replace some current procedures. The recent knowledge of the great benefits to patients with rheumatoid arthritis from certain hormones, especially the adrenal cortical hormone, cortisone, and the pituitary adrenocorticotropic hormone, ACTH, is enthusiastically welcomed by everyone. The certainty, completeness and speed of the action of these new substances in controlling rheumatoid arthritis are remarkable. Patients and physicians throughout the world hope that use of these hormonal substances may soon become practical.

As therapeutic improvements develop they should be put into practice. An advertisement which appeared about 1880 characterized a rheumatic remedy as "better than gold." Now, seventy years later, it is hoped that cortisone will become the medicament which may be referred to as truly "better than gold" in the treatment of rheumatoid arthritis. When therapeutic procedures are developed that are more effective than gold salts, all physicians should abandon this form of treatment. Investigators who have been studying gold preparations will be among the first and happiest to discontinue the use of such compounds in favor of superior agents. Until improved therapy is available measures at hand must be employed. When gold salts are used, they should be given wisely with a full knowledge of their effects, limitations and potential toxicity as well as their potential benefits.

ABSTRACT OF DISCUSSION

DR. LESLIE J. A. PARR, Sidney, Australia: In 1936 in conjunction with Dr. E. A. Shipton of Australia, I began gold therapy, and in 1937 we published our first results—70 cases with 1 death, which occurred after we gave 200 mg. of a gold compound. At that stage, we reduced our dosage to 50 mg. Dr. Freyberg has detailed the most important facts concerning gold therapy and has stressed in particular dosage and maintenance dosage. We found early that results were as good with 50 mg. of a gold salt as with 200 mg. Although the improvement was slower, the toxicity went from 45 to 25 per cent, and that has been our average throughout the years. We have not observed any especially severe reactions. A number of exfoliative dermatitides responded rapidly to 2,3-dimercaptopropanol (BAL). Chrysotherapy was our main method of attack in rheumatoid arthritis until 1938, but we began to encounter so many relapses that we started giving a small maintenance dose of the gold salts at that period. In 1944 our patients were given a maintenance dose of 50 mg. once a week, later every second week, third week, fourth week and, finally, every six weeks. Some patients have gone four, five or six weeks on maintenance therapy with complete control of the disease and without relapse. We found that many cases of arthritis were refractory to gold therapy, and in consequence of some results with prontosil (diacetylaminoazotoluene), which the Germans investigated many years ago, we began looking for a sulfonamide preparation to supplement the action of gold, and we used benzyl sulfanilamide (proseptazine) in 1938. The war interrupted our work, and in 1943 we began more extended trials. Benzyl sulfanilamide is slightly different from all the other sulfonamide drugs, and today our method of procedure is, first, to attack the disease with benzyl sulfanilamide and then use a gold compound as a second method of attack. We find that benzyl sulfanilamide in conjunction with liver extract will give results much more rapid and spectacular than those with gold, and we have kept some of our patients on a benzyl sulfanilamide regimen for three years. We have had a 10 per cent rash-type reaction necessitating desensitization, but toxicity in many patients can be controlled with 1 to 1½ Gm. of benzyl sulfanilamide per day. Then we found that in some cases relapse of arthritic symptoms began during sulfonamide therapy, so we gave a gold compound in addition; today we give benzyl sulfonamide initially, and if the patient does not respond we may give a gold preparation. In the last eighteen months we have also used epinephrine and intravenously administered calcium. If one does not get any result using benzyl sulfanilamide within two months, I would advise trying the effect of epinephrine in oil. Some physicians will be amazed at the reaction that takes place. Since Dr. Thorn proved that epinephrine has some effect on the adrenal cortex, it may be that we were using the equivalent of small doses of adrenocortical hormones. That may be the explanation. We have found—and we have tried this over a period of ten years—that treatment with gold salts takes second place to benzyl sulfanilamide therapy in conjunction with epinephrine but that gold is still a valuable remedy. There are two important considerations, the small dosage and the maintenance dosage.

DR. RICHARD H. FREYBERG, New York: I have had no experience with the type of treatment discussed by Dr. Parr. Some physicians have felt that gold therapy has been of value because of the toxicity it produces and that it is desirable to produce toxicity to get the best result. I disagree. I am sure that good results can be obtained without producing toxicity.

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 [1] of 1947 and 1949 were on the use of diphenhydramine (benadryl®) hydrochloride, tripelennamine (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

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 [2] of December 1948 concerned the use of diphenhydramine, tripelennamine 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 ☐ aching ☐ nasal obstruction ☐ sore throat ☐ in bed ☐ 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 ☐ shorter ☐ about the same ☐ more severe ☐ 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 effectivness 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 [3] reported that tripelennamine 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 [4] 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 doses 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 [5] 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

Name ..... Group .....

Address (or P. O.) ..... Age ..... Sex .....

Number of colds in previous years (average) .....

Evidence of allergy .....

SUMMARY OF DATA

Week	Date	Days of Cold	Severity S.O.[1]	Severity SYMP.[2]	Severity C.W.P.[3]	Week	Date	Days of Cold	Severity S.O.[1]	Severity SYMP.[2]	Severity C.W.P.[3]	Week	Date	Days of Cold	Severity S.O.[1]	Severity SYMP.[2]	Severity C.W.P.[3]
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					

[1] Student's opinion: 1, Mild. 2, Moderate. 3, Severe. 4, Very severe.
[2] Symptomatology: A, Mild (coryza without fever, aching, or bed). B, Moderate (with one of 3). C, Severe (with two of 3). D, Very severe (all of 3).
[3] 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 [6] 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 Antihistaminic 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.) 1949.

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 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 medicaments were given out in strict rotation to the students as they enrolled, as follows[7]: 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., 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 medicament 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 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

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

	Group 1 (Placebo)	Group 2 (Ascorbic Acid)	Group 3 (Phenindamine Tartrate)	Group 4 (Ascorbic Acid plus Phenindamine Tartrate)	Group 5 (Tripelennamine Hydrochloride)
Number of subjects in group at completion of study	76	77	73	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	198	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 (Phenindamine Tartrate)	Group 4 (Ascorbic Acid plus Phenindamine Tartrate)	Group 5 (Tripelennamine Hydrochloride)
1. Student's opinion as to severity					
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
2. Based on symptoms *					
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
3. Student's opinion as to comparison with previous colds					
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
4. Percentage of colds lasting less than 4 days	47	39	44	43	45
5. Percentage of colds lasting only 1 or 2 days	33	25	25	24	29

* See text for basis of classification

7. The special tripelennamine 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 antihistaminic 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 (*d*) 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 nonallergic 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.

ORALLY GIVEN MEPHENESIN IN INFANTILE CEREBRAL PALSY

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The treatment of cerebral palsy at the present time centers about muscle relaxation and reeducation. The modalities employed in training a child are well defined and are executed in specific phases during the progress of a patient. The training period is long and tedious and may well be compared in chronicity to the educational program of a normal child in his primary school. Surgical procedures, external bracing and medication are considered adjuncts only.

Many children manifesting the various types of cerebral palsy have been subjected to the administration of barbiturates, belladonna, scopolamine, stramonium, neostigmine and other preparations in the hope of release from the abnormal state. The results over a long period of time have been variable if not indifferent.

A definite aid in treatment might be a nontoxic drug with few or no undesirable effects. Such a preparation should be palatable to children. It should produce the desired degree of relaxations or stability for a sufficient period of time to allow a child to acquire new motor patterns or to perfect existing ones. The recent reports on the effect of mephenesin (tolserol®[3-ortho-toloxy-1,2-propanediol]) in spastic and athetoid states are interesting and suggest that this drug may be a precursor of progressive developments in this field of therapy.

The British pharmacologists Berger and Bradley found that mephenesin produced muscle relaxation without unconsciousness. Stimulated by their observations Stephen and Chandy,[1] Schlesinger and others [2]

Mephenesin (tolserol®) for this study was supplied by E. R. Squibb & Sons.

1. Stephen, C. R., and Chandy, J.: Canad. M. A. J. **57**: 463 (Nov.) 1941.

2. Schlesinger, E. B.; Drew, A. L., and Wood, B.: Clinical Studies in the Use of Myanesin, Am. J. Med. **4**: 365 (March) 1948.