PAPERS AND ORIGINALS

Steroid Aerosols in Asthma: An Assessment of Betamethasone Valerate and a 12-month Study of Patients on Maintenance Treatment

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Summary

Betamethasone valerate aerosol is a new compound for the treatment of asthma. Its clinical effectiveness was established in a double-blind cross-over trial in non-steroid-dependent asthmatic patients. At a dosage of 400 to 800 μg/day for three months there was no evidence of suppression of hypothalamic-pituitary-adrenal function, as assessed by tetracosactrin and insulin stress tests.

A 12-month follow-up study of 120 patients using steroid aerosols (betamethasone valerate or beclomethasone dipropionate) indicated that tolerance does not develop and that a daily maintenance dose of 200 μg/day was adequate in most patients. Temporary lack of response was observed during episodes of sputum production or of heavy exposure to antigen.

There were no observed side effects other than fungal infections of the respiratory tract. However, the incidence of candidiasis of the pharynx (13%) and particularly of the larynx (5%) in apparently immunologically normal patients was disturbing. These infections were not seen in patients taking 200 μg/day. Though there is yet no evidence that fungal infections associated with steroid aerosols may penetrate the trachea and bronchi the possibility of this indicates that caution should be exercised in their use, particularly in long-term high dosage.

Introduction

Attempts to substitute inhaled corticosteroids for oral preparations in the treatment of asthma have until recently met with little success. Despite several early reports in which at least a modest response to inhaled powders of hydrocortisone and prednisolone was claimed, this route of administration has never found favour.

So far, only with beclomethasone dipropionate (Clark, 1972; Lal, 1972; Morrow Brown *et al.*, 1972; Gaddie *et al.*, 1973; Morrow Brown and Storey, 1973) has there been any indication that inhaled steroids may have an important part to play in the management of asthma. This compound has a high topical activity on the skin and apparently also in the lung, and it is effective in asthma in a dosage which is low enough to avoid the risk of suprarenal suppression. There have, however, been no adequate reports so far of its effect on the hypothalamic-pituitary end of the axis. Another question that remains to be answered is whether undesirable side effects could emerge in the long term, particularly in respect of fungal infections of the respiratory tract.

Betamethasone valerate is another halogenated corticosteroid which has a high topical potency relative to its systemic activity and which has not so far been assessed as an aerosol treatment for asthma.

This paper presents, in part A, a double-blind, cross-over trial with a three-month follow-up of inhaled betamethasone valerate compared with placebo and assessed by sequential analysis. We have attempted to establish its effectiveness in a dose which is without risk of hypothalamic-pituitary-adrenal (H.P.A.) suppression. H.P.A. function has been studied by tetracosactrin stimulation tests before and after four weeks, and by insulin stress tests after three months' treatment.

In part B we report a further and larger series of patients taking aerosol treatment with either beclomethasone dipropionate or betamethasone valerate whom we have followed up for 12 months. In this series we looked for long-term side effects with particular reference to fungal infections of the respiratory tract.

Part A—Clinical Trial of Betamethasone Valerate Aerosol

Patients

Altogether 23 adults with daily, perennial moderately severe asthmatic symptoms who were not taking oral corticosteroids

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were admitted to the trial. Patients taking oral steroids during the previous three months were also excluded so that the full effect of the inhaled steroid on the H.P.A. axis could be assessed.

Five patients were withdrawn from the trial, two because of exacerbations of asthma needing oral steroid treatment during the introductory period, and three because they did not keep satisfactory records.

The patients studied in this cross-over trial were all asthmatics not dependent on steroids, and it might, therefore, be assumed that they had trivial symptoms. But this was not so, as 10 of them had readings for forced expiratory volume in one second of less than 50% of their predicted normal, and 12 of them had previously needed oral steroids to control their asthma. Indeed, if they had not responded to the steroid aerosol many of them would have needed long-term steroids by mouth.

Methods

Two identical aerosol canisters, one containing betamethasone valerate and the other a placebo consisting of the propellants alone, were assigned to every patient, in random order, to be used for 28 days each. Neither the physician nor the patient knew their identity until the trial was finished. The first period of treatment was preceded by two weeks on placebo, which was known to the physician but not to the patient. This was to accustom the patients to using a peak flow meter and completing a daily symptom record form. The records made in this period were not included in the assessment.

The dose of betamethasone valerate was 800 μg/day taken as two puffs four times a day. This seemingly rather high dosage was deliberately chosen so that a good clinical response could be expected and H.P.A. function could be assessed at the upper limit of the likely clinical dose.

The propellants were dichlorodifluoromethane *B.P.C.* and trichlorofluoromethane *B.P.C.* in the proportion of about three parts to four.

Tetracosactrin tests for adrenal function were done after four weeks in order to include the maximum number of patients taking the full dosage of 800 μg.

Insulin stress tests, for more adequate assessment of H.P.A. function, were not thought justifiable in all patients as they are not without hazard. It was therefore decided to use them only in those patients who were likely to continue aerosol treatment for a long period. The tests were therefore done on five patients who were still on treatment three months after the end of the cross-over trial and who were the only ones who could come into hospital for the tests.

Assessment of Response

The following criteria were used to assess the effects of the treatment.

Preference for Active or Placebo Material.—Both the patient's and the physician's choice was given retrospectively but before the records were decoded. An independent observer decoded the results and plotted them sequentially by the method of Armitage (1960).

Ventilatory Function.—Every patient had a peak flow meter to take home. The best of three readings was recorded, both on rising in the morning and again at bedtime, every day, and not less than two hours after the last dose of any bronchodilator drug. The significance of differences between the active and placebo treatments was assessed by paired *t* tests.

Symptom Score.—Symptoms for each 24 hours were marked on a 10-point scale ranging from 0 (no asthma) to 10 (maximum severity). Significance of differences was assessed by paired *t* tests.

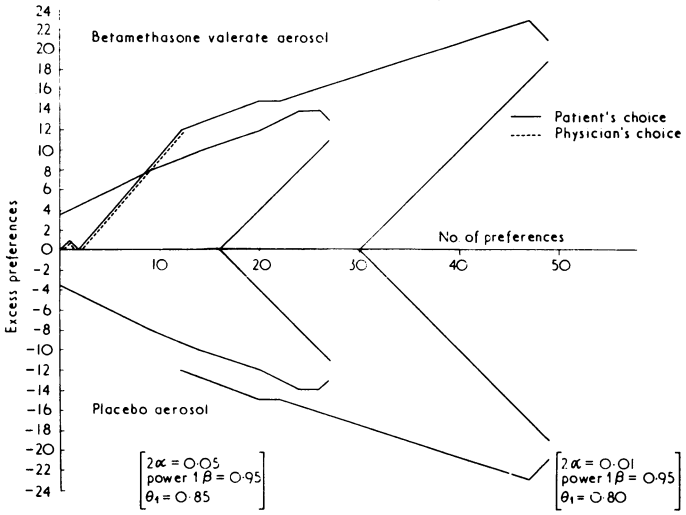
Daily Bronchodilator Dosage.—A record was kept of all drugs taken. The significance of differences in bronchodilator requirements was assessed by paired *t* tests.

Suprarenal Function Tests.—Thirty-minute tetracosactrin tests were performed on all patients on admission to the trial and again immediately after the second 28-day treatment period.

Insulin Stress Tests.—Five patients were further investigated by hypoglycaemic stress tests after three months on known active treatment at a dosage of not less than 400 μg/day (three took 800 μg and two took 400 μg).

Results

Sequential Analysis of Preferences.—The sequential analysis is shown in the graph. The trial was stopped when patient's preferences reached the 1% significance line. At this point 18 patients had completed the two treatment periods.



Sequential analysis of preferences for betamethasone valerate aerosol 800 μg/day, or placebo.

Ventilatory Function and Symptomatic Response.—The results obtained in the last 14 days only of each treatment period have been analysed in order to minimize any "carry-over" effect from the active treatment when it was given before the placebo. Sixteen of the 17 patients for whom daily peak flow readings were properly recorded had significantly higher readings on the active treatment, either in the morning, or in the evening, or both (table I). The mean daily peak flow readings for the group as a whole were also higher on active treatment ($P < 0{\cdot}01$). Symptom scores and bronchodilator requirements were both significantly reduced on the active treatment ($P < 0{\cdot}01$ and $< 0{\cdot}05$ respectively).

Suprarenal Function Tests.—The results of the short tetracosactrin tests were available before and after treatment in 17 patients. The responses were all normal according to the criteria of James and Landon (1969). There were no differences between those measured immediately after the active aerosol and those after the placebo aerosol (table II).

Failure to Respond to Betamethasone Valerate Aerosol.—Four patients (cases 2, 3, 7, and 18) failed to respond to the active treatment by one or more of the criteria. Their lack of response appeared to be unrelated to age, sex, age at onset, or duration of asthma, to the severity of the airways obstruction, and to the type of disease (extrinsic or intrinsic as determined by skin testing). The presence of sputum, however, probably influenced the outcome, as three of the four patients in whom it was noted (cases 2, 7, 14, and 18) were among the least responsive to treatment.

TABLE I—*Comparison of Ventilatory Function of Placebo Versus Active Treatment with Betamethasone Valerate*

Case No.	Mean Morning Peak Flow (± S.D.)			Mean Evening Peak Flow (± S.D.)		
	Placebo (l./min)	Active (l./min)	P*	Placebo (l./min)	Active (l./min)	P*
1	285 (45·3)	396 (63·3)	<0·001	343 (40·9)	396 (19·3)	<0·001
2	179 (32·5)	207 (35·0)	<0·05	217 (41·0)	204 (50·4)	N.S.
3	308 (7·0)	274 (58·0)	Worse	361 (18·6)	267 (44·6)	Worse
4	235 (78·8)	350 (39·4)	<0·001	297 (51·4)	386 (42·5)	<0·001
5	309 (48·8)	414 (69·7)	<0·01	331 (28·8)	448 (36·6)	<0·001
6	Incomplete records			Incomplete records		
7	118 (17·6)	126 (19·1)	N.S.	121 (18·8)	114 (17·8)	<0·05
8	176 (14·0)	192 (12·5)	<0·01	177 (22·0)	196 (16·0)	<0·05
9	302 (33·9)	318 (28·6)	N.S.	299 (21·5)	346 (17·8)	<0·001
10	240 (64·2)	270 (25·7)	<0·01	265 (62·0)	307 (30·0)	<0·02
11	314 (46·7)	356 (34·9)	<0·01	362 (26·7)	339 (32·7)	N.S.
12	108 (19·0)	114 (21·3)	N.S.	121 (19·8)	141 (15·4)	<0·05
13	153 (14·8)	211 (15·2)	<0·001	172 (14·6)	219 (13·7)	<0·001
14	88 (7·0)	111 (25·4)	<0·01	120 (25·9)	151 (27·4)	<0·02
15	168 (49·2)	264 (35·5)	<0·001	250 (33·5)	279 (35·6)	<0·02
16	414 (12·3)	447 (25·0)	<0·01	420 (18·8)	467 (38·9)	<0·01
17	95 (15·4)	102 (21·5)	N.S.	119 (21·8)	143 (16·3)	<0·01
18	119 (13·5)	128 (6·1)	<0·02	140 (19·4)	136 (9·1)	N.S.
Whole group P <0·01				Whole group P <0·01		

*Significance of differences calculated by paired *t* tests.
N.S. = Not significant.

TABLE II—*Plasma Cortisol Levels (μg/100 ml) in Short Tetracosactrin Tests for Adrenal Function before and after 28 Days Treatment with Betamethasone Valerate*

Case No.	Before Treatment			After Treatment		
	Resting	30 min after Tetracosactrin	Increase	Resting	30 min after Tetracosactrin	Increase
1	19	33	14	15	31	16
2*	20	38	18	16	32	16
3	13	32	19	16	43	27
4*	11	34	23	10	28	18
5*	15	32	17	20	32	12
6*	12	28	16	18	29	11
7	13	36	23	11	31	20
8*	9	22	13	11	27	16
9	7	28	21	6	28	22
10*	12	25	13	9	23	14
11	7	20	13	9	24	15
12	8	25	17	13	29	16
13*	11	22	11	9	25	16
14	14	25	11	14	23	9
15*	11	29	18	12	29	17
16	7	25	18	9	28	19
18*	10	31	21	13	37	24

*Tests carried out immediately after 28 days on betamethasone valerate aerosol. In the other patients the tests were done 28 days after stopping the steroid aerosol.

Review after Three Months' Treatment.—At the end of three months five patients had stopped the treatment because they preferred bronchodilators and two had been lost to follow-up. The remaining 11 patients continued on maintenance steroid aerosol (three took 800 μg/day (cases 10, 11, and 12), six took 400 μg/day (cases 1, 5, 6, 13, 14, and 15), and two took 200 μg/day (cases 16 and 17)). Good control of their asthma was maintained in all of them.

Insulin Stress Tests were carried out in five of those on maintenance treatment (cases 5, 6, 10, 11, and 12). After an intravenous injection in the fasting patient of 0·15 units/kg of soluble insulin at 9 a.m. the blood sugar was reduced to ⩽ 30 mg/100 ml. The criteria used for determining a normal response to hypoglycaemia were those of James and Landon (1969) (an increment of at least 7 μg/100 ml plasma cortisol and a final level of at least 20 μg). The response in all five patients was normal (table III). In no patient was there any unpleasant effect from the test other then sweating and hunger. Pulse and blood pressure remained normal.

Side Effects.—No untoward side effects of the treatment were observed in nine of the patients. Two, who were taking 800 μg/day, however, developed sore throats and huskiness of the voice towards the end of the third month of treatment. On examination typical "thrush" lesions with white centres and red surrounds were seen on the fauces and posterior pharyngeal wall; in one (case 12) similar lesions were seen on the vocal cords, and in the other (case 11) the cords were reddened, but no white spots were seen. Throat swabs from both these patients grew profuse *Candida albicans* on culture. Intradermal tests for delayed (24-hour) hypersensitivity and lymphocyte transformation tests with candida antigen were done and were positive in both these patients. They both also had immediate positive (10-minute) skin reactions to the same antigen. Treatment for the candida infections with amphotericin lozenges in full dosage did not clear the infections while the dosage of betamethasone valerate was left at 800 μg/day, but when the dose was reduced to 200 μg/day and amphotericin was repeated both the throat and laryngeal symptoms disappeared and the throat swab cultures became negative.

TABLE III—*Results of Insulin Stress Tests in Five Patients after 12 Weeks Continuous Treatment with Betamethasone Valerate Aerosol*

Case No.		Minutes after Insulin				
		0	30	45	60	90
5	B.S.	87	20	42	44	52
	P.C.	20	17	30	33	30
6	B.S.	73	21	35	40	45
	P.C.	19	17	29	29	26
10	B.S.	82	16	31	41	60
	P.C.	22	17	27	29	26
11	B.S.	75	30	28	28	40
	P.C.	17	22	28	31	32
12	B.S.	60	11	19	21	33
	P.C.	10	10	26	32	31

B.S. = Blood sugar in mg/100 ml. P.C. = Plasma cortisol in μg/100 ml.

Part B—Twelve-month Follow-up Study

Patients

A total of 120 patients (15 children and 105 adults) on treatment with either betamethasone valerate or beclomethasone dipropionate aerosol (40 and 80 respectively) were observed for 12 months. In view of the similarity of action of the two compounds their results have been assessed together. The 120 patients included 10 who were treated in part A of this paper, 31 other moderately severe non-steroid-dependent asthmatic adults, 64 adults on long-term maintenance oral prednisone, eight children on regular corticotrophin (ACTH) injections, and seven other children with severe asthma.

All the patients in this study had normal chest radiographic appearances and had shown an initial satisfactory response to steroid aerosols as judged by increased ventilatory function.

Methods

Withdrawal of oral steroids was attempted if the response to the aerosol was good. The patients were then maintained on the lowest dose which would control their asthma, and other treatment was adjusted accordingly. After stabilization of treatment interviews were at about four-week intervals and ventilatory function tests were made at these times.

A watch was kept for throat and laryngeal symptoms, and throat swabs for culture were taken from those who admitted to sore throats or husky voices. All patients were told to wash out the mouth and throat with water after each inhalation of steroid, hoping to minimize any local adverse side effects of the aerosol on the posterior pharyngeal wall which takes the full force of the pressurized spray.

In patients where positive cultures for *C. albicans* were obtained, skin tests for immediate and delayed (24-hour) responses to candida extract were done when possible. The strengths used were 100 mg/ml for prick tests and both 1 mg/ml and 100 μg/ml for intradermal tests (Bencard's extracts).

Results

Satisfactory long-term control of asthma was achieved in 88

out of the 120 patients. A maintenance dose of 200 μg/day was adequate in all but 35 of these who required 300 to 400 μg/day. Five patients, all children, required only 100 μg/day. These doses were arrived at by starting with 400 to 800 μg/day and lowering the dose after a full response had been achieved. This usually took less than four weeks, but efforts were made in the less responsive patients for up to three months.

Results of treatment and the incidence of fungal infections of the respiratory tract are set out in table IV. This is broken down to show the relation of oral steriod treatment to other factors.

TABLE IV—*Twelve-month Follow-up of 120 Patients on Steroid Aerosols*

	No. of Patients	Not on Oral Steroids or ACTH (n = 48)	Adults On Prednisone (n = 64)	Children On ACTH (n = 8)
Satisfactory maintenance on steroid aerosol	88	41	39	8
Withdrawn (preferred bronchodilators)	27	7	20	None
Withdrawn (to control persistent candidiasis)	5	nil	5	None
Total incidence of respiratory candidiasis	16	7	9	None
Patients able to reduce or (discontinue) prednisone or ACTH	47 (18)	—	39 (10)	8 (8)

Temporary lack of response to steroid aerosol occurred in 15 patients during the course of upper respiratory tract infections with sputum (presumed to be viral), but these patients regained their good response in about three weeks. Other temporary lack of response occurred in four patients, who had specific extrinsic asthma, during heavy exposure to antigen. One during the grass pollen season, two who were sensitive to airborne fungal spores during the late summer, and one during exposure to house dust. These patients also recovered their response when they were no longer exposed to the respective antigens.

The prevalence of fungal infections of the respiratory tract was a problem. Sixteen patients (13%) developed infections of the pharynx or larynx or both with *C. albicans;* only nine of these were on oral steroid treatment, and none had recently been taking antibiotic drugs. The appearance of the lesions was typical of thrush and the most intense lesions were on the posterior pharyngeal wall. Fourteen of these patients also complained of severe soreness of the throat and huskiness of the voice, and two of them could hardly speak. In six patients (5%) white monilial spots were seen on the vocal cords on indirect laryngoscopy. There was no evidence that the infections involved the trachea or bronchi, though, of course, bronchoscopy could not be done to exclude this. No patient developed cough or wheeze which was thought to be due to the steroid aerosol and no radiological changes suggestive of fungal infections of the lungs were seen.

Cultures from posterior pharyngeal throat swabs grew *C. albicans* in all 16 patients who admitted to sore throats. Swabs from a random 25 patients without symptoms were all negative.

The development of these candida infections may have been dose-related because we did not see them in any patients who were taking less than 400 μg/day of either aerosol. However, only two out of three patients in part A who had taken as much as 800 μg/day for 12 weeks became infected, whereas, in part B, four patients who started with only 400 μg/day developed candida infections in less than four weeks. All but five of the patients became symptom free and culture negative when the dose of steroid aerosol was reduced to 100 or 200 μg/day and amphotericin throat lozenges were taken, whereas the amphotericin had no effect on the patients before the aerosol dose was reduced. Five patients had to stop the aerosol before they recovered. The details of the 16 patients who developed candida infections are shown in table V. There did not appear to be a higher incidence of these infections in patients on oral steroids, in those taking disodium chromoglycate who might have had some pharyngeal and laryngeal irritation from this drug, or in female patients who could have been vaginal carriers of the organism.

The results of skin tests for both immediate and delayed sensitivity to candida were available in seven of the 16 patients (cases 1, 2, 3, 9, 11, 13, and 15). The immediate response was positive in all, and the late (24-hour) response was positive in all but one (case 15, who was taking oral steroids). Lymphocyte transformation tests were positive with candida extract in two patients who were examined for this (cases 2 and 9, who are also discussed in part A).

Discussion

The chance of success of steroid aerosol treatment in asthma depends on the choice of a compound with a topical activity which is high relative to its systemic activity. Both betamethasone valerate and beclomethasone dipropionate are such compounds.

There seems to be a popular misconception that these topically-active steroids are not absorbed through the lung or gut. This is untrue. Adrenal suppression has been found when large doses of both betamethasone valerate and of beclomethasone dipropionate are inhaled in man (4 mg and 2 mg respectively) (L. C. Wilson, personal communication, 1971; Choo-Kang *et al.*, 1972). Adrenal suppression has also been shown when large doses of betamethasone valerate are taken by mouth (8 mg/day) (Friedman *et al.*, 1967). It is therefore evident that these drugs are readily absorbed by both routes and that their absorption and systemic activity differ very little from that of the most commonly-used oral corticosteroid, prednisone. The virtue of the steroid aerosols lies simply in their very high topical activity, which enables them to be effective at a dose which is well below their H.P.A. suppressive level.

TABLE V—*Details of Patients who Developed Thrush Lesions of Respiratory Tract*

Case No.	Age (years)	Sex	Daily Dose Aerosol (μg)	Time on Aerosol (weeks)	Prednisone Oral Dose (mg/day)	DSCG 20-mg Capsules (No./day)	Pharyngeal Thrush Lesions Present	Laryngeal Thrush Lesions Present on Cords	Symptoms of Laryngitis	Culture Positive*
1	18	F.	400	4	10	4	Yes	Yes	Yes	Yes
2	43	F.	800	10	None	4	„	„	„	„
3	55	F.	400	4	None	4	„	No	„	„
4	42	F.	400	8	10	0	„	Yes	„	„
5	26	M.	400	8	None	4	„	No	No	„
6	31	F.	400	14	10	0	„	„	Yes	„
7	49	M.	400	12	None	4	„	„	„	„
8	35	F.	400	8	10	0	„	„	„	„
9	24	M.	800	12	None	4	„	„	„	„
10	30	F.	400	12	None	4	„	„	„	„
11	32	F.	400	12	10	4	„	Yes	„	„
12	62	M.	800	7	None	0	„	„	„	„
13	43	F.	400	4	15	0	„	No	„	„
14	36	F.	400	8	10	0	„	„	No	„
15	24	F.	400	12	15	4	„	Yes	Yes	„
16	52	M.	800	8	10	0	„	No	„	„

**Candida albicans* grown from throat swab.
DSCG = Disodium Cromoglycate.

It is apparent from the published work on beclomethasone dipropionate that non-steroid-dependent patients respond more readily to steroid aerosol than do those on maintenance oral treatment. Our experience has been the same in our long-term study. The reason for this better response in patients not dependent on steroids is not necessarily because their asthma may be less severe, but may be because they are less likely to have long-standing asthmatic disease with a large complement of fixed airways obstruction. Almost all of our failures of response to inhaled steroids were in patients with severe chronic asthma which was poorly controlled by as much as 15 mg/day of prednisone and in those with sputum. Most of these patients were steroid-dependent.

On the other hand, some of the most responsive patients were children with very severe asthma. These children might have been treated with oral corticosteroids by some doctors, but we believe that ACTH is preferable in children and this is what they were given. They had failed to respond to disodium cromoglycate and had previously needed excessive amounts of bronchodilators to control their symptoms. In almost all of them the response to steroid aerosols was spectacular and the ACTH could be stopped.

It is evident from our follow-up results that the response to inhaled steroids is maintained and that tolerance does not develop for at least 12 months. Temporary loss of response, however, has been noted when patients have been exposed to a heavy dose of antigen, or have developed an episode of sputum production, usually due to an infective cold.

Any long-term side effects of inhaled steroids have not yet been reported. It would not be expected that systemic side effects such as osteoporosis would be seen in the absence of H.P.A. suppression, but it might be suspected that local atrophic changes similar to those seen in the skin after excessive use of topically-active steroid ointments could develop in the respiratory mucosa, particularly in the posterior pharyngeal wall which takes the full force of the aerosol burst. In animal experiments (D. M. Harris, personal communication 1973), however, no histological abnormalities have been detected in the lungs of dogs exposed to beclomethasone dipropionate aerosol in doses high enough to induce gross Cushingoid changes. In man there is as yet no information abut the histology of the respiratory mucosa exposed to steroid aerosols. However, L. Reid stated (personal communication, 1973) that no lung mucosal changes which might be attributable to systemic steroid treatment have been reported in biopsy or necropsy material, despite the fact that thinning of the skin is a commonly seen side effect of prolonged high oral dosage. Though both the foregoing observations are of interest, this problem awaits direct investigation.

Even if histological changes in the respiratory mucosa are absent it is possible that local immunological responses are altered. Sixteen (13%) of our patients developed pharyngeal thrush and in six (5%) of these the larynx was also involved. Though candida infections of the pharynx are sometimes seen in otherwise normal patients, particularly after antibiotic treatment, it is unusual to see candida in the larynx. This and other parts of the respiratory tract are seldom affected by this organism except in conditions of deficiency of cell-mediated immunity, in chronic mucocutaneous candidiasis, and in patients with terminal disease.

Of our 16 patients who developed candida infections seven were taking oral steroids and none had recently taken antibiotics. Also, no patient had shown any evidence of impairment of systemic immunological response. In view of these observations and the high prevalence of the infection in our series, we must suggest that steroid aerosols increase susceptibility to fungal infection of the pharynx and larynx. This could be due either to histological damage or to local immunological changes from the direct action of the topically-active steroid on the respiratory mucosa.

The development of laryngeal candidiasis is a cause for concern because it is not known how far down the respiratory tract the infection may penetrate. For this reason caution with steroid aerosols would seem advisable, particularly in respect of long-term high dosage, and we suggest that their use in patients with lung damage such as bronchiectasis, in which fungal infections could be difficult to eliminate, should be avoided until it can be established that the increased susceptibility to fungal infections does not involve the lung.

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