No chloramphenicol was detected in the blood serum in six babies, one of whom had vomited half an hour after its dose. No cause for the remaining five negative results was found. Failure of absorption was discounted, as one of these cases showed a reasonable serum level in a repeat test the following day.

We recommend a dosage as set out in the Table: this represents 33–50 mg. per lb. (73–110 mg. per kg.) per dose, given twice daily.

We would like to thank the paediatricians, paediatric registrars, and nursing staff for their co-operation in this investigation. We are also grateful to Messrs. Parke Davis for generous supplies of chloramphenicol.

REFERENCES

- Claudon, D. B., and Holbrook, A. A. (1952). *J. Amer. med. Ass.*, 149, 912.
 Fleming, A. (1944). *Lancet*, 2, 620.
 Hawkins, L. A., and Lederer, H. (1952). *British Medical Journal*, 2, 423.
 Hewitt, W. L., and Williams, B. (1950). *New Engl. J. Med.*, 242, 119.
 Kelly, R. S., Hunt, A. D., and Tashman, S. G. (1951). *Pediatrics*, 8, 362.
 Ley, H. L., Smadel, J. E., and Crocker, T. T. (1948). *Proc. Soc. exp. Biol., N.Y.*, 68, 9.
 Murray, J., and Crawford, E. M. (1951). *Lancet*, 2, 147.
 Smellie, J. M. (1950). *Proc. roy. Soc. Med.*, 43, 766.
 Smiley, R. K., Cartwright, G. E., and Wintrobe, M. M. (1952). *J. Amer. med. Ass.*, 149, 914.
 Sturgeon, P. (1952). *Ibid.*, 149, 918.
 Wolman, B. (1952). *British Medical Journal*, 2, 426.

SUMMER HAY-FEVER AND ASTHMA TREATED WITH ANTIHISTAMINIC DRUGS

BY

A. W. FRANKLAND, M.A., B.M., B.Ch.

AND

R. H. GORRILL, M.D.

*The Wright-Fleming Institute of Microbiology,
St. Mary's Hospital Medical School, London, W.2*

In the early summer of 1948 a trial of a new antihistaminic drug was carried out in the hay-fever clinic. It has since been named chlorcyclizine hydrochloride ("histanin"). Each tablet contains 25 mg. of N-methyl-N-(4-chlorobenzhydryl) piperazine dihydrochloride. After this trial it was suggested (Frankland, 1949) that, although antihistamines could help the mild case of hay-fever, they might precipitate the onset of asthma in the more severe cases. This was commented on in the review of hay-fever literature for 1949 (Kaplan and Ehrlich, 1951). It was, however, pointed out that a statistical survey of hay-fever patients treated with antihistamines must be carried out before it could be taken as proved that asthma was more apt to occur in such patients. It is interesting that in another trial (Gay *et al.*, 1948) the high incidence of asthma in hay-fever patients treated with antihistamines had been noted, but not commented upon. There is now fairly widespread belief that hay-fever patients who receive antihistaminic drugs as the only form of therapy are more liable to develop asthma than those who receive no treatment (*British Medical Journal*, 1952).

An experiment was designed to test not only the efficacy in hay-fever and hay-asthma of an untried antihistaminic drug, but also whether there was any statistical difference in the incidence of asthma in treated and untreated hay-fever patients. In the first enthusiasm

that greeted the preparation of many new antihistaminic drugs, the published reports suggested that antihistamines do benefit many cases of asthma. Southwell (1948) commented on the non-critical assessments in many of the published papers from France and America. He concluded as a result of a trial of mepyramine maleate ("anthisan," pyranisamine maleate, or "neo-antergan") in the treatment of asthma that it "conferred no apparent benefit upon 25 specially selected and carefully observed asthmatic patients." Hunter and Dunlop (1948) also concluded that mepyramine maleate was of no value in the prevention of asthma. Frankland (1952) and Watkins (1952) agree with these views.

Scheme of Trial and Methods of Assessment

The patients were treated with three different kinds of tablets: (1) mepyramine maleate, which has had extensive trials and clinical use; (2) a new antihistaminic preparation which has as yet no name and will be referred to as 405-c-49 (chemically it is 3-pyrrolidino-1-(4'-chlorophenyl)-1-(2-pyridyl) prop-1-ene maleate); and (3) inert tablets. It was considered essential that the box of tablets given by the doctor to the patient should be numbered and not named. The consecutive-numbered boxes were given to the patients in the order they reported. Previously the three kinds of tablets had been allocated to the numbered boxes by use of a random-number table. Twin girls who both received the same tablets were the only exception to this random distribution. Anthisan (mepyramine maleate) is normally coloured green, but for the purposes of the trial Messrs. May & Baker kindly supplied white tablets. The inert tablets, which contained 5 gr. (0.32 g.) of lactose, looked similar to but differed in taste from the antihistamine under trial. Each tablet of 405-c-49 contained 10 mg. of the antihistaminic drug, which was thought to correspond clinically to a dose of the 100-mg. tablet of mepyramine maleate. The doctor did not know which type of tablet he gave to the patient (except for the few patients who asked for a change of tablet). It was not until all the results of treatment had been tabulated that the kind of preparation used was entered on the card. Each patient was given a chart and asked to keep a daily record, from the time the symptoms of hay-fever began, of the number of tablets taken each day, and whether the results were good, moderate, or poor so far as the hay-fever was concerned. The letters G, M, and P were used to designate the daily result of taking the tablets.

The patients were told that they were taking part in a trial of a new drug for hay-fever, and that it was believed that the side-effects, if any, would probably not be annoying, but that the dose was not known. It was suggested that up to four tablets a day was probably the correct dose for relief of symptoms, but more or fewer tablets might be necessary. As a third of all patients were to receive inert tablets when first seen, all of them were told that if they thought the tablets given to them were not effective they could either come back for a stronger tablet or use any other preparation that was considered from previous years' treatment to be more effective.

Normally a patient used the same tablet throughout the hay-fever season, though a few patients who were seen more frequently were given the chance of a change of tablet if they so desired. If a patient did ask for a change of tablet, in each case the new antihistaminic tablet 405-c-49 was given. This allowed a direct comparison with either the inert or the mepyramine maleate tablets. In practice only a few patients came back for what was euphemistically called the stronger tablet.

When the patients were first seen at the beginning of the trial they were accepted as suitable for it so long as their complaint was one of seasonal hay-fever. Before the diag-

nosis could be made, symptoms of irritation of the eyes with rhinorrhoea and sneezing during the month of June had to be present. In many the symptoms lasted longer than one month. In many cases the symptoms began in May and continued until the beginning of August or longer. Interestingly, the daily charts often indicated a season much shorter than had been given at the first interview. Many of the women and nearly all the children were very vague about the week and sometimes even the month of the onset and disappearance of symptoms. Every patient was also carefully questioned at the beginning and at the end of the trial regarding symptoms of asthma. If there was any suggestion of a non-seasonal allergic rhinitis or asthma the patient was excluded from the trial.

During the last week in August and the first week in September the patients were reviewed. They brought back their completed daily charts and any unused tablets. For reasons unconnected with this experiment they had their skin reactions retested. For various reasons, but generally because of distance from London, some of the patients undergoing the trial did not return for the final interview. Each one of these was written to and requested to return the daily chart and answer a questionnaire. The following information was obtained from all patients. They were asked whether the overall results of the treatment were good, moderate, or poor; whether they had noticed any side-effects from the tablets, and, if so, what these were; and whether they preferred the new tablets to any previous antihistamine used.

The daily record of the chart indicated the number of tablets taken and whether they produced good, moderate, or poor relief. If the total number of "good" days exceeded the total number of "moderate" and "poor" together the result was called "good." So, too, if the total number of "poor" days exceeded the "moderate" and "good" days the result was called "poor." Moderate relief as shown from the chart nearly always corresponded to the patient's overall impression of the treatment. The heading includes most of those who obtained good results at the start of the hay-fever season but at the height of the pollen cloud found that the tablets were not effective. When the side-effects from the tablets were such that normal everyday occupations could not be continued the results were designated "poor." In five cases the results according to the chart and to the patient's statement did not correspond. The patient, who in each case was a child, stated that the tablets had not helped, while the chart showed good results. The child's impressions were accepted rather than the wishful thinking of the mother that had caused her to fill in a faulty card. Even so, as is described later, some of the patients did obtain good results from the inert tablets.

The diagnosis of asthma in all the patients was based on subjective observations. Grading of asthma according to severity of symptoms was not carried out.

The clinical diagnosis of summer hay-fever was confirmed in every case by means of skin tests. The method used was to prick through a small amount of testing fluid with a sharp needle so that momentary pain was felt but no blood was produced. It has been shown that under standard conditions about 0.000003 ml. is introduced into the skin (Squire, 1950). For the diagnosis of a grass-pollen sensitivity a mixed pollen extract ("pollacine") of a strength of 20,000 Noon units was used.

Results

In all, 174 patients took part in the trial, and the preliminary analysis shows that the three groups are comparable regarding sex ratio, age, age of onset of hay-fever, and follow-up (Table I). The results of the use of the three different tablets in the treatment of hay-fever, together with the results of those who changed their tablets, are given in Table II. Few patients elected to change their type of

tablet during the trial: the figures show that no patient on 405-c-49 tablets changed, three patients on mepyramine maleate changed and were given 405-c-49, and four patients on control changed and were given 405-c-49 tablets. The results following change of tablet are interesting, but owing to the numbers being so small no statistical analysis can be made.

In each group records were made of the incidence of asthma and the history of previous antihistaminic treatment for hay-fever. The results are shown in Table III. All patients who had had asthma in previous summers developed asthma again in the summer of 1951 except one patient who previously had had a summer hay-fever and associated asthma but had noticed no asthma for the last five years. As will be seen, the results show no evidence for a correlation between drug-taking and asthma. The same number of patients developed asthma for the first time in the summer of 1951 whether they took antihistaminic or control tablets.

TABLE I.—Composition of Three Groups of Cases

		Mepyramine Maleate (55)	405-c-49 (59)	Control (60)
	Male	31	37	33
	Female	24	22	27
Age of patient	Years			
	0-9	2	4	3
	10-19	12	9	14
	20-29	22	22	21
	30-39	12	18	16
	40-49	7	5	2
	50+	0	1	4
Age at onset	0-9	13	12	14
	10-19	17	24	22
	20-29	20	16	19
	30-39	4	6	2
	40+	1	1	3
Follow-up:	Attended interview	48	45	50
	Replied by letter	7	12	7
	Defaulted	0	2	3

TABLE II.—Results of Treatment of Hay-fever

Results	Mepyramine Maleate	405-c-49	Control
Good	28	25	11
Moderate	10	16	4
Poor	16	16	42
Total	54*	57	57

Statistical analysis:

- (1) Mepyramine maleate v. control: $\chi^2=21.18$, $P<0.001$
- (2) 405-c-49 v. control: $\chi^2=24.18$, $P<0.001$
- (3) Mepyramine maleate v. 405-c-49: $\chi^2=1.26$, $P\approx 0.5$

Changed Tablets

	Original Status	Results on 405-c-49
Mepyramine maleate	3 poor	2 good, 1 moderate
Control	4 "	4 good

* Although all the mepyramine maleate patients were successfully followed up one failed to take any tablets during the season.

TABLE III.—Incidence of Asthma

	Present Before this Year	First Time this Year	Absent
Mepyramine maleate	17	6	31
405-c-49	18	6	33
Control	18	7	32
Total	53	19	96

Overall % = 42.86

History of Previous Use of Antihistaminic Drugs

Mepyramine maleate	{ 23 with asthma	..	13 had used drugs before (57%)
	{ 31 without asthma	..	24 " " " " (77%)
405-c-49	{ 23 with asthma	..	17 " " " " (74%)
	{ 34 without asthma	..	22 " " " " (65%)
Control	{ 25 with asthma	..	20 " " " " (80%)
	{ 32 without asthma	..	25 " " " " (78%)

TABLE IV.—*Duration in Years of Hay-fever in Asthma and Non-asthma Cases*

Duration of Hay-fever in Years	Mepyramine		405-c-49		Control		Pooled Data	
	Asthma Cases	No Asthma	Asthma Cases	No Asthma	Asthma Cases	No Asthma	Asthma Cases	No Asthma
0- ..	7	14	8	14	3	14	18	42
5- ..	5	7	4	7	8	10	17	24
10- ..	6	2	3	7	6	6	15	15
15- ..	3	4	6	4	4	1	13	9
20+ ..	2	4	3	1	4	1	9	6
Total ..	23	31	24	33	25	32	72	96

χ^2 on pooled data = 9.51, $P = 0.05$.

Also when the *past* history of the asthma cases is compared with the unaffected cases it will be seen that there is no difference in the incidence of asthma whether antihistaminic drugs had or had not been taken previously.

In view of these findings the importance of duration of hay-fever on the onset of asthma was examined. The results are set out in Table IV. It will be seen that in all three groups of patients asthma is more likely to occur with long durations of hay-fever. The figures have accordingly been pooled and analysed, and the results are just significantly different.

The value of treatment of hay-fever by antihistamines might depend upon the presence or absence of hay-asthma. With this in mind the figures in Table V were obtained, and, as each group shows the same trends, two groups of pooled data are also shown. The statistical analysis shows that the results are significantly better in non-asthma cases than in asthma cases. This observation is emphasized by including the control group, which makes the significance much bigger. The explanation is that inert tablets had very little effect in cases with hay-asthma but seemed to have some effect in mild cases not complicated by asthma.

The figures collected in this trial of the incidence of asthma in the three treatment groups allows an investigation into the number affected with asthma and the number with relief of symptoms. There seems to be no difference in results between the two potent antihistamines and lactose in the treatment of hay-asthma (Table VI).

The side-effects from taking the three different kinds of tablets are shown in Table VII. In 10 patients mepyramine maleate caused such a marked soporific effect that hay-fever was preferred. Other patients with less severe side-effects reported that these lessened after the first few days. If the patient complained of any other effect which was believed to be due to the tablets and not to the hay-fever, this was recorded. Some of the patients who developed asthma for the first time when taking tablets not unnaturally blamed the treatment. Two of the patients who attributed

TABLE V.—*Results of Treatment of Hay-fever in Asthma and Non-asthma Cases*

Results	Mepyramine Maleate		405-c-49		Mepyramine Maleate and 405-c-49 Pooled		Control		Pooled Data All 3 Groups	
	A.P.	N.A.	A.P.	N.A.	A.P.	N.A.	A.P.	N.A.	A.P.	N.A.
Good ..	8	20	11	14	19	34	3	8	22	42
Moderate ..	1	9	6	10	7	19	0	4	7	23
Poor ..	14	2	7	9	21	11	22	20	43	31

χ^2 pooled data of all 3 groups = 13.63, $P = 0.001$.
 χ^2 2 active groups = 10.63, $P = 0.01$.
 A.P. = Asthma present. N.A. = No asthma.

TABLE VI.—*Results of Treatment of Hay-asthma*

Drug	No. of Patients with Asthma	No. Obtaining Relief
Mepyramine maleate ..	23	3
405-c-49	24	4
Control	25	3

TABLE VII.—*Side-effects of Tablets*

Side-effects	Control	Mepyramine Maleate	405-c-49
Soporific { Mild .. 4 } 5 { Severe .. 1 } 10		11 } 21 10	9 } 10 1
Any other effects* { Constipation (1) Headache (1) Diarrhoea (1)		Depression (1) Nausea (1) Headache (1) Diarrhoea (1)	Depression (1) Dizziness (1) Thirst (1)
Catarrh	0	3	3
Asthma	2	1	2

* The number in parentheses refers to the frequency of complaints and not to the number of patients.

TABLE VIII.—*Preference of Tablet for Hay-fever Treatment*

Tablet	Preferred Tablet to Any Other	Preferred Others	The Same	No Opinion	Never Used Tablets	Total
405-c-49 ..	24	5	7	3	18	57
Mepyramine ..	22	6	10	3	14	55
Control ..	15	27	1	4	10	57

their asthma to the treatment were on control tablets, one was on mepyramine maleate, and two were on the new antihistamine.

Table VIII shows the preference of patients for various kinds of tablets. Ten of the patients preferred control tablets to all other tablets tried because they produced no side-effects. Even so, the control tablets gave such poor results that 27 patients preferred any other tablets. There is little to choose between the preferences of the groups on the two antihistaminic drugs, though Table VII would indicate that because of fewer side-effects the new preparation is preferable.

Conclusions

The purpose of the trial in 1951 was twofold: (1) to carry out a clinical trial of a new antihistaminic drug in cases of hay-fever; and (2) to see whether the incidence of asthma in seasonal cases of hay-fever was altered when symptomatic treatment with antihistaminic drugs was used. This paper is concerned mainly with the latter problem.

The new antihistaminic drug 405-c-49 compared favourably with mepyramine maleate, though weight for weight it was ten times more potent.

The number of patients who had asthma with their seasonal hay-fever for the first time in their life was the same or similar in the three groups, as was the number who never had asthma but who had had previous antihistaminic drugs. In Table III it will be seen that the overall incidence of asthma for the whole group was 42.86%, which compares with a figure of 55% given by Williams (1950) for South Wales. Table VII shows that in each group a few patients thought that their asthmatic symptoms were due to the tablets.

The prognosis in hay-fever is difficult to gauge except to say that Table IV indicates that the longer hay-fever is present the more likely is it that the patient will develop asthma with it. The presence of asthma makes it less likely that antihistamines will help the hay-fever, as shown in Table V, though if specific hyposensitization is given, and this helps the pollen asthma, any remaining hay-fever is helped by antihistamines (Frankland, unpublished work). Finally, it will be seen (Table VI) that, contrary to the observations of the earlier literature on the subject, there is no evidence in a carefully controlled selected group of seasonal (pollen) asthmatic patients that the antihistaminic drugs are of any benefit to the asthma when used as the only form of treatment.

Summary

A clinical trial has been made with antihistaminic drugs in the treatment of seasonal cases of hay-fever and asthma.

Suitable antihistaminic drugs help many of the mild cases of seasonal hay-fever. These drugs do not increase the incidence of asthma, nor do they help the symptom of asthma when it occurs.

REFERENCES

- British Medical Journal*, 1952, 1, 380.
 Frankland, A. W. (1949). *Med. Ill.*, 3, 193.
 — (1952). *Practitioner*, 168, 57.
 Gay, L. N., et al. (1948). *Bull. Johns Hopk. Hosp.*, 83, 356.
 Hunter, R. B., and Dunlop, D. M. (1948). *Lancet*, 1, 849.
 Kaplan, M. A., and Ehrlich, N. J. (1951). *Ann. Allergy*, 9, 105.
 Southwell, N. (1948). *British Medical Journal*, 1, 877.
 Squire, J. R. (1950). *Clin. Sci.*, 9, 127.
 Watkins, A. G. (1952). *Practitioner*, 168, 33.
 Williams, D. A. (1950). *Int. Arch. Allergy*, 1, 172.

PYLEPHLEBITIS AND SEPTICAEMIA TREATED WITH AUREOMYCIN

BY

F. GRAHAM MARSON, M.D., M.R.C.P.

Senior Medical Registrar

AND

M. J. MEYNELL, M.D., M.R.C.P.

Clinical Pathologist

with a Note on the Surgical Findings by

F. WELSH, F.R.C.S.

The General Hospital, Birmingham

Recovery from systemic infection with organisms of the *Bacteroides* group is worth recording in view of the high mortality. In well-established infections the case mortality is over 50% (Topley and Wilson, 1946). Brown *et al.* (1941) reported the recovery of one of fifteen patients with septicaemia due to bacteroides. Comparably poor results were recorded by Thompson and Beaver (1932), Reid *et al.* (1945), Ruys (1947), and McVay *et al.* (1949). The last-named, in their report of six cases, had four deaths despite chemotherapy. The last two cases recovered after large dosage of aureomycin and supportive treatment.

A case of pylephlebitis with septicaemia, from which both *Bacteroides fragilis* and *Streptococcus haemolyticus* were isolated, was recently admitted to this hospital. The patient was originally treated with penicillin, chloramphenicol, and streptomycin with no apparent benefit. The regimen of McVay *et al.* was adopted, with final recovery of the patient.

Topley and Wilson include the bacteroides in the genus *Fusiformis*. They define the latter as follows: "Obligate parasites. Anaerobic or microaerophilic. Cells frequently elongated and fusiform, staining somewhat unevenly. Filaments sometimes formed; non-branching; sometimes highly pleomorphic. Non-motile. No spores. Reaction to Gram variable, but mainly Gram-negative. Growth in laboratory media feeble." They term infections with the genus *Fusiformis* as necrobacillosis.

Bergey (1948) separated the bacteroides from the fusiform bacilli and defined them as motile or non-motile Gram-negative bacilli which are obligate anaerobes.

Beigelman and Rantz (1949) emphasize the ubiquitous character of the group. They state that these organisms have been isolated from gangrenous lesions of practically all the organs of the human body as well as from

normal mucous membranes. They are commonly present in the mouth, tonsils, large bowel, and female genital tract. The general opinion is that they are of low virulence in man and act as secondary invaders. Blood-stream infection is probably not uncommon, but spontaneously terminates as soon as the primary focus is treated. Rarely, a septicaemia arises which ends fatally. It is stated by Reid *et al.* that pylephlebitis of the regional veins draining the primary focus is a common occurrence; arthritis, jaundice, and pulmonary emboli are frequent accompaniments.

Case Report

A man aged 32 was admitted with an illness of one month's duration. Whilst at work he was seized with severe upper abdominal pain, which later radiated to the right iliac fossa. This continued for four days and was accompanied by some diarrhoea. On the fifth day the pain began to abate, but he suffered a rigor. For the three weeks before admission he had two or three rigors a day.

On examination he appeared extremely ill, and was pale, thin, and sallow. His pulse was 120; temperature 102.8° F. (39.3° C.). No abnormality of the cardio-respiratory system was detected apart from a haemic murmur. The upper abdomen was tender; no mass was palpable. The liver and spleen were not palpable. A rectal examination was negative.

The blood count showed: haemoglobin, 54%; red cells, 3,060,000 per c.mm.; white cells, 19,800 per c.mm., 82% being polymorphonuclears. There were many target red cells in the stained films. The other laboratory examinations were negative, apart from a serum alkaline phosphatase of 35 units, and the Van den Bergh was immediate positive. On admission blood cultures in various media, including Robertson's meat, were taken. These were repeated with each rigor for the first 24 hours. From all cultures two organisms were isolated—a β -haemolytic streptococcus belonging to Lancefield's Group A, and *Bacteroides fragilis*. The latter was agglutinated by the patient's serum to a titre of 1 in 250. The streptococcus was fully sensitive to penicillin.

Bact. fragilis, by the ditch-plate method, was insensitive to penicillin but fully sensitive to chloramphenicol and streptomycin. As a result the penicillin treatment which he had had since admission was stopped and chloramphenicol and streptomycin were given. Chloramphenicol was administered as follows: 4 g. the first day and 2 g. daily subsequently. In addition 2 g. of streptomycin in divided doses was given subcutaneously each day. His temperature continued to swing, at times reaching 105° F. (40.6° C.). A laparotomy was performed on the sixth day after admission and an appendicular abscess was found and drained; the necrotic remnant of the appendix was removed. Examination of the pus revealed, in addition to various organisms, a β -haemolytic streptococcus and *Bact. fragilis*. There was no appreciable change in his condition.

Six days after the first operation another laparotomy was performed in order to ligate the ileo-colic vein. The patient's condition was critical and no further procedure was attempted. On this day he was given aureomycin, 1 g. four-hourly by mouth, and all other antibiotic therapy was stopped. In three days, after 18 g. of aureomycin, his temperature fell to normal and remained so. He received a total of 80.5 g. in approximately 14 days. During this period he had 4 pints (2.3 litres) of blood and a high-protein diet with additional vitamins. His only complaints were a slight soreness of the mouth and some difficulty in swallowing.

After all treatment was stopped he became less cadaverous and began to put on weight. For a few days a pseudo-chylous fluid drained from his operation wound, but this rapidly cleared up. He was discharged to a convalescent home.