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BECLOMETHASONE DIPROPIONATE AEROSOL IN LONG-TERM TREATMENT OF PERENNIAL AND SEASONAL ASTHMA IN CHILDREN AND ADULTS: A REPORT OF FIVE-AND-HALF YEARS' EXPERIENCE IN 600 ASTHMATIC PATIENTS

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1 Clinical experience in the long-term treatment of allergic asthma with beclomethasone dipropionate aerosol (BDA) during the past five-and-half years is reviewed. A total of 600 patients from National Health Service and private practice, including 176 children, was treated.

2 A total of 241 patients, including 57 children, was corticosteroid-dependent for 1–18 yr. Of these patients, 70% were successfully transferred to BDA, 21% could be only partially transferred, and 9% could not. Over the years, 12% had to revert to oral corticosteroids, but 4% were able to stop BDA without relapse. Oropharyngeal thrush was observed in 16%, but in only two cases did treatment have to be withdrawn on that account. There were no deaths from asthma, and seven normal births.

3 A total of 359 non-corticosteroid-dependent asthmatics, including 119 children, were also treated with BDA. Successful control of symptoms was achieved in 99%, but 4% eventually became corticosteroid-dependent. There were three deaths from asthma and 13 normal births. Fifteen per cent were able to stop treatment without relapse. Five per cent developed oropharyngeal candidiasis, but treatment did not have to be stopped on that account.

4 In 35% of both groups, a preliminary course of oral corticosteroid at high dosage was required before the introduction of BDA therapy. Sixty-two patients were treated for over 5 yr, and approximately 1350 patient-years of BDA have been given without evidence of side-effects.

5 Thirty-one corticosteroid-dependent and 73 non-corticosteroid dependent patients with perennial asthma had 231 seasonal episodes, effectively controlled in 68%, and 38 purely seasonal asthmatics had 100 episodes, with good control in 80% of cases.

Introduction

Since our first clinical trial was published (Brown *et al.*, 1972), many other investigators have confirmed that beclomethasone dipropionate aerosol (BDA) is effective in the control of asthma. We have confirmed our original findings in children with seasonal asthma and hay fever, and have reported our long-term experience in the treatment of perennial and seasonal asthma, and also allergic rhinitis (Brown & Storey, 1973, 1974, 1975; Brown *et al.*, 1977). The place of any new remedy in therapeutics can be established only after long experience, and the purpose of this report is to review our results for the five-and-half year period from June 1970 to December 1975.

Case selection and methods

The indications for treatment with BDA have not altered since the first clinical trial, excess of eosinophil cells in the sputum or nasal smears being demonstrable in all cases (Brown, 1958). Intensive investigation of allergic factors, using methods described previously, was undertaken in every case (Brown, 1970). Objective data on the severity and diurnal patterns of airways obstruction and response to treatment were obtained by issuing peak flow meters (PFM) for individual use. The minimum pretreatment control period on PFM monitoring was 2 weeks, but many patients were monitored before treatment for months or even years. All patients had been suffering

from asthma for at least one year.

Dosage and administration of BDA

BDA was administered by metered aerosol (50 μg per 'puff'). After preliminary complete expiration, the aerosol was discharged simultaneously with a sudden deep inspiration. This is essential to ensure that BDA reaches the bronchi. Personal instruction was given in the use of the aerosol, and the patient's technique was checked at several visits until satisfactory. The patients were told that BDA does not act immediately, that it must be taken on a regular daily basis, and that reduction in dosage must be made gradually. Many patients had already had a trial of the treatment on the advice of their general practitioners, but few of them had benefitted from it because of incorrect usage of the aerosol or inadequate dosage. Placebo aerosols are useful for demonstration purposes, since many patients use bronchodilator aerosols incorrectly. A salbutamol aerosol used shortly before the inhalation of BDA helps to ensure that the corticosteroid aerosol reaches the bronchi.

It must be emphasized that if a patient is short of breath, he will have difficulty in achieving effective inhalation of an aerosol. When airways obstruction is severe, BDA may cause bronchial irritation, and the asthma may become worse. In this situation it is necessary to relieve the airways obstruction by an adequate course of oral corticosteroids in high dosage before introducing BDA. Doses of prednisolone of up to 40 mg daily for a week or more are frequently necessary in these circumstances.

In the past 3 yr we have found that the most practical dosage of BDA is three metered doses three times daily. Initially, we used two doses four times daily, but the mid-day dose was often forgotten, or was inconvenient to take at school or at work. In children, and in adults where there is a difficulty in usage, it is advisable to prescribe three metered doses four times daily initially, since very little may reach the bronchi until the correct technique is used.

Corticosteroid-dependent group (241 cases)

This group comprised 229 asthmatics who had been corticosteroid-dependent for 1–18 yr, and 12 who had been given corticotrophin for 1–5 yr. Many attempts to withdraw corticosteroids had been unsuccessful, the degree of airways obstruction varied widely, and the age range was from 2.5–68 yr. Daily dosages were 0.5–1.5 mg betamethasone phosphate (Betnesol), a soluble corticosteroid unlikely to produce gastric side-effects (Brown, 1961).

Method of transfer

Transfer from oral to aerosol corticosteroids was effected by adding BDA to the regimen, and gradually phasing out oral treatment. In our initial studies (Brown *et al.*, 1972) corticosteroids were withdrawn too quickly. Our present practice is to transfer the patients to 1-mg prednisolone tablets, equivalent to their usual total daily maintenance dose, and then to reduce the dose by 1 mg daily with regular PFM monitoring. Much slower withdrawal is necessary when corticosteroids have been used for a long period, the speed of withdrawal being a matter of clinical judgment. An obvious recurrence of symptoms was seldom observed until the maintenance dose of prednisolone was down to 3 mg daily.

All ex-corticosteroid-dependent patients were given a personal supply of prednisolone for emergency use, with clear instructions on the dosage to be taken in the event of an asthmatic attack. A yellow warning label was affixed to their 'steroid cards' regarding suppression of adrenal function for up to 2 yr.

Table 1 Results in 229 corticosteroid-dependent and 12 corticotrophin-dependent cases (31 also seasonal)

Age commenced treatment with BDA (yr)	*2–14*		*15–29*		*30–44*		*45–59*		*60+*		*Overall result*	
	Number	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Total completely transferred	51	90	18	64	47	73	38	59	13	48	167	70
Increase in average PEF	23	40	0	0	18	28	13	20	2	7	56	24
100%+	19	34	6	21	16	25	9	14	7	26	57	24
50–100%												
0–50%	9	16	12	43	13	20	16	25	4	15	54	22
Partial transfers	3	5	9	32	12	19	19	29	9	33	52	21
Failed transfers	3	5	1	4	5	8	8	12	5	19	22	9
Totals	57		28		64		65		27		241	
Late failures	3	5	3	12	9	14	13	20	1	4	29	12

Results

Table 1 shows that the best results were obtained in the younger age groups. The large number of patients in whom the peak expiratory flow (PEF) was more than doubled suggests that the maintenance dose of oral corticosteroids in these cases may have been inadequate for full control, although the optimum dose would undoubtedly have produced unacceptable side-effects.

Oral corticosteroids were withdrawn in 70%, and the failure rate was only 9%. In the remaining 21%, the dose of oral corticosteroid was reduced, indicating that BDA had a corticosteroid-sparing effect. Dosage in this group varied from 3–5 mg prednisolone daily. The data show that the degree of reversibility decreases, and the incidence of failure and partial transfer increases, with advancing years. Even those in the older age groups, who could be only partially transferred to BDA were, however, much better controlled. Partial transfers became more common as larger numbers joined the group. Late failures are a new category, where control by BDA alone was eventually lost in 12% and a return to oral corticosteroids was unavoidable.

Relief of side-effects and complications on transfer Table 2 summarizes these aspects of transfer, the most obvious beneficial effect being loss of Cushingoid features. Atrophic changes in the skin were slow to recover, and were never complete, but the tendency to bruise often became less marked within a month of transfer. Improvement in osteoporotic changes in the vertebrae could be assessed only by the disappearance of back pain. Reduced insulin requirements in two cases with concomitant diabetes have already been reported (Brown & Storey, 1973), but the child whose diabetes was unmasked only when he had to be given high doses of oral corticosteroid has now become an established diabetic.

Withdrawal rhinitis, eczema and nasal polypi caused problems in 65 patients. Oral corticosteroid therapy must have suppressed these allergic phenomena, which were unmasked on transfer to BDA. Long-term results of BDA therapy in nasal allergy are being reported separately (Brown & Storey, 1977).

Table 2 BDA in treatment of corticosteroid-dependent asthma, relief of side-effects and complications of transfer in 241 cases

Regression of moon face and loss of weight	85
Diabetes mellitus: reduced insulin requirements	2
Steroid-induced dyspepsia	15
Osteoporosis	10
Unmasking of allergic rhinitis	37
Exacerbation of eczema	20
Tiredness, lassitude, and aches and pains	80
Recurrence of polypi	8
Regression of skin atrophy and bruising	24

Eighty patients experienced obvious corticosteroid withdrawal symptoms lasting for various periods, being most severe after many years of treatment. Two patients refused to endure such symptoms, preferring to continue on oral corticosteroids, and 52 of the whole group of 241 became partial transfer cases, remaining well controlled on prednisolone 3–4 mg daily plus BDA.

Corticotrophin seemed ineffective in alleviating withdrawal symptoms, although perhaps it was not continued for a sufficiently long period, as suggested by Hugh-Jones *et al.* (1975). Tetracosactrin zinc produced acute hypokalaemia in two patients, possibly because of the differential effect of stimulating an intact and functioning zona glomerulosa and an atrophic zona fasciculata of the adrenal glands. Encouragement and reassurance that patience would have its reward seemed the best approach. All these effects have been noted in previous publications, and have become familiar to all who have been involved in using this treatment in corticosteroid-dependent asthmatics.

Long-term dosage levels and value of clinical allergy techniques Table 3 summarizes maintenance dosage levels of BDA required after transfer. A few patients required larger doses of 600 µg daily, the usual dose being 450 µg daily. In 29% a smaller dose proved adequate.

As shown in Table 6, 80 (33%) patients in this group had been taking BDA for over 3 yr, 131 (54%) for over 2 yr and 169 (74%) for over 1 yr. Twelve patients were able to stop treatment without relapse, but 20 have been lost to follow-up. Twenty-five of the original series have now been maintained on BDA for over 5 yr, without loss of control except for an occasional exacerbation requiring a short course of oral corticosteroid. The incidence of infection has not been higher than before BDA therapy, and in some cases it has been lower.

At this Centre, intensive allergy studies are carried out on all patients, but specific hyposensitization is undertaken only if objective proof is indicated by nasal provocation tests (Brown, 1970). It would have been unethical to withhold such treatment in long-term patients, and the use of hyposensitization made possible the transfer to BDA of 51 (21%) patients in this group. Thus, the failure rate without hyposensitization would have been 30% in this group of corticosteroid-dependent patients. A further six patients were able to stop all treatment because of avoidance of known allergens or hyposensitization, whereas another six stopped treatment without relapse for no ascertainable reason.

Oropharyngeal candidiasis The incidence of

oropharyngeal candidiasis is noted in Table 3, where it is clear that this problem, along with hoarseness, is much more common in corticosteroid-dependent patients. There was no doubt that this side-effect was dose-dependent, and usually responded rapidly to amphotericin B lozenges; but in two cases BDA had to be withdrawn. Evidence of infection was not sought routinely, nor were routine mycological investigations carried out, as in the studies of McAllen *et al.* (1974), Brompton Hospital/MRC Collaborative Trial (1974) and Milne *et al.* (1974). Patients are now instructed to drink or gargle immediately after inhaling BDA to prevent the aerosol from being deposited on the pharyngeal mucosa. Hoarseness was troublesome in some cases, but laryngoscopy disclosed no evidence of *Candida albicans* infection of the larynx.

Miscellaneous aspects Table 4 illustrates that in 37% of patients the airways obstruction was so severe as to require initial treatment with oral corticosteroids in high dosage. The dose was then tapered off, and BDA introduced when the dose of prednisolone was down to 15 mg daily. At this stage, the airways obstruction had usually been substantially relieved, and the patient had no difficulty in inhaling the aerosol.

Out of 57 corticosteroid-dependent children 34 (60%) began to regain the growth they had lost while on oral corticosteroid therapy. In this group seven normal babies have been born. No patient died from asthma, two died from myocardial infarction and two from other causes.

Table 3 BDA in treatment of asthma

Maintenance dosage level and other data	*241 Corticosteroid-dependent cases*	%	*359 Non-corticosteroid-dependent cases*	%
600 µg	36	15	25	7
450 µg	115	48	173	48
300 µg	35	15	85	24
200 µg or less	33	14	71	20
Difficulty in transfer or in stabilization before hyposensitization	51	21	52	14
Stopped without relapse without hyposensitization	6	2	35	10
Stopped without relapse because of hyposensitization or avoidance	6	2	19	5
Candida albicans infection once or more	38	16	17	5
Hoarseness	16	7	5	1

Table 4 BDA in treatment of asthma (miscellaneous data)

		241 Corticosteroid-dependent cases		*359 Non-corticosteroid-dependent cases*	
		Number	%	*Number*	%
Initial high dose oral corticosteroids necessary		89	37	122	33
Growth restarted		34	14	12	3
Sodium cromoglycate	Effective	28	12	45	13
	Ineffective	146	60	139	39
	Not tried	67	28	170	47
Aspergillosis effectively treated		7	3	6	2
Aspergillosis not effectively treated		9	4	0	0
Died of asthma		0	0	3	1
Died of cardiac causes		2	1	3	1
Died of other causes		2	1	0	0
Normal babies delivered		7	3	13	3

Causes of failure to transfer to BDA Table 5 shows that infection and hypersecretion, which must prevent the aerosol from penetrating to the bronchial mucosa, are the most common causes of failure, partial failure or late failure to transfer from oral to aerosol therapy. The irreversible allergic group had sputum containing abundant eosinophils, but no improvement in airways obstruction was obtained either with large doses of oral corticosteroid or with BDA. A few cases admitted to the study in error without sputum examination were later found unresponsive, and were shown to have typical bronchitic sputum cytology, with excessive numbers of macrophages but no eosinophils (Brown, 1958).

Table 7 compares the results of BDA in 'extrinsic' and 'intrinsic' types of asthma. A better response was usually obtained in the 'extrinsic' group.

Allergic bronchopulmonary aspergillosis In 22 cases of allergic bronchopulmonary aspergillosis,

Table 5 BDA in treatment of allergic asthma (causes of failure)

	Corticosteroid-dependent			*Non-corticosteroid-dependent*	
	Initial failure	*Partial transfer*	*Late failure*	*Initial failure*	*Late failure*
Frequent infection and hypersecretion	4	24	16	3	6
Persistent thrush	2	—	—	—	—
Irreversible allergic	9	28	11	2	8
Not allergic	3	—	—	—	—
Passed from allergic to bronchitic phase	—	—	2	—	—
Irritation in use	2	—	—	—	—
Totals	20	52	29	5	14

Table 6 BDA in treatment of perennial asthma (duration of treatment to 31 December, 1975)

	241 Corticosteroid-dependent cases		*359 Non-corticosteroid-dependent cases*	
Duration of treatment	*Number*	*%*	*Number*	*%*
5–5.5 yr	25	10	37	10
4–5 yr	22	9	76	21
3–4 yr	33	14	77	21
2–3 yr	51	21	61	17
1–2 yr	38	16	23	6
6–12 months	40	17	6	2
Stopped without relapse	12	5	54	15
Lost to long-term follow-up, presumably still on treatment	20	8	25	8

Table 7 BDA in treatment of asthma (comparison of results in extrinsic and intrinsic classes)

	241 Corticosteroid-dependent				*359 Non-corticosteroid-dependent*			
	Intrinsic	*%*	*Extrinsic*	*%*	*Intrinsic*	*%*	*Extrinsic*	*%*
Over 100% increase in PEF	19	18	37	27	40	40	85	33
50–100% increase in PEF	17	17	40	29	33	33	105	41
0–50% increase in PEF	24	23	30	22	27	27	64	25
Partial transfer	30	29	22	16	–	–	–	–
Complete failure	13	13	9	1	1	1	4	1
Totals	103		138		101		258	

good results were obtained (Table 4) without any overgrowth of fungus in the sputum. Only three of this group were excreting *Aspergillus fumigatus* in sputum, but all had at one time the appropriate X-ray findings, and Type 3 skin reactions. Not all had precipitins in the serum, and our experience was similar to a previous report (Hilton & Chatterjee, 1975), using the same diagnostic criteria.

Non-corticosteroid-dependent group (359 cases)

Table 8 summarizes the overall results, by age groups and by degree of reversibility. In many cases the degree of airways obstruction was more severe than in the corticosteroid-dependent patients. In 33% oral corticosteroids in high dosage were required to relieve the airways obstruction before introduction of BDA.

The results were better than in the corticosteroid-dependent group, with fewer failures and a greater degree of reversibility in the older age groups. Late failure after initial success in 14 cases was again a feature which has gradually become more apparent with long-term experience.

Dosage requirements (Table 3) were lower in this group, 43% requiring less than 450 μg daily. Thirty-five patients (10%) were able to stop treatment without relapse, and another 19 (5%) after hyposensitization or avoidance of allergens. As in the corticosteroid-dependent group, there was difficulty in obtaining adequate control in 52 cases (14%) until hyposensitization was undertaken.

Oropharyngeal candidiasis (Table 3) was a lesser problem, possibly because of the smaller doses, and hoarseness was less frequent. Twelve children (10% of this group) had growth retardation, presumably as an effect of chronic asthma, because their growth rate increased after the introduction of BDA. There were three deaths from asthma in this group, as compared with none in the corticosteroid-dependent group.

Failure (Table 5) was usually associated with hypersecretion and frequent bronchial infection, and with irreversible allergic airways obstruction. Late failure after initial success was again a feature.

As shown in Table 6, 190 (53%) of this group had been treated for over 3 yr, 251 (70%) for over 2 yr, and 274 (76%) for over 1 yr. Fifty-four (15%) were able to stop treatment without relapse, three times the proportion in the corticosteroid-dependent cases.

Seasonal asthma

The results for 331 seasons in 142 patients are summarized in Table 9, which includes 38 purely seasonal cases who were not otherwise included in this report. Care was taken to ensure that no other treatment, except bronchodilators, was used, so as to

Table 8 Results in 359 non-corticosteroid-dependent asthmatics (including 73 with seasonal factors)

Age commended treatment with BDA (yr)	*2–14*		*15–29*		*30–44*		*45–59*		*60+*		*Overall result*	
	Number	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Total established BDA	119	100	44	96	90	97	79	100	25	100	354	99
Increase in average PEF												
100%+	43	36	18	39	26	29	31	39	7	28	125	35
50–100%	53	45	14	30	36	40	25	32	10	40	138	38
0–50%	23	19	12	27	25	28	23	29	8	32	91	26
Failed to establish	0	0	2	4	3	3	0	0	0	0	5	1
Totals	119		46		90		79		25		359	
Late failures	2	2	1	2	7	8	3	4	1	4	14	4

assess the value of BDA alone. This summary is an extension of our previous report (Brown & Storey, 1974). The pollen and spore counts are monitored daily at this Centre, so that peaks of allergen challenge are known and can be correlated with the PEF recordings. The counts obtained in Derby are consistently much higher than those reported in London, often by a factor of three or even four.

Perennial asthma, well controlled by BDA in winter, can be seriously affected by seasonal factors in very sensitive cases. Specific hyposensitization may be required to diminish or abolish seasonal exacerbations. In purely seasonal cases, results are much better, but abrupt falls in PEF and exacerbations of symptoms often coincide with peaks of the pollen or mould spore counts.

Pregnancy and BDA

Twenty of our 600 patients became pregnant, and were delivered of normal children. There were no abortions, spontaneous or therapeutic.

Discussion

This report, involving the treatment of 600 patients with BDA, 241 previously corticosteroid-dependent, for up to five-and-half years, is reassuring in that no new side-effects have appeared in a total of approximately 1350 patient-years of treatment. Oropharyngeal candidiasis has not been a significant problem in this series, but was commoner in the corticosteroid-dependent group. The incidence is similar to that in other reports, with one notable exception. McAllen *et al.* (1974) reported a 13% incidence of *C. albicans* infection of the pharynx, larynx or both. Milne & Crompton (1974) found yeasts in 41% of throat swab cultures, but clinical thrush in only 5.5%, and the Preliminary Report of the Brompton Hospital/MRC Collaborative Trial (1974) reported a dose-dependent cumulative increase in clinical thrush increasing to 45% at 28 weeks in patients on 400 μg daily, and 77% at 800 μg daily; but the thrush was never severe enough to necessitate stopping treatment. It is difficult to assess the true significance of these reports, or of the contentious correspondence (Grant *et al.*, 1974) which followed the last publication, but from the clinical point of view there has fortunately been no problem of any significance in our series. Our impression is that a drink or a simple gargle after the inhalation of BDA, and improved dental hygiene, has resulted in fewer cases of clinical thrush in recent years.

The major problems were all concerned with corticosteroid withdrawal symptoms and unmasking of other allergic manifestations. The policy of providing each patient, or the parents of children, with an emergency supply of corticosteroid for immediate use without medical advice has undoubtedly proved of value in the corticosteroid-dependent group. Disaster might otherwise have occured, as in three of the five sudden asthma deaths recently reported from Australia by Mellis & Phelan (1977). Their detailed case reports suggest that the timely administration of an effective dose of corticosteroids might have averted the fatal outcome in some of these cases, that normal tetracosactrin tests can be deceptive, and that occasional sophisticated pulmonary function tests may be inferior to frequent PEF recordings, which provide an early warning system. Continuity of care and immediate access to a chest physician when problems arise are other factors which we believe are vital to success. It is notable that all asthma deaths occurred in the non-corticosteroid-dependent group, illustrating the unpredictable nature of the disease and its constant dangers.

The availability of large numbers of PFMs is considered essential for accurate monitoring. Many patients are quite unaware of the severity of their airways obstruction until it is monitored in this

Table 9 BDA in treatment of seasonal asthma (results in 142 cases for seasonal aspects only)

	Total cases	*Total seasons*	*Good control*		*Poor control*	
			Number	*%*	*Number*	*%*
From corticosteroid-dependent group	31	88	58	66	30	34
From non-corticosteroid-dependent group	73	143	99	69	44	31
From purely seasonal group	38	100	81	81	19	19
Totals	142	331	238	72	93	28

All cases had positive nasal challenges before season and had no desensitization therapy.
Good control means no asthma, or transitory breakthrough only.
Poor control means repeated attacks requiring other therapy.

way. Relief of airways obstruction by means of a course of oral corticosteroid at high dosage before the introduction of BDA is a technique which has undoubtedly contributed greatly to successful treatment.

Our long experience with BDA, allied with similarly encouraging reports from most countries in the world, indicates that the efficacy of this treatment in asthma has now been fully established, and offers hope of independence from oral corticosteroid therapy and its side-effects to many thousands of asthmatics. Our data suggest that the effectiveness of BDA is in proportion to the degree of reversibility of the airways obstruction, and whether the bronchi can be rendered sufficiently patent for the aerosol to be effectively inhaled.

Although BDA is clearly an important advance in treatment for the corticosteroid-dependent asthmatic, its place in the treatment of milder cases is less clear. It is generally assumed that bronchodilators and sodium cromoglycate should be tried first, and that BDA should be introduced only if these drugs are ineffective. In the light of our own experience, however, it seems justifiable to suggest that in cases of chronic asthma of moderate severity BDA should be used as soon as it is apparent that bronchodilator requirements are increasing.

The absence of long-term side-effects and the reversal of airways obstruction usually obtained with BDA suggests that it is now the treatment of choice for asthma of moderate severity, particularly in younger patients who have a greater chance of spontaneous recovery.

It must be emphasized that, with the exception of patients who are able to stop treatment with BDA without relapse, this method of treatment is still only a means of suppressing the allergic reaction without disturbing pituitary–adrenal function (Harris *et al.*, 1973; Buisseret, 1973; Maberly *et al.*, 1973). Although its proper use may enable many patients to lead a normal life for the first time in many years, such results should not obscure the fact that the cause or causes of the asthma are still present and often unidentified. The long-term results presented here would have been less satisfactory without the use of specialized diagnostic methods and hyposensitization.

We thank Dr D.M. Harris of Allen & Hanburys Research Ltd for constant help and encouragement, and for supplying the Becotide aerosols and PFMS. Without the help of the Clinic staff, particularly Sisters Murray, Wellings and Simmill, such a long-term clinical study would have been impossible. We also thank the Midlands Asthma and Allergy Researh Association for help and facilities, and above all, the patients who cooperated so well and for so long.

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A neglected breakthrough In asthma therapy

Sir-In the Seminar on Asthma (Oct 26, p 1313),1 no mention was made of the value of examination of sputum for eosinophil cells, which 44 years ago showed that the presence of . many eosinophils predicted responsiveness to oral steroids,' and 14 years later enabled me to select patients with asthma who were most likely to benefit from inhaled steroids. Techniques to induce sputum for diagnosis and monitoring of asthma, which have been greatly refined and developed in recent years, were not mentioned either.

Beclomethasone dipropionate (BDP) aerosols have been improved by dissolving this substance in .hydrofluoroalkane propellant (HFA) instead of suspending it in chloro- fluorocarbons (CFCs). This technical development has enabled improved delivery systems, producing steroid aerosol particles of average size 1 micron.

Results of studies of radiolabelled BDP suspended in CFCs have shown that only 13% *of* inhaled BDP is retained in the lung, mostly in the larger bronchi. With BDP dissolved in HFA, an ultrafine aerosol is produced, of which 53% is deposited evenly throughout the lungs, thus reaching the peripheral airways.. The importance of this finding is that the smaller bronchi can be accessed and treated with inhaled corrlcosteroids.

The peripheral airways have been shown to be a major site of inflammation and obstruction in asthma, therefore treating the whole bronchial tree should prevent some patients with reversible asthma from slowly developing irreversible chronic obstructive pulmonary disorder over many years.' Furthermore, these ultrafine aerosols ought to improve long-term outlook of children with chronic asthma who need indefinite steroid aerosols.

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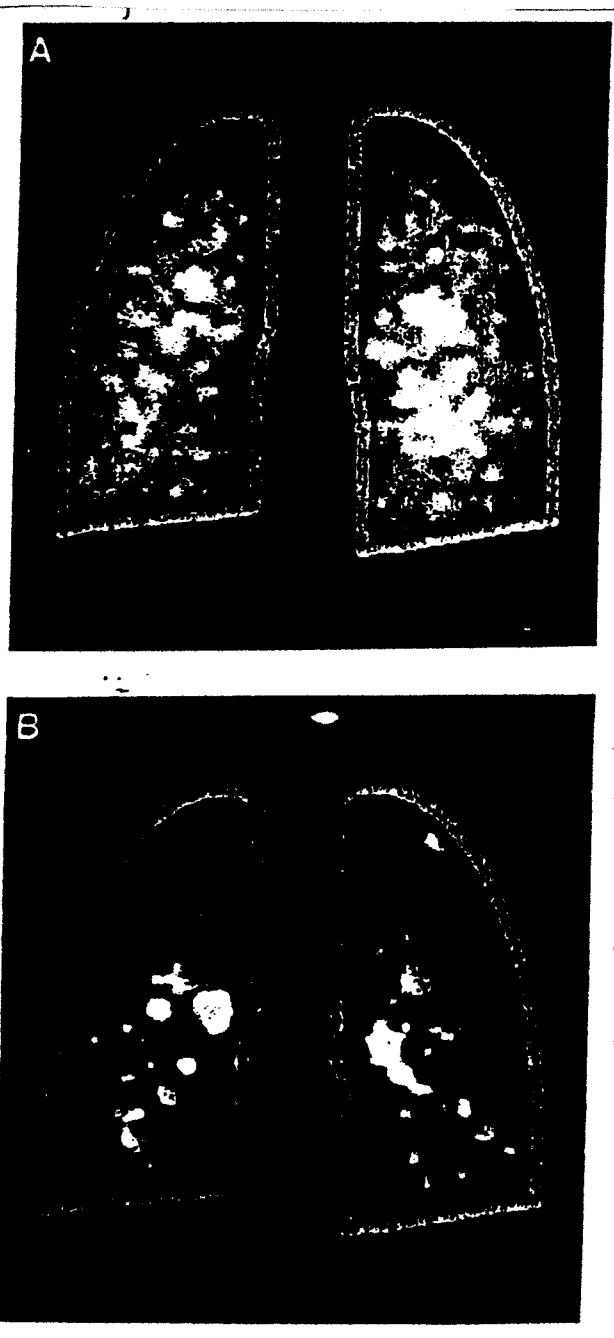

Figure 4. Differential pulmonary deposition of radiolabeled BDP with HFA-134a-BDP MDI (*panel A*) vs CFC-BDP MDI (*panel B*). Panels A and B are gamma scintigraphic images. Reprinted from Reference 18.

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Beclomethasone dipropionate aerosols in the treatment of asthma in childhood

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Clinical trials of beclomethasone dipropionate aerosols for the treatment of asthma began at the Derby Chest Clinic in the summer of 1970. The most dramatic improvements were found amongst children (Brown *et al.*, 1972; Brown and Storey, 1973). The effectiveness of beclomethasone in allergic asthma at all ages has been repeatedly confirmed by many investigators, but anxiety persists regarding possible long-term side effects on the bronchial or nasal mucosa. For this reason long-term follow-up of patients on continuous treatment is very important. Surveys of 600 asthmatics treated with beclomethasone for up to five and a half years, and of 315 patients with allergic rhinitis for up to five years, have already been published (Brown *et al.*, 1977a and b). The present study is specifically concerned with the fate of children who started treatment between the ages of two and 14 years, and who have been treated with beclomethasone for from two to eight years to July 1978.

Subjects and methods

Case selection

Excessive numbers of eosinophil cells in sputum or nasal mucus (Brown, 1958), difficulty in controlling the asthma and especially dependence on oral corticosteroids were the major indications for beclomethasone therapy. Other evidence of atopy, such as a positive reaction to common allergens, was usually present and intensive investigation for allergic factors using methods previously described (Brown, 1970) had been undertaken in every case.

Monitoring

Objective data on the severity and the diurnal patterns of airway obstruction, and of the response to treatment, were obtained by issuing peak flow meters to each patient for use three times a day. The minimum

TABLE I.—Long-term treatment with beclomethasone dipropionate aerosols for asthma in childhood

Treatment groups (n)	Increase in average peak expiratory flow rate after transfer to beclomethasone						Failed transfer	
	>100%		50–100%		0–50%			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Steroid-dependent children (48)	19	40	16	33	6	12	7	15
Steroid independent children (107)	39	36	47	44	18	17	3	3

TABLE II.—Long-term treatment with beclomethasone dipropionate aerosols for the treatment of asthma in childhood from July 1970 to July 1978

Success rates as assessed 1978 (n)	Good control (n)	(%)	Moderate control (n)	(%)	Poor control (n)	(%)	Partial transfer (n)	(%)	Outright failure (n)	(%)	Late failure (n)	(%)
Ex-steroid dependent children (48)	21	44	13	27	3	6	4	8.5	4	8.5	3	6
Steroid independent children (107)	67	63	27	25	10	9	0	0	1	1	2	2
Combined results (155)	88	57	40	26	13	8	4	3	5	3	5	3

pre-treatment control period on peak flow monitoring was two weeks, but many patients had been monitored in this way for months or even years, and all had been asthmatic for at least one year. The average of all peak expiratory flow readings for the control two weeks was taken as the baseline, regardless of steroid or other therapy at this time. This figure was compared with the average peak expiratory flow over a stable two-week period after becoming established on beclomethasone. The results are shown in table I.

At each visit peak expiratory flow records, symptoms and treatment charts, dosage and usage of beclomethasone, height, weight and general clinical condition were checked. Parents were supplied with oral steroids and given instructions for using them on their own initiative when necessary. Occasionally it was also necessary for parents of children subject to very sudden attacks to possess and to be able to give subcutaneous injections of salbutamol or terbutaline (Brown, 1977). Special warning labels were affixed to our patients' steroid cards regarding probable suppression of adrenal function for up to two years, and the necessity for steroid cover during times of stress..

Beclomethasone was administered by metered aerosol using techniques previously described in detail. The most practical dosage for children is three puffs of 50μg each three times per day—this avoids taking the aerosol to school and enables a parent to supervise the usage of the aerosol on every occasion.

Assessment methods

Our assessment was based on all available data for each patient over all the years they had been attending the clinic or consulting rooms. Frequency of exacerbations necessitating short-term use of oral steroids, bronchodilator requirements, symptom scores on our special charts, athletic performance, actual compared with predicted peak expiratory flow for height according to Nairn and his colleagues (1961), growth rate (Tanner *et al*, 1966) and any other relevant information, together with a clinical assessment, were all taken into account. Table II gives the broad success ratings based on these data.

Adrenal function tests were considered unnecessary in view of the results of our investigations in adults (Brown *et al.*, 1972), and those of other workers (Buisseret, 1973; Harris *et al.*, 1973; Maberley *et al.*, 1973) who have shown that there is no evidence of adrenal suppression with doses up to 1000μg per day (20 puffs).

Transfer from steroids

Transfer in the steroid dependent group was carried out by adding beclomethasone to the regimen, and then phasing out the oral corticosteroids, using 1mg prednisolone tablets for easy adjustment of dosage. In many cases the dose could be reduced by 1mg per day under peak flow monitoring, but children who had been receiving oral steroid therapy for long periods and in higher doses had to be handled with great care, the speed of withdrawal being a matter for clinical judgement. Tests of adrenal function were found neither helpful nor reliable.

In approximately one third of both steroid-dependent and steroid-independent groups we found it essential to clear the airways by a preliminary course of high dosage oral steroid to ensure that the beclomethasone could be inhaled easily and deeply and could exert its topical effects on a bronchial mucosa free from excess secretion.

The allergic factor

Intensive allergy investigations are routine at this centre, but specific hyposensitization is undertaken only if objective proof of the responsible allergen is obtained by means of nasal, and recently also bronchial, provocation tests and avoidance is not possible. It would have been unethical to withhold this type of therapy in long-term patients, and in the final assessment 40 (26%) of our young patients were considered to be successfully controlled with beclomethasone as a result of hyposensitization. These were cases in which we had had considerable difficulties in control using beclomethasone alone; thus the two methods of therapy were complementary.

Results

Corticosteroid-dependent group

The most severe problems were encountered in this group of 48 children and four patients could not be established on the aerosol and four more had to be satisfied with continuing on a minimal dosage of oral steroid as well as beclomethasone. In a further three patients initial success was followed after varying periods of time by failure of beclomethasone to keep the asthma under control. Corticosteroid withdrawal symptoms were much less of a problem than in adults, only 11 of the children complaining of headaches, lassitude and tiredness for about a week. This group of children contained the hard core of problem asthmatics attending this centre.

A 15-year-old girl, who had been steroid-dependent for 11 years was successfully transferred to beclomethasone dipropionate aerosol (BDA), but allergic rhinitis was unmasked. Nasal provocation tests revealed sensitivity to dog, cat and house dust; the pets were removed and hyposensitization against house dust and mites introduced. It later became possible to stop BDA and all other treatment without relapse. She is now aged 24 but her height on entry to the trial, (140cm) never increased.

A 13-year-old boy had been on a five-year-course of oral steroids for asthma/eczema syndrome. Average peak expiratory flow rate was 92 l/min before, and 227 l/min after, being established on BDA, rising to 400 l/min after one year, and later to 500 l/min. He is now an athlete, plays rugby football, and has won silver and gold Duke of Edinburgh awards for mountain endurance tests. His chest was distorted and he was stunted but, in the first 18 months on BDA alone he grew 12.8cm, and at 19 years he was 174cm. The chest deformity improved but, removal of a dog and hyposensitization against house dust mites and pollen made an additional contribution. He has had BDA for eight years and still takes 3 puffs daily.

Late failures.—Over the years a new category of case has emerged in which, after a period of some years of excellent control, the situation becomes uncontrollable and oral steroids have to be used again. These patients responded dramatically to oral steroids, and were easy to transfer to beclomethasone, until they became suddenly unresponsive. This may occur at any age.

After being steroid-dependent for five years a ten-year-old girl was transferred to BDA and received hyposensitization against grass pollen, house dust and house dust mites. Her average peak expiratory flow rate rose from 95 l/min to 400 l/min, and, within a year, she was swimming and normally active, gaining 7½cm in height over three-and-a-half years. After an exacerbation triggered by infection, the peak expiratory flow rate fell to between 100 and 150 l/min. She no longer responds dramatically to high dosages of corticosteroids, and is again steroid-dependent with the usual side effects.

TABLE III.—Growth in children on long-term treatment with beclomethasone dipropionate for chronic asthma

Treatment groups (cases assessed)	Growth along same percentile (n)	(%)	Growth rate increased (n)	(%)	Growth rate decreased (n)	(%)
From steroid-dependent group (23)	11	47	9	39	3	13
From steroid-independent group (52)	34	65	12	23	6	12
Overall (for those with sufficient data)	45	60	17	28	9	12

Corticosteroid-independent group

The corticosteroid-independent group of 107 children would be expected to include only the relatively mild cases, but on objective assessment by peak flow monitoring many were found to be just as severely affected as those in the steroid-dependent group. This was undoubtedly due to reluctance to use oral steroids and underestimation of severity on the part of their medical attendants, who seldom had a peak flow meter. As shown in tables I and II, the response to beclomethasone in this group was better and control was easier, but high-dose steroid therapy was often required to clear the airway of secretion and allow the beclomethasone to be fully effective. The growth of some children was retarded, presumably as a result of the chronic asthma, since the rate increased after the introduction of the beclomethasone (table III).

Apart from those patients in whom it was necessary to clear the airways by means of a short course of oral steroids in high dosage, the usual method of introduction was to add the beclomethasone to the treatment regimen, and when the peak expiratory flow rate had reached a satisfactory level other therapy, except for bronchodilators, was usually withdrawn. The requirement for aerosol bronchodilators usually decreased dramatically, provided the technique of inhalation was satisfactory. Sodium cromoglycate could normally be withdrawn and there was no objective evidence that the two inhalational treatments potentiated or added to the improvement in peak expiratory flow rate obtained with one alone.

Side effects and other problems

The only side effect encountered was oropharyngeal thrush on eight occasions; this was easily treated with amphotericin lozenges and treatment never had to be abandoned on this account.

The one death in this series can probably be attributed to high-dosage steroid therapy being begun too late, so that the situation was irreversible by the time the boy was admitted for intensive care.

Growth.—Unfortunately adequate data on growth were only available for 75 children and the results are presented in table III. Definite stunting due to continuous steroid therapy or to the effects of severe asthma was present in some children, as shown by obvious rapid growth when they were off steroids and their asthma was well controlled.

Failure to establish on beclomethasone.—In spite of abundance of eosinophil cells in the sputum there were four patients in the steroid-dependent group and one in the steroid-independent group whose reversibility was very poor when given large doses of corticosteroid orally for prolonged periods. These were also the patients who were liable to frequent infection and who proved impossible to establish on beclomethasone.

Long-term maintenance dosages and duration of treatment

Table IV summarizes the maintenance dosages. Only five patients required 12 puffs per day; the commonest dose was three puffs three times a day (450μg). These

TABLE IV.—Maintenance dosages required for the long-term treatment of asthma in childhood with beclomethasone dipropionate

Dosage (μg/day)	No.	%
600	5	3.5
450	64	44
300	49	34
200 or less	27	18.5
Total successfully treated	145	100

TABLE V.—Duration of long-term treatment with beclomethasone dipropionate aerosols for chronic asthma in childhood

Duration of continuous treatment up to July 1978 (Years)	(n)	Ceased treatment without relapse after (Years)	(n)
2-3	8	<1	3
3-4	21	1-2	6
4-5	29	2-3	6
5-6	37	3-4	3
6-7	19	4-5	5
7-8	7	5-6	1
Total	121	Total	24

dosage levels could perhaps have been lower in many cases, but in the almost total absence of side effects it is unreasonable to press for reduction of dosage at every opportunity as in patients taking oral corticosteroids.

Table V shows the duration of treatment. Very few children began treatment in 1970, but as by 1973 we were much more certain of the benefits and lack of side effects of beclomethasone therapy many children were started then. The only problems have been the inevitable sudden exacerbations which require to be controlled promptly with oral steroids and sometimes antibiotics.

The 24 cases in which beclomethasone therapy could be stopped without relapse of the asthma are also shown in table V. Some patients could stop after less than a year, others took longer and one took over five years. Many children stopped and restarted treatment several times, but most have been able to reduce the dose over the years. A few cases were initially classed as failures, but attempts to establish on beclomethasone were eventually successful—this was often due to the removal of a major factor, such as a pet, or to hyposensitization.

Seasonal asthma

Fifty children were also subject to seasonal allergies superimposed on their perennial asthma. A child who would be easily controlled in winter might be a difficult problem in the summer and might even require short-term oral corticosteroids. These 50 children endured 183 seasons between them and 61 of the summers were very poor in spite of beclomethasone. Hyposensitization may be the key to the problem and we have already published on seasonal aspects of beclomethasone therapy (Brown and Storey 1974).

Discussion

This long-term survey appears to confirm that beclomethasone is a significant advance in treatment which can be used without side effects in any child who can be trained in its effective use. We found that steroid withdrawal symptoms and unmasking of latent allergic symptoms were more of a problem than the occasional candida infection, but the biggest difficulties were undoubtedly in training children to use beclomethasone correctly. Without expert tuition by the clinic nurses and checking at each visit for sloppy use the results could not have been as reported. Preliminary experience with a dry powder inhaler has shown that children can use this device much more easily than the aerosol, thus confirming the report by Carmichael and his colleagues (1978).

The predicted peak expiratory flow rate for height was seldom attained in the early stages of treatment with beclomethasone, even though, as shown in table I, it was surprisingly common for the rate to be doubled or more than doubled within a short period. This is simply because the average pre-beclomethasone peak expiratory flow rate was so low that it was less than half the predicted figure. In children who were growing rapidly the increase in peak expiratory flow rate might lag behind the predicted figure, although eventually some would catch up as they developed. Growth and improvement in airway, plus the effects of hyposensitization and avoidance, interact in a bafflingly complex manner. Some of the improvement may also have been spontaneous, especially at puberty. The effects of complete freedom from asthma for the first time since infancy were often very dramatic and accompanied by a remarkable blossoming of self-confidence.

The policy of supplying the parents with emergency drugs for use at once pending medical advice has undoubtedly proved of great value, particularly in the steroid-dependent group and in unstable cases. Disaster might easily have struck otherwise, as happened in possibly three of five sudden asthma deaths in ex-steroid-dependent children reported from Australia by Mellis and Phelan (1977). As has been pointed out (Brown 1977) our methods might have averted these deaths although continuity of care and immediate access to advice when problems arise must also have contributed to our good safety record. The widespread use of peak flow monitoring may also have helped, as both patients and their doctors are often quite unaware of the severity of the airway obstruction.

Accelerated growth in ex-steroid-dependent patients after transfer was previously reported (Brown and Storey, 1973) but not confirmed by others (for instance, Godfrey *et al.*, 1978). In spite of a regrettable lack of data in many cases, there was, as shown in table III, no doubt that growth was resumed in some of our children. The 19 children followed for from three to five years by Godfrey and his colleagues (1978) had all been receiving an alternate-morning steroid regimen before transfer, so that neither positive nor negative effects on growth would be expected. The present survey applies to a much larger patient population over a longer period, and the steroid-dependent group had all had continuous treatment.

We would seem to be unusual amongst the many investigators of the effects of beclomethasone in recent years in the emphasis that we

have always placed on adequate investigation of the allergic factors, with a view to avoidance or hyposensitization. It is impossible to estimate the difference that this approach to the problem has made to our results, but individual case histories provide good examples of instances in which obvious environmental factors have been overlooked.

Regrettably, the effectiveness of beclomethasone may often be decreased or even negated by lack of attention to removable factors in the environment. We find that a combination of the investigative and the suppressive approach is undoubtedly the most effective in management, but it is sometimes difficult to persuade patients and general practitioners of, for instance, the importance of pets in the home. The major allergen in most cases, however, is the house dust mite, which is most difficult to avoid in the UK. The evidence will be published separately, but we have found that hyposensitization with pure mite preparations is effective provided that the procedure is adequately monitored and objective provocation tests used as a guide to results.

The real importance of the advance in treatment offered by beclomethasone is indicated by the fact that in the past two years there have been no fresh corticosteroid-dependent cases in children attending this centre—the rare exceptions are those who have proved to be late failures of treatment. It was not until we began to analyse the data that we realized that the whole scene had changed slowly so that steroid dependence is now an unusual problem.

We wish to thank all the staff at the Derby Chest Clinic, involved in these observations over the years, for their help, and Dr D. M. Harris of Allen and Hanburys for his unstinting support.

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My memories of the introduction of inhaled steroid therapy

In 1970, use of a steroid aerosol transformed the lives of many asthma patients previously dependent on oral steroids to control their symptoms: Dr Morrow Brown pioneered this effective suppressive therapy, but calls for more attention to the causes of allergic asthma.

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The story really begins in 1950 with my MD thesis on 'Adaptation and Adaptive Dysfunction', which concluded that allergic reactions are essentially manifestations of maladaptation to the environment.[1] There was no opportunity to develop this concept until 1957, when I found myself in acute disagreement with the conclusion of the Medical Research Council's controlled trial of oral steroids in long-term asthma that steroids were no better than bronchodilators![2] But who was I, working in a deprived ex-TB Chest Clinic with no equipment, to say that the MRC was wrong?

Nevertheless I began my own open trial and found after 3 months that while some patients were no better, those who had improved had done so to such a remarkable extent that it seemed as if they had a different disease. My studies on adaptation suggested that this disease was allergic asthma. However the laboratory staff could find no eosinophil cells in the sputum, when I was certain they should be present in abundance.

IDENTIFYING STEROID RESPONDERS

I retrieved from the attic my old student's microscope and improvised a rapid wet-smear method for sputum cytology. I then found that, while the steroid responders had many eosinophils in the mucoid part of the sputum, the non-responders had mostly macrophages. This result was striking because 56 of the 63 patients with many eosinophils were dramatically improved on steroid therapy, but only one of 27 with macrophages.[3]

Thus sputum cytology was the key to identifying individuals with steroid-responsive allergic asthma and distinguishing them from those with chronic bronchitis. This observation resulted in many happy asthma patients in my clinic, but I felt very reluctant to continue steroid tablets indefinitely because of side-effects, and sought an acceptable alternative. The most logical approach seemed to be to attempt to identify the responsible allergens, in the hope that specific avoidance or specific immunotherapy would allow steroids to be withdrawn without the return of symptoms. Accordingly, from 1958 onwards I embarked upon an intensive programme of allergy research,[4] and followed a steep learning curve in a completely strange specialty.

EARLY TRIALS OF AEROSOL ADMINISTRATION

The ability to select truly allergic asthma patients was crucial to the success of the first trial of beclomethasone dipropionate (BDP) administered as an aerosol. The drug was nearly discarded after trials in Edinburgh in 1968 had shown that BDP was ineffective and caused adrenal suppression.[5] However, Dr Wilfred Simpson, Medical Director to Allen & Hanburys, had such faith in the drug because of its intense surface activity that, hours before leaving to take up another appointment, he wrote asking me to try BDP again.

Trials began in summer 1970; we selected patients with eosinophils in sputum or nasal smears and positive skin prick tests, and monitored their progress with individual peak flow meters. The results were soon obvious, and many patients who had been dependent on steroid tablets were weaned on to BDP, with complete relief from steroid side-effects. The main problem was that withdrawal of steroid tablets often caused recrudescence of allergic rhinitis and polyps, but this could be controlled by using BDP intranasally as well. The use of individual peak flow meters enabled us to record striking objective data for each patient.

These data were submitted to Allen & Hanburys, with the result that the late Dr David Harris, who had taken over as Medical Director, wrote in

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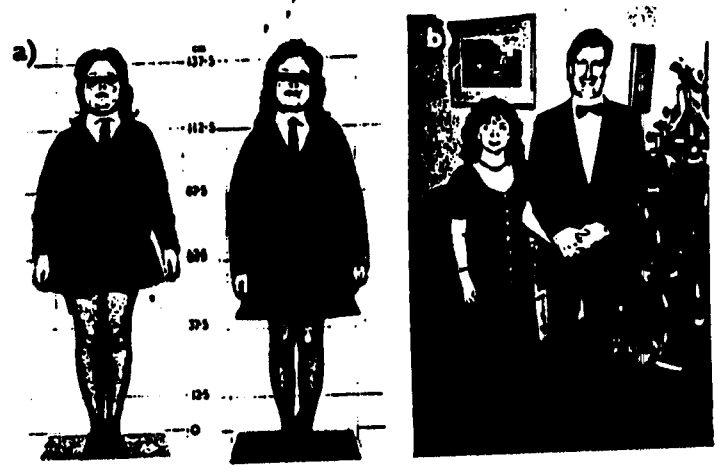

Figure 1. a) Changed appearance of a 16-year-old girl (weight loss 11 kg, height gain 1.3 cm) after 5 months on aerosol steroid alone. Previously she had been dependent on oral steroids or corticotrophin for 11 years to control her asthma. b) Same patient aged 40 years with her policeman husband. Her final height was 144.5 cm. She stopped taking beclomethasone dipropionate altogether between the ages of 20 and 35 years, but had to resume a minimal dosage of 100 µg at bedtime when aged 39. Causative allergens were never identified.

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THE FIRST ANNOUNCMENT →

192. A new steroid aerosol for the treatment of allergic asthma

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Beclomethasone Dipropionate Aerosol (Allen and Hanbury's Ltd.) has been used for the first time in the treatment of 60 cases of allergic asthma. The results have exceeded all expectations in that 32 cases dependent on oral steroid therapy have been successfully transferred to this method of treatment. Difficulties were experienced with steroid withdrawal symptoms in cases who had had oral steroid therapy for 5 yr or more. Transfer was unsuccessful in 8 cases. The optimum dosage appears to be 100 μg 4 times a day, and control, as judged by peak flow readings, was often better than on oral steroids. 20 cases who had never had steroids were also treated most effectively by this means. Peak flow meters were issued to all cases so that objective data were obtained for a control period before and for months after the introduction of the steroid aerosol. Data on any adrenal suppression caused by adsorption of the aerosol is being obtained, but the marked steroid withdrawal syndromes and unmasking of allergic symptoms in patients previously maintained on low dosages of steroids, suggest that adrenal suppression is minimal or absent. This new therapeutic agent shows promise of being a real therapeutic advance, especially in paediatrics.

THE FIRST PUBLICATION

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

H. MORROW BROWN, G. STOREY, W. H. S. GEORGE

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), Herxheimer *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.

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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
	Ineffective	31
	Helpful	4
Steroid therapy side effects evident		28
Corticotrophin	Ineffective (200 units)	14
	Responsive	10
	Not known	13

Response to Aerosol		
Peak flow	Better	25
	No change	7
	Worse	4
Successful transfer to aerosol		28
Occasionally needed short-term steroids		13
Failed transfer		9
Failed on account of frequent infections		2

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THE FIRST ANNOUNCMENT →

192. A new steroid aerosol for the treatment of allergic asthma

MORROW BROWN, H. and STOREY, G., *Derby, United Kingdom*

Beclomethasone Dipropionate Aerosol (Allen and Hanbury's Ltd.) has been used for the first time in the treatment of 60 cases of allergic asthma. The results have exceeded all expectations in that 32 cases dependent on oral steroid therapy have been successfully transferred to this method of treatment. Difficulties were experienced with steroid withdrawal symptoms in cases who had had oral steroid therapy for 5 yr or more. Transfer was unsuccessful in 8 cases. The optimum dosage appears to be 100 μg 4 times a day, and control, as judged by peak flow readings, was often better than on oral steroids. 20 cases who had never had steroids were also treated most effectively by this means. Peak flow meters were issued to all cases so that objective data were obtained for a control period before and for months after the introduction of the steroid aerosol. Data on any adrenal suppression caused by adsorption of the aerosol is being obtained, but the marked steroid withdrawal syndromes and unmasking of allergic symptoms in patients previously maintained on low dosages of steroids, suggest that adrenal suppression is minimal or absent. This new therapeutic agent shows promise of being a real therapeutic advance, especially in paediatrics.

THE FIRST PUBLICATION

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

H. MORROW BROWN, G. STOREY, W. H. S. GEORGE

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), Herxheimer *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.

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TREATMENT OF CHRONIC ASTHMA WITH PREDNISOLONE

SIGNIFICANCE OF EOSINOPHILS IN THE SPUTUM

H. MORROW BROWN
M.D. Edin., M.R.C.P.E.

COMMENT IN MARCH 2000

Would this paper, depending solely on clinical and subjective observations, be accepted for publication today? Probably not, but the NHS authority had actually refused to authorise the purchase of a spirometer costing about £100, and the Peak Flow meter had not been invented.

They would certainly not have agreed to buy a microscope, so it was fortunate that I had found pathology and haematology so interesting that I had not sold it, as most students did pre-war. The reason for the failure of the bacteriology laboratory to find eosinophils was that technicians are trained to look in the pus, not the mucus, where the eosinophils are to be found.

The most important consequence of this investigation was that it provided a means of identifying the asthmatics where the cause was allergy, and who would respond to steroids. The ability to do this was to be crucial for case selection when the opportunity came to conduct the first successful clinical trial of beclomethasone dipropionate three years later.

I still practise with a microscope beside me to this very day, because the crude cytology is most informative, . It also provides a basis for decision-making on the spot without waiting for a result from a nameless and faceless technician in a distant laboratory. Induced sputum is in vogue today, but how much information is lost by excessive processing?

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TREATMENT OF CHRONIC ASTHMA WITH PREDNISOLONE
SIGNIFICANCE OF EOSINOPHILS IN THE SPUTUM

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THE Medical Research Council subcommittee on clinical trials in asthma found no real advantage in cortisone acetate in the treatment of chronic asthma, compared with bronchodilator drugs (Medical Research Council 1956)—a result which surprised those whose experience indicated that corticosteroids are often of great value. Analysis of the M.R.C. trial suggested that its methods were not beyond criticism; so general practitioners in the Derby area were asked to refer chronic asthmatic patients to the chest clinic to take part in another trial on different lines using prednisolone. This began in January, 1957, and included patients who were already receiving steroid therapy, as well as those who joined the trial later. There were 90 patients in all.

To produce a clear-cut result, entry to the trial was limited to those patients who had had chronic bronchospasm for at least a year, and who had proved refractory to all other forms of treatment over at least one month. The only exceptions were a few cases in which the general practitioner had already given bronchodilators an adequate trial, and in which bronchospasm was very severe. Severe chronic bronchial infection and bronchospasm of cardiac origin were excluded, but cor pulmonale, even with congestive failure, was not considered a contraindication. Prednisolone was thus used as a last resort only, so that its efficacy could be as sternly tested as possible.

Early in the trial it was found that the distinction between asthma and chronic bronchitis with predominant bronchospasm was extremely difficult, especially in elderly men, in whom the results of steroid therapy seemed generally poor and totally unpredictable. In fact, a few months after the trial began the results were about half good and half bad, mainly because of this type of patient being included.

At the same time there was a group of younger patients distinguished by recurrent infection and bronchospasm who responded temporarily to antibiotics, only slightly to bronchodilators, and in whom sputum culture and sensitivity testing proved a most unhelpful guide to treatment. The finding of eosinophilic sputum in some chronic bronchitics (May 1954) suggested cytological examination of their sputum, and it was eventually found that no less than 16 patients with this clinical picture, who had been confidently thought to be chronic bronchitics for up to three years, had eosinophilic sputum and responded dramatically to prednisolone, with relief of bronchospasm and usually cessation of recurrent bronchial infections.

Negative laboratory reports when eosinophils were expected to be abundant prompted the improvisation of a quick and easy method of examining the sputum and made it possible to separate the true asthmatics with eosinophilic sputum from the others with ease and accuracy.

The success of this method suggested that it might be interesting to examine the sputum of patients having prednisolone. Corticosteroids clear the blood of eosinophils, but it was soon found that this did not happen in the sputum. What was even more interesting was that the results indicated that eosinophils in large numbers in the sputum were associated with a good response to prednisolone, and few or no eosinophils with a poor response.

With experience, certain aspects of clinical examination became evident. Often bronchospasm could be demonstrated only by forced exhalation through the open mouth. Others would not admit a single wheeze, breath sounds and respiratory excursion were both much diminished, and extremely high-pitched capillary bronchospasm could be elicited only by expressing the residual air by forcible manual expression (Power 1958) while continuing to auscultate with a diaphragm-type stethoscope. These patients were often the most dyspnœic and the lack of physical signs had led to the suspicion of cardiac disease. This may be the type of case referred to (Stuart-Harris and Hanley 1957) as " some patients with bronchospasm do not wheeze, though their distress is greatly improved by broncho-dilator drugs ".

Treatment

Except when bronchospasm was very severe, the dose given was 5 mg. thrice daily for a week, followed by reassessment and adjustment of dose.

Patients were told that if wheezing disappeared during the first week they could reduce the dose after a few days, but the majority did not do so. In favourable cases wheezing had ceased when they were seen a week later, and the dose could then be reduced. It was seldom necessary to increase the dose. All patients were given brief notes warning them of the dangers involved in prednisolone therapy. As a further safeguard notes on the dangers of treatment were issued to family doctors, and patients were given another copy of the notes in a sealed envelope to be given to their doctor if he did not have the case-notes to hand, as, for instance, when he was called at night.

Each patient was told to take as little prednisolone as possible to keep him free from wheezing. When wheezing had ceased for a few days the dose was reduced by 2·5 mg. every three days until wheezing returned slightly. It should then be increased by 2·5 mg. so that wheezing disappeared again, and then continue at that level for about ten days, when a further attempt should be made to reduce the dose. Thus, the patient was constantly trying to reduce the dose and finally stop treatment. Many remained free of symptoms on from 7·5 to 2·5 mg. per day, and others were able to stop altogether; though few could remain symptom-free for long.

Cooperation was remarkably good, and often patients were too enthusiastic in reducing dosage, so that spasm got out of hand and 15 mg. a day was needed for a week or so to control it. Any acute spasm was dealt with by increasing the dose abruptly until it was controlled, and then immediately beginning to reduce again. Patients were told to do this on their own, and not one has had any difficulty or catastrophe.

With these methods and by careful supervision and the use of antibiotics when needed, the risk of side-effects and complications was minimised, and suppression of endogeneous secretion and possible adrenal atrophy were unlikely. When necessary however, much higher doses were given for short periods, and a good working rule was found to be to double the dose at once if in doubt. If the sputum was purulent, a course of tetracycline always preceded the beginning of prednisolone therapy.

Eosinophils in the Sputum

Large numbers of eosinophil leucocytes, and sometimes Charcot-Leyden crystals and Kurschmann's spirals, are to be found in the sputum of asthmatic patients, but these findings have so far had no bearing on treatment.

Collection of Specimens

The rapid consulting-room method which was evolved depends on persuading the patient to produce a sample of genuine sputum in a petri dish, where it is much easier to pick out with forceps against a dark background the most

promising piece of sputum. Only by insisting on the production of a specimen before the patient left the clinic could suitable samples be obtained, and much encouragement was often needed.

Many asthmatics have great difficulty in producing sputum, especially later in the day. Quite often only a tiny piece of mucus, not much bigger than a pin head, swimming in saliva, could be produced. This would almost certainly have been overlooked in the usual container, but proved to be crowded with eosinophils. Patients seldom produce a satisfactory specimen unless they are supervised, especially children, and specimens sent by post were seldom satisfactory and sometimes disgusting. Children, encouraged by a little postural coughing, can often produce a minute but diagnostic sample when the parents swear that the child has never coughed anything up in its life. Occasionally it was necessary to visit the home early in the morning to get a diagnostic specimen.

Macroscopic Appearances

Only when the typical " boiled sago " sputum was produced could the microscopic findings be predicted with confidence. This type was also very firm and elastic, and a lump of any size usually had to be squeezed out under the cover-slip. The appearances associated with an excess of eosinophils varied widely from the green sputum described by May (1954), through mucopurulent and mucoid, to what seemed only stringy mucus. The " boiled-sago " type, and the eosinophilic green sputum were both rare, and on the whole the commonest was mucoid sputum which was sticky and gelatinous. Residual sputum of this type, associated with bronchospasm and persisting after pus had subsided with the use of antibiotics, was very often eosinophilic.

Screening Technique for Eosinophils

The piece of sputum is placed on a slide. It may be spread out with forceps, but it is not spread into a film because this tends to break up eosinophils and casts. Thin films also give a very much smaller and less representative sample. One drop of Leishman stain is applied with an eyedropper, followed by one drop of distilled water; a cover slip is dropped on top, and the specimen is examined after from ten minutes to several hours. At first only the edges of the specimen are well stained, but later any eosinophils in the centre pick up the stain while the rest of the cells in the interior of the lump are still unstained. It was often possible, when an established case of asthma was seen for the first time, to take the specimen first so that it was ready for examination by the time the clinical assessment was completed. Slides and coverslips can be used straight from the box without cleaning, thus saving valuable time in a busy clinic. An old-fashioned students' microscope was found quite adequate, and all requirements can easily be fitted inside the case in spring clips for domiciliary use. A simple microscope is also much easier to carry about and set up.

This crude method of examination often took about the same

time as writing out a form to send the specimen to the laboratory. A similar method has been described by Mulder (1956), but the sputum is washed in buffered saline before staining with eosin. Rawlins (1955) has also shown that examination of thin smears is of little value because of the irregular distribution of these cells. He homogenised the sputum with pancreatin, and carried out total and differential counts, but this would be difficult to do in tiny specimens and has the defect of breaking up any small casts.

Microscopic Appearances

The eosinophilic portions of the specimen can easily be located under the 2/3 in. objective with a no. 3 eyepiece, and the typical coarse eosinophilic granules confirmed by examination with the 1/6 in. objective. It was found that daylight was far better than any other form of illumination, because the eosinophils are much more obvious and the significant portions of the specimen can be located swiftly.

The numbers of eosinophils varied enormously from occasional scattered eosinophil cells to streaks, clumps, casts, or sputum in which there were few other cells. Occasionally they were hard to find, either because the specimen was poor or because they were in isolated clumps and several specimens had to be examined. This applied particularly to cases in which treatment with prednisolone had been dramatically successful before the routine examination of sputum was introduced, and confirmation of their presence or absence was required to complete this survey.

With purulent sputum the eosinophils may be found in clumps, or as occasional tiny casts, and re-examination after antibiotic treatment will show no pus and many eosinophils, which had previously been swamped by pus cells (Helm et al. 1954, Stuart-Harris and Hanley 1957).

Bronchial casts of any size were seen only once, but small eosinophilic casts of the terminal bronchioles were a common finding. Kurschmann's spirals and Charcot-Leyden crystals, which are only signs of the severity and chronicity of the condition, were rare.

Eosinophils were scattered irregularly throughout the sputum, the number undoubtedly varying from day to day, from specimen to specimen, so any attempt to carry out differential counts (Rawlins 1955) seemed pointless; but a rough system of expressing the degree of eosinophilia was used.

Significance of Eosinophils

Once it was realised that excessive numbers of eosinophils meant that treatment with prednisolone would be effective, it seemed likely that steroid therapy could be placed on a much more scientific basis. But it soon became clear that large numbers of eosinophils in the sputum were not necessarily associated with severe asthma or a failure to respond to antispasmodics which justified the

use of prednisolone. A boy of eight, with simple recurrent bronchial catarrh and many rhonchi but no definite bronchospasm, had only eosinophil cells in his sputum; and his brother of nine with no signs in his chest at all produced a tiny piece of sputum crowded with eosinophils. Obviously it was unjustifiable to suggest anything more than the simplest remedies. The deciding factor was the severity of the bronchospasm and *not* the findings in the sputum.

Results

The findings summarised in the accompanying table show the striking improvement in the eosinophilic cases

90 CASES OF CHRONIC ASTHMA TREATED WITH PREDNISOLONE

Relief of bronchospasm	Cases with eosinophilic sputum	Cases with a few or no eosinophils
Complete	56	1
Partial	7	3
Slight	—	7
No relief	—	16
Total	63	27

and the poor results in other patients. In general, the greater the numbers of eosinophils, the more certain was the result.

Some patients have had to stay on prednisolone for a long time. Which is the lesser evil, disabling asthma or the dangers of long-term prednisolone treatment? All patients who had to make this choice chose to continue treatment in the knowledge that there are certain dangers.

A man of 29 has been taking prednisolone, plus occasional doses of antispasmodics, for three years. Previously he had been totally incapacitated for four months, in spite of intensive treatment with bronchodilators and a short course of cortisone acetate. The prognosis seemed grave after sixteen years of chronic asthma and after all other drugs had lost their effect. With antibiotics and larger doses of cortisone acetate, which were gradually reduced as his condition improved, he was finally able to return to work. Residual dyspnœa is slight, but radiologically the emphysematous change is severe, and has not altered. He has been taking prednisolone instead of cortisone for the past two years (10–5 mg. daily). He has remained well. Sputum is scanty but always contains many eosinophils. Bronchospasm becomes severe a short time after stopping therapy. As a safeguard, however, he is now having weekly injections of long-acting corticotrophin.

The elderly bronchitic with severe bronchospasm rarely benefited, but there were a few surprise results in patients for whom nothing else seemed possible. Younger

patients who obtained complete relief from bronchospasm usually had little or no residual dyspnœa once the bronchospasm had disappeared. On the other hand, the older asthmatics in whom emphysema had developed were still dyspnœic to a varying extent.

Experience showed that if there was no improvement in the course of two weeks on 15 or 20 mg. of prednisolone per day in the absence of purulent sputum, no significant benefit would be derived from continuing treatment. Cases of chronic bronchospasm who fulfilled the criteria for entry to the trial, but who had negative sputum findings, were, therefore, admitted to the trial for a short course only, followed by tapering off before they could become dependent on the hormone. As a result sufficient cases have been included to make it clear that in the absence of excess of eosinophils seldom can even partial relief be expected.

Results in Children

In children only the very worst cases were treated, and then only after the demonstration of eosinophils in the sputum had put therapy on a sounder basis. It was decided that it was quite unjustifiable to use prednisolone unless antispasmodics were of no avail and there was definite evidence of emphysema and a poor prognosis. So far there has been no occasion to regret this decision, and the most dramatic results have been in children and young people. It must be emphasised that prednisolone was not considered unless the child had constant bronchospasm punctuated by exacerbations. The results in children reported by Kennedy and Thursby-Pelham (1956) and Thursby-Pelham and Kennedy (1958) were encouraging, but the doses may have been on the high side, especially for long-term therapy.

Excess of eosinophils in the sputum and nasal smears has been a relatively common finding in children. The usual history was of frequent respiratory infections but no obvious asthmatic symptoms beyond occasional wheezing. Sometimes, however, the history suggests bronchiectasis, and can be most misleading. My observations so far suggest that recurrent bronchitis or frequent colds in children should be suspected of having an allergic basis, and that sputum examination may often give a true diagnosis.

Complications

The most serious complication was glycosuria, of which there were 3 instances, 1 in a mild diabetic.

Treatment with prednisolone definitely appeared to

make attacks of purulent bronchitis more common in 3 patients. Purulent sputum had been a prominent feature for years, and it was decided that prednisolone should be stopped because of the risks involved with the persistence of chronic infection.

Defects of the Trial

This trial is open to much criticism because the patients all knew the nature of the treatment and some of its dangers, and even regulated their own dosage. Moreover, the doctor-patient relationship was very strong. The only objective findings were in the sputum and the correlation of the sputum results with those of treatment. Attempts were made to introduce placebo tablets to patients who were apparently having homœopathic doses, but this could not reasonably be done in those who were taking a greater quantity because of the known dangers of sudden cessation of treatment, firstly because they regulated their own dosage, and secondly because they could have an acute attack requiring an increased dose. It was also very difficult to ensure that the family doctor was fully aware that placebo was being given, because his partners might not know, and endless difficulties could arise in the event of an acute attack. In 3 cases it was shown that placebos were not a substitute for 2·5 or 1·25 mg. per day.

The unpredictable results of steroid therapy in asthma which have bedevilled other trials, and the difficulties in diagnosis between bronchitis and asthma, seem from these data to be due to an unknown degree of dilution of the test sample with bronchitics. The assessments were not based on scientific evidence, and clinical assessment in emphysema has been shown by Fletcher (1952) to vary widely from observer to observer. Also subjective evidence in asthmatic patients is notoriously subject to psychosomatic influences. It is, however, difficult to credit that the data given here can be entirely erroneous. At least the trial sample of true allergic asthmatics has been purified, and it is well established that the steroids will suppress allergic phenomena.

Summary

90 patients with chronic asthma were treated with prednisolone. Only those in whom bronchodilator drugs had failed to produce a satisfactory response were included.

The results indicate that prednisolone is very useful in the treatment of chronic asthma *provided* the sputum contains large numbers of eosinophils. In the absence of an eosinophilic sputum a satisfactory response is unlikely, and the use of prednisolone is contraindicated.

A method of self-regulated dosage ensured that only the smallest possible effective dose was taken so that side-effects and complications were less likely.

Though prednisolone is an effective treatment in suitable cases it never does more than suppress the asthmatic state and it does not abolish eosinophils in the sputum, though the quantity is much reduced.

I wish to thank Dr. E. V. Morton, of Boots Pure Drug Co., for a most generous supply of prednisolone, Mr. E. Roe, laboratory technician, Derwent Hospital, Derby, for his assistance, and general practitioners in the area whose support made this trial possible.

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