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Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease

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Abstract

Inhaled corticosteroids are known to reduce respiratory symptoms and airway responsiveness in allergic patients with asthma. The aim of the present randomised, double blind study was to assess the effect of eight weeks' treatment with inhaled budesonide in non-allergic smokers with chronic obstructive lung disease. Twenty four subjects (23 male) entered the study. Their ages ranged from 40 to 70 (mean 57) years, with a mean of 35 (range 9–80) pack years of smoking; the mean FEV_1 was 53% (range 32–74%) predicted and geometric mean PC_{20} (histamine concentration causing a 20% fall in FEV_1) 0·96 (range 0·07–7·82) mg/ml. After a two week washout, single blind, placebo period, 12 patients were allocated to treatment with budesonide 1600 μg/day and 12 to placebo for eight weeks. The only additional drug to be taken was ipratropium bromide "if needed." Twenty one patients completed the study, 10 in the budesonide group and 11 in the placebo group. The standard deviation of the difference between duplicate measurements of PC_{20} histamine and citric acid cough threshold made two weeks apart was below one doubling dose step. There was a significant reduction in dyspnoea in the budesonide group, but otherwise no change in symptom scores or use of ipratropium bromide over the eight weeks of treatment within or between the two groups. No significant differences in spirometric values, peak expiratory flow, PC_{20} histamine, or citric acid cough threshold were found between the groups. Although differences were not significant, some of the changes showed a trend in favour of budesonide. Whether a longer observation period would show a significant influence of inhaled corticosteroids in patients with chronic obstructive lung disease remains to be determined.

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Inhaled corticosteroids are widely used as maintenance treatment both in patients with sudden attacks of dyspnoea and almost completely reversible airflow obstruction (asthma) and in patients with persistent airflow obstruction that is not fully reversible but may vary in intensity (chronic obstructive lung disease). Several investigators have shown that maintenance treatment with inhaled corticosteroids decreases airway responsiveness in patients with allergic asthma,[1–7] possibly because of an effect on inflammatory processes within the airways.[8]

The role of oral and inhaled corticosteroids in the treatment of smokers with chronic obstructive lung disease remains controversial, however.[9 10] Short term treatment with oral corticosteroids caused no overall improvement in patients with chronic obstructive lung disease in several studies[9–14]; but in some double blind crossover, placebo controlled studies "responders" were distinguished from "non-responders," one of the features of a responder being a higher peripheral blood eosinophil count.[11–14] Inhaled corticosteroids, such as beclomethasone dipropionate and budesonide, have a strong topical effect and far fewer systemic side effects than oral corticosteroids. There are only a few reports on the effect of inhaled corticosteroids on patients with chronic obstructive lung disease.[15–18] In a recent study 12 out of 34 patients with chronic obstructive lung disease responded, with a 10% or more increase in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), or peak expiratory flow (PEF), to 1500 μg of inhaled beclomethasone dipropionate a day.[18] In this study, however, some allergic individuals were also included, to judge by IgE values and skin test responses. Recently it has been suggested that little or no change in airway responsiveness occurs after 800 or 1200 μg of inhaled corticosteroids.[15 16]

The aim of our study was to investigate the effects of treatment with a high dose of an inhaled corticosteroid on airflow obstruction, airway responsiveness, and cough threshold in current non-allergic smokers with moderate, partially reversible airflow obstruction.

Methods

PATIENTS

Twenty four patients (23 male), with a mean age of 57 (range 40–70) years, participated in the study. Inclusion criteria were: smoking at least one cigarette a day for at least five years; FEV_1 30–75% predicted; reversibility, in terms of the difference between FEV_1 % predicted before and after 0·5 mg inhaled terbutaline, of less than 20%; a provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) of less than 16 mg/ml. Skin test responses to 12 common allergens and IgE

specific for house dust mite had to be negative, total serum IgE had to be below 470 IU/ml, and the peripheral blood eosinophil count had to be below $0{\cdot}2 \times 10^6$/l. The patients had no upper respiratory tract infection or any oral corticosteroids in the two months before the study. Inhaled corticosteroids were stopped two weeks before the start of the double blind study period.

STUDY DESIGN

Patients were seen in the outpatient department at two week intervals over 12 weeks. The first two visits were before and after a single blind placebo treatment period of two weeks (four puffs twice daily administered via the Nebuhaler, Astra). They were then allocated at random to one of two parallel groups in a double blind design. Twelve patients received 1·6 mg/day budesonide (four puffs twice daily via the Nebuhaler) for eight weeks; and the other 12 were treated with a placebo inhaler. Measurements of FEV , response to 0·5 mg terbutaline, PC_{20} histamine, and citric acid threshold were carried out every two weeks for eight weeks. For controlling any symptoms the only bronchodilator drug allowed, besides the study drugs, was ipratropium bromide "as needed." All other bronchopulmonary medication was discontinued two weeks before entry to the study. Drug canisters were weighed at each visit to assess the patients' compliance. The protocol was approved by the hospital medical ethical committee and written consent from each patient was obtained.

DIARY CARDS

The patients made daily recordings of morning and evening expiratory peak flow (PEF; Mini Wright, best of three attempts) and scored the symptoms of coughing and dyspnoea on a 0–3 scale (0 = none, 3 = severe). Sputum volume was estimated on a 0–5 scale (0 = none, 5 = more than one coffee cup) and the number of ipratropium bromide puffs inhaled was recorded.

MEASUREMENTS

All medication was stopped 12 hours before each visit, which took place at the same time of day. Inspiratory slow vital capacity (VC) and FEV_1 were measured with a water sealed spirometer (Lode BV, Groningen, The Netherlands). After baseline FEV_1 measurements a histamine inhalation provocation test was carried out. When the FEV_1 had returned to a value above 85% of the highest value on that day a citric acid cough challenge was performed. After this challenge VC and FEV_1 manoeuvres were performed before and 20 minutes after inhalation of 0·5 mg terbutaline to assess reversibility. Whenever a fall in FEV_1 occurred after the citric acid challenge, reversibility was measured when the FEV_1 had returned to the baseline value. FEV_1 was expressed as % predicted.[19]

PC_{20} histamine

Histamine challenge was performed by a modification of the method of De Vries[20] with a Wiesbadener doppelinhalator and an airflow of 8 l/min (output 0·12 ml/min, mean particle size less than 5 μm). Inhalation of phosphate buffered saline (PBS) was followed by doubling doses of histamine from 0·03 mg/ml until there was a 20% fall in FEV_1 from the post-PBS value or the maximum dose of 16 mg/ml was reached. The inhalation took two minutes (during tidal breathing) with intervals of at least five minutes between doses. FEV_1 was measured 30 and 90 seconds after each inhalation. PC_{20} was estimated by linear interpolations on a log dose-response plot.

Citric acid cough threshold

Citric acid was nebulised in the same way as histamine. After a control measurement with saline the subject inhaled doubling concentrations of citric acid diluted in saline (from 1 to 512 mg/ml) during tidal breathing for one minute. FEV_1 was measured 30 and 90 seconds after each inhalation. The interval between doses was at least five minutes. The cough threshold was defined as the first concentration of citric acid that induced cough during inhalation, provided that the following concentration also led to cough. Cough was registered with a pressure transducer connected to the spirometer. When no cough occurred with the highest citric acid concentration the cough threshold was arbitrarily set at 1024 mg/ml.

Withdrawals

Eleven of the 12 placebo treated and 10 of the 12 budesonide treated patients completed the trial. One patient in the actively treated group (No 4) was admitted to hospital with congestive heart failure on visit 3. One patient in the placebo group (No 11) and one in the budesonide group (No 10) had to be withdrawn after visits 3 and 4 respectively, owing to a respiratory tract infection that required treatment with oral corticosteroids, bronchodilators, and antibiotics.

STATISTICAL ANALYSIS

Logarithmic transformation of PC_{20} histamine values and the citric acid threshold values was carried out before analysis. Reproducibility was assessed as the standard deviation (SD) of the difference between duplicate measurements (d):

$$(\mathrm{SD})^2 = \frac{\sum d^2}{2k},$$

where k is the number of patients.

Diurnal variability of PEF values was calculated for each day as (afternoon reading − morning reading/mean of the two readings) = 100%; the mean for seven days was then calculated.

Student's unpaired t test was used to compare values for the two treatment groups. Changes within each group were analysed by paired t test. Means symptom scores for two week periods were compared by Wilcoxon's signed rank test. A p value of 0·05 or less was

Table 1 Clinical data at entry to the study

Patient No	Age (y)	Pack years* (y)	VC (l)	FEV_1 (l)	FEV_1 (% pred)	Reversibility† (%)	PC_{20} histamine (mg/ml)	Citric acid cough threshold (mg/ml)	Treatment before study
BUDESONIDE									
1	46	19	4·30	2·15	54·9	5·1	0·87	256	BCT
2	62	15	4·70	2·50	71·5	5·7	0·23	>512	A
3	53	38	4·00	1·80	53·4	5·9	0·37	512	AC
4	63	26	4·18	1·30	34·9	10·7	1·00	>512	ABC
5	62	47	3·30	1·05	32·0	7·6	0·81	512	A
6	56	14	2·90	1·70	59·2	5·2	2·64	128	AC
7	67	22	2·55	1·65	60·0	−1·8	0·68	128	A
8	55	40	4·25	2·40	67·2	14·0	1·54	256	AC
9	66	21	4·00	1·90	58·5	9·2	3·03	128	AC
10	56	63	4·35	1·60	45·2	14·1	0·33	>512	AC
11	48	24	3·45	1·80	51·9	5·8	0·47	>512	AC
12	66	32	4·20	1·45	42·9	4·4	0·07	64	AC
Mean	58·3	30·1	3·85	1·78	52·6	7·2	GM 0·65	GM 341	
SD	7·1	14·6	0·65	0·43	12·0	4·4			
PLACEBO									
1	63	61	4·20	2·00	59·9	12·0	2·10	512	AC
2	57	71	3·30	1·80	55·3	9·2	5·53	4	A
3	50	59	3·85	2·30	64·9	7·1	0·10	256	AB
4	62	41	2·35	1·60	53·7	3·4	0·78	64	AC
5	50	9	2·40	1·25	34·4	6·9	0·83	>512	AC
6	45	27	2·80	1·95	55·5	5·7	1·46	256	ABC
7	51	35	3·00	1·20	35·5	4·4	0·48	64	A
8	52	37	4·40	2·90	74·1	5·1	7·82	512	A
9	40	18	4·85	2·55	67·3	5·3	3·19	256	AC
10	63	38	3·50	1·75	51·8	3·0	5·00	>512	ACT
11	70	80	3·75	1·90	56·0	4·4	2·34	256	AC
12	66	12	3·15	1·25	40·6	6·5	0·41	>512	AC
Mean	55·8	40·7	3·46	1·87	54·1	6·1	GM 1·41	GM 228	
SD	9·1	19·6	0·28	0·53	12·3	2·5			

*One pack year was defined as the number of packs of cigarettes smoked per day multiplied by the number of years (1 pack = 25 cigarettes).
†Difference between FEV_1 % predicted before and after 0·5 mg inhaled terbutaline.
VC—vital capacity; PC_{20}—provocative concentration causing a 20% fall in FEV_1; GM—geometric mean; A—anticholinergic; B—beta agonists; C—inhaled corticosteroid; T—theophylline.

regarded as statistically significant. Values are presented as means with standard deviations in parentheses.

Results

PATIENTS

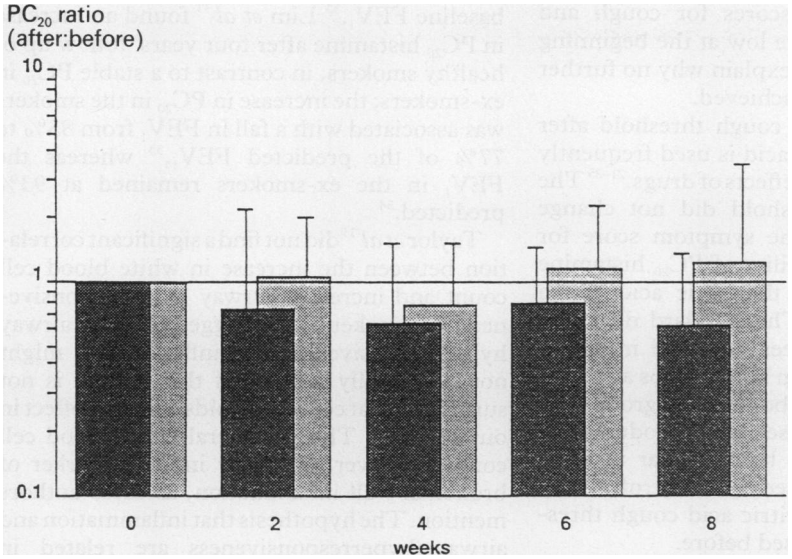
The clinical characteristics of the patients are shown in table 1. There were no statistical differences between the two groups with regard to baseline FEV_1, FEV_1 % predicted, reversibility, PC_{20} histamine, or citric acid cough threshold. Diurnal PEF variability in the run in period was low and did not differ between groups, the mean (SD) percentage variation being 9·9 (4·2) in the budesonide group and 8·5 (4·2) in the placebo group. Compliance, as measured by weighing the cannisters, was similar in the two arms of the study, ranging from 80% to 89% in the budesonide group and from 79% to 91% per two weeks of usage in the placebo group.

SPIROMETRY

Individual values of FEV_1 % predicted during the trial, obtained after withdrawal of bronchodilators for 12 hours or more and before any challenge procedure, are shown in table 2. Spirometric values did not change significantly in either group in the two week run in period.

Table 2 Individual FEV_1 % predicted values during the trial

Patient No	Placebo: week 0	2	4	6	8	Patient No	1600 μg budesonide: week 0	2	4	6	8
1	54	63	51	58	51	1	57	66	74	69	60
2	55	52	55	58	40	2	64	76	62	69	69
3	73	69	62	68	64	3	61	56	50	50	55
4	47	54	52	57	47	4	40	40	40	—	—
5	34	36	36	36	34	5	26	21	23	27	23
6	55	54	69	54	57	6	63	64	64	59	61
7	35	35	33	33	27	7	55	55	58	53	56
8	72	69	77	69	63	8	69	66	66	67	67
9	66	66	66	67	66	9	55	58	62	62	58
10	56	50	58	53	53	10	55	37	45	—	—
11	56	52	44	—	—	11	50	52	55	55	52
12	39	34	39	36	49	12	41	38	47	47	44
Mean	53·5	52·8	52·8	53·5	50·1	Mean	53·0	52·4	55·1	55·8	54·5
SD	13·0	12·7	13·0	13·1	12·5	SD	12·1	15·6	13·7	12·8	13·2



Mean (SD) ratios of PC_{20} histamine (provocative concentration causing a 20% fall in FEV_1) at follow up to baseline PC_{20} histamine. ■ Budesonide group (n = 10); ■ placebo group (n = 11).

The mean (SD) percentage change in FEV_1 % predicted over the eight weeks of treatment (from visit 2 to visit 6) was −3·4 (6·9) for the placebo group and +0·4 (3·3) for the budesonide group. These changes did not differ significantly between the two groups (p = 0·12). The mean absolute change in FEV_1 between visit 2 and visit 6 was −0·12 (0·23) litres (p > 0·05) for the placebo group and +0·015 (0·11) l for the budesonide group—an increase that was just below significance (p = 0·098). The difference between the two groups was not significant.

VC improved over the eight weeks of treatment in both groups. Although the increase in the budesonide group was greater (0·29 (0·23) l; p = 0·08) than that in the placebo group (0·10 (0·43)), the difference was not significant.

REVERSIBILITY

There was no significant difference in reversibility, expressed as the difference between FEV_1 % predicted before and after 0·5 mg terbutaline, between the groups at any time. There were no significant change in reversibility after the eight weeks budesonide compared with the pretreatment values. The mean percentage change in FEV_1 before and after terbutaline treatment was 6·1 (2·5) and 7·4 (1·5) in the placebo group and 7·2 (4·4) and 6·5 (5·0) in the budesonide group.

Table 3 Diary card data (mean (SD) values): improvements during the trial up to the day the patient was in the trial (day 43–74 minus day 8–14)

	Budesonide (n=12)	*Placebo (n=11)*
Peak expiratory flow (l/min):		
Morning	− 2·83 (47·0)	+2·0 (33·3)
Evening	−13·18 (36·2)	−5·7 (21·4)
Dyspnoea (0–3)	− 0·22 (0·30)*	+0·10 (0·61)
Cough (0–3)	− 0·24 (0·47)	−0·15 (0·77)
Sputum (0–5)	+ 0·03 (0·19)	−0·33 (0·95)
Ipratropium bromide (No of puffs/day)	+ 0·48 (1·75)	+0·65 (1·07)

*p < 0·05 within group (t test).

REPRODUCIBILITY OF PC_{20} HISTAMINE AND CITRIC ACID THRESHOLD MEASUREMENTS

The standard deviations of the difference in duplicate measurements for citric acid threshold and PC_{20} histamine were 0·77 doubling doses (DD) and 0·96 DD respectively (comparison of values before and after the two weeks' single blind placebo period). Reproducibility, expressed in terms of doubling dose, after six weeks of placebo treatment was 0·82 DD for histamine and 1·5 DD for citric acid.

PC_{20} HISTAMINE

The ratios of PC_{20} histamine values after and before eight weeks' treatment with placebo and with budesonide are presented in the figure. No significant differences were seen over the eight weeks of treatment within or between the treatment groups. The ratio of PC_{20} histamine after eight weeks to the initial value was above 1 for placebo and less than 1 for budesonide; the differences were just less than significant. The mean change in $\log^{10}$ PC_{20} histamine after eight weeks' treatment was +0·086 (0·504) mg/ml in the placebo group and −0·208 (0·348) mg/ml in the budesonide group.

CITRIC ACID COUGH THRESHOLD

The mean changes in $\log^{10}$ citric acid threshold after eight weeks' treatment were −0·14 (0·45) DD for the placebo group and −0·18 (0·47) DD for the budesonide group. There were no significant changes within or between the two groups.

DIARY CARD

Morning and evening PEF and symptom scores (dyspnoea score, coughing, and sputum production) were analysed by comparing days 8–14 with days 43–74 (table 3). There were no significant changes except in the dyspnoea score, which improved significantly during budesonide treatment (p < 0·05), whereas it increased only slightly in the placebo group (p = 0·08 for budesonide versus placebo). The use of ipratropium bromide as needed increased slightly, but was similar in the two groups during the whole study.

Discussion

The present study was carried out in non-allergic current smokers with chronic obstructive pulmonary disease. We were unable to find a statistically significant effect of eight weeks' treatment with budesonide 1·6 mg/day on lung function, reversibility, PC_{20} histamine, or citric acid threshold, to judge by the similarity between the treated group and the placebo group.

The improvement in FEV_1 almost reached significance after eight weeks of active treatment, so the question arises whether a longer treatment period would have shown a difference between the two groups. Symptom scores for dyspnoea but not for coughing and sputum production showed a significant improvement. Reduced dyspnoea may be the first indicator of a slow improvement in lung function that otherwise may need more time to become

detectable. Symptom scores for cough and sputum production were low at the beginning of the study. This may explain why no further improvement could be achieved.

Measurement of the cough threshold after provocation with citric acid is used frequently to assess the antitussive effects of drugs.[21-25] The citric acid cough threshold did not change significantly nor did the symptom score for cough. The reproducibility of PC_{20} histamine was good and that of the citric acid cough threshold acceptable. The standard deviation of the difference between repeated measurements two weeks apart in both groups and after 10 weeks in the placebo treated group was around one doubling dose. The reproducibility for PC_{20} histamine has been similar in some other studies, summarised by Cockcroft.[26] The reproducibility of the citric acid cough threshold has not been assessed before.

In the present study we could not distinguish "responders" from "non-responders" in the actively treated group. This may be because patients with features that might favour a response to corticosteroids, such as sputum eosinophilia and allergy, were excluded.

The results of our study are in keeping with those of recently published short reports of a Danish and a British group that indicated no improvement or only a small improvement in lung function or airway hyperresponsiveness after treatment for three months with 0·8 mg and 1·2 mg budesonide daily.[15 16] Effects may be smaller in smokers than in non-smokers or ex-smokers, as the ongoing deleterious effect of smoking may prevent a response.

There are other possible explanations for the lack of effect of high doses of inhaled budesonide in these patients. Firstly, corticosteroids are known to be potent anti-inflammatory drugs but, in contrast to the "allergic asthmatics," where inflammation is dominated by eosinophils, neutrophilic infiltration has a major role in smokers.[27-29] The two types of inflammation may react differently to treatment with corticosteroids and the duration of the treatment may have been too short to result in clinical improvement. On the other hand, most of our patients were longstanding middle aged smokers, and such a chronic inflammatory stimulus may need longer treatment than allergic stimuli in young asthmatic patients. This hypothesis may be supported by findings of Postma *et al*,[30 31] who showed in a retrospective study that long term use of more than 7·5 mg prednisolone a day was associated with a slower decline in FEV_1 or even improvement in patients with chronic obstructive lung disease and moderate to severe airflow obstruction. The association with decline in FEV_1 was, however, seen only after 6–24 months of follow up. Another explanation could be the relation between FEV_1 and airway hyperresponsiveness. In allergic asthmatic patients FEV_1 and airway hyperresponsiveness appear to be mainly independent phenomena: patients with normal baseline lung function may be very hyperresponsive. In smokers with chronic airflow obstruction the relation is stronger: in most studies the degree of airway hyperresponsiveness correlates with baseline FEV_1.[32] Lim *et al*[33] found an increase in PC_{20} histamine after four years' follow up of healthy smokers, in contrast to a stable PC_{20} in ex-smokers; the increase in PC_{20} in the smokers was associated with a fall in FEV_1 from 83% to 77% of the predicted FEV_1,[33] whereas the FEV_1 in the ex-smokers remained at 93% predicted.[34]

Taylor *et al*[35] did not find a significant correlation between the increase in white blood cell count and increased airway hyperresponsiveness in smokers and suggested that airway hyperresponsiveness and inflammation might not be causally related. If this is so it is not surprising that corticosteroids had little effect in our patients. The peripheral white blood cell count, however, is a very indirect marker of bronchial wall inflammation, as these authors mention. The hypothesis that inflammation and airway hyperresponsiveness are related in patients with chronic obstructive lung disease is therefore still not refuted.

In conclusion, we found that inhalation of 1·6 mg budesonide a day for eight weeks did not improve airway hyperresponsiveness as assessed by inhalation of histamine and citric acid. The increase in FEV_1 after eight weeks was just below significance, whereas the symptoms of dyspnoea improved significantly. The implication of this and other studies is that longer observation periods are required to establish whether inhaled corticosteroids have a beneficial influence on the outcome of chronic obstructive lung disease. Whether doses of budesonide above 1·6 mg would provide an earlier and better response, without side effects, is a further question that has to be answered.

1 Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987; 79:653–9.

2 Kraan J, Koeter GH, vd Mark ThW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: A comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985;76:628–36.

3 Kraan J, Koeter GH, vd Mark ThW, *et al*. Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis* 1988;137:44–8.

4 Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 μg/day) and budesonide (1600 μg/day,) for chronic asthma. *Thorax* 1986;41:869–74.

5 Jenkins CR, Woolcock AJ. Effect of prednisone and beclomethasone dipropionate on airway responsiveness in asthma: a comparative study. *Thorax* 1988;43:378–84.

6 Gaddie J, Petrie GR, Reid IW, Sinclair DJM, Skinner C, Palmer KNV. Aerosol beclomethasone diproprionate: a dose-response study in chronic bronchial asthma. *Lancet* 1973;ii:280–1.

7 Ryan G, Latimer KM, Juniper EF, Robert RS, Hargreave FE. Effects of beclomethasone dipropionate on bronchial responsiveness to histamine in controlled nonsteroid-dependent asthma. *J Allergy Clin Immunol* 1985;75:25–30.

8 Lundgren R, Soderberg M, Horstedt P, Sterling R. Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. *Eur Respir J* 1988;1:883–9.

9 Evans JA, Morrison IM, Saunders KB. A controlled trial of prednisone, in low dosage, in patients with chronic airways obstruction. *Thorax* 1974;29:401–6.

10 Eliasson O, Hoffman J, Trueb D, Frederick D, McCormick JR. Corticosteroids in COPD. *Chest* 1986;89:484–90.

11 Mendella LA, Manfreda J, Warren PW, Anthonisen NR. Steroid response in stable chronic obstructive pulmonary disease. *Ann Intern Med* 1982;96:17–21.

12 Mitchell DM, Gildeh P, Rehahn M, Dimond AH, Collins JV. Effects of prednisolone in chronic airflow limitation. *Lancet* 1984;ii:193–6.

13 Shim C, Stover DE, Williams MH. Response to corticosteroids in chronic bronchitis. *J Allergy Clin Immunol* 1978;**62**:363–7.
14 Stokes TC, Shaylor JM, O'Reilly JF, Harrison BDW. Assessment of steroid responsiveness in patients with chronic airflow obstruction. *Lancet* 1982;ii:345–7.
15 Engel T, Heinig JH, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. *Eur Respir J* 1989;**2**: 935–9.
16 Watson A, Lim TK, Joyce H, Pride NB. Trial of the effect of inhaled corticosteroids on bronchoconstrictor and bronchodilator responsiveness in middle aged smokers [abstract]. *Thorax* 1988;**43**:231P.
17 Harding SM, Freedman S. A comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response. *Thorax* 1978;**33**:214–8.
18 Weir DC, Gove RI, Robertson AS, Sherwood Burge P. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax* 1990;**45**: 112–7.
19 Quanjer PhH. Standardized lung function testing. *Clin Respir Physiol* 1983;**19**(5):45–51.
20 De Vries K, Goei JT, Booij Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962;**20**:93–101.
21 Belcher N, Rees PJ. Effects of pholcodine and salbutamol on citric acid induced cough in normal subjects. *Thorax* 1986;**41**:74–5.
22 Bickerman HA, Barach AL. The experimental production of cough in human subjects induced by citric acid aerosols. Preliminary studies on the evaluation of antitussive agents. *Am J Med Sci* 1954;**228**:156–63.
23 Cox ID, Wallis PJW, Apps MCP, *et al.* An electromyographic method of objectively assessing cough intensity and use of the method to assess effects of codeine on the dose response curve to citric acid. *Br J Clin Pharmacol* 1984;**18**:377–82.
24 Pounsford JC, Birch MJ, Saunders KB. Effect of bronchodilators on the cough response to inhaled citric acid in normal and asthmatic subjects. *Thorax* 1985;**40**:662–7.
25 Rees PJ, Clark TJH. Assessment of antitussive effects by citric acid threshold. *Br J Dis Chest* 1983;77:94–7.
26 Cockcroft DW. Measurement of airway responsiveness to inhaled histamine or methacholine: method of continuous aerosol generation and tidal breathing inhalation. In: Hargreave FE, Woolcock AJ, eds. *Airway responsiveness, measurement and interpretation.* Hamilton, Ontario: Astra Pharmaceuticals, 1985:22–8.
27 De Monchy JGR, Kauffman H, Venge P, *et al.* Bronchoalveolar eosinophilia during allergen induced late asthmatic reactions. *Am Rev Respir Dis* 1985;**131**:373–6.
28 Mullen JBM, Wiggs BR, Wright JL, Hogg JC, Paré PD. Nonspecific airway reactivity in cigarette smokers. *Am Rev Respir Dis* 1986;**133**:120–5.
29 Reynolds HY, Newball HH. Anaylsis of protein and respiratory cells obtained from human lung by bronchial lavage. *J Lab Clin Med* 1974;**84**:559–73.
30 Postma DS, Steenhuis EJ, Van de Weele LTh, Sluiter HJ. Severe chronic airflow obstruction: can corticosteroids slow down progression? *Eur J Respir Dis* 1985;**67**:56–64.
31 Postma DS, Peters I, Steenhuis EJ, Sluiter HJ. Moderately severe chronic airflow obstruction. Can corticosteroids slow down progression? *Eur Respir J* 1988;**1**:22–6.
32 Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresposiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; **132**:25–9.
33 Lim TK, Taylor RG, Watson A, Joyce H, Pride NB. Changes in bronchial responsiveness to inhaled histamine over four years in middle aged male smokers and ex-smokers. *Thorax* 1988;**43**:599–604.
34 Pride NB, Taylor RG, Lim H, Joyce H, Watson A. Bronchial hyperresponsiveness as a risk factor for progressive airflow obstruction in smokers. *Bull Eur Physiopathol Respir* 1987;**23**:369–75.
35 Taylor RG, Gross E, Joyce H, Holland F, Pride NB. Smoking, allergy, and the differential white blood cell count. *Thorax* 1985;**40**:17–22.