

## PAPERS AND ORIGINALS

# Beclomethasone Dipropionate: A New Steroid Aerosol for the Treatment of Allergic Asthma

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## Summary

Beclomethasone dipropionate was used in pressurized aerosols for the treatment of 60 cases of chronic allergic asthma for up to 15 months. Twenty-eight out of 37 cases were transferred to this treatment after being dependent on oral steroids for up to 16 years. Nineteen out of 23 other asthmatics not dependent on steroids were also completely controlled. No biochemical evidence of adrenal suppression was found. Steroid withdrawal symptoms were often a problem, suggesting absence of systemic absorption. The precise mode of action and metabolic fate of this corticosteroid are not yet known.

## Introduction

It has been obvious since the very early days of steroid therapy for allergic asthma that the deposition of the active drug directly on to the bronchial mucosa by means of an aerosol could be an advantageous method of treatment. The drug would be delivered only at the site where it was required. The local concentration could be high, yet systemic absorption minimal and the side effects of steroid therapy avoided.

Attempts to establish this method have been the subject of reports by many investigators from Gelfand (1951) onwards, including studies by Brockbank *et al.* (1956), Brockbank and Pengelly (1958), Helm and Heyworth (1958), Herzheimer *et al.* (1958), Smith (1958), Bickerman and Itkin (1963), Brown (1963), and a further publication, including a review of nine others, by Kravis and Lecks (1966). Hydrocortisone was used as powder by early investigators, and later dexamethasone phosphate in pressurized aerosols by others, with varying degrees of success. However, systemic absorption of dexamethasone with

typical steroid side effects was noted by Siegel *et al.* (1964), Novey and Beall (1965), and Toogood and Lefcoe (1965). Biochemical evidence of adrenal suppression was reported by Linder (1964). Systemic absorption of dexamethasone thus proved an insuperable problem which rendered administration of this steroid by aerosol rather pointless.

Beclomethasone dipropionate, which has already been used for some years as a topical ointment for eczema, does not suffer from this defect. This compound was used in aerosol form for the present trial.

## Case Selection

Sixty patients were selected for the trial from both National Health Service and private practices. All except one were stable perennial asthmatics, as shown by observation over a period of from six months to 16 years. Sputum examination in 59 cases showed a significant excess of eosinophil cells. Intensive investigation of allergic factors and treatment, when indicated, using the methods described by Brown (1970) had been ineffective or unhelpful. Thirty-seven of the patients had been continuously dependent on steroid therapy for from 1 to 16 years, taking total daily doses of from 0.5 to 1.5 mg of betamethasone or 5 to 15 mg of prednisolone. Repeated attempts at steroid withdrawal had resulted in relapse. Thirty-five of the steroid-dependent group had previously taken part in a trial (unpublished) of disodium cromoglycate but only four had improved.

The cases were not classified as intrinsic or extrinsic, but simply as perennial allergic asthma. The extent of the reversibility of the airways obstruction in each case varied widely, and steroid-dependent patients were well indoctrinated to take the minimum dose possible. As shown in Table I 14 patients were

TABLE I—Steroid-dependent Group (37 Patients)

Steroid withdrawal symptoms . . . . .	17			
Worsening of eczema . . . . .	4			
Unmasking of allergic rhinitis . . . . .	5			
Disodium cromoglycate { Not tried . . . . .	2	Peak flow {	Better . . . . .	25
{ Ineffective . . . . .	31		No change . . . . .	7
{ Helpful . . . . .	4	{ Worse . . . . .	4	
Steroid therapy side effects evident . . . . .	28	Successful transfer to aerosol . . . . .		28
		Occasionally needed short-term steroids . . . . .		13
Corticotrophin { Ineffective (200 units) . . . . .	14	Failed transfer . . . . .		9
{ Responsive . . . . .	10	Failed on account of frequent infections . . . . .		2
{ Not known . . . . .	13			

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period of at least two weeks preceded the introduction of the aerosol. Many patients had already been keeping peak flow records for long periods as part of an intensive investigation. When the patient was seen again, if record-keeping was good aerosol therapy was started, but if record-keeping was inadequate the case was rejected as unsuitable.

In steroid-dependent patients the aerosol, 100 µg four times a day, was added to the usual daily dose of oral steroids for four days, after which the oral steroid was gradually phased out over the next three to four days. For example, a patient taking 10 mg of prednisolone daily would reduce the dose by 2.5 mg/day, or if on betamethasone 1 mg daily, by 0.25 mg/day.

Peak flow readings were averaged over at least two weeks before the aerosol was introduced, readings over periods of many months being available in those patients who were being studied intensively. The average readings after the introduction of the aerosol were taken from a two-week period beginning from two weeks after the transfer to the aerosol or from the point at which the peak flow rate had become stabilized.

**Results**

**STEROID-DEPENDENT GROUP (37 CASES)**

These 37 cases are summarized in Fig. 2 and Table I, which also shows the "side effects" encountered in introducing the aerosol. Seventeen steroid-dependent patients experienced withdrawal symptoms to a greater or lesser degree. These consisted of tiredness, lassitude, headache, aches and pains, depression, and occasionally emotional instability, lasting for a week or longer. All but three were already known not to respond to cortico-

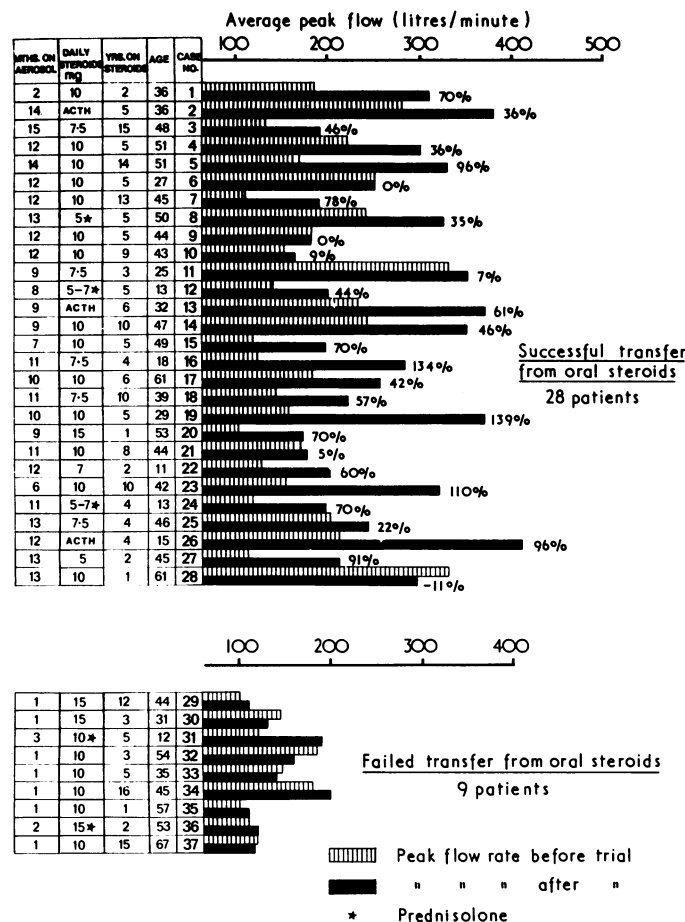


FIG. 2—Steroid-dependent group. The steroid usually preferred was betamethasone but the dosage has been expressed as an equivalent dose of prednisolone to render evaluation easier; 0.5 mg of betamethasone has been taken to equal 5 mg of prednisolone. Cases treated with prednisolone are indicated by an asterisk. Comparative averages of peak flow readings taken from two-week periods before and for two weeks after established on aerosol.

trophin. This was so common that we soon began to warn patients in advance that they might have to endure all the discomforts of relative adrenal insufficiency even though their peak flow meter readings might be the same or even much better than before. No serious episodes of adrenal insufficiency occurred in any case.

Five patients complained bitterly of allergic rhinitis and four of a worsening of eczema after transfer to the aerosol steroid. This surprising finding suggests that lack of exogenous oral corticosteroid in the blood stream, contrasting with local suppression of the bronchial allergy, had unmasked latent allergic symptoms in the nasal mucosa or skin. This finding contrasts markedly with the reports of Novey and Beall (1965) and of Toogood and Lefcoe (1965), who observed (and photographed) pronounced Cushingoid effects from dexamethasone phosphate aerosols. Moonface became less evident in those in whom this side effect was prominent. One patient who had been on steroids for 10 years was delighted by the fact that many of her friends failed to recognize her in the street. On their own these effects suggest that systemic absorption of the steroid is negligible, quite apart from the results of tetracosactrin and insulin tests shown in Fig. 3.

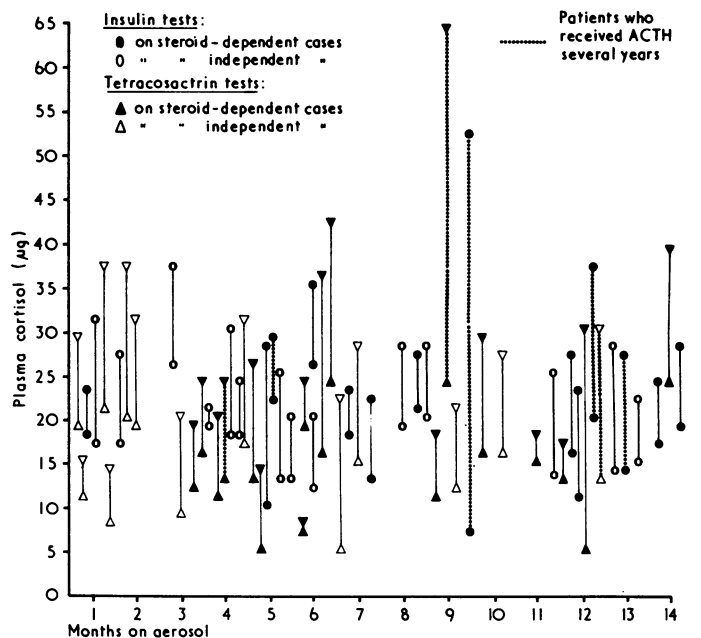


FIG. 3—Adrenal function tests in 29 patients, at up to over a year on aerosol steroid, showing the rise in plasma cortisol achieved as a result of direct and of indirect adrenal stimulation. There is no evidence of decrease in response with duration of treatment. Twelve patients had serial tests at wide intervals, again with no evidence of adrenal suppression.

We are particularly interested in this surprising effect because nasal provocation tests can still be carried out without the usual difficulty of the masking of positive results by oral steroids. Previously it had been necessary to omit steroids on the day of a provocation test.

If the patient cannot inhale enough air it follows that he cannot inhale enough aerosol of any kind for it to be effective. This simple fact should be obvious, but surprisingly this is not always so. Thus if a patient had severe airways obstruction, whether on or off steroids, it was essential to use high-dosage steroid therapy for a short time to clear the bronchi and thus allow the aerosol to become fully effective.

The best example of this type of case is illustrated in Fig. 4 which refers to a case of late-onset asthma of three years' duration in a man aged 45. During the control period he became progressively worse. As shown, the aerosol was first introduced in an attempt to gain control without using oral steroids, but it had an irritant effect, causing severe bronchospasm lasting half an hour or more, and it became obvious that oral steroids were essential. However, once his peak flow had risen markedly on oral steroids

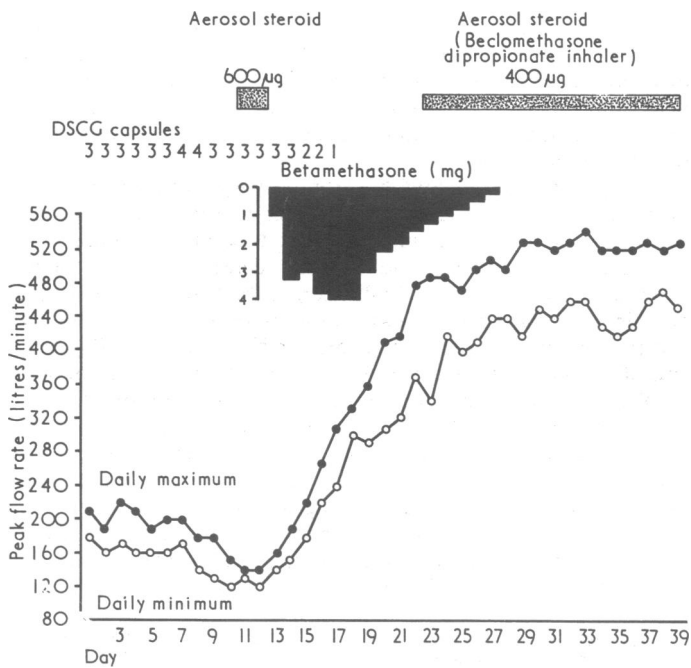


FIG. 4—Man aged 45. Late-onset asthma—allergens unknown. A good example of the uselessness of aerosol therapy until airways cleared by high-dosage steroids. Disodium cromoglycate (DSCG) had been used for a year but was no longer effective. High level maintained to date on aerosol alone. The aerosol actually caused bronchospasm when first introduced. This case is not included in the present series as the patient was seen subsequently, but it is shown on account of its outstanding interest.

it became possible to phase them out and take over control with aerosol alone.

It is relevant to mention that our normal practice in recent years has been to assess reversibility of allergic asthma under peak flow meter control by giving 4 mg of betamethasone, or 40 mg of prednisolone, daily until no further increase in readings takes place. Betamethasone has been preferred for many years for most cases, mainly because of freedom from peptic ulceration, as reviewed by Brown (1961). To assess reversibility with isoprenaline aerosols has not, in our hands, been a useful manoeuvre.

Three cases were transferred from corticotrophin and 10 were known to respond well to corticotrophin gel or long-acting tetracosactrin. It was notable that none of them had any with-

drawal symptoms. In contrast, all 14 of those known not to respond to these hormones had severe withdrawal symptoms.

The failures in both groups, as can be seen from the relatively poor peak flow, were rates in cases where a good result would have been surprising as they were already known to be almost completely irreversible. Careful exclusion of such cases would obviously have produced a much better result in this trial, but it was considered more ethical to give them a chance. Other cases of this type (Cases 6, 9, 11, 21, and 28) did not show objective improvement on aerosol, but the fact that they became independent of oral steroids was regarded as most gratifying and they were considered successful transfers.

STEROID-INDEPENDENT GROUP (23 CASES)

There were seldom difficulties in establishing these patients on the aerosol, except in the failures. The results are shown in Table II and Fig. 5. No side effects whatever were noted in this

TABLE II—23 Patients Requiring Occasional Steroid Therapy or Never Required Steroid Therapy

Intermittent steroids	..	16	Completely established on aerosol	..	19
Never given steroids	..	7	Occasional loss of control during infections	..	4
Disodium cromoglycate	{	6	Failure to transfer	..	4
	{	2			
	{	15			

group of cases. The failures were undoubtedly due to lack of reversibility and a dominant factor of permanent structural damage or chronic infection. Stricter selection of patients would have excluded these unfortunate patients from the trial.

A striking feature which is not illustrated or counted, and which applies to all successful cases, is the very remarkable reduction in requirement for bronchodilator drugs and aerosols. Most patients finally required only the steroid aerosol on its own. One patient commented that when he found that he had forgotten his bronchodilator one evening he did not panic as he would previously have done, and thereafter never bothered to carry it at all.

EFFECTS OF AEROSOL ON PEAK FLOW READINGS

Extreme examples of one of the major differences between the effects of oral and aerosol administration of steroids are given in

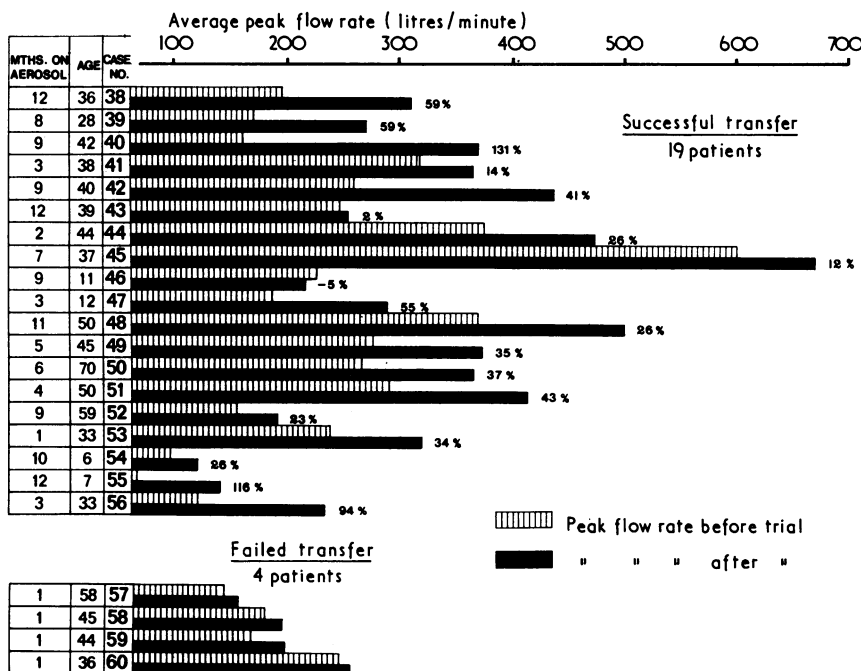


FIG. 5—Steroid-independent cases. Comparison of average peak flow readings for 14 days before and 14 days after establishment on aerosol. Case 45 would not seem severe enough to justify this treatment, but the main complaint was incessant cough which responded only to oral steroids. The cough was completely suppressed by the aerosol in 24 hours.

Figs. 6 and 7. This is the virtual abolition of the violent diurnal variations in peak flow which commonly occur in the labile asthmatic.

Many cases are certainly much better controlled by this aerosol than by oral steroid, a surprising finding that is possibly related to the effects of this compound on the bronchial mucosa. It should be clear that the increases in average peak flow are in many cases surprisingly great, suggesting that the local effect of the aerosol was much greater than that of their usual dose of oral steroid. The dosage which would have been required to maintain an equivalent peak flow could not have been continued on a long-term basis without serious side effects.

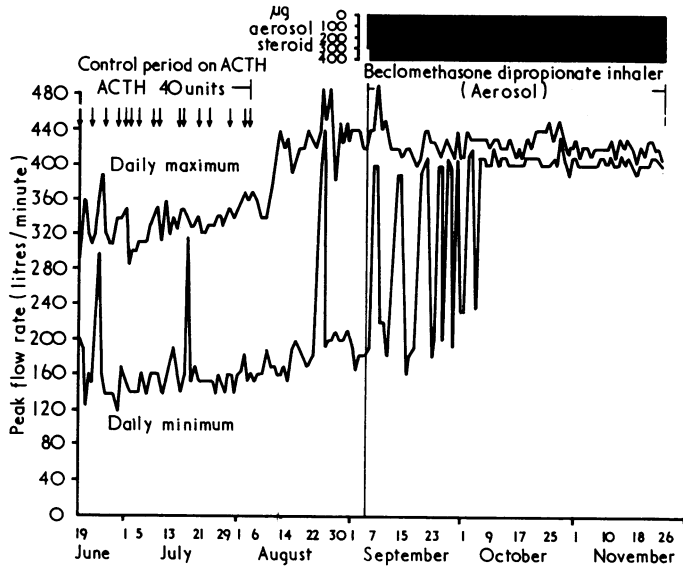


FIG. 6—Boy aged 14. Perennial asthma since age of 3. Steroid therapy for five years and transferred to corticotrophin (ACTH) two years previously. Example of abolition of diurnal variation on aerosol. Known allergens—penicillium and aspergillus. Desensitization only partly successful.

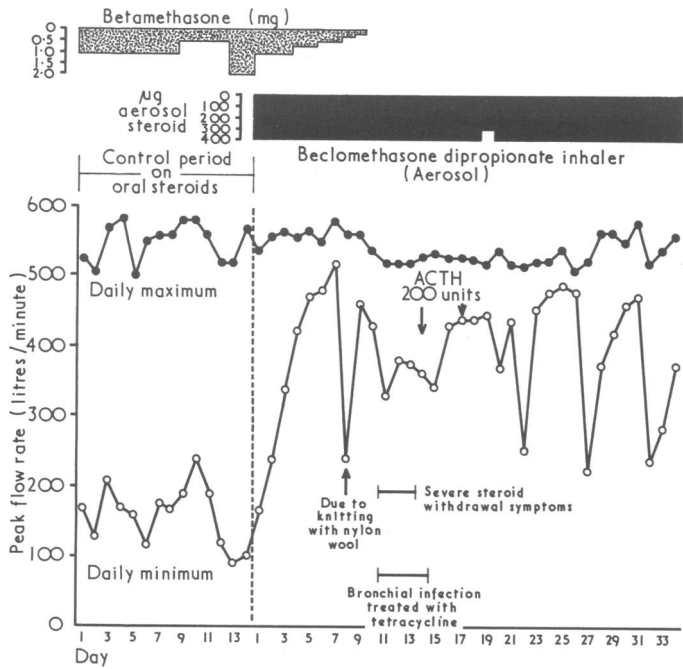


FIG. 7—Married woman aged 28. Severe chronic perennial asthmatic. Frequent episodes of status asthmaticus. Steroid-dependent six years. Usual maintenance dosage 1-1.5 mg of betamethasone. Moonface, osteoporosis, and bruising. Marked withdrawal symptoms and no response to 200 units of corticotrophin gel. Allergens unknown, but coal-tar derivatives strongly suspect. Swings of peak flow from 60 l./min at 6 a.m. to 600 l./min at 6 p.m. were a constant feature of this patient on oral steroids. Subsequently proved difficult to maintain on aerosol alone because of frequent infections.

USE OF AEROSOL STEROID IN CHILDREN

We are most impressed with the results in nine children who were trained to use a pressurized aerosol from the age of 6. Five had been on oral steroids, with serious effects on growth, for periods of some years before referral, and attempts to identify the responsible allergens were unsuccessful so that there was no prospect of cessation of steroids. Resumption of growth was remarkable, two children gaining 2 in (5 cm) in six months and another 3 in (7.5 cm) in a year. Measurements on the others were unfortunately omitted but growth had obviously been resumed. Control of the asthma was complete in four of the cases; the other child was liable to frequent infections. Unmasking, or increase in, atopic manifestations such as eczema has been troublesome in two cases.

The four children who were not steroid-dependent were all markedly improved and completely controlled. One of the striking examples is illustrated in Fig. 8, where serial records of

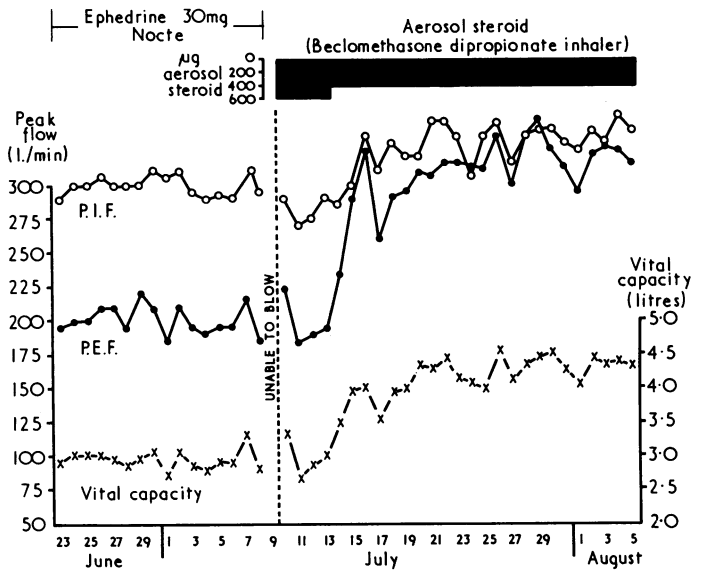


FIG. 8—Boy aged 12. Chronic perennial asthma five years. Never required steroids but seemed likely to do so just before aerosol began. Allergens unknown in spite of extensive investigation. Wright Respirometer used for serial vital capacity measurements. Peak inspiratory flow obtained by use of peak flow meter modified according to Nairn and McNeill (1963). Note the effects of the aerosol on the peak expiratory flow which soon becomes almost equal to the peak inspiratory flow.

peak inspiratory and expiratory flow, using a meter modified according to Nairn and McNeill (1963), and also vital capacity, using a Wright Respirometer, were obtained, thanks to the very high degree of co-operation from his mother. The relationships of these measurements as shown are of great interest.

EVIDENCE OF LACK OF SYSTEMIC ABSORPTION

Tetracosactrin tests and insulin hypoglycaemia stress tests, as described by Landon *et al.* (1963), were carried out in 27 cases and the results are presented in Fig. 3. Plasma cortisol was estimated by the method of Mattingly (1962). Two or more serial adrenal function tests were carried out at intervals of from 6 to 14 months in 12 patients. We would have preferred to do more serial tests, but for a multiplicity of reasons this was impossible. However, in none, whether steroid-dependent or not, was there any evidence of adrenal suppression with either type of test.

Apart from the biochemical data, the steroid withdrawal symptoms and the unmasking of allergic manifestations can be reasonably assumed to indicate absence of significant absorption

of the aerosol steroid. Serial liver function and full blood examinations have disclosed no abnormality in any of the cases.

In order to obtain further evidence regarding possible adrenal suppression three volunteer subjects inhaled excessive quantities of the aerosol daily for two days, following several daily basal cortisol estimations. The results are shown in Fig. 9, and from

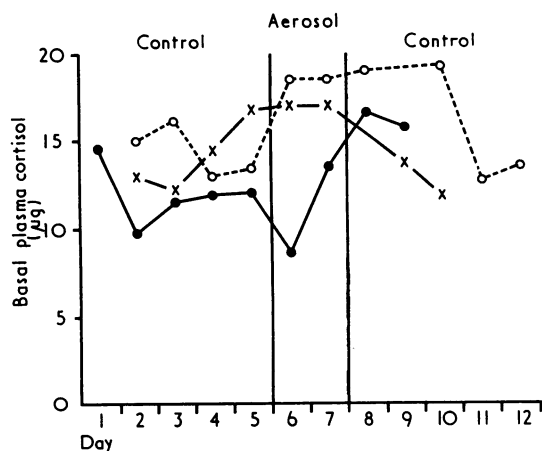


FIG. 9—Effects of inhaled beclomethasone dipropionate on the morning basal cortisol. An aerosol delivering 250 µg per puff was used eight times a day, for two days, in one healthy volunteer (X-X) and a patient (●-●), who had already been on 400 µg daily for six months. Another volunteer (O---O) took 4 mg daily for two days.

this it is clear that in at least three subjects there is no evidence whatever of the occurrence of adrenal suppression in higher dosages than have been used normally in the treatment of patients.

### Conclusions and Discussion

Beclomethasone dipropionate aerosol would seem to provide an alternative to long-term oral steroid therapy in many cases of chronic perennial asthma. Effective control of the asthma is achieved with no evidence of systemic absorption or of steroid side effects. The exact mode of action of this compound remains to be fully elucidated.

The best results are in the younger and more reversible cases. The abolition of diurnal fluctuation is a surprising feature. It is possible to substitute this therapy for long-term oral steroids even when taken for many years. Steroid withdrawal symptoms, and unmasking of hitherto suppressed allergic manifestations, have presented interesting problems.

Selection of pure allergic asthmatics, or cases where the allergic factor is dominant, is a sine qua non of this, or any other,

trial of a steroid preparation in allergic asthma. Care has been taken to exclude seasonal cases, where daily fluctuations of airborne allergens can cause wide variation in peak flow.

It cannot be overemphasized that these patients are in a precarious condition in the event of trauma or infection. It is essential that they be instructed to resume oral steroids in high dosage without delay, when obviously necessary, without waiting for medical advice. They must carry warning cards clearly indicating their potentially dangerous situation.

Such serious problems do not arise in relation to patients who have had only occasional steroid therapy, or have never required it. On the data presented here there seems to be no contra-indication to the use of this preparation by mild asthmatics who would not normally be considered for the use of corticosteroids. As many of them had already failed to respond to disodium cromoglycate this new therapeutic approach may have much to offer, especially in paediatrics. In all types of case considerable clinical expertise and experience of the management of allergic asthma may be required during the transfer period.

This method of treatment has no place whatever in status asthmaticus. Those unable to inhale air surely cannot inhale enough aerosol to have any effect. The presence of excess bronchial mucus and often pus must also form a barrier the aerosol cannot penetrate. The future role of aerosol therapy is clearly confined to maintenance of airway patency and prevention of attacks.

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