

A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy

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Because of several controversial reports concerning the efficacy of cromolyn sodium in the treatment of asthma, the Drug Committee of the American Academy of Allergy instituted a collaborative study in November, 1969. The protocol was designed to select patients according to age, cooperativeness, severity of asthma, and type of asthma—extrinsic, intrinsic, or mixed. The basic design of the study involved a baseline period of one week in which inert filler (lactose) was administered in the Spinhaler apparatus and during which the patient could be familiarized with the complex record keeping. The basal period was followed by two 4 week crossover periods during which cromolyn sodium was alternated with placebo. Symptom scores, drug intake, physician evaluation, patient preference, and simple pulmonary function tests were subjected to statistical analysis. Results gleaned from 252 completed patients indicated a favorable response for the drug as compared to placebo in patient symptom scoring, ephedrine-like drug scores, physician evaluation, and patient preference. A drug carry-over effect extending over a period of 4 weeks created difficulty in assessing results of the placebo period in patients who received active drug during the first 4 week period. Although a favorable drug effect was usually observed when cromolyn sodium was the first drug in the trial sequence, efficacy was more clear-cut during active drug administration in patients who received placebo during the first 4 weeks of the study. The mechanism of this carry-over effect was not apparent. The amelioration index tended to be higher in the pediatric group and in those patients whose asthma was classified as mixed. No change in the objective indices of one-second forced expiratory volume or peak expiratory flow measured once every 2 weeks was obtained. No serious side effects were noted by the participating investigators. These results indicate that cromolyn sodium will be a useful adjunct to the pharmacological treatment of asthma.

In 1965, a bis-chromone compound was synthesized by linking two chromone molecules derived from the Eastern Mediterranean herb, *Ammi visnaga*. This drug, cromolyn sodium, though lacking in smooth muscle-relaxing activity, was found to possess the unique property of preventing mast cell degranulation induced by antigen-antibody reactions.¹ After preliminary ameliorative effects were observed in human asthma,² an extensive series of clinical trials were undertaken in various medical centers throughout the world.³

Presented in part at The 27th Annual Meeting of the American Academy of Allergy, February 22, 1971, Chicago, Ill.

Received for publication April 19, 1972.

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Although the majority of these studies reported favorable results, particularly in extrinsic (reagin-mediated) asthma, the conclusions of several investigators were less enthusiastic.⁴⁻⁷ Thus a large scale clinical study utilizing the resources and experience of the Drug Committee of the American Academy of Allergy was deemed advisable and was begun in 1969. The objectives of this study were to determine the short-term therapeutic effectiveness and safety of cromolyn sodium by means of a double-blind crossover trial, comparing it with a matching placebo preparation. This is a report of results in 252 patients who had satisfactorily completed the clinical trial by May 1, 1971.

METHODS AND MATERIALS

Selection of subjects

Ages of the patients ranged from 5 to 73. Children were defined as age 5 through 16 inclusive. Wherever possible, patients over 50 years of age were excluded in order to minimize the effects of complicating diseases such as chronic bronchitis, emphysema, and various cardiovascular conditions. Patients over 50 years of age could be included provided they had well-documented asthma for at least 5 years and the physician was able to provide sufficient clinical evidence which excluded the above-mentioned diseases. Pregnant women were not accepted into the clinical trial. Although the primary purpose of the study was to evaluate asthma, an attempt was made to classify asthma on the basis of extrinsic, intrinsic, or mixed forms. Duration of asthma in all patients was at least one year. Furthermore, the participating physician must have supervised treatment for at least 6 months, and all patients must have manifested symptoms for at least 2 months before starting the trial. Patients who were asymptomatic on a stable steroid dosage regimen were allowed to enter the trial by tapering the steroid drug to a level which allowed the appearance of symptoms. In such cases, minimal symptoms must have been observed for 2 weeks prior to inclusion in the study. Patients who were on minimal steroid dosage were asked to maintain the same dose initially and throughout the 9 week study period. Drugs other than steroids could be reduced or increased. However no new drug therapy or hyposensitization could be started during the trial period. Conventional methods of treatment such as bronchodilators, expectorants, etc., were continued throughout the study on an as-needed basis.

Drugs and dosage

In the active drug period 20 mg. of cromolyn sodium was inhaled 4 times a day by means of a special Spinhaler apparatus. During the placebo period, a matched placebo powder consisting of lactose plus sodium sulfate was administered by means of the same device. Similar capsules containing pure lactose were supplied for use in the base-line period.

Plan of study

The study commenced with a practice period of one week, the base-line week, during which time the patient became familiar with the effects of inhalation of powdered lactose and the complex routine of record keeping. If the patient's performance was satisfactory during this week, he was then entered into the formal study during which cromolyn sodium and placebo were each taken for 4 weeks, the sequence being derived from tables of random numbers. Clinical and laboratory assessments were obtained at the beginning and end of the basal period and at 2 week intervals thereafter. At the conclusion of the 8 week total treatment period, the patient was given an option to continue or discontinue treatment by means of the following questionnaire:

Would you prefer to:

- (1) Stop all treatment?
- (2) Continue with capsules of first 4 week period?

(3) Continue with capsules of second 4 week period?

or, do you have:

(4) No special preference.

After this choice was made, the individual's code was broken. If the patient's preference was active drug, he was permitted to remain on an extended study with cromolyn sodium. Because of ethical considerations, patients were not maintained on placebo capsules.

Records

Instruction forms were provided for both patients and clinicians. All patients were required to sign an informed consent form. Initial evaluation forms were completed on each patient entering the study. The following information was obtained from these forms: age, sex, age at onset of asthma, duration of asthma, and type of asthma, i.e., intrinsic, extrinsic, mixed. Patients kept a comprehensive record of symptoms of a daily diary form. Symptoms of wheeze, breathlessness, chest tightness, cough, sputum, and number and duration (hours) of attacks were rated separately during day and night according to the scales shown in Table I. The average day and night scores for the days recorded were computed by dividing the total scores for the period by the number of days less the blank days in which records were not obtained. On the reverse side of this form, concomitant medications for each 24 hour period were recorded. At the conclusion of the study, drug scores were obtained by multiplying the milligrams consumed by factors which accounted for short- and long-acting oral preparations as well as parenteral and rectal medications. An average daily drug dosage score was then computed. Physician evaluation forms were also completed at the end of each 2 week period. Data on these forms included the physicians' evaluation of patient's symptoms according to the same numerical scale shown in Table I, physical examination findings, pulmonary function testing, side effects, and other significant events during the preceding 2 weeks. On the same form the physician was required to evaluate the patient's current asthma according to the following scheme: (1) no change, (2) slightly worse, (3) very much worse, (4) slightly better, (5) very much better. Prior to the study there were 4 teaching seminars during which all cooperating investigators were instructed in methods of assessment, which included the subjective responses of the patients without referring to the patient diary card, uniform methods of evaluating physical signs, and assessment of daily activities of patients which were affected by asthmatic symptoms. The patient's over-all symptom response during each 4 week crossover period was also evaluated on a separate form. At this time the patient was asked to evaluate his symptoms during the preceding 4 weeks by means of the following scale: (1) very much worse, (2) definitely slightly worse, (3) about the same, (4) definitely slightly better, (5) very much better, (6) completely absent.

Laboratory investigations

Hematologic, urine, and blood chemistry surveys were obtained before and after each treatment period. All laboratory procedures were performed in a central laboratory. Chest x-rays were also performed before each crossover period. One-second forced expiratory volume (FEV₁) and/or peak expiratory flow rate (PEFR) were also recorded on a biweekly basis.

Data collection and analysis

All reports were mailed to the Chairman of the Drug Committee who in turn submitted them to the Department of Biomedical Statistics of the University of Cincinnati Medical Center for programming and final statistical evaluation. Symptom and drug scores were analyzed by means of a linear covariate model. All analyses were based upon data from the base-line period and the periods of active drug and of placebo, respectively.

In order to verify the comparability of the two treatment sequence groups (active drug first versus placebo first), parameters of age, sex, age at onset of asthma, duration of asthma, and type of asthma were compared by means of the chi square statistic. Pretrial responses of symptoms (wheeze, breathlessness, tightness, cough, sputum, and asthma attacks), physi-

TABLE 1. Numerical scores of symptoms, sputum, and asthma attacks

Score	Chest symptoms	Sputum	Asthma attacks
0	None	None	Total
1	Trivial or doubtful	Few specks only	number
2	Mild, clearly present but causing little or no discomfort	Approximately 1 table-spoon	of
3	Annoying but not causing marked discomfort	Approximately 2 table-spoons	attacks
4	Moderately severe, causing marked discomfort but not interfering with routine	Approximately 4 table-spoons	and duration
5	Severe, some interference with sleep or activities but not incapacitating	More than 4 tablespoons	in hours
6	Very severe, intolerable		

cians' assessment of the symptomatology (dyspnea, chest tightness, wheeze, and cough), and medication scores were compared by means of a *t* test for unpaired samples. The covariate model was further designed to consider the following factors simultaneously: (1) sex—male, female; (2) age—less than 17, 17 to 40, greater than 40; (3) type of asthma—intrinsic, extrinsic, and mixed; (4) duration of asthma: less than 5 years, greater than 5 years; (5) age at onset of asthma—less than 4, 4 to 40, greater than 40; (6) pollen season—present or absent in preceding trial period, or present or absent in present trial period; (7) concomitant medications—average daily usage in preceding and present period compared to base-line drug usage; (8) Spincap usage (placebo or cromolyn sodium)—average daily usage in preceding and present period compared to the amount required by initial protocol; (9) pretrial score: average daily score of symptoms and medication.

The statistical model assumed that each patient had some level of symptom score for each 2 week period during the trial. This score was the function of the trial period (placebo or cromolyn), the patients' demographic data, the type and onset of asthma, concomitant medications, presence or absence of pollen season, and pretrial score for the individual involved. Thus all information pertaining to a given patient was included in the model to help explain why different symptom scores were observed both within and between patients.

RESULTS

By May 1, 1971, 300 patients had been entered into the trial. Thirty-eight patients either did not complete the 9 week trial or had record forms which were illegible or incomplete. Ten patients were eliminated from the analyses because of unusually large increases in concomitant corticosteroid therapy which occurred in the same frequency during drug and placebo periods. Data contained in the study records of the remaining 252 patients were included in the statistical analysis. Preliminary analysis revealed that there was a strong sequence or carry-over effect of active drug into the placebo period. Because of this obvious drug order effect, it was necessary to divide all patients into 2 major groups—those receiving the active drug first, and those receiving placebo first. In the preliminary analysis, it was then necessary to ascertain if there were significant differences between the 2 drug sequence groups for such variables as age, sex, age at onset of asthma, duration and type of asthma (intrinsic, extrinsic, and mixed), pollen season, the effect of pretrial symptom score, concomitant medications, and the actual number of Spincap usage for all patients. The treatment sequence groups were shown not to differ with respect to the distribution of age, sex, age at onset, duration of asthma, and type of asthma. Twenty of the 22

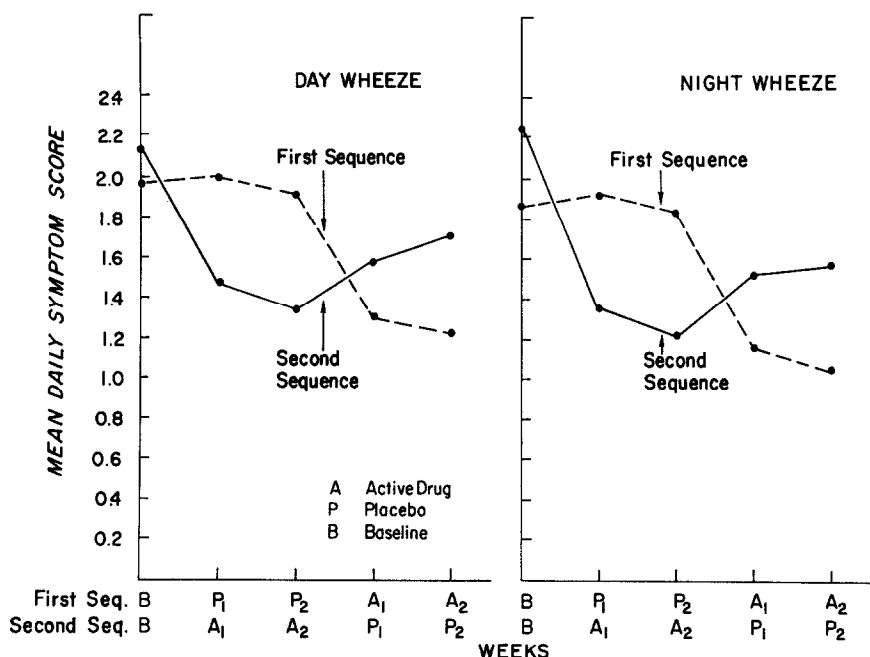


FIG. 1. The relationship of mean daily scores to drug order effect for symptoms of day and night wheeze in 252 patients. First sequence signifies administration of placebo first; second sequence refers to administration of drug first.

pretrial symptom and medication scores did not differ significantly ($p < 0.05$) between the 2 drug order groups. The presence or absence of pollen seasons in the 2 drug sequence groups before the trial began did not differ significantly. Furthermore, dose levels of pretrial medications and Spincap usage did not differ between the 2 treatment groups. Thus the tests for group pretrial comparability revealed that the 2 drug order groups (active-placebo, placebo-active) contained the same type of patients with generally comparable pretrial symptom and medication levels and were unaffected by variability of pollen seasons during the study. The similarity of the 2 groups indicated that any difference in the treatment effect between a group receiving active drug first and the group receiving placebo first must be due to factors other than pretrial differences between the 2.

The main analysis by the linear covariate model considered all the above factors simultaneously. For the group receiving placebo first, a significant treatment effect was seen for a vast majority of the patients (approximately 80 per cent) in 15 of the 16 symptom scores and in 2 of the 4 concomitant medications analyzed. Significant treatment effect was not seen for the group receiving the active drug first except in the analysis of all ephedrine-like medications, where 70 per cent of the patients taking these drugs were shown to take significantly fewer doses in the active drug period as compared to the placebo period. Fig. 1 depicts the change from base-line scores throughout the placebo period and the active drug periods for symptoms of day wheeze and night wheeze

in the total patient population. In the placebo-first group it should be noted that symptom scores remain steady during the placebo periods but drop significantly during the four weeks of active drug administration. In the second drug order sequence (active drug first) symptom scores drop during the 2 cromolyn sodium periods and tend to increase slightly in the following 2 week placebo periods, but not to base-line levels. These results were typical of most of the symptom and medication scores analyzed. Variation in the frequency of active or placebo capsule dosing was adjusted for in the analysis model and was shown not to greatly influence the treatment effect one way or the other. Similarly, the presence or absence of the pollen seasons during the trial periods was shown to have little influence on the treatment effect. The effect of pretrial levels of symptom and drug scores on treatment showed that when the pretrial level of symptoms was greater the treatment effect was also greater. Obviously it was more difficult to show a significant reduction in symptom scores when the symptom scores were low at the beginning of the trial. In the over-all analysis, results in the group receiving placebo first demonstrated that scores after active treatment were consistently 25 per cent lower than scores after placebo treatment. Certain types of patients were shown to differ significantly in their response to treatment as compared to the rest of the trial population. Patients whose age at onset of asthma was less than 4 showed a greater treatment effect than the others. Subjects under 17 years of age demonstrated a more marked treatment effect than those subjects older than 17 years; subjects with asthma for at least 5 years also showed a greater treatment effect. A similar effect was noted for type of asthma in that the mixed group showed consistently better results. However it should be emphasized that this category accounted for 79 per cent of the placebo-active group and 80 per cent of the active-placebo group, a reflection of the difficulty of classifying asthma into purely extrinsic or intrinsic types on the basis of selection criteria used in the study.

Other analyses included physicians' evaluations of asthma, patients' symptom responses, and patients' final preferences. Table II shows physicians' evaluations of asthma for both drug trial sequences. For the group receiving the placebo first, 34 per cent of the patients were evaluated as improved after placebo treatment (in comparison with the preceding period) as opposed to 74 per cent judged to be improved after receiving the active treatment. For the group receiving the active drug first, 30 per cent of the patients were assessed as being better after placebo treatment as opposed to 71 per cent evaluated as being better after receiving the active treatment. Table III illustrates the patients' symptom responses for the 2 trial sequences. For the group receiving placebo first, 39 per cent of the patients reported improvement of symptoms after placebo treatment as opposed to 81 per cent who considered their symptoms improved after receiving the active treatment. For the group receiving the active group first, 38 per cent of the patients noted a decrease in symptoms after placebo treatment as opposed to 77 per cent who experienced improvement after receiving the active treatment. The patients' final preferences are presented in Table IV, both over-all and then stratified into the different variables analyzed in the linear covariate model. After receiving both treatments, 70 per cent of the patients indicated that they

TABLE II. Comparison of physicians' evaluations of asthma during placebo-active and active-placebo sequences

Trial sequence	Physician evaluation			
	Placebo period		Active period	
	No. patients	%	No. patients	%
<i>Placebo-active</i>				
Very much worse	9	66	1	26
Slightly worse	26		12	
No change	45		19	
Slightly better	33	34	32	74
Very much better	9		58	
<i>Active-placebo</i>				
Very much worse	12	70	2	29
Slightly worse	42		13	
No change	33		21	
Slightly better	17	30	35	71
Very much better	20		53	

TABLE III. Comparison of patients' symptom reports during placebo-active and active-placebo sequences

Trial sequence	Patient assessment			
	Placebo period		Active period	
	No. patients	%	No. patients	%
<i>Placebo-active</i>				
Very much worse	7	61	4	19
Definitely slightly worse	23		5	
About the same	47		15	
Definitely slightly better	38	39	28	81
Very much better	11		67	
Completely absent	0		7	
<i>Active-placebo</i>				
Very much worse	19	62	1	23
Definitely slightly worse	39		7	
About the same	20		21	
Definitely slightly better	23	38	33	77
Very much better	22		61	
Completely absent	3		3	

preferred to continue on the active medication, while 19 per cent showed a preference for continued treatment with placebo. Of the 11 per cent who "very much" preferred placebo, 89 per cent had received the active drug first. It should also be noted that a greater preference for the active drug was indicated by patients of all categories, except for those with the "pure" intrinsic variety of asthma.

No significant changes in FEV₁ and/or PEF_R before or after bronchodilators were obtained in either trial sequence categories. No significant hematologic, blood chemistry, or urine abnormalities could be attributed to active drug administration. Chest x-rays were unchanged from pretrial levels throughout the course of the study.

To the present, 196 patients have elected to continue in an open trial study.

TABLE IV. Patients' final preferences for drug or placebo at the conclusion of the study

Patient category	Very much prefer placebo		Slightly prefer placebo		Stop all treatment	
	No.	% *	No.	%	No.	%
Placebo-active sequence	3	2.3	10	7.9	12	9.5
Active-placebo sequence	25	20	10	8	6	4.8
Age < 17 yr.	11	7.2	12	7.9	8	5.3
Age 17-40 yr.	11	22.7	4	8.4	2	4.1
Age > 40 yr.	6	11.5	4	7.6	8	15.4
Male	17	11.7	10	6.8	8	5.4
Female	11	10.5	10	9.5	10	9.5
Onset < 4 yr.	14	10.1	11	7.9	7	5
Onset 4-40 yr.	11	11.4	8	8.3	6	6.2
Onset > 40 yr.	3	18.7	1	6.2	5	31.2
Duration < 5 yr.	4	10.2	1	2.5	4	10.2
Duration > 5 yr.	24	11.3	19	8.9	14	6.6
Extrinsic	4	13.7	5	17.2	1	3.4
Intrinsic	5	22.7	0	0	5	22.7
Mixed	19	9.5	15	7.5	12	6.0

*All per cents are those of subgroup totals.

†Number of patients in each category in the total patient population of 251. An opinion was

One hundred three of these patients have continued keeping their diary and drug scores, but these have not been analyzed as yet.

DISCUSSION

The protocol of the American Academy of Allergy cromolyn study was severely restrictive in the selection of patients. Since chronic asthma of an ongoing type was required, patients universally fell into a "perennial" category with or without seasonal influences. The age range requirements placed the entire group in a range in which positive family history of allergy, a personal history of allergy, and/or positive skin tests were almost universally present. This was manifested in the small number of "pure" intrinsic asthmatic patients selected for study. The fact that the overwhelming majority of patients were of the "mixed" type merely indicated that many of these patients had infectious or other contributing factors. Since the total study duration was for a 9 week period, chronicity of asthma was required. Finally, asthmatic symptoms in all patients were of sufficient magnitude to require medical attention of a long-term nature. In this sense the test population could be considered homogeneous in that it represented a group of ambulatory, chronic asthmatic patients of relatively severe grade with an "atopic" background. Although no isolated marker of the course of the disease manifestations could be identified, the general pattern of response as represented by numeric scores of wheeze, cough, tightness of the chest, breathlessness, frequency and duration of isolated attacks, and sputum production was favorably influenced by cromolyn sodium therapy. This favorable influence on the symptoms of asthma was often accompanied by a decrease in the use of symptomatic medications such as bronchodilators and corticosteroids. The results of the analysis on the group receiving placebo first showed that the

Continue with either		Slightly prefer active		Very much prefer active		Category† totals
No.	%	No.	%	No.	%	
5	3.9	20	15.8	76	60.3	126
4	3.2	24	19.2	56	44.8	125
6	3.9	25	16.5	89	58.9	151
1	2.1	10	20.8	20	41.6	48
2	3.7	9	17.3	23	44.2	52
5	3.4	23	15.7	83	56.8	146
4	3.8	21	20.0	49	46.6	105
4	2.8	23	16.5	80	51.5	139
5	5.2	21	21.8	45	46.7	96
0	0	0	0	7	43.7	16
3	7.7	7	17.9	20	51.2	39
6	2.8	37	17.4	112	52.8	212
2	6.9	7	24.1	10	34.4	29
3	13.6	4	18.1	5	22.7	22
4	2.0	33	16.5	117	58.5	200

not obtained from one patient.

scores after active treatment were consistently 25 per cent lower than the scores after placebo treatment. The strong carry-over effect was considered to be the reason for not demonstrating a significant treatment effect for the group receiving cromolyn sodium first. However, even in this group the placebo scores were shown to be increasing toward the pretrial scores in the last 2 weeks of the placebo period and were higher than the scores recorded in the active period. Further evidence of the efficacy of cromolyn sodium was demonstrated by the facts that a large majority (70 per cent) of patients expressed a preference for the active drug, 72 per cent of the patients were evaluated by their physician as improved after active treatment, and 79 per cent of the patients assessed their chest symptoms as better after the active treatment. Certain other factors also interacted with efficacy of treatment. As reported in other studies,³ subjects under 17 years of age showed a more marked treatment effect than did subjects over 17. This increased efficacy in children was also reflected in the fact that patients whose age of asthma at onset was less than 4 years also showed a greater treatment effect than did other patients in the population. However, the reason that patients with asthma of greater than 5 years' duration showed a better interaction with treatment effect is not readily apparent.

Because this was a large multicenter study, complete and detailed physiologic studies could not be performed. However, simple pulmonary function studies were included in the study in order to provide a possible objective index of response. It was well recognized before the study that there are diurnal and day-to-day variations in PEF_R and FEV₁ procedures. For this reason it was also postulated that a single test performed at 2 week intervals might have no significance at all. Indeed, this was the case when the results were finally analyzed. However, other investigators^{8, 9, 14} have observed significant improve-

ment in pulmonary function when more complete studies were evaluated.

Except for mild throat irritation in some cases, there were no significant side effects encountered in this study, both in the drug and placebo groups. Two deaths were reported in patients who had participated in this study. One of the deaths occurred quite suddenly in a child who had been receiving placebo capsules and who had not yet received the drug. The other death occurred in an adult 8 months after she had completed the full study. Her death occurred suddenly at home. She had not participated in the extended trial study.

Although stabilization of *in vitro* mast cell preparations by cromolyn sodium has been demonstrated,¹ the mechanism of drug action *in vivo* has not been fully elucidated. The strong carry-over effect of the drug is also difficult to explain satisfactorily. In some cases the carry-over effect must be presumed to have lasted at least 4 weeks, a much longer period than had been described in earlier clinical trials. The drug's effects on immunologic reactions mediated by reaginic or Arthus-type antibodies could hardly account for such long-term persistence, suggesting that other nonimmunologic effects may be involved. Inhibition of exercise-induced asthma,¹⁰ histamine hypersensitivity,¹¹ and hyperventilation-induced asthma¹² by prior inhalation of cromolyn sodium have all been demonstrated. Recently Altounyan and associates¹³ postulated that desensitization to specific antigens under the protective cover of cromolyn sodium may also account for long-term drug effects in extrinsic asthma. Kerr and associates¹¹ suggested that cromolyn sodium may exert a specific protective effect upon the bronchial smooth muscle membrane. The clinical results of this investigation cannot be interpreted as favoring any one or more of these hypotheses.

In summation, this controlled study has revealed that short-term administration of cromolyn sodium results in symptomatic improvement in asthma. This was reflected by reduced dosages of concomitant medications. Under these conditions and with relatively infrequent measures, no statistically significant changes of pulmonary function were observed. Children tended to respond better than adults. There were no significant side effects. The drug may have a persistent effect for as long as 4 weeks. This study has also demonstrated that cooperative multicenter investigations of asthma are feasible and perhaps advantageous as compared to single center trials. We recommend that any promising antiasthmatic agent should be studied in a similar fashion and that a Multi-center Drug Study Group should be retained as a permanent subcommittee of the Drug Committee of the American Academy of Allergy.

The authors wish to thank Fisons Corporation, Bedford, Massachusetts, for supplying record forms and drugs. The diligent assistance of Greta Lee Splansky, Lottie Kwiatek, Martha Held, Joy Eckhardt, and eleven other "girls Friday" is gratefully acknowledged.

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