

From the asthma centre Eijkeloord in Groesbeek, The Netherlands.

TREATMENT OF CHILDREN
IN AN ASTHMA CENTRE WITH
DISODIUM CROMOGLYCATÉ

Double-blind Crossover Trial

By

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Since the original publication by *Howell & Altounyan* (1967) a great number of investigators have reported the results with disodium cromoglycate in the treatment of asthma patients (1-8, 10-13, 15-17).

Of the studies in asthmatic children the trial of *Strick et al.* (1970) is the only one that refers to patients who were treated in a home for asthmatic children (3. Abstract): 27 out of 36 children completed the study satisfactorily; 18 improved on disodium cromoglycate, 6 on placebo, 3 remained unchanged. These results were based on medication score and wheeze score.

Morrison Smith & Devey (12) performed a double-blind trial in outpatients aged 5 to 16 years. In 24 out of 44 cases the active period was considered better than the placebo period; in 7 cases the placebo period was preferred; 13 times no decision could be made.

Jones & Blackhall (6) in a double-blind trial on 16 children, obtained no significant results. 77 children were treated on an open basis during a long period. A good response was seen in a proportion of the patients, but not in those cases where the lung function was impaired between attacks.

Aims of Trial

In this study we intended to check on three main points:

1. the possible therapeutic effect of disodium cromoglycate in the special population of a children's asthma centre;
2. the grade of improvement, if any;
3. the characteristics of patients suitable for this therapy, by comparing patients who did, with those who did not, improve.

The therapeutic effect of disodium cromoglycate was measured with the same methods as normally used in this centre to evaluate the progress of our patients (9).

In this way it was possible to use the pre- and post-trial periods as an internal check on both the degree of improvement obtained, and the experimental design.

PLAN OF THE TRIAL AND METHODS

The trial was carried out during the period of September to December 1969. The subjects involved are in-patients in the asthma centre; generally they stay for a period of 1 to 3 years. At the centre they are ambulant, attend the resident school and lead, as far as possible, a normal life. Because of the fact that during their stay in the centre a proportion of the patients becomes (nearly) free of complaints, we admitted to the trial only the patients who regularly showed significant asthma symptoms. Children who were too young or who were unsuited in any other way to cooperate sufficiently were excluded from the trial. 30 patients were treated according to the double-blind crossover method for 4 weeks with active capsules containing 20 mg disodium cromoglycate and for 4 weeks with matching placebo capsules, containing lactose + 5 mg anhydrous sodium sulphate. The capsules were inhaled 4 times a day, using the "Spinhaler".¹ One patient was excluded shortly after the beginning of the trial because of a lung-infection (it is assumed that this had nothing to do with this therapy). Out of the remaining 29 patients 18 were boys and 11 were girls. Their ages were 6-16 years with an average of 11.3 years; 14 children belonged to the middle group of 10-12 years.

The following data were collected on each patient:

a) *Asthma score*. It is a matter of routine that every day the staff make 4 records (morning, afternoon, evening and night) of asthma according to a

¹ Fisons Ltd., Loughborough, England, kindly provided the material.

numerical code. The following scores are used for complaints during each period.

0: no symptoms at all during the period observed.

1: minimal asthma symptoms: wheeze just audible or very slightly disturbed respiration.

2: slight asthma symptoms.

3: moderate to severe asthma symptoms.

4: gross dyspnoea.

The *highest* score, out of the four scores per day, is used for further calculations.

b) *Peak expiratory flow rate*, recorded several times a week or every day, always at the same time, viz. at 12.00 p.m. (using the Wright P.E.F. meter).

In a previous study (16) the correlation between these two method (a) and (b) and their usefulness in evaluating the course of the disease, has been demonstrated.

c) Requirements of drugs, namely:

× *antibiotics*, most of the time used for short periods of about one week for episodes of lung infections;

× *symptomatics*: aminophylline, promethazine, thiazinamium, isoprenaline. Because of the fact that generally a combination (aminophylline suppositories and promethazine) is given in attacks of severe dyspnoea the *number of days* during which this therapy is used is a better score than the quantity of the drug.

× *corticosteroids*.

From the data collected figures for 14-day periods were computed, generally 7 such periods per patient, viz. period 1 and 2 immediately prior to the trial; period 7 immediately after the trial; periods 3 to 6 covering the trial proper. After finishing the trial it appeared that the active drug had been given 15 times in the periods 3 and 4; 14 times in the periods 5 and 6. The asthmascore per 14 days was calculated by taking the sum of the asthmascores per day (as defined above). Peak flow rates for the 14 day period were averaged. In each of the periods 3 to 6, a blood count was made for eosinophil leucocytes (per mm³ blood; measurements were made at 12.00 p.m.). The remaining data came from the usual routine methods and will be discussed later on.

RESULTS

The results per case are shown in the Figs. 1 and 2. Fig. 1 deals with the 14 patients, in which the treatment with cromoglycate followed after the placebo. Fig. 2 deals with the 15 patients in which cromoglycate preceded placebo. Only one patient, no. 25, used corticosteroids continuously during

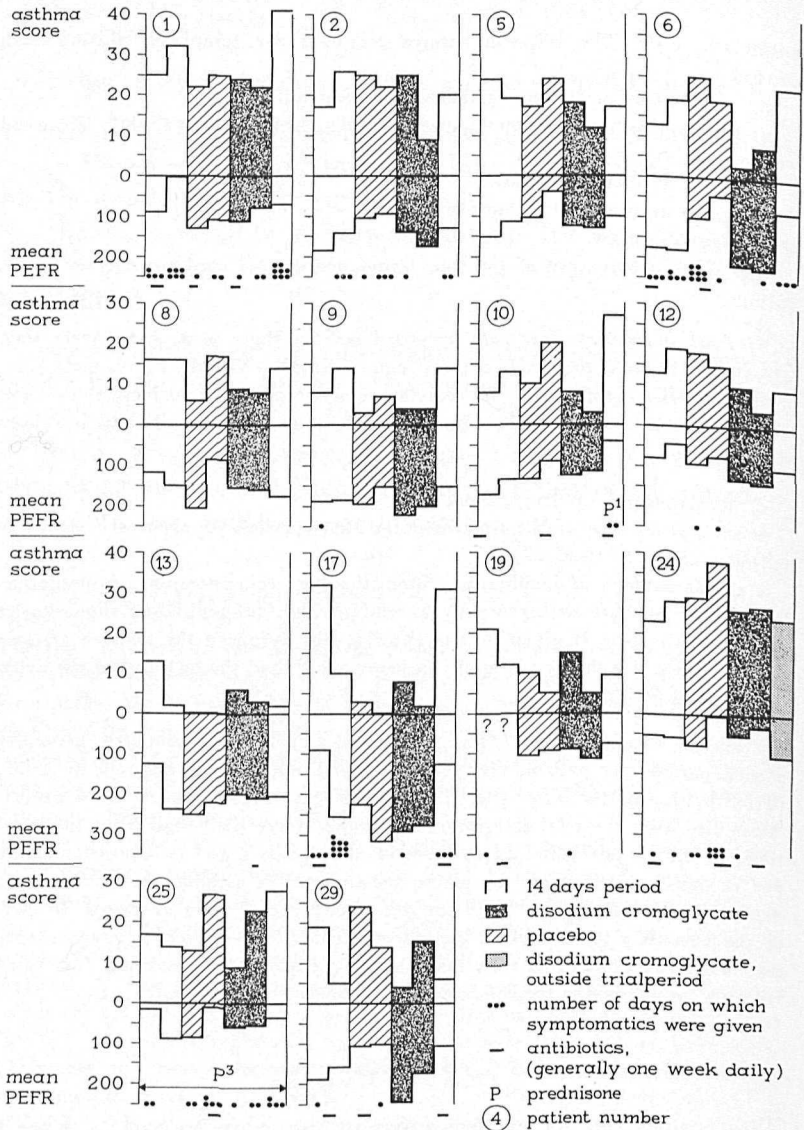


Fig. 1.

Asthma score, mean peak flow and the number of days (per period of 14 days) with symptomatic therapy, antibiotics and corticosteroids.

Cases in which cromoglycate followed after placebo.

P₁ (patient 10): 3 days 5 mg prednisone in period 7.

P₃ (patient 25): every other day 5 mg prednisone.

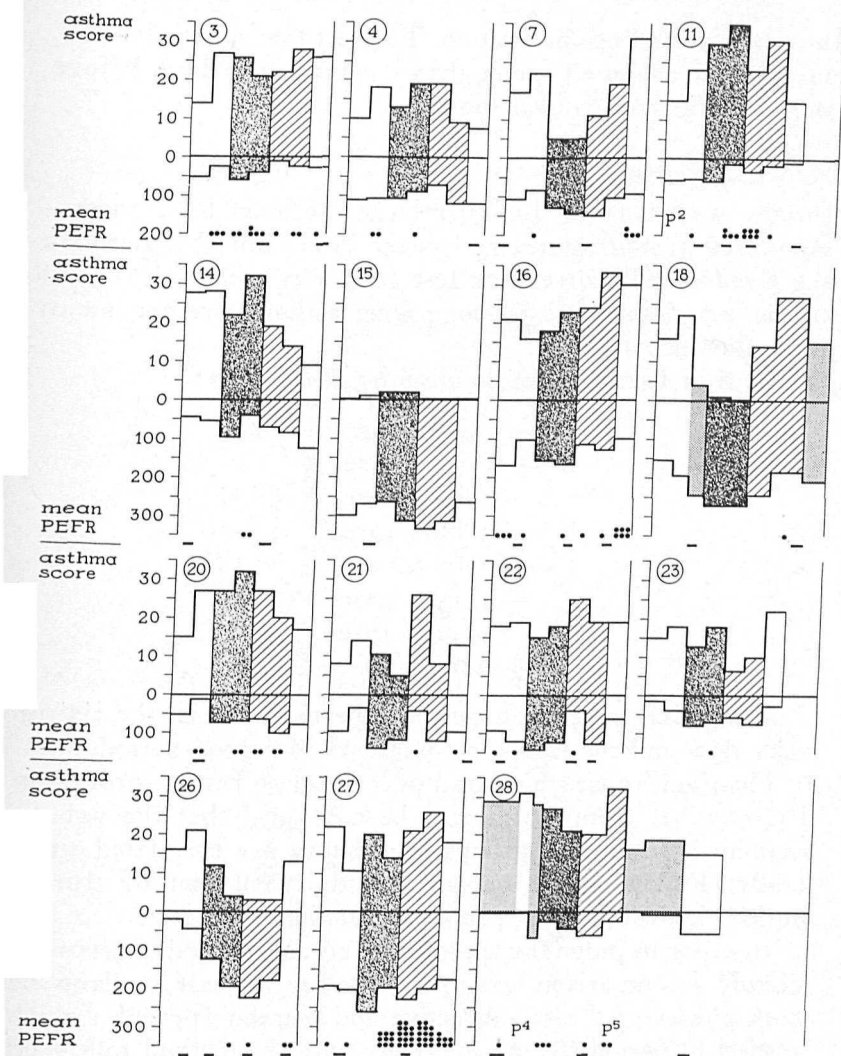


Fig. 2.

(Cfr. Fig. 1). Cases in which cromoglycate preceded placebo.

P₂ (patient 11): 5 mg prednisone per day in period 1.

P₄ and P₅ (patient 28): 3 respectively 5 days 5 mg prednisone in periods mentioned.

(In the Figs. the average peak flow is put under the line, the asthmascore above the line; improvement is shown in the fall of the whole "block" which stands for one period).

the whole period of observation. The fact that 3 patients (no. 24, 18 and 28) used cromoglycate on an open base before and after the trial is also shown.

Statistical Evaluation

Firstly, we examined for correlation between both parameters used (asthmascores and peak flow). For that purpose the *Kendall* rank correlation test (17) was used with regard to the 4 periods (3 to 6) comparing asthmascore and mean peak flow per 14 days.

The S of Kendall (maximum 6 by $N = 4$) is:

— 6	in 2 cases
— 5	in 3 cases
— 4	in 6 cases
— 3	in 3 cases
— 2	in 6 cases
— 1	in 4 cases
0	in 3 cases
+ 2	in 2 cases

A negative correlation can be expected between the rising peak flow and the falling asthmascore in a good period.

The significance, calculated over these 29 results, produces $P < 0,00001$, from which may be concluded that the values examined, within the groups considered, are correlated generally. Following the same method, calculation of the 7 periods known per case produces a similar result.

In order to judge the therapeutic effect of disodium cromoglycate a comparison was made between the last 14 days of both phases of treatment, active and placebo (period 4 with respect to period 6), in accordance with the method followed by other authors. This was done because of a possible continuation of the therapeutic effect of disodium cromoglycate during the first part of the placebo period and also because there may be a time lapse in the appearance of the clinical effect of cromoglycate.

Considering the asthma score only, 18 cases improved dur-

TABLE 1
Difference Between Observation Periods in "Student's" t-test for Paired Data
 (N = 29 for Period 4 and 6; N = 25 for Periods 1, 2, 7).

	Mean difference	Asthmascore SD	t	P	Mean difference	SD	Mean PEFR t	P
Period 4 and 6 (Placebo versus active)	-4,0	9,4	-2,30	<0,05	23,8	46,9	2,74	<0,02
Period 1 versus 2	0,89	8,5	0,54	n.s.	— 1,3	54,6	0,12	n.s.
Period 2 versus 7	0,96	9,9	0,50	n.s.	-10,0	55,7	0,90	n.s.

ing the active period, 10 during the placebo; in 1 case there was no difference. According to the average peak flow the figures are 17, 11 and 1 respectively. When both criteria are combined it appears that the asthmascore as well as the average peak flow are in favour of the active drug 14 times and 7 times in favour of the placebo. These numbers are not significant in the chi-square-test.

Seeing that the differences in favour of disodium cromoglycate are larger than those in favour of the placebo the following tests produce significant results.

Wilcoxon's matched pairs signed ranks test shows that with respect to:

mean peak flow rate $T = 205$; $P < 0,02$ (Two tailed)
 asthma score $T = 193$; $P < 0,05$ (Two tailed)

TABLE 2
*Mean and SD of Asthmascore and Mean Peak Flow Rate
 in Observation Periods (N = 25).*

	Asthmascore		Mean PEFR	
	Mean	SD	Mean	SD
Period 4 and 6				
Active	13,6	10,3	140,4	75,2
Placebo	16,4	9,8	117,2	78,5
Period 1	16,2	6,9	115,2	69,7
Period 2	17,3	7,9	113,8	76,9
Period 7	18,0	10,1	103,8	59,5

With "Student's" t-test for paired data the same results were obtained (Table 1). This test was also used to determine the stability of the basal condition, that is, to check that the pre- and post-trial periods did not differ systematically. For that reason the two 14 days periods before the trial (1 and 2) were compared, and the period immediately before the trial was compared with the one after the trial (2 and 7). The differences in asthmascore and mean peak flow rate are small and not significant (Table 1).

Table 2, in which the mean and the standard deviation of the asthma score and the peak flow during the critical periods are stated, may be of help in the assessment of the grade of improvement under the influence of cromoglycate. (Patient 19, from whom no peak flow is known during the periods 1 and 2, and patients 18, 24 and 28 with an active treatment pre- and post-trial are excluded from this calculation).

The data with respect to the use of drugs, produced in Figs. 1 and 2, are compatible with the results of the asthma score and peak flow; statistically they have not been worked out separately.

Eosinophilia: no difference has been found between the placebo and disodium cromoglycate phase.

Side-effects: were minimal. Sometimes a slight stimulation causing coughing immediately after inhalation was reported. 3 Patients complained of multiple coughing-fits during the trial. One patient (no. 28) only coughed during the placebo period, perhaps because of irritation; on the other hand two patients were coughing less when they were using the active drug (no. 24 and 27).

DISCUSSION

The first of the three points listed in the introduction can be answered positively: in the asthma centre for children a therapeutic effect of disodium cromoglycate was proved in the double-blind crossover trial. Also in selected cases treated on an open base we found good results. Two of these cases are illustrated. Fig. 3 gives the whole progress during the attendance at the centre of patient 18; he started with an open treatment (early in 1968), later on he was involved in the double-blind trial, and after the trial he was treated again on an open base, which has been continued after his discharge. Fig. 4 shows an open treatment of almost 3 months in patient 26.

Our results are inferior to those of *Morrison Smith & Devey* (12), who, using the chi-square test, showed a predomi-

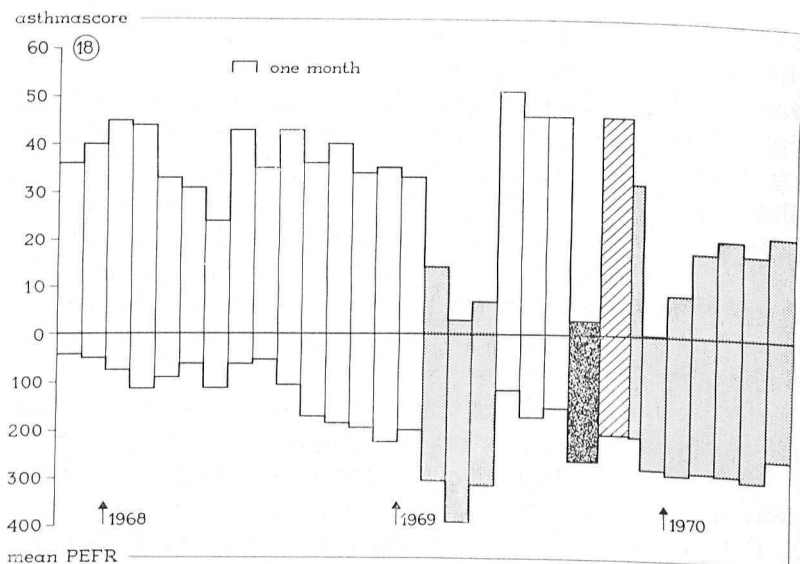


Fig. 3.

Patient 18, boy, 16 years. Asthma symptoms in a period of 2½ years.
Open treatment and trial are indicated as in Fig. 1.

nant number of positive responses to the drug. Studying this publication further, it seems likely to me that their patients were less serious than ours.

Some authors (3, 5, 10, 15) did see an improvement in symptoms or in the medication score, but not with respect to a significant increase in the lung function. On the contrary, in our group of patients, there is generally correlation between the asthma score and the mean peak flow, which is apparent from the results of the previously mentioned Kendall-test.

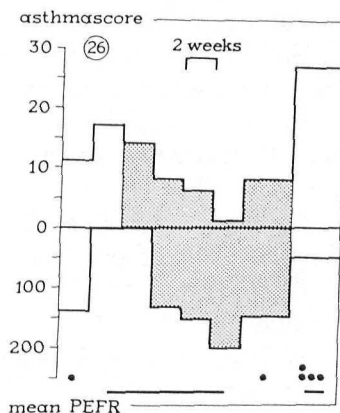
The answer to the second point, concerning the grade of improvement under the influence of disodium cromoglycate, is to be obtained from the data of Table 2 and Figs. 1 and 2. In this trial the effect of the treatment was impressive in some cases, small in others and not infrequently absent.

A further look at the Figs. 1 and 2 shows some more details.

In the cases in which treatment with the active drug fol-

Fig. 4.

Patient 26, girl, 13 years.
Open treatment with disodium
cromoglycate.



lowed the placebo (Fig. 1) a good effect was to be seen more often than in the cases in which the active drug was given first (Fig. 2), a difference, however, which is not significant. Something similar is mentioned by *Kennedy* (7); in a double-blind trial 40 out of 57 patients improved, but the ventilatory capacity showed a significant improvement only in those cases who received disodium cromoglycate after placebo. I am not able to give an explanation for these differences. Seeing the basal condition has not changed (cf. Table 1) it is permissible to judge the active phase with the whole period of observation as a background. In this context it is striking that, for instance, patient 1 already improved with placebo and remained the same for periods 3 to 6. In my opinion this might be interpreted as a placebo effect, which is probably also playing a role in patients 9 and 17.

In the statistical results, patient 26 is a doubtful case (active period 4, with respect to placebo period 6: score worse, peak flow better), according to the Figs. 2 and 4 she reacted well.

In patients 8 and 28 the useful effect of cromoglycate is doubtful, although they appear as good cases in the statistical results. This is because of a bad phase during the last 14 days of the placebo period.

Because of the absence of a sharp difference between nega-

tive and positive cases, the third point, concerning the characteristics of the type of patients who reacted favourably to the treatment, was not suitable for statistical running.

In order to get some insight into this matter, the material was divided into 3 groups on the basis of the data in the Figs. 1 and 2.

Group A: patients who clearly improved during the treatment with disodium cromoglycate.

Group B: patients in whom the improvement was small or doubtful.

Group C: patients without any effect or with an apparently negative effect during the therapy. (Table 3).

TABLE 3
Differentiation Between Three Groups of Patients.

Group	A	B	C
Number of patients	12	11	6
Boys/Girls	8/4	5/6	5/1
Mean age (years)	11,1	11,7	11,0
Asthma thorax	5	9	4
Mean blood eosinophilia			
$\leq 500/\text{mm}^3$	3	1	0
$500 \leq 1000/\text{mm}^3$	3	8	3
$> 1000/\text{mm}^3$	6	2	3
Group mean	950	820	870
House dust positive	9	4	3
Human dander positive	7	8	5

A: clear effect of therapy; B: doubtful effect; C: no or "negative" effect.
Average level of blood eosinophilia in 4 counts during the trial period.
Intracutaneous tests with 0,1 per cent allergen extracts (made by Hal).

One indication of the previous severity of asthma is the presence of an asthmatic thorax deformation; this was found relatively less often in the patients of group A.

In the long-term treatment of 100 adults *Altounyan* &

Howell (1) did not see any effect in 6 "non-allergic" patients (criterion was: no sputum eosinophilia). On an average the sputum of our patients contained in 1 out of 5 tests, a ratio of eosinophils of at least 10 per cent in the smear preparation. In this respect there was not a remarkable difference between the groups. Two patients had, on a number of occasions, no sputum eosinophilia (patient 2 and 22); they belong to our Group A. Also the frequency of eosinophils in the nasal secretion (on an average positive 1 in 4 times per patient) did not differ remarkably. In some patients no eosinophilia was found in several smears of nasal secretion: 2 in group A, 3 in group B and 1 in group C.

However, there was some difference with respect to the level of blood-eosinophils using the average of 4 tests during the trial period (Table 3).

Chen et al. (3) mentioned a non-significant difference in favour of the patients with positive skin tests. *Moran et al.* (11) made a distinction between asthmatic and bronchitic symptoms in the patients and found a strong association between allergic asthma and improvement on cromoglycate.

According to Table 3 a relatively greater frequency of positive house dust reactions was found in our group A; no difference in the number of reactions to human dander.

No positive reaction with a series of allergens (pollen, groups of fungi, danders, dusts) was found in 3 patients, of which 1 belonged to Group A and 2 to Group B.

Positive sputum: on an average 1 out of 4 sputa per patient contained pathogenetic micro-organisms: in this respect the groups were completely equal.

Jones & Blackhall (6) described a better therapeutic result with cromoglycate in what they term "labile" cases, who generally have a normal or almost normal lung function between attacks.

In our patients we examined three spirograms, carried out in 1969, each time before and after an injection with thiazinamium. If at least one spirogram was normal immediately this was called "spontaneous" reversible; if all three spiro-

grams were outside the normal range after thiazinamium this was called "non-reversible"; if at least one became normal it was called "reversible".

TABLE 4
Reversibility of Spirograms. Groups as in Table 3.

Group	A	B	C
"Non-reversible"	2	6	3
"Reversible"	7	5	2
"Spontaneous"	3	—	1

The bronchial hyper-reactivity, measured with increasing doses of histamine aerosol, was raised in all patients, with no difference between groups; no patient required a higher level than 8 mg/ml histaminebisulphate to cause a minimum fall of 10 per cent in the V.C.; in the majority of cases the dose was 2 or 4 mg/ml. Before admission 19 out of 29 patients used corticosteroids, 8 during the admission; in this respect also, there was no difference between the groups.

We conclude that in this material there are no significant differences between the patients who responded more and those who responded less, to treatment with disodium cromoglycate. The most that can be said from these figures is that in the group that reacted more favourably there are less patients with a deformed thorax and there are more patients with spontaneous reversible spirograms, with high blood-eosinophilia and positive housedust tests.

When we consider this discussion and the data presented we come to the conclusion that our material is rather too homogeneous for the differences to be easily seen. Moreover it consists of relatively serious cases, being children that are sent to a centre because of their asthma. The trial cases came from children not improving spontaneously. In addition they were examined in Autumn, the period in which the asthma symptoms tend to increase. On the other hand only one patient had to be treated with corticosteroids continuously during the trial. Furthermore it is our experience that children,

sent to an asthma centre, are often selected on the ground of co-existing psycho-social difficulties. This fact may be taken into account in estimating the comparatively small response to treatment in our group of children.

Our overall impression is that the clinical usefulness of this sort of drug, which is non-symptomatic and, generally, neither immediate nor very powerful in its actions, cannot easily be studied with this kind of experimental design, when the disease is as variable as asthma.

SUMMARY

In 29 asthmatic children in the age of 6-16 years, admitted to a home for asthmatic children, a double-blind crossover trial was carried out with inhalations of disodium cromoglycate during 4 weeks and placebo during 4 weeks. A statistically significant therapeutic result of the active drugs as compared with placebo could be proved. The peak flow rate generally showed a good agreement with the symptoms (asthmascore) as indices of the asthmatic condition during the different periods of the trial. There were no side-effects of importance. Differences between the type of patients who did respond and those who did not were unclear. This, and the limited effect, may be connected with the selection of the material.

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