

### ANTIHISTAMINIC AGENTS AND ASCORBIC ACID IN THE EARLY TREATMENT OF THE COMMON COLD

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Recently there has been widespread interest in the use of antihistaminic drugs in the treatment of the common cold. Several enthusiastic papers have appeared in the medical literature. These reports have been widely publicized in the lay press, and, since some of the antihistaminic drugs have been released for over-the-counter sale, a tremendous advertising campaign has gotten under way.

Brewster's reports<sup>1</sup> of 1947 and 1949 were on the use of diphenhydramine (benadryl®) hydrochloride, tripeleminamine (pyribenzamine®) hydrochloride, pyranisamine maleate (neo-antergan®) and methapyrilene (histadyl® and thenylene®) hydrochloride. He was the first to emphasize the importance of the early use of these drugs in the treatment of the common cold. In his 1949 series, all symptoms were aborted in 19 of 21 patients who started medication within the first hour and in 48 of 55 patients who started medication within two hours of onset. One may reasonably ask how many of these patients actually would have continued to have symptoms if no treatment whatsoever had been given. His control series was inadequate to answer this question, -since only 2 patients received the "control" (codeine-papaverine) medication during the first hour and none during the second hour of symptoms. Thus, it would appear from his graphs that, of all patients treated with either antihistaminic agents or codeine-papaverine during the first twelve hours of symptoms, only 9 per cent of the controls (2 patients) began treatment during the first two hours, while 20 per cent of the experimental group did so. When the graphs are referred to again and when only those colds treated after the symptoms had lasted at least two hours but before the cold was twelve hours old are considered, the results would appear to be as follows: of 215 patients receiving antihistaminic therapy, 111 (52 per cent) were "cured," 100 (46 per cent) were improved

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From : the Students' Health Service, University of Minnesota, Minneapolis.

1. Brewster, J. M.: Benadryl as Therapeutic Agent in Treatment of the Common Cold, U. S. Nav. Med. Bull: 47:810 (Sept.-Oct.) 1947; Antihistaminic Drugs in the Therapy of the Common Cold, U. S. Nav. Med. Bull. 49:1 (Jan.-Feb.) 1949,

and 4 (2 per cent) were not improved; of 20 patients receiving codeine-papaverine, 6 (30 per cent) were "cured," 11 (55 per cent) were improved and 3 (15 per cent) were not improved.

Gordon's report<sup>2</sup> of December 1948 concerned the use of diphenhydramine, tripeleminamine and phenind-

**Name** \_\_\_\_\_ **P.O.** \_\_\_\_\_ **Report for week (beginning Sunday)** \_\_\_\_\_ **Date** \_\_\_\_\_

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

Check here if you have had no symptoms of a cold during the week of this report.

Check here if you have had symptoms of a cold at any time during the week of this report and fill in the following:

Date of onset of the cold \_\_\_\_\_

Are this week's symptoms a continuation from the previous week? Yes  No

How many days of the week of this report have you had symptoms? \_\_\_\_\_

Severity:  mild;  moderately severe;  severe;  very severe

Symptoms:  nasal discharge  sneezing  itching  
 nasal obstruction  sore throat  hoarse  
 cough  fever  Other \_\_\_\_\_

Medicine: How many of the cold tablets did you take during this cold? \_\_\_\_\_

Have you used the medicine exactly as prescribed? \_\_\_\_\_

Any reactions from the tablets? \_\_\_\_\_ What? \_\_\_\_\_

Comments: \_\_\_\_\_

If, during the week of this report, you have recovered from a cold, indicate whether, in retrospect, you consider that, compared with your colds in previous years, this last one was:  
 very much milder  somewhat milder  about the same  more severe  longer, than average  longer, than average

Date of report \_\_\_\_\_ Signature \_\_\_\_\_

Fig. 1. Card on which subjects reported the presence or absence of symptoms, the severity of symptoms and the effectiveness of the medication during the week of the report.

amine tartrate (thephorin®) in the treatment of infections of the upper respiratory tract among 500 patients. He, too, was enthusiastic. Other forms of treatment were combined with the antihistaminic therapy in at least some of his patients, and he had no control series.

Murray<sup>3</sup> reported that tripeleminamine produced more so-called cures and more relief from annoying symptoms of the common cold than any other treatment used in the medical department of the Dennison Manufacturing Company in the past twenty-eight years. His conclusions were based on an uncontrolled study in which he treated 510 patients with early head colds.

The most dramatic results were reported by Arminio and Sweet<sup>4</sup> in December 1949. They used thonzylamine (neohetramine®) hydrochloride in the prophylaxis and treatment of the common cold in three institutions—a large state penitentiary, a convent and a seminary. In the prophylaxis experiment, 300 patients took courses of thonzylamine hydrochloride every day over a period of about six months. At the same time, 300 control subjects took placebo tablets at the same rates. Of the former group, 200 took either 100 or 150 mg. of thonzylamine hydrochloride daily, and, of these, 91 per cent had no cold symptoms whatever during the entire period, 6.5 per cent had first phase colds lasting only twenty-four to forty-eight hours and only 2.5 per cent had second and third phase colds. One hundred subjects took 50 mg. of thonzylamine hydrochloride every day, and, of these, 83 per cent had no symptoms of colds during the entire period, 5 per cent had first phase colds and 12 per cent had second and third phase colds. In not one of the 300 patients taking thonzylamine regularly did cough, malaise, nasal obstruction or fever develop over the entire six month period. Reactions to thonzylamine were practically nonexistent: mild reactions developed in 11 of the 100

subjects who took 150 mg. per day, but none of the other 200 subjects taking thonzylamine complained of any ill effects whatever. Among the 300 control subjects, 241 had one or more colds—some as many as five or six; 179 of these were severe colds and "practically all eventually required extensive therapy"; complications such as pneumonitis, bronchitis and sinusitis, developed in 11 subjects.

The treatment group reported by Arminio and Sweet contained over 300 patients. One third of these received 50 mg. of thonzylamine hydrochloride three times a day for three days, another third received the placebo medication and the rest received the usual cold treatment (acetylsalicylic acid, nose drops and lozenges). It was noted that 100 per cent of the subjects who began thonzylamine treatment during the first forty-eight hours after the onset of symptoms responded to therapy. This treatment, when begun within the first twenty-four hours, relieved colds in one-fifth the time, as compared with the placebo series, and, if the drug was given during the second twenty-four hours, the time required for complete relief was reduced by half, as compared with the placebo series. It was pointed out that thonzylamine is of no value once there has been secondary invasion.

Phillips and Fishbein<sup>5</sup> used caubren® compound (25 mg. chlorothen citrate, 320 mg. acetophenetidin and 32 mg. caffeine) for the treatment of colds in an industrial plant. They controlled their experiment by giving acetylsalicylic acid tablets to about an equal number of subjects. The average duration of the colds was about half as long for the group given the caubren® compound as for the group given acetylsalicylic acid, and again these authors point out that the earlier the antihistaminic therapy is begun, the better. Reactions were more frequent among those taking acetylsalicylic acid than in the experimental group.

OUTLINE OF PRESENT STUDY

In the fall of 1948, we began a controlled experiment in an attempt to evaluate the antihistaminic agents as a method of treatment of the common cold. We were

SUMMARY OF DATA											
Week	Date	Days of Cold	Severity			Week	Date	Days of Cold	Severity		
			A.A. <sup>1</sup>	B.B. <sup>2</sup>	C.W.S. <sup>3</sup>				A.A. <sup>1</sup>	B.B. <sup>2</sup>	C.W.S. <sup>3</sup>
1						31					
2						31					
3						30					
4						30					
5						25					
6						26					
7						27					
8						28					
9						29					
10						30					

<sup>1</sup> Student's estimate: 1, Mild; 2, Moderate; 3, Severe; 4, Very severe.  
<sup>2</sup> Symptomatology: A, Mild (sneezing without fever, itching, or hoarse); B, Moderate (with one of 3); C, Severe (with two of 3); D, Very severe (all of 3).  
<sup>3</sup> Compared with previous colds: 1, Very much milder; 2, Milder; 3, Same; 4, More severe; 5, Much more severe.

Fig. 2.—Individual master sheet for each student, on which weekly information from each subject on cold prevention in 1948-1949 was summarized.

interested, also, in trying large doses of ascorbic acid, since one of our earlier experiments<sup>6</sup> indicated a possible (though slight) effect of this substance in the prevention of colds.

2. Gordon, J. S.: Antihistaminic Drugs in the Treatment of Upper Respiratory Tract Infection, Laryngoscope 58:1265 (Dec.) 1948.

3. Murray, H. G.: The Treatment of Head Colds with an Anti-histaminic Drug, Indust. Med. 18:215 (May) 1949.

4. Arminio, J. J., and Sweet, C. C.: The Prophylaxis and Treatment of the Common Cold with Neohetramine, Indust. Med. 18:509 (Dec.)

5. Phillips, W. F. P., and Fishbein, W. I.: An Antihistaminic Analgesic Preparation in the Therapy of Colds, Indust. Med. 18:526 (Dec.) 1949.

6. Cowan, D. W.; Diehl, H. S., and Baker, A. B.: Vitamins for the Prevention of Colds, J. A. M. A. 120:1268 (Dec. 19), 1942.

We had intended to make this a two year study, but, because the antihistaminic drugs have now been released for over-the-counter sale, it is obvious that some difficulty might be encountered in keeping the control group strictly controlled; therefore, we are reporting the relatively small series observed during the school year 1948-1949, before antihistaminic drugs were available without prescription.

The subjects were University of Minnesota students who volunteered to join the group because they were especially susceptible to colds and because colds constituted a real problem to them. On enrolment in the

plus citric acid, lactose and binders; group 4—ascorbic acid, 667 mg., plus phenindamine tartrate, 25 mg., plus binders, and group 5—tripelennamine hydrochloride, 50 mg., plus citric acid and binders, in special large white tablets to look like the others. Each subject was instructed to return for more of his medication whenever needed so that it would always be available for the early treatment of any cold that might occur.

Each week the subject received a report card (fig. 1) for reporting the presence or absence of symptoms during the week of the report, the severity of symptoms and the effectiveness of the medication. These weekly

TABLE 1.—Antihistaminic Drugs and Ascorbic Acid in Treatment of Colds

	Group 1 (Placebo)	Group 2 (Ascorbic Acid)	Group 3 (Phenind- amine Tartrate)	Group 4 (Ascorbic Acid plus Phenind- amine Tartrate)	Group 5 (Tripele- namine Hydro- chloride)
Number of subjects in group at completion of study.....	76	77	78	71	70
Average number of colds per year in previous years *.....	5.4	5.6	5.2	5.1	5.2
Total number of colds treated in study.....	207	213	108	172	190
Average duration of colds in previous years (days) *.....	13.0	12.2	11.5	10.8	13.0
Average duration of colds treated in this study (days).....	5.1	5.6	5.7	5.6	5.2
Percentage of "reduction" in duration.....	61	54	50	48	60
Number of patients reporting reactions.....	7 (9%)	7 (9%)	12 (16%)	13 (18%)	13 (19%)

\* Reported from memory.

TABLE 2.—Severity of Treated Colds in This Study (Percentage of Total Colds in Group)

	Group 1 (Placebo)	Group 2 (Ascorbic Acid)	Group 3 (Phenind- amine Tartrate)	Group 4 (Ascorbic Acid plus Phenind- amine Tartrate)	Group 5 (Tripele- namine Hydro- chloride)
<b>1. Student's opinion as to severity</b>					
Mild .....	54	51	49	48	57
Moderate .....	28	26	35	35	30
Severe .....	13	19	11	12	11
Very severe.....	5	4	5	5	2
<b>2. Based on symptoms *</b>					
Mild .....	75	72	73	69	78
Moderate .....	19	18	16	25	17
Severe .....	4	8	8	5	3
Very severe.....	2	2	3	1	2
<b>3. Student's opinion as to comparison with previous colds</b>					
Much milder.....	42	40	35	34	37
Somewhat milder.....	33	32	38	33	32
About the same.....	17	20	18	22	25
More severe.....	8	8	9	11	6
Shorter .....	27	23	28	28	35
Longer .....	4	6	5	7	4
Presumably neither shorter nor longer than usual.....	69	69	67	65	61
<b>4. Percentage of colds lasting less than 4 days.....</b>					
	47	39	44	43	45
<b>5. Percentage of colds lasting only 1 or 2 days.....</b>					
	33	25	25	24	29

\* See text for basis of classification

group, each subject was asked to fill out a questionnaire. Then, after a brief discussion, he was given a box of medicine with written instructions to take one dose at the first symptoms of a cold and to repeat the dose every four hours until the cold was definitely "cured" or until the medicine (10 doses) was used up. The medications were given out in strict rotation to the students as they enrolled, as follows: group 1—placebo (citric acid to simulate the taste of ascorbic acid, lactose, cornstarch, sugar, talc and stearic acid); group 2—ascorbic acid, 667 mg., plus the binders and fillers previously mentioned; group 3—phenindamine tartrate, 25 mg.,

reports were summarized on a master card (fig. 2) for each student, and the data from the master cards were used to tabulate the results of the entire study.

Of the 430 subjects enrolled at the beginning of the study, the records of 367 (85.4 per cent) were used in tabulating the final results. These 367 students treated 980 colds during the period of the study (December 1948 to April 1949). The reasons for dropping the other students were as follows: 1. It was found during the course of the study that 12 enrollees were definitely allergic, although, by questioning each applicant as he applied, we had tried to keep out of the group all those whose colds were probably allergic in nature. These 12 were referred to an allergy clinic for study and treatment. 2. Twenty-five students failed to send in their

7. The special tripeleennamine hydrochloride tablets were furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J. The other preparations, including the placebo, were furnished by Hoffmann-LaRoche, Inc., Nutley, N. J.

reports, either because of cancellation from school or failure to cooperate. 3. Twenty-four students reporting regularly had no colds during the entire period of the study and, therefore, had no opportunity to try the medicine given them. 4. Two students refused to continue to take the medicine because of "reactions." One of these complained only of the bad taste of the tablet (tripelennamine), and the other became weak and dizzy on each of two attempts to take the medicament (phenindamine). In our series (table 1), the anti-histaminic agents alone, ascorbic acid alone, or phenindamine plus ascorbic acid did not shorten the average duration of colds in their groups of subjects. It is emphasized that all students were instructed to start the medication at the earliest symptom. Some students no doubt waited for several hours to begin medication, but we have no reason to believe that the time interval factor would not have operated the same for all groups, including the group taking placebo.

It is interesting that 7 of the subjects taking placebo reported "reactions." Two reported headache from the placebo tablets (1 stated that it occurred every time he took the medicament) ; 2 reported a mild sedative effect; 1 reported increased frequency of urination; 1 reported nausea, and 1 reported angioneurotic edema of the lip. Seven patients in the group taking ascorbic acid also reported reactions: dryness of the mouth, 2; increased frequency of urination, 1; nausea, 1; headache, 1; sleeplessness, 1, and "bad taste," 1. Phenindamine caused the following reactions in 12 patients: stomach upset, 4; headache, 3; sleeplessness, 2; "dopey" feeling, 1; dizziness, 1, and difficult and painful urination, 1. In addition, it will be remembered that 1 patient dropped out of the study because of severe dizziness and fainting after taking phenindamine. Reactions to the ascorbic acid and phenindamine combination occurred in 13 patients: headache alone, 2; headache, sleepiness and loss of appetite, 1; drowsiness, 3; sleeplessness, 2; dizziness, 2; excessive perspiration, 1; increased frequency of urination, 1, and slight weakness and faintness, 1. The reactions to tripelennamine in 13 patients were: drowsiness alone, 6; dizziness alone, 2; dizziness and drowsiness, 1; dizziness and headache, 1; stomach irritation, 1; increased frequency of urination, 1, and sleeplessness, 1. In addition, 1 subject refused to continue the experiment because of the bad taste of the tripelennamine hydrochloride tablets.

Table 2 represents an attempt to compare the relative severity of the treated colds in each of the five groups. This is presented in five different ways: 1. The student's own opinion as to the severity of his symptoms. 2. Our estimate, based on the symptoms checked on the report card by the student; this classification was (*a*) mild if there was coryza but no fever and no aching and the patient did not have to go to bed with the cold, (*b*) moderate if either fever or aching was present or bed rest was required, (*c*) severe if two of these criteria were met and (*rf*) very severe if all three of these criteria were met. 3. Comparison with previous colds (student's opinion) : after the cold was completely over, the subject was asked to tell whether he thought it had been much milder, somewhat milder, about the same, or more severe and whether it had been shorter or longer than the usual previous colds. 4. The proportion of all colds in each group which lasted less than four days each. 5. The proportion of

colds in each group which lasted less than three days. None of these comparisons indicates that any of the experimental groups fared better than the control group.

We received many enthusiastic reports, both written and oral, from the subjects of the cold study. However, some of the most glowing testimonials came from members of the control group. The first request we received this fall concerning information on the availability of our "cold pills" came from a student who had been in the study series and who had since been graduated. We answered that the material was not yet available commercially in the form administered here but that we still had some in stock and would give him some, if he liked. He made a special trip from the northern part of the state to get the drug, whereupon it became necessary for us to look up his record. He had been in the placebo group.

#### SUMMARY

Under the conditions of this controlled study, in which 980 colds were treated in 367 supposedly non-allergic students, there is no indication that ascorbic acid alone, phenindamine tartrate (thephorin®) alone, ascorbic acid plus phenindamine, or tripelennamine (pyribenzamine®) hydrochloride have any important effect on the duration or severity of these infections of the upper respiratory tract.