		Avg change in preceding 24 hrs	Avg divergence from normal		
Falling or subnormal temperature; avg daily precipitation of > 0.17 in:					
S 19–23	5	−5	−10	0.32	12.3
24–29	6	0	−18	.31	16.1
O 3– 5	3	−4	+3	.28	10.0
J 31– 1	2	−4	+2	.19†	11.8
My 6– 8	3	−8	−5	1.68	7.3
11–15	5	+1	−6	.42	10.1
16–20	5	−3	−5	1.00	15.4
Total.....	29				12.5 ±.6*
Falling or subnormal temperature, avg daily precipitation of <0.17 in:					
O 9–11	3	−3	+3	0	8.1
16–26	11	−3	−4	.01	6.6
29– 3	6	−2	+2	.08	5.6
N 21– 8	18	−2	−6	.10	7.4
D 11–14	4	−2	−8	.03	5.8
J 17–20	4	−6	−20	.05	8.0
23–26	4	−9	−8	0	6.9
F 10–16	7	−5	−8	.01	7.4
21–26	6	−4	+5	0	7.9
M 1– 8	8	−2	−17	.04	6.5
16–22	7	−2	−10	.12	4.6
31– 6	7	−3	+3	0	4.8
A 9–14	6	−7	−1	.15	5.0
17–22	6	−1	−8	.11	3.9
30– 1	2	−7	−2	0	6.6
My 23–25	3	−2	−6	.04	10.2
Total.....	102				6.5 ±.2
The 48 hrs following 3 days or longer of falling or subnormal temp.:					
Total.....	36	+7	+3	.05	6.8 ±.4
The remaining intervals (between Sept 15 and May 5):					
Total.....	58	+3	+10	.06	5.2 ±.3

* The probable error. † Rain.

to 61. Heavy rain fell. The temperature continued to drop or to hold at a low level until the 29th. A rise began on the 30th to a level which, by Oct. 2nd, was 8 degrees above the normal.

The changing colds-incidence

Between Sept. 15th and 18th, the 1600 students had an average of 5.9 new colds per day per thousand. Only a slight increase occurred on the 19th—to 7.1 new colds per day per thousand. A sharp increase to 16.3 occurred on the 20th. Day-to-day variation was evident over the period of dropping or subnormal temperature between Sept. 20th and 29th, but a rate near 16 was sustained throughout, and for 24 hours beyond. Recession back to the initial level began on Oct. 1st and was complete on Oct. 2nd.

Significance

Only one certain way was available for determining whether or not these changes, so closely paralleling the weather changes, could be considered to be suggestive of a relationship. It was necessary to examine the year as a whole; divide it into intervals clearly separating the weather changes; group together the intervals of falling temperature accompanied by heavy rainfall, the intervals of falling temperature not accompanied by heavy rainfall, the intervals of neither falling temperature nor heavy rainfall, etc.; find the average colds-incidence for the combined intervals in each contrasted classification, together with the probable modifying errors; and then observe whether those averages were sufficiently different from one another, in relation to the errors involved, to indicate significance.

The odds against an observed difference being a matter of chance altogether are given by the "Handbook of Chemistry and Physics" (Chemical Rubber Publishing Co., Cleveland, 1941, p. 199) as 22 to 1 when the difference is 3 times the probable error; 142 to 1 when the difference is 4-fold; 1341 to 1 when the difference is 5-fold; and 65 billion to 1 when the difference is 10-fold.

Table 1 presents the summarized comparison for the year as a whole. The total of 29 days of falling temperature accompanied by heavy rains had an average of 12.5 new colds per day per thousand, with a modifying probable error of 0.6. The 102 days of equivalently falling temperature, without heavy rainfall, had an average of 6.5 $\pm$ .2 new colds per day per thousand. The average number of new colds per day per thousand for the eighteen 48-hour periods immediately following cessation of sustained temperature drop was 6.8 $\pm$ .4, and for the 58 days free from either associated or recent, sustained temperature drop, 5.2 $\pm$ .3. The difference in average number of new colds per day per thousand for the days of presumed maximal and minimal weather effect was 7.3 $\pm$ .7—ten times the modifying probable error and unquestionably significant.

Nature of the weather effect

Whatever effect or effects may be exerted by the weather, they may be as frequently in a direction decreasing the risk of infection as in a direction increasing it. The net result would then be one affecting timing more than total number.

This timing effect was utilized for a further examination of the day-to-day incidence figures for information bearing on such questions as the following:

II. DO THE MOST SUSCEPTIBLE MEMBERS OF THE GROUP DEVELOP THE FIRST COLDS?

Susceptibility was gauged in terms of number of colds reported for the year as a whole. Twelve per cent of the girls remained free of common cold for the year 1942–3, 22 per cent had 1 cold; 24 per cent had 2; 20 per cent had 3; and 23 per cent had more than 3. The latter group had 45 per cent of the total number of colds—that is, approximately double its pro rata allotment. The development of the September wave of common cold in this, most susceptible group reached its half-point two days in advance of that in the group with but 1 or 2 colds for the year (table 2). The ratio of colds developed in the more susceptible and less susceptible groups, per thousand, between Sept. 15th and 18th, was 3.6 to 1 and, between Sept. 19th and Oct. 2nd, 2.4 to 1. On the day after the heavy rain of Sept. 19th, the incidence of common cold rose for the less susceptible group only to fall back again two days later, rising again on the day after the second heavy rain on Sept. 25th and 26th. Over these same intervals, the colds-incidence rose smoothly and without interruption in the more susceptible group. The indication, as a whole, was one of greater and more sustained increase in colds-incidence in the group with the greater number of colds for the year.

During the spring wave of common cold, the temperature changes were smaller and spread over a longer time interval. The number of new colds per day per thousand increased to levels comparable to those reached in September, only in the more susceptible group.

Smoking

A slightly increased tendency toward common cold, in that fraction of the student body accustomed to the use of cigarettes, had been noted during the preceding year (5). The beginning change of weather, on Sept. 19th, produced a change in colds-incidence from 6.4 to 10.8 in the group of 830 smokers, without parallel increase in the group of 771 nonsmokers. The response to weather change by the latter group appared to be, in general, slower, less sustained and less extreme (table 2).

Most of the smoking was done in smoking rooms, encouraging congregation and facilitating spread. A possible effect of smoking on fitness, and through fitness on susceptibility to common cold (6) is suggested in section III.

The analyses presented in tables 2 and 3 are exploratory in character; the relationships brought out are suggestive rather than conclusive. They do recall, strongly, the attention directed by Teague to the droplet dispersions which carry air-borne infection from one person to another, to the marked effect of drying on the ability of those dispersions to convey infection, and on the retarding effect of falling temperature and condensing moisture on such drying. Such infection might be presumed to affect the more susceptible fraction of the population first and then build up, in the air,—from the coughing, sneezing, etc. of that group—to a concentration able to affect the less susceptible fraction.

Time, also, may be required for the building up of an air-contamination of threatening proportions.

Time of arrival

As is indicated in table 3, 452 of the 708 girls resident on the south campus were second-year girls, arriving Sept. 10th; 521 of the 597 girls on the north campus were first-year girls, arriving Sept. 15th.

The September common cold wave passed the half-way point for the more susceptible group on the south campus on Sept. 22nd; and for the more susceptible group on the north campus on Sept. 24th. It passed the half-way point for the less susceptible group on the south campus on Sept. 24h and for the less susceptible group on the north campus on Sept. 26th.

TABLE 2

Greater and more sustained rise in colds-incidence (during the period of weather effect) in the fraction reporting a total of 4 to 6 colds for the year than in the fraction reporting 1 to 2. Use of cigarettes as a complicating factor

PERIOD	MEAN TEMP., F	AVG DAILY RAINFALL, IN.	NO. OF NEW COLDS REPORTED PER DAY PER 1000 BY THE		NO. REPORTED PER DAY PER 1000 BY THE GROUP WITH THE INDICATED NO. OF COLDS FOR THE YEAR	
			Smokers	Nonsmokers	1 to 2	4 to 6
S 15–18	80	0.15	6.4	5.6	3.4	12.3
19	61	1.59	10.8	3.9	4.1	13.7
20–21	57	0	15.1	14.3	11.0	26.0
22–24	53	T*	15.2	10.8	6.4	27.4
25–26	44	.92	18.6	9.7	8.9	32.9
27–28	46	0	19.7	17.5	13.0	34.5
29–30	63	0	20.9	12.3	15.8	27.4
O 1– 2	69	0	7.2	9.1	6.2	12.3
A 25–27	61	.19	2.7	3.5	1.8	6.3
28– 1	60	0	8.1	4.9	3.8	13.7
M 2– 5	68	.01	8.3	10.2	6.2	20.0
6– 9	57	1.27	9.0	5.8	5.8	15.1
10–14	58	.31	13.0	9.4	6.6	24.7
15–16	66	.87	15.6	9.1	9.6	24.7
17–18	61	1.39	16.2	19.5	8.9	32.9
19–20	60	.88	13.2	9.1	8.2	20.6
21–22	63	T	6.0	3.2	2.7	12.3

* Trace.

Menstruation, fatigue

Information permitting an appraisal of the extent of influence from the menstrual cycle was given by 730 of the girls reporting. Only 105 of these had colds

coinciding with a menstrual period—a proportion which would appear to have been within the range of chance occurrence.

Fatigue, worry, and lack of sleep frequently were cited as contributing causes but could be assessed objectively only for the small percentage in whom these factors represented fixed habits contributing to a deterioration in physiological fitness great enough to be revealed by the modified Flack test (section III).

Immunity

Only two observations were made with possible bearing on this highly debatable aspect of the problem. The first is summarized in table 4, which gives an indication of the average elapsed time between the successive colds reported. The second possibly represents no more than a coincidence: The change from a predominating percentage of first colds in the fall to a predominating percentage of second and third colds in the winter was accompanied by a change in the percentage with symptoms of a "head-cold" or coryza.

TABLE 3

*Comparative development of the first wave of common cold on the south campus, with a predominance of arrivals on September 10, and on the north campus, with a predominance of arrivals on September 15**

PERIOD	NO. OF NEW COLDS PER DAY PER THOUSAND IN THE GROUP WITH THE INDICATED NO. OF COLDS FOR THE YEAR			
	South campus		North campus	
	4 to 6	1 to 2	4 to 6	1 to 2
S 10–14	6.5	2.1	3.2	0
15–18	13.0	5.1	17.9	1.0
19–24	29.4	8.0	22.5	6.2
25–29	26.1	11.6	38.1	10.3
30– 1	9.8	18.5	27.8	15.9
Date by which 50 per cent of the September colds had developed:				
	S 22	S 24	S 24	S 26

* Sixty four per cent of the total number of girls living on the south campus were seniors, arriving September 10; 87 per cent of the total number resident on the north campus were juniors, arriving Sept. 15.

Frost and Gover already had called attention to the differing general character of the respiratory disease most prevalent during the fall and winter. They had found the peak incidence for coryza to be in the early autumn, with only secondary rises during the winter and spring—despite the increases, during those periods, in prevalence of respiratory disease as a whole. Influenza was observed to have its highest prevalence in February and March (7).

Table 4 indicates the shifting from a predominance of first colds in the fall, to a predominance of seconds and thirds in the winter and of thirds, fourths, fifths and sixths in the spring. Only an extremely small percentage of the colds followed a preceding cold by less than 3 weeks.

A high percentage of the fall colds had one or more of the following predomi-

nating characteristics: reddened nasal mucous membranes, swollen turbinates, "stopped-up head," sneezing, and nasal discharge—with a dry, scratchy, sore or congested throat as a modifying rather than a dominant part of the picture. During the winter months, few colds conforming to this description were seen at the health center. The colds had taken on a "winter" character difficult to

TABLE 4

Spacing of the colds

WEEK BEGINNING	TOTAL NO. OF NEW COLDS REPORTED				
	First colds	seconds	thirds	fourths	fifths-sixths
S 13	59				
20	156				
27	154				
O 4	83	2			
11	62	7			
18	56	20			
25	46	14			
N 1	28	25			
8	28	19	1		
15	29	23	3		
22	30	30	3	1	
29	56	31	8	1	
D 6	33	47	5	0	
vacation					
J 13	11	25	29	9	
20	18	41	24	3	1
27	20	33	25	12	3
F 3	15	24	16	13	1
10	20	30	17	13	3
17	22	34	35	17	1
24	15	19	25	19	6
M 3	11	22	16	6	6
10	10	22	19	13	5
17	8	14	17	5	7
24	4	5	9	7	4
31	4	10	19	12	8
A 7	9	8	20	8	7
14	5	8	13	12	8
21	4	7	5	7	8
28	4	21	22	22	19
M 5	8	24	17	21	23
12	13	28	42	41	30
19	9	27	23	20	26

define but appearing to be more advanced at time of first report and with predominating involvement of the throat.

III. THE SEASON-TO-SEASON CHANGES IN PHYSIOLOGICAL FITNESS

The observations reported below were obtained with a modification of the Flack test (8) placing emphasis on pulse rise rather than breath-holding time

and requiring performance in the standing position. Every effort was made to eliminate sources of transient fluctuation, in order to obtain a picture of the average, composite change in the group as a whole—a change which, while revealing a slight extent of the deterioration inevitably accompanying the lapse of time between one vacation and another, proved to be almost negligibly small in dimension.

Not every girl of college age can, with her breath, raise the mercury in a small manometer to the 40 mm level. One percent of the group examined for the study reported below was unable to support a pressure of 20 mm. The latter pressure was adopted as that most practicable for the group as a whole and would appear, from the relatively small proportion of minimal pulse rises indicated in table 5, to have imposed—together with the standing position—a sufficient circulatory handicap to satisfy the requirements of the test for all but a small minority.

TABLE 5

Range of pulse rise and breath-holding time observed during the total of 560 modified Flack tests made during the year 1942–3 on normal girls of college age

BREATHHOLDING TIME	NUMBER OF TESTS WITH A PULSE RISE, IN BEATS PER MIN., OF:					TOTAL NUMBER IN GROUP	% DEVELOPING DIZZINESS
	0–4	6–12	14–24	26–36	>36		
sec.							
<15	2	4	2	1	3	12	83
15–24	12	15	48	33	12	120	12
25–35	19	48	98	78	37	280	5
36–45	11	25	36	36	20	128	2
>45	3	4	7	4	2	20	0
Total no. in group	47	96	191	152	74		
% becoming flushed	0	8	8	15	19		

Procedure

Subjects were selected who were free of recognized circulatory abnormality. They were instructed to report for test when feeling "average" and free from the more immediate effects of ingested food, carbonated beverages, unusual exercise or excitement, and cigarettes. The pulse rate was taken by the examiner after 5 minutes of quiet sitting. The subject then rose, drew a full breath, expelled it slowly, drew a second full breath and held that for as long as was comfortably possible against a pressure of 20 mm of Hg. During this breath-holding period, the pulse rate was followed continuously, in 5 second intervals. The total rise in pulse rate from the level observed during quiet sitting to the maximal level reached during the breath-holding period was recorded, together with the total time in seconds that the breath was held.

Dizziness, faintness, flushing. Faintness was observed during only 1 of the 560 tests summarized in table 5; dizziness in 42; and flushing in 59. Eighty-six per cent of the dizziness and 75 per cent of the flushing occurred during tests

producing a pulse rise of more than 24 and or a breath-holding time of less than 25. Flushing occurred approximately twice as frequently in the smokers as in the nonsmokers.

Average reaction elicited. The average pulse rise produced was 22.4 ± .5 beats per minute. The average breath-holding time was 30.5 ± .4 seconds.

Effect of habitual use of cigarettes

No substantial difference was apparent in the average breath-holding time of the smokers and nonsmokers. A small but probably significant difference was apparent in the average pulse rise produced (23.0 ± .5 for the smokers and 19.7 ± .5 for the nonsmokers). The increased average pulse rise carried with it a suggestion of greater average impairment in fitness, rather than a shift in the position of the normal for this group, since it was paralleled by an equivalently small but probably significant, increased incidence of common cold (3.38 ± .06 for the smokers and 2.98 ± .06 for the nonsmokers).

TABLE 6

Maximal average incidence of common cold in the high pulse rise group

PULSE RISE, BEATS PER MIN	NUMBER OF TESTS	AVG ASSOCIATED INCIDENCE OF COMMON COLD*
14 to 24	191	2.68 ±.08†
<14	141	3.12 ±.07
>24	226	3.39 ±.07

* Number of colds per person between Sept. 15, 1942, and May 28, 1943, as determined by day-to-day inquiry, observation and record.

† The estimated, probable error.

Range of pulse rise associated with minimal average incidence of common cold

The range of pulse rise associated with minimal average incidence of common cold, for the group reported in table 6, appeared to be midway between the extremes of pulse rise observed rather than in association with the lowest range observed. Because, for some of the subjects tested, the breath may not have been held long enough to bring out a capacity response, it could not be concluded that this apparently central tendency was more than suggestive. The difference of 0.71 ± .11 in associated incidence of common cold, between the group with pulse rises between 14 and 24 and the group with pulse rises in excess of 24 was of greater weight than the difference of 0.44 ± .11 between the central and lower pulse rise group and less subject to reservation in interpretation.

Changes with the progress of the school year

No change was observed in average breath-holding time. A minimal, average pulse rise was observed in the fall, increasing slightly through the winter to a maximal in the spring (table 7). An additional series tested only twice (once in the fall or winter and again in the winter or spring) showed a parallel trend. A total of 24 persons, from the two series, reacted with a pulse rise 24 or more

beats per minute higher in the winter or spring than was observed during the preceding determination. Twelve reacted with a decrease of 24 or more. The average colds-incidence for the group with the increase of 24 or more was 3.9 ± .2. That for the group with the contrasted decrease was 2.2 ± .2. These figures, together with the increased proportion of pulse rises accompanied by flushing, during the spring tests, imply a progressive slight deterioration in average fitness, as a source of the higher average pulse rise obtained in the spring, rather than a progressive adaptation or other nonsignificant modification in response toward the test. The implied deterioration was, of course, not uniform throughout the group; reached practically significant proportions in only a small fraction; and was, in part, balanced by the instances of contrasted improvement above mentioned.

TABLE 7

Heightening of the average pulse rise with the progress of the year

TIME	NO. OF SUBJECTS	AVG BREATH-HOLDING TIME	AVG PULSE RISE, BEATS PER MIN	% WITH A PULSE RISE OF > 24	% BECOMING FLUSHED
		sec.			
Fall	113	30.4 ±.5	20.1 ±.7	31	9
Winter*	113	30.4 ±.4	22.0 ±.8	40	11
Spring	113	30.7 ±.4	24.8 ±.8	50	15

* A one-month vacation, possibly nullified by the stresses of travel and the holiday season, intervened between the fall and winter determinations.

IV. ASCORBIC ACID

Ascorbic acid has been studied by others for its possibilities vs. common cold mainly as a substance capable of overcoming vitamin C-deficiency and such predisposition to common cold as may result from vitamin-C-deficiency.

The vitamin C-deficient individual is likely to be deficient in other principles, also, and in vitality. Crandon observed no deterioration in ability to avoid common cold during a self-imposed, 6-month interval of controlled ascorbic acid deficiency (9). An actual lessening of duration and severity was observed which is the expectation in any study requiring a degree of watchfulness assuring early recognition, and imposing some degree of restriction of risk.

Bergquist (10), in an investigation conducted in Sweden during 1939–40, found a higher percentage of vitamin C-deficiency and a higher percentage of time lost from work as a result of colds than is observed in this country. Vitamin C-saturation followed by 30 mg of ascorbic acid 3 times daily, together with quinine, appeared to produce a lessening of time lost from work, as a result of colds, not clearly stated but appearing to be from a level approximating 7 per cent to a level approximating 1.5 per cent.

Glazebrook and Thomson (11) gave 50 mg of ascorbic acid daily to 335 boys, following a preliminary saturation. Common cold developed in 21.2 per cent. Among the 1100 controls, common cold developed in 26 per cent. The average number of days lost due to infection was 2.5, per boy, in the ascorbic acid group,

and 4.98, per boy, in the control group. Seventeen instances of pneumonia and 16 of "acute rheumatism" occurred in the control group and none in the ascorbic acid group.

Cowan, Diehl and Baker (12) gave 200 mg of ascorbic acid daily throughout the colds season. The average colds-incidence for the 208 students given ascorbic acid was 1.9 ± .07. That for the 155 students given a placebo was 2.2 ± .08. The percentage with no colds, for the ascorbic acid group, was 11.5; that for the placebo group was 8.4.

Cowan, Diehl and Baker encountered one difficulty in balancing their treated and control groups met with, also, in the study reported below. Only 79.9 per cent of the students given the placebo stayed with the study to completion as compared with 89.3 per cent for the ascorbic acid group (12).

Clinical observations of effect from ascorbic acid, given *following* onset of common cold, have been made by Ruskin (13) and van Alyea (14).

No clear-cut, unchallenged demonstration has yet been made that ascorbic acid can exert a direct effect against bacterial infection. An unpublished test by one of us, with Miss Alice McIlroy (at The Western Pennsylvania Hospital), of the effect of ingested ascorbic acid on outcome in normal, healthy, uninjured mice infected intravenously with a sufficient number of fully virulent, type I pneumococci to produce a mortality (in the absence of treatment) of 50 per cent, showed a difference in mortality, between the 273 members of the control group and the 289 members of the ascorbic acid group, of 0 ± 3 per cent. The ascorbic acid was freshly dissolved in water, in a concentration of 2 to 5 mg in 0.1 ml, and introduced directly into the throat through a glass tube, 20 minutes prior to the infection. A further test, by R. B. Locke, of the effect of injected ascorbic acid on blood culture and survival in rabbits infected intravenously with the type I pneumococcus, also showed no substantial, direct effect. Of the total of 25 rabbits given ascorbic acid, 32 ± 7 per cent survived as compared with the survival percentage of 23 ± 6 for the 26 controls. The ascorbic acid, for the rabbit test, was given intravenously as a freshly prepared, neutral solution containing 75 mg in a total volume of 2 ml, injected 1 to 5 minutes before the infection.

A recent leading article in the Lancet makes this pertinent statement concerning the relative parts played in the development of common cold by bacterium and virus: "The common cold is probably due to a virus. . . . The portal of entry is the nasal mucosa, whence absorption takes place into the subepithelial lymphatics and thence into the blood stream. In the true cold that is the end of the matter. After a brief period the resisting mechanism of the body overcomes the invasion and resolution follows: this may take from 2 or 3 up to 10 or 12 days. But the process is rarely as simple as that, because the virus infection lays the victim open to attack by his own and other people's bacteria. As a rule, then, secondary bacterial invasion follows, and goes through essentially the same process of local and general spread" (15).

Ascorbic acid has been found to have an inactivating action vs. purified influenza virus under *in vitro* conditions possibly not applicable to the problem of

actual infection (16). An inactivating action, *in vitro*, also has been reported vs. poliomyelitis virus (17).

Any presumptive effect by ascorbic acid, if directed against the virus of common cold rather than the bacterial agents producing secondary invasion, would have to be accomplished early.

Procedure

A call was issued for volunteers to report to the health center at the first recognized indication that a cold might be in process of development. An examination was made, the initial symptomatology noted and recorded, and an estimate made of the probable number of hours elapsed since presumed onset. Those recommended for inclusion in the ascorbic acid study were then given either one gram of that substance, by mouth, in water, or an equivalent amount of citric acid as a placebo.[2] The ascorbic acid and placebo were given alternately insofar as was practicable and without knowledge on the subjects' part that placebos were being given.

The desirability of rest was emphasized but not made mandatory. Opportunity was given to go immediately to bed. The subjects not admitted to the infirmary—and the majority were not—were asked to keep warm, retire as early as possible, push fluids, and take no other medication for 48 hours.

On the following morning, report was again made to the health center and an additional gram of ascorbic acid or citric acid given. A small percentage, greater for the citric acid group than for the ascorbic acid group, failed to report for second dosage and reexamination.

Decision was made as to outcome on the second day, 48 hours after the beginning of the management described, when examination revealed that the cold either had not developed or had persisted.

Table 8 compares the percentages of nondeveloping colds reported for the groups given ascorbic or citric acids, on a basis of symptomatology present and time treatment was begun.

Initial symptoms

Two symptom groupings only are presented; one indicating nose involvement with or without accompanying throat involvement, and the other indicating throat involvement only. The instances of throat involvement, only, appeared to be so responsive to the basic management given as to leave no margin for demonstration of possible ascorbic acid effect. Development was checked to an extent probably approaching the uppermost limits of realization, whether or not ascorbic acid was given. The percentage of nondeveloping colds for the 123 instances of nose involvement given ascorbic acid was 62 ± 4; that for the 83 comparable instances given citric acid was 37 ± 4 (a difference of 25 ± 6). One hundred thirty members of this group were studied during the 1942–3 season,

[2] We are indebted to Chas. Pfizer and Co. for the ascorbic and citric acids used and to Mrs. Frances Whitesides for taking over the uncompleted phases of the ascorbic acid-common cold investigation, following Mrs. Niedringhaus' death.

by Mrs. Niedringhaus; 76 were studied during the autumn of 1943 by Mrs. Whitesides. The comparative percentages of nondeveloping colds found by the two investigators for the two different seasons were: following ascorbic acid, 61 (Mrs. N.) and 63 (Mrs. W.) and, following citric acid, 38 (Mrs. N.) and 36 (Mrs. W.).

Promptness of recognition and treatment

The instances of nose involvement recognized and given either ascorbic or citric acid within 7 hours of presumed onset appeared to be satisfactorily responsive to the basic management alone. The first hours after onset would appear to give the greatest opportunity for a rapid, spontaneous checking of further development. The percentage of spontaneous recoveries for colds involving the nose and not cared for until 8 to 28 hours after presumed onset was, for the citric acid group, 21 ± 4 per cent, as compared with 58 ± 7 per cent when cared for promptly (a difference of 37 ± 8).

TABLE 8

Duration of common cold in relation to initial symptoms present, time treatment was begun, and ascorbic acid

BASIS FOR COMPARISON	TEST GROUP, ASCORBIC ACID GIVEN*		CONTROL GROUP, CITRIC ACID GIVEN*	
	No. of colds studied	% which did not develop	No of colds studied	% which did not develop
Initial symptoms:†				
Nose, with or without accompanying throat involvement	123	62 ±4	83	37 ±4
Throat, with no observed nose involvement	56	63 ±5	36	61 ±7
Time treatment was begun:‡				
Within 1 to 7 hours of presumed onset	54	65 ±5	36	58 ±7
Within 8 to 28 hours of presumed onset	69	59 ±5	47	21 ±4

* One gram at time of first examination and, again, 24 hours later.

† Nose: reddened nasal mucous membranes and/or swollen turbinates, "stopped-up" head, sneezing or nasal discharge; Throat: dry and/or reddened, sore, scratchy, or congested.

‡ Girls *with* nose involvement, only.

The time of presumed onset was estimated by the examiner at time of first examination and decision was made as to whether the cold had or had not developed, at the time of third examination, 48 hours later.

Ascorbic acid. The percentage of spontaneous checking of further development of the colds with nose involvement not reported until 8 to 28 hours after presumed onset, was 59 ± 5 per cent for the group given ascorbic acid and 21 ± 4 per cent for the group given citric acid—a ratio of 3 to 1 and a difference of 38 ± 6.

Discussion

The high percentage of spontaneous checking of further development of common cold found for the controls given early care may be sufficiently unexpected to many of the readers of this report to require a restatement of the fact that all of the colds taken for the ascorbic-citric acid study were sufficiently established at time of report to bring the student to the health center and to warrant acceptance by the examiner as a cold suitable for inclusion in the ascorbic-citric acid series.

The colds distributed through any given group presumably differ in severity. Many, possibly, produce effects so slight as to escape recognition and report. Many of those studied for table 8 perhaps would have escaped recognition had they not been watched for, because of the special attention being given to the common cold problem as a whole. Approximately 60 per cent would appear to have been sufficiently mild to permit of satisfactory disposition within 24 to 48 hours, providing the total load on the individual was lightened, soon enough, through restriction of activity, conservation of warmth, etc.

If the common cold is to be presumed to involve a sequence of 1) virus invasion followed by 2) bacterial invasion, the probability is high that not more than 60 per cent of the students volunteering for the ascorbic acid evaluation reported for first examination *before* secondary bacterial invasion had begun. A 60 per cent checking of further development would, in such case, have been the maximum realizable through any procedure not able to affect, materially, the course of a bacterial invasion already in progress, *but able to counteract or modify effects of the preceding virus invasion on the host* to an extent preventing the development of the cold, from the status of a virus infection only, to the status of a combined viral and bacterial infection.

The increased tendency to fatigue and chilling commonly reported during onset of common cold, while less suggestive of shock that the beginning stages of influenza, draws attention to the fact that restriction of activity and conservation of warmth are measures useful vs. shock. Ascorbic acid in massive dosage has been reported to increase the ability of animals to withstand the shock of severe injury (18), extreme loss of blood (19) and prolonged subjection to the gravitational stresses of the upright position (20).

SUMMARY

A study was made of the spread of common cold through a group of 1600 girls of college age, as affected by the weather, use of cigarettes, and relative susceptibility to common cold; of the season-to-season changes in physiological fitness as appraised by a modified Flack test; and of the effect, on duration of common cold, of early recognition and care, and ascorbic acid in massive dosage.

Sharp increases in number of new colds per day occurred during periods of falling temperature accompanied by heavy rain. The increases began and were most steadily sustained in the girls with a total of 4 or more colds for the year. The smokers, also, had a tendency to precede the nonsmokers. The weather-precipitated rises in colds-incidence tended to begin 24 to 48 hours after the beginning of the weather change and to persist for 24 to 48 hours after its cessation. The total number of colds, for the September wave, reached its halfway-point 2 days earlier for the more-susceptible fraction than for the less-susceptible fraction.

Only a slight deterioration in average physiological fitness occurred with the progress of the year. The deterioration was not uniform but restricted to a small fraction, partially balanced by a smaller group showing improvement. The smokers appeared to be slightly less fit, on the whole, than the nonsmokers. Nose involvement predominated in the fall colds and throat involvement in the winter colds which were, mainly, seconds and thirds rather than first colds.

A total of 298 colds was studied for the ascorbic acid appraisal; 119 of which were controls given placebos of citric acid. Approximately 60 per cent of the colds with throat involvement only appeared to respond to the basic management given both the control and ascorbic acid groups—restriction of activity, precaution against chilling, and increased fluid intake—with a spontaneous checking of further development. The colds with nose involvement were equally responsive to management, alone, if recognized and submitted to care within 7 hours of presumed onset. For those not recognized and submitted to care until 8 to 28 hours after presumed onset, the percentage of spontaneous checking of further development was, for those given one gram of ascorbic acid at time of first examination and again 24 hours later, 59 $\pm$ 5 and, for those given citric acid, 21 $\pm$ 4.

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ADDENDUM

A report has just come to attention by D. F. Smiley, Am. J. Hyg., **9,** 477-479, 1929, entitled "A study of the weekly incidence of colds in normal and in colds-susceptible groups throughout a winter". Smiley asked for a showing of hands, in his hygiene classes, for each new cold developed during the winter of 1926-1927. A total of 1625 students cooperated. His normal group consisted of those with 3 colds or less during the preceding year. The remainder were classed as the susceptibles. The fluctuations from week to week were much wider in the colds-susceptible group than in the normal group. The conclusion was drawn that "Among the normal group of students, there was no marked epidemic peak of colds. . . . It would seem probable that the ordinary winter or spring epidemic of colds among college students is a phenomenon almost entirely limited to the colds-susceptible group of students and involving very little the larger normal group of students."

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