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Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality

ALAN J WILLIAMS, MS BAGHAT, DE STABLEFORTH, RM CAYTON, PM SHENOI, CRAIG SKINNER

From the Departments of Thoracic Medicine and ENT Surgery, East Birmingham Hospital, Birmingham

ABSTRACT Nine of 14 asthmatic patients who presented with persistent dysphonia while taking inhaled corticosteroids had a bilateral adductor vocal cord deformity with bowing of the cords on phonation. This causes the dysphonia and usually occurs without candidiasis. It was seen with beclomethasone dipropionate (in both pressurised aerosol and dry powder preparations), betamethasone valerate, and budesonide. It was related to the dose and potency of inhaled steroid and may represent a local steroid myopathy. It was reversed when the inhaled steroid was stopped, although resolution sometimes took weeks. Laryngeal candidiasis may have contributed to the vocal cord abnormality in two of these nine patients. Of the five patients without vocal cord deformity, laryngeal candidiasis was the sole cause of dysphonia in three. In the remaining two dysphonia was thought to be psychogenic. The vocal cord deformity may exist subclinically. Of nine patients who started to take aerosol steroid and who were examined monthly for one year, three developed vocal cord deformity but only one had persistent dysphonia. Vocal abuse did not appear to contribute to dysphonia.

Inhaled steroids have an important and well established role in the treatment of chronic asthma.[1–6] Troublesome side effects include candidiasis, sore throat, and dysphonia. These complications occur with all inhaled steroids [7–10] and are probably dose related.[4 8 11–15] The incidence of these side effects is uncertain. The reported incidence of candidiasis ranges from zero[16–19] to 91%[20] and that of sore throat and dysphonia from zero to 55%[4 8 11 21] of patients receiving inhaled steroids. It is not clear whether candidiasis is the sole cause of sore throat and dysphonia as there is no predictable association between these symptoms and candidiasis. Moreover, confusion arises owing to different diagnostic criteria for candidiasis; incomplete ear, nose, and throat examination in most reported studies; and failure to distinguish between the symptoms of sore throat and dysphonia. The two present studies were undertaken to clarify these problems; they included detailed analysis of voice recordings, a detailed history with formal assessment of vocal abuse, and both indirect and direct (fibreoptic) laryngoscopy.

Address for reprint requests: Dr AJ Williams, East Birmingham Hospital, Birmingham B9 5ST.

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Patients and methods

STUDY 1

The first study included all patients who presented to the ENT and thoracic medicine departments with severe and persistent dysphonia while receiving inhaled steroids for asthma. A careful history of dysphonia was recorded, with particular reference to the onset and its relation to the start of treatment with inhaled steroids. The type and total daily dose of inhaled and oral treatment were noted and the patient's inhaler technique was scrutinised and graded "efficient" or "inefficient." "Efficiency" was recorded if the following criteria were fulfilled: (1) mixture of the aerosol contents by shaking; (2) depression of the actuator shortly after the start of a deep inspiration, followed by (3) breath holding for at least four seconds.

In each patient an independent assessment of dysphonia was made by two speech therapists after an interview and analysis of the patient's voice recordings. Specific inquiry was made about smoking, shouting, coughing, loud voice, noise during work, family deafness, and excessive throat clearing. The patient was considered to have vocal abuse if three or more of these factors were present. The same criteria for vocal abuse were applied to a

random sample of people attending a hospital outpatient department. The severity of dysphonia was scored for each patient on a scale of 0–4, zero denoting normal phonation and 4 the most severe dysphonia short of aphonia.

In all cases an examination of the pharynx and larynx was undertaken. Naked eye appearances were documented and a throat swab was taken for mycological study. The presence of fungus was recorded if colonies were grown in Sabouraud's medium after culture for 24–48 hours. The larynx was examined by standard mirror (indirect) laryngoscopy supplemented by direct fibreoptic examination, the latter after the application of local anaesthetic (25% cocaine paste) to the nasal fossae and lignocaine spray to the oropharynx and postnasal space. Care was taken that no anaesthetic was applied to the larynx. The appearances and movements of the vocal cords were documented and photographs taken during deep inspiration (abduction) and phonation (adduction).

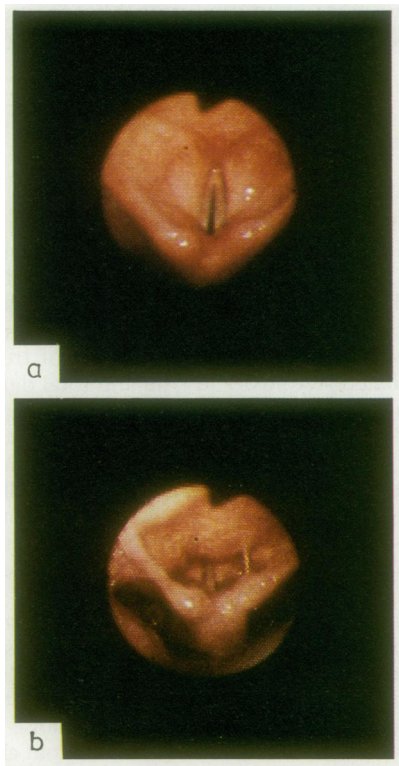

Fig 1 *Laryngoscopic appearances during phonation: (a) showing the bilateral adductor vocal cord abnormality; (b) showing normal appearance (full adduction).*

In all patients the effects of discontinuing inhaled steroid were assessed, the laryngeal appearances and dysphonia being recorded at intervals of two to four weeks. During this follow up period beta agonist inhaler treatment was continued, with an increased dose in some cases and the addition of inhaled ipratropium bromide in others. The modified medication was intended to maintain control of the asthma and also served to replace and match the total quantity of propellant in the discontinued steroid inhaler.

STUDY 2

Patients with chronic asthma of sufficient severity to warrant treatment with inhaled steroids were studied before or within two months of starting treatment with inhaled steroids and monthly thereafter for about one year. At each clinic visit inquiries into the presence of symptoms of sore throat and dysphonia were made, followed by full ENT examination. Patients with a past history of dysphonia were excluded.

Results

STUDY 1

During 18 months 14 patients (seven male) presented with persistent dysphonia while receiving inhaled steroids for chronic asthma. Their mean age was 58 years (range 38–73).

There was excellent agreement between the two speech therapists in their scoring of the grade of dysphonia. On only one occasion in one patient did their assessments differ and then by only one grade.

Direct laryngoscopy invariably gave a good view of the larynx whereas indirect examination failed to give any view in three patients because the epiglottis obscured vision. In nine patients a characteristic bilateral adductor vocal cord abnormality ("bowing" on phonation) was seen on laryngoscopy. An example of this abnormality with normal vocal cord appearances for comparison is shown in figure 1. The type and total daily dose of inhaled treatment, duration of inhaled steroid treatment and duration and grade of dysphonia in these nine patients are shown in table 1. Patient 6 received inhaled steroids on two separate occasions and developed dysphonia on both. Four patients were also receiving oral medication: slow release aminophylline (450 mg/day) in two patients, terbutaline sulphate in one patient (15 mg/day), and prednisolone (5 mg/day) in one other. The duration of inhaled steroid treatment ranged from four to 156 weeks with a mean of 37 weeks. The delay between the start of the treatment and the onset of dysphonia was highly variable; one patient (No 3) commented that dysphonia began

Table 1 *Details of nine patients developing an adductor vocal cord abnormality while taking inhaled steroids*

Patient No	*Age (y)*	*Sex*	*Inhaled steroid (total daily dose in μg)*	*Additional inhaled treatment (total daily dose in μg)*	*Duration of steroid inhalation (w)*	*Duration of dysphonia (w)*	*Grade of dysphonia*
1	70	M	BDP (400)	Salbutamol (200)	92	32	2
2	51	M	BDP (400)	Terbutaline (2 mg) DSCG (160 mg)	8	3	1
3	73	M	BDP (400)	Salbutamol (800)	28	28	2
4	52	F	BDP (200)	Salbutamol (600) DSCG (120 mg)	156	44	2
5	63	F	BDP (R) (800)	Salbutamol (R) (1600)	28	12	4
6	64	M	BDP (400) BV (800)	Salbutamol (600) Ipratropium (160) Fenoterol (1600)	8 10	6 6	1 1
7	55	F	BV (800)	Salbutamol (1600)	30	6	3
8	69	M	Budesonide (400)	Salbutamol (800)	6	4½	1
9	57	M	Budesonide (400)	Salbutamol (800)	4	2½	3
Mean					37	14·4	2·0

BDP—beclomethasone dipropionate; BV—betamethasone valerate; (R)—inhaled via rotahaler; DSCG—sodium cromoglycate.

Table 2 *Appearances of pharynx and larynx, results of fungal studies, and presence or absence of sore throat in the nine patients*

Patient No	*Appearance of pharynx*	*Appearance of larynx*	*Candida albicans cultured*	*Sore throat*
1	Normal	Normal		
2	Normal	Hyperaemia		
3	Normal	Normal		
4	White patches	White patches, hyperaemia, vocal cord oedema	+	+
5	White patches	White patches	+	+
6	Normal Normal	Normal Normal		
7	White patches	Normal	+	
8	Normal	Normal		
9	Normal	Slight vocal cord oedema		

Table 3 *Possible factors contributing to the adductor vocal cord deformity*

Patient No	*Candida albicans cultured*	*Efficient inhaler technique*	*Vocal abuse*	*Cigarette smoking (No/day)*
1	−	+	−	
2	−	+	−	
3	−	+	+	
4	+	−	+	3
5	+	+	+	2
6	−*	+ +	− −	
7	+†	+	−	6
8	−	+	−	
9	−	+	−	

*On two occasions.
†Pharynx only.

immediately while in another (No 4) it appeared only after 112 weeks. There was no significant correlation between the duration of treatment and the grade of dysphonia at presentation. Table 2 summarises the appearances of the pharynx and larynx, the results of fungal cultures, and the presence or absence of sore throat. In most cases the pharynx and larynx appeared normal apart from the vocal cord deformity. There was no suggestion of mucosal atrophy. Three patients had pharyngeal thrush, with the larynx affected in two of them; these two had a sore throat.

Factors which might have a role in the pathogenesis of the vocal cord deformity are shown in table 3. The inhaler technique was efficient in all but one case. Vocal abuse was present in three cases; in our control group 13 out of 50 hospital outpatients had vocal abuse.

With cessation of steroid inhalation the dysphonia and vocal cord deformity resolved. The typical course of events is shown in figures 2 and 3. Patient 1 (fig 2) had taken 400 μg beclomethasone dipropionate for 23 months and had had dysphonia for eight months. The vocal cord abnormality and dysphonia improved and had resolved by 12 weeks after the inhaled steroid had been stopped. Patient 5 (fig 3) had taken beclomethasone dipropionate inhaled as a dry powder for seven months and had

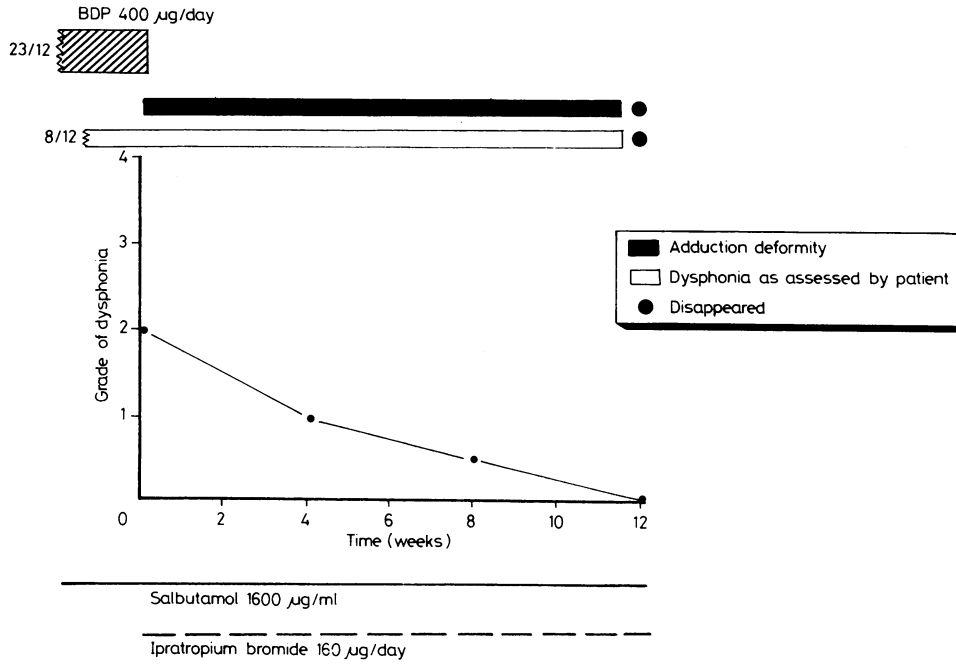

Fig 2 *Resolution of dysphonia and vocal cord deformity after withdrawal of inhaled beclomethasone dipropionate (BDP) treatment in patient 1.*

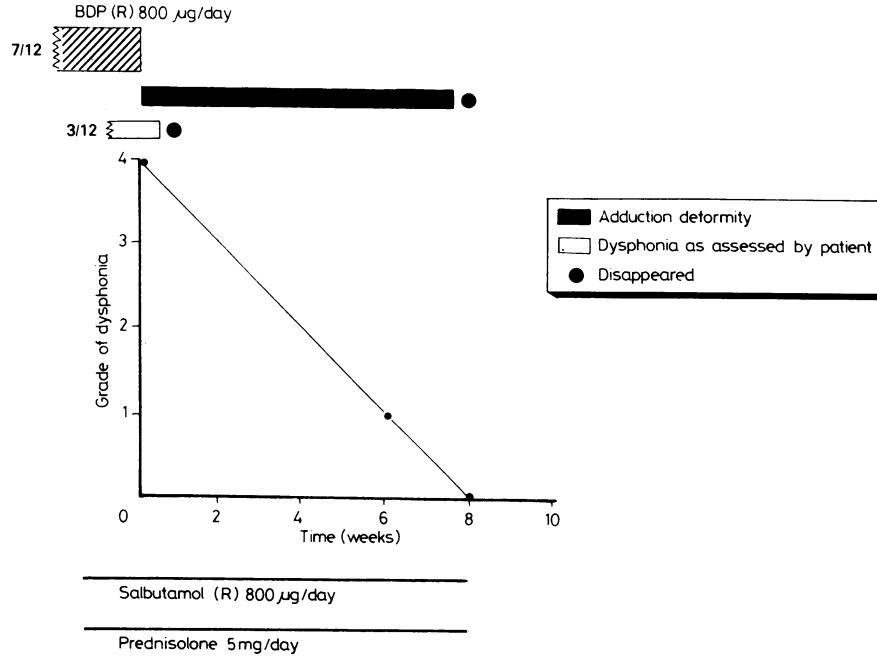

Fig 3 *Resolution of dysphonia and vocal cord deformity after withdrawal of inhaled beclomethasone dipropionate (BDP) treatment in patient 5. (R)—inhaled via rotahaler.*

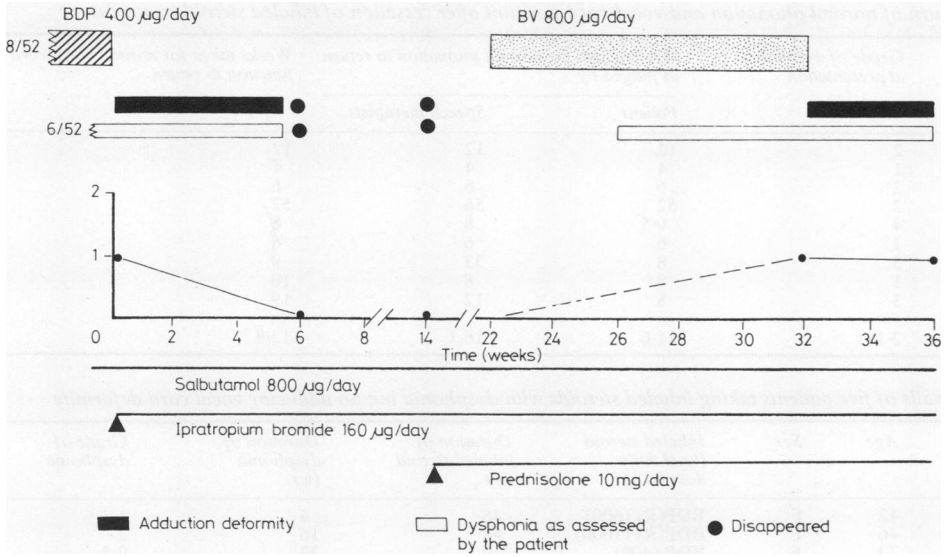

Fig 4 *Dysphonia and vocal cord deformity in patient 6: resolution after withdrawal of beclomethasone dipropionate (BDP) and reappearance after introduction of betamethasone (BV).*

had dysphonia for three months. The adduction deformity had resolved by eight weeks after the inhaled steroid had been stopped. The patient thought that his voice had returned to normal within the first week after he had stopped inhaling steroid, although dysphonia as assessed by speech therapists persisted for eight weeks. Inhalation of salbutamol as a dry powder was continued throughout and the dose of prednisolone remained unchanged. In patient 6 (fig 4) the patient had received beclomethasone dipropionate for eight weeks and had had dysphonia for six weeks. Discontinuation of inhaled steroid led to the improvement and eventual disappearance of the dysphonia and the vocal cord deformity at six weeks. At follow up examination eight weeks later the patient remained symptom free with a normal laryngeal appearance. Commencement of treatment with another inhaled steroid, betamethasone valerate, led to a return of the adduction deformity and dysphonia. A summary of events for all nine patients is shown in table 4. There was a strong correlation between the times taken for the recovery of normal vocal cord function and of normal phonation as judged by the patients ($r = 0{\cdot}97$) and speech therapists ($r = 0{\cdot}87$). The time taken for normal vocal cord function to return ranged from four weeks to one year (mean 13·8 weeks) and was not related to the initial grade or duration of dysphonia at presentation. Full recovery of phonation and vocal cord function was seen in all patients.

In patient 6 betamethasone has been continued for the last seven months, and vocal cord deformity and mild dysphonia (grade I) persist. Likewise resumption of beclomethasone dipropionate inhalation in patient 1 led to a return of the laryngeal abnormality within six weeks, with occasional dysphonia.

There were five dysphonic patients in whom no adduction deformity of the vocal cords was seen at laryngoscopy. Details of these patients are shown in tables 5 and 6. They had milder dysphonia (mean grade 1.1). Three had laryngeal candidiasis. The other two had normal laryngeal appearances but were judged to be tense and anxious, with psychogenic dysphonia.

STUDY 2

Nine patients (five female) with a mean age of 51 years (range 33–69) have been followed for up to 21 months (mean 13 months) after starting inhaled steroids. Patients were examined at monthly intervals. Four patients were examined before starting inhaled steroids, while the other five had the initial

Table 4 *Return of normal phonation and vocal cord function after cessation of inhaled steroid treatment*

Patient No	Grade of dysphonia at presentation	Weeks taken for normal phonation to return as judged by		Weeks taken for normal vocal cord function to return
		Patient	Speech therapists	
1	2	12	12	12
2	1	4	4	4
3	2	6	6	6
4	2	52	56	52
5	4	0·5	8	6
6	1	6	6	6
7	3	8	33	9
8	1	8	8	10
9	3	8	12	19
Mean	2·1	11·6	16·1	13·8

Table 5 *Details of five patients taking inhaled steroids with dysphonia but no adductor vocal cord deformity*

Patient No	Age	Sex	Inhaled steroid (total daily dose in μg)	Duration of inhaled steroid (w)	Duration of dysphonia (w)	Grade of dysphonia
10	42	F	BDP(R) (600)	48	4	1
11	46	F	BDP(R) (1600)	44	16	2
12	73	F	BDP (400)	224	32	0·5
13	38	F	BDP (400)	12	12	1·5
14	59	M	BDP (450)	72	24	0·5
Mean				80	17·6	1·1

BDP—beclomethasone dipropionate; (R)—inhaled via rotahaler.

Table 6 *Appearances of pharynx and larynx and results of fungal studies in five patients taking inhaled steroids with dysphonia but no adductor vocal cord deformity*

Patient No	Appearance of pharynx	Appearance of larynx	Candida albicans cultured	Sore throat
10	White patches	White patches	+	−
11*	Normal	White patches Vocal cord oedema	−	−
12	White patches Erythema	White patches Vocal cord oedema	+	−
13	Normal	Normal	−	−
14	Normal	Normal	−	−

*Receiving oral antifungal treatment.

examination within eight weeks (mean five weeks) of starting treatment. During the follow up period six patients remained symptom free with no pharyngeal or laryngeal abnormality, while three patients developed some abnormalities. Details of these patients follow.

Patient 1 A 53 year old woman started to take beclomethasone dipropionate (400 μg/day) by pressurised aerosol. She was instructed in aerosol technique and at each clinic visit was judged to have an efficient technique throughout the study of 20 months. There was no past history of dysphonia. An ear, nose, and throat examination before treatment started showed nothing abnormal. Twelve weeks after she had started inhaling beclomethasone dipropionate an adduction abnormality of the vocal cords was observed, although the patient was symptom free. The dose of beclomethasone was reduced to 300 μg/day and normal vocal cord function was restored one month later. After a further eight months the abnormality reappeared (no dysphonia being noticed), but it had disappeared one month later. Her dose of beclomethasone was increased two months later to 800 μg/day; the abnormality subsequently returned and has persisted while she has been having this treatment for the last six months. Occasional dysphonia has been noticed by the patient after prolonged conversation.

Patient 2 A 52 year old woman started to take beclomethasone dipropionate 800 μg/day, delivered as a dry powder. There was no past history of dysphonia and an ear, nose, and throat examination before treatment began showed nothing abnormal. Three months later an adduction abnormality of the vocal cords without dysphonia was noted and the steroid inhalation was stopped. One month later the appearances were normal and remained so over the next six months.

Patient 3 A 57 year old woman was examined seven weeks after starting beclomethasone dipropionate at a dose of 400 μg/day. There was no past history of dysphonia. An adductor vocal cord abnormality was observed without dysphonia.

Steroid inhalation was continued for the next three months and the abnormality persisted but without symptoms. The drug was then discontinued and one month later the abnormality had disappeared. Beclomethasone dipropionate was then reintroduced at the same daily dose. Ten weeks later the patient became dysphonic and the abnormality was detected at examination two weeks later. The steroid inhalation was again discontinued. Normal phonation returned one week later but the laryngeal abnormality took 14 weeks to resolve.

Discussion

Local complications of inhaled steroids include candidiasis, sore throat, and dysphonia. The interrelationship and pathogenesis of these three conditions have previously not been clear.

We have recognised for the first time a characteristic laryngeal abnormality which appears to underlie most cases of persistent dysphonia. In nine out of 14 patients there was a bilateral vocal cord adduction deformity, the cords assuming a bowed or elliptical appearance during phonation. We believe this deformity to be causal—firstly, because the laryngeal abnormality developed and resolved in parallel with dysphonia and, secondly, because an identical abnormality, "phonasthenia," is a well described cause of dysphonia in myopathic disorders such as myasthenia gravis and dystrophia myotonica. In these conditions there is considered to be a paresis of the phonatory muscles, the internal tensor muscle group being the most commonly affected. Dysphonia arises from failure of the vocal cords to approximate completely during phonation, a gap being left for escape of air. We believe that this abnormality has not previously been recognised in dysphonic patients receiving inhaled steroids for three reasons. Firstly, interest has centred around candidiasis as a cause of dysphonia and laryngoscopy has usually been performed simply to verify or exclude the presence of candidiasis rather than to assess vocal cord mobility. Secondly, until the advent of fibreoptic techniques laryngoscopy has been limited in the conscious patient to an indirect mirror examination, a technique we have found to be inferior for recognising the abnormal laryngeal appearances. Thirdly, direct laryngoscopy with rigid instruments under general anaesthesia cannot assess vocal cord mobility.

Some cases of dysphonia appear to be due to candidiasis without any vocal cord abnormality. In five patients with persistent dysphonia and normal vocal cord mobility, three had laryngeal candidiasis (table 6). We diagnosed the latter when there were typical white, raised plaques with underlying erythema. In two of the three cases fungal cultures for *Candida albicans* were positive. In the third patient fungal cultures were negative but she was taking an oral antifungal agent at the time of the examination. Candidiasis is a well known complication in patients receiving inhaled steroids. Its reported incidence varies from zero to 91%. This variation depends partly on the diagnostic criteria adopted by the authors and partly on whether single or repeated examinations of the pharynx are made. *Candida albicans* is part of the normal oropharyngeal flora and has been cultured from throat swabs in 28%[22] and 57%[23] of normal subjects: hence the diagnosis of candidiasis must be a clinical one. When the strict criteria of typical naked eye appearances together with positive fungal cultures are used, as in our study, the reported incidence of pharyngeal candidiasis is much less variable, although it still shows a range from zero to 32%.[5 7 8 16 20 24]

As well as being the sole cause of dysphonia, candidiasis may contribute to the vocal cord abnormality by adding an inflammatory component to the myopathic one. Two of our nine patients with vocal cord deformity (table 2) had laryngeal candidiasis.

In some patients with persistent dysphonia no vocal cord deformity or candidiasis is seen. We had two patients in this category. Both appeared unduly tense and anxious and we believe that their dysphonia was psychogenic.

Various mechanisms have been suggested for the occurrence of dysphonia with inhaled steroid treatment, including a non-specific mucosal irritation caused by the freon propellants[24] and drying action of the spray.[17] We have shown a consistent vocal cord deformity, however, to underlie most cases of persistent dysphonia. The mechanism of the laryngeal abnormality we believe to be related to the steroid rather than the propellant component of the inhaled steroid preparation. Firstly, the laryngeal adduction deformity resolved after the inhaled steroid had been stopped, even though the total quantity of inhaled propellant was maintained by an appropriate increase in inhaled bronchodilator beta agonist and ipratroprium bromide treatment; the fluorocarbon propellants in aerosols do not differ significantly in either type or quantity. Secondly, resumption of inhaled steroids in two patients (patients 1 and 6) without any increase in total propellant intake led to a return of the abnormality. Thirdly, one patient (patient 5) was taking dry powdered preparations of steroid and bronchodilator, which contain no propellants. In a recent study it was also concluded that dysphonia was due to the steroid rather than the propellant.[11] In this study it was suggested that vocal cord abuse

might be an important contributory factor. But although vocal abuse was present in some of our patients it was no more common than in a control group of medical outpatients.

It is clear that all available inhaled steroid preparations can cause the laryngeal abnormality and that a change to a different one at an equivalent dose is unlikely to influence the problem. Probably the risk of dysphonia due to the adductor vocal cord deformity is related to the total dose and potency of inhaled steroid preparation. For instance, the two patients (8 and 9) taking budesonide, which is two to three times as potent as beclomethasone dipropionate,[25] both developed dysphonia less than two weeks after starting the drug; while the patient taking the smallest dose of inhaled steroid, beclomethasone dipropionate 200 μg (patient 4), took the longest time (112 weeks) to develop dysphonia. Possibly the vocal cord deformity represents a local steroid myopathy, but we have no direct evidence for this. Interestingly dysphonia is seldom reported in children during inhaled steroid treatment and this may be explained by the use of a lower total daily dose, as has been suggested;[19] perhaps too the anabolic influence of growth counteracts any detrimental myopathic effect of the steroid.

In our dysphonic patients sore throat occurred only when candidiasis was present, although it is clear that most patients with candidiasis are symptom free. The efficiency or otherwise of the patient's inhaler technique may have a bearing on the vocal cord abnormality. An efficient technique was found in 90% of patients, a higher percentage than anticipated from previous surveys, in which usually 30–40% of patients have been judged to have an inept technique.[26 27] Theoretically patients with an efficient technique may be at greater risk of developing this abnormality for the following reason. The branching system of the airways provides an extremely efficient aerodynamic filter and only 10% of the total dose emitted from an aerosol reaches the conducting airways of the lung.[28–31] The remainder is deposited by inertial impaction, usually in the mouth and pharynx. Patients who have an inefficient inhaler technique will therefore deposit more of the drug in the oropharynx. In contrast, patients with an efficient technique will deposit more of the drug in and around the larynx from the stream of particles en route to the lung.

After discontinuation of the inhaled steroid the laryngeal appearances and the voice invariably returned to normal, although this sometimes took months.

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