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Asthma and irreversible airflow obstruction

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ABSTRACT To determine whether asthma alone can cause irreversible airflow obstruction 42 men and 47 women with chronic asthma (mean duration 22 (SD 13) years) without evidence of other disease likely to cause irreversible airflow obstruction were treated with theophylline orally and a beta agonist both orally and by inhalation for four weeks. After two weeks of treatment the FEV_1 was less than 85% of the predicted normal value (%P) in 48 patients and these individuals then received prednisolone 0·6 mg/kg/day for two weeks. Duration and severity of asthma and smoking history were quantified by questionnaire; 38 patients were current smokers or ex-smokers. FEV_1 was measured at 0, 2, and 4 weeks. The mean difference between the best FEV_1 during the study and the predicted normal value was 0·29 l ($p < 0·001$); FEV_1 %P decreased with age ($r = -0·30$, $p < 0·01$) and with the duration ($r = -0·47$, $p < 0·001$) and severity ($r = -0·55$, $p < 0·001$) of asthma. Similar findings were noted when the results for non-smokers and those whose asthma started in adult life were analysed separately. We conclude that asthma alone can cause irreversible airflow obstruction and that the degree of obstruction is a function of the duration and severity of previous asthma. The results suggest the possibility that irreversible airflow obstruction in asthma may be preventable by minimising the degree of persistent asthma.

Evidence from several studies suggests that chronic asthma may be associated with the development of irreversible airflow obstruction. Firstly, pulmonary function is frequently abnormal during clinical remission from asthma;[1–7] secondly, the airways of patients with chronic asthma dying from non-respiratory causes show changes including mucous plugging, chronic inflammatory and eosinophilic infiltration, basement membrane thickening, and smooth muscle hypertrophy,[8 9] which could cause persistent narrowing; and, thirdly, many patients with asthma by definition have persistent airflow obstruction, which is not reversed by intensive treatment including corticosteroids.[10 11] Despite this evidence, a relationship between asthma and irreversible airflow obstruction has not been firmly established because there has been no large scale study of ventilatory function in patients with asthma in which reversible obstruction has been minimised by intensive treatment and in which other conditions likely to cause irreversible obstruction, such as emphysema, cigarette smoking, and occupational airway disease, have been either considered or excluded. This paper reports such a study, the aims of which were to determine whether asthma alone can cause irreversible airflow obstruction and whether factors such as cigarette smoking, age of onset of asthma, and duration and severity of previous asthma were associated with any irreversible obstruction.

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Patients and methods

One hundred patients with asthma of more than three years' duration who were attending outpatient clinics of the department of respiratory medicine at the Sir Charles Gairdner Hospital were studied. The patients had a clinical diagnosis of asthma with variability in the FEV_1 of at least 20% within a period of six months before the study; 70% showed marked variation of FEV_1 with changes of over 50% in this period. The patients had no clinical or radiographic evidence of bronchiectasis, pulmonary eosinophilia, allergic bronchopulmonary aspergillosis, or emphysema. Gas transfer, measured on admission to the study by the single breath carbon monoxide technique, was normal in all. Patients thought to have an occupational cause for their asthma or a history of environmental exposure likely to cause chronic bronchitis and those in whom oral cortico-

steroid treatment was contraindicated were excluded from the study.

All patients received inhaled and oral beta agonists (salbutamol 200 μg four hourly and 4 mg three times daily) and oral theophylline (125 mg four times daily) for a minimum of four weeks. Two weeks after commencing this treatment 48 patients in whom the postbronchodilator FEV_1 was less than 85% of the predicted normal value (%P) received additional treatment with prednisolone 0·3 mg per kg twice daily (dosage range 35–55 mg/day) for a minimum of two weeks. Inhaled corticosteroids or cromoglycate or both were continued in the 40 patients being treated with these drugs on admission to the study. Plasma theophylline concentrations were measured after two weeks' treatment in 35 randomly selected patients to ensure that the concentration was in the therapeutic range of 55–110 μmol/l. Seven patients who developed intercurrent asthma during the study continued treatment until the FEV_1 value had returned at least to the level found before deterioration. FEV_1 was measured with a calibrated electronic spirometer (Monaghan M403) on entry to the study and after two and four weeks of treatment; the FEV_1 was taken as the highest value from three forced vital capacity readings in which the FEV_1 varied by 3% or less. Values were corrected to BTPS. All measurements were made after inhalation of an aerosol of isoprenaline sulphate, 200–300 μg, between 1400 and 1500 hours.

Patients completed a modified Medical Research Council questionnaire on respiratory symptoms (1966) to ascertain smoking history, presence of cough and sputum, and duration and severity of asthma. A score representing the severity of asthma, similar to that used by others,[12 13] was obtained by summing the scores from each of the following: (1) frequency and persistence of "usual" wheezing multiplied by the duration in years of these symptoms (7 grades, maximum score 450*); (2) impairment of daily activities (7 grades, maximum 70 points); (3) hospital admissions and loss of time from school and work due to asthma (maximum 200 points*); (4) usual medication multiplied by the number of years taken (maximum 300 points*); (5) patients' assessment of severity of asthma on a self-rating scale (100 points). Scores greater than 300 indicated asthma of considerable clinical severity with a high incidence of persistent wheeze, effort dyspnoea, and hospital admission.

The highest FEV_1 for each individual during the study was compared with the predicted normal value derived from the data of Knudson *et al*[14] and Burrows *et al*[15] and based on age, sex, height, and cigarette smoking. Use of these data to predict the FEV_1 of an Australian population, however, could be inappropriate. We therefore also compared the highest FEV_1 of asthmatic subjects who had never smoked with that predicted from FEV_1 data obtained during the 1972 Busselton (W Australia) population survey on 514 men and 1024 women over 18 years of age who had never smoked and had no history of lung or heart disease[16] (also N Stenhouse, personal communication); data on symptom free Australian smokers were not available for comparison. The relationships between FEV_1 and age, age at onset and duration of asthma, the score for severity of asthma, cigarette consumption, and chronic cough and sputum were examined by linear regression and multiple regression analyses. Differences in these relationships between subgroups were examined by comparison of regression lines.[17]

*Maxima quoted were the highest scores obtained.

Results

Eighty nine of the 100 patients completed the study; 10 did not attend for review appointments and one patient withdrew because of tremor induced by salbutamol. Tremor caused 22 patients to discontinue oral salbutamol; in 12 of them terbutaline, 5 mg three times a day, was successfully substituted. Ten patients discontinued theophylline because of gastrointestinal side effects. All patients treated with prednisolone completed two weeks of treatment; no adverse effects were noted. Table 1 summarises the principal characteristics of the 89 patients who completed the study. Table 2 summarises the response to treatment. The mean FEV_1 increased with treatment in the entire group ($p < 0·001$) and in both those treated with steroids ($p < 0·001$) and those not treated with steroids ($p < 0·001$); in the latter group the mean FEV_1 on completion of treatment was not significantly different from the predicted normal value.

The mean difference between the predicted normal FEV_1 and the highest value observed during treatment was 0·29 l ($p < 0·001$). The highest FEV_1 %P decreased with increasing age ($r = -0·26$, $p < 0·05$) and with increasing duration (fig 1) and severity (fig 2) of previous asthma. The highest FEV_1 observed during the 12 months before conclusion of the study was also significantly less than predicted (mean difference 0·24 l, $p < 0·01$) and highly correlated ($p < 0·001$) with both the duration and the severity of asthma ($r = -0·48$ and $-0·56$ respectively). Similar results were obtained in 47 of the patients whose asthma had started after their 16th birthday (adult onset asthma) and in the 51 patients

Table 1 *Principal characteristics of patients*

	No of patients	*Height (cm)**	*Age (y)**	*Asthma*		*Smoking history*		*Chronic cough and sputum‡*
				*Age at onset (y)**	*Duration (y)**	*Number†*	*Pack years**	
Male	42	173·5 (6·1)	43·0 (14·9)	23·4 (19·2)	20·6 (14·2)	27 (8C, 19E)	21·8 (15·1)	19 [5]
Female	47	162·1 (6·0)	41·4 (13·8)	17·9 (15·6)	23·4 (11·5)	11 (4C, 7E)	8·1 (7·7)	13 [8]
Total	89	167·5 (8·3)	42·2 (14·3)	20·5 (17·5)	22·1 (12·9)	38 (12C, 26E)	17·9 (14·7)	32 [13]
Male-female differences		p < 0·001	NS	NS	NS		p < 0·01	

*Mean values with standard deviations in parentheses.
†Includes number of current smokers (C) and ex-smokers (E).
‡Number with cough and sputum who had never smoked in square brackets.
NS—not significant.

Table 2 *FEV_1 before and during treatment as percentage of predicted normal values[14 15] (means with standard deviations in parentheses)*

	Initial	*After 2 weeks' treatment*	*After 4 weeks' treatment*	*Best in study*	*Best in previous year*
All patients (n = 89)	77·3 (24·0)	79·1 (25·1)	87·9 (23·1)	89·9 (22·7)	91·6 (22·6)
No steroids (n = 41)	96·8 (13·9)	101·2 (11·0)	104·3 (12·7)	106·7 (11·8)	108·3 (11·7)
Steroids (n = 48)	60·5 (17·1)	60·1 (17·3)	73·9 (20·7)	75·6 (19·6)	77·4 (19·8)

who had never smoked (table 3). In those who had never smoked the mean difference between the highest observed and the predicted normal FEV_1 and the relationship between FEV_1 and duration and severity of asthma were similar whether the data of Knudson *et al*[14] or of the Busselton population survey[16] were used to predict FEV_1 (table 3). The decrease of FEV_1 %P with age and with the duration and severity of asthma was not significantly different between smokers and those who had never smoked, between those with childhood onset of asthma and those with adult onset, or between those with and those without chronic cough and sputum. Women showed a greater decrease of FEV_1 %P with age than males ($p < 0·05$); but the decreases associated with increasing duration and with increasing severity of asthma were similar in men and women.

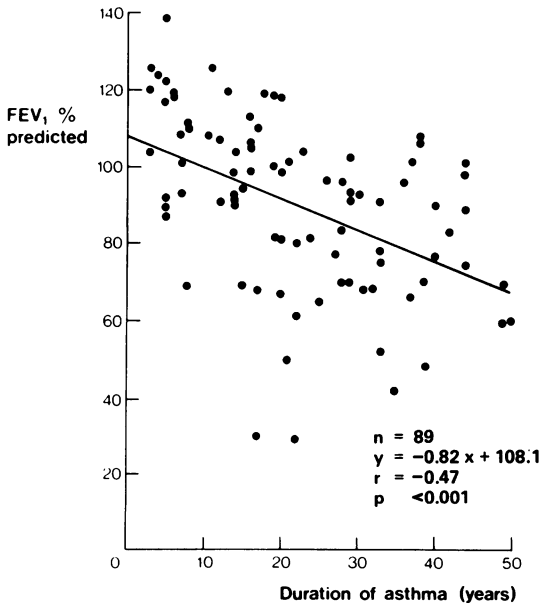

Fig 1 *Relationship between duration of asthma and the highest FEV_1 (percentage of predicted value) during treatment in each of the 89 patients completing at least four weeks' treatment.*

There were no significant correlations between age and duration or age and severity of asthma, between duration and self-assessment of asthma severity or between FEV_1 %P and age of onset of asthma, or between FEV_1 %P and smoking history, either for all subjects or men and women separately. The mean severity score was significantly higher ($p < 0·01$) in women (317 ± 148) than in men (235 (SD 144)). FEV_1 %P was significantly correlated ($p < 0·01$ or $< 0·001$) with the score for impairment of daily activities ($r = -0·33$), hospital admissions ($r = -0·31$), the patients' self-assessment of asthma severity ($r = -0·29$), usual medication requirements ($r = -0·42$), and duration and severity of wheeze ($r = -0·43$). Total severity score and the patients' self-assessment of the severity of asthma were highly correlated ($r = 0·56$, $p < 0·001$).

Discussion

The results of this study suggest that asthma alone can cause irreversible airflow obstruction and that

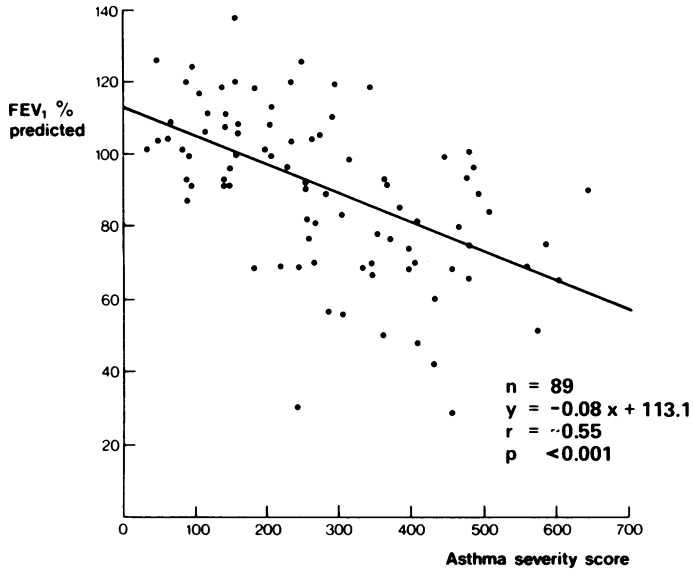

Fig 2 *Relationship between total score for severity of asthma in arbitrary units and the highest FEV_1 (percentage of predicted value) during treatment.*

the degree of obstruction is a function of the duration and severity of previous asthma. The validity of these conclusions depends on the way in which any persistent reversible airflow obstruction affected the results, the suitability of the data used to predict normal values, and the accuracy of our assessment of the severity of asthma. In any group of patients with chronic asthma a proportion will have diurnal fluctuations in airway function which are not abolished by treatment,[18 19] while others may develop intercurrent exacerbations. Several factors suggest that any persistent reversible obstruction in our patients was small and not responsible for the results: (1) The dose and duration of steroid treatment were sufficient to define corticosteroid responsiveness.[20] (2) Patients in the group which did not receive steroids achieved a normal FEV_1. (3) The highest FEV_1 during the study was little different from the highest value during the previous 12 months (mean difference 0·05 l) and use of this latter value in analysing the results did not alter the findings. (4) The effect of diurnal variation of FEV_1 was minimised by the study protocol. (5) Only seven patients developed symptomatic asthma during the study; in these treatment was prolonged and in five the final FEV_1 was greater than the best FEV_1 in the preceding 12 months. (6) It is unlikely that any reversible component of airflow obstruction would have been systematically greater in older people and in those with the longer duration of asthma, particularly as age and duration of asthma were not correlated with each other or with the patients' assessment of the severity of asthma.

Table 3 *Difference between highest FEV_1 during treatment and predicted normal value and relationship between FEV_1 (% predicted) and duration and severity of asthma*

	All patients	*Adult onset*	*Never smoked*
Number	89	47	51
FEV_1 P–FEV_1 H: mean difference (l)	0·29§	0·22†	0·42§ (0·46§)*
FEV_1 H as %P *v* duration of asthma (r)	−0·47§	−0·44‡	−0·42 (−0·42)*
FEV_1 H as %P *v* severity of asthma (r)	−0·55§	−0·56§	−0·55§ (−0·51§)*

*Analysis based on FEV_1 predicted from Busselton population survey.[16]
Significance of differences and correlations: †$p < 0·05$; ‡$p < 0·01$; §$p < 0·001$.
P—predicted; H—highest value during treatment.

We used the data of Knudson *et al*[14] and Burrows *et al*[15] to predict the FEV_1 of the healthy population because these studies included large numbers and took account of the effect of cigarette smoking. It is unlikely that use of these data resulted in overestimation of the difference between the FEV_1 of asthmatics and healthy people or of the effect of age and duration of asthma on FEV_1. In the asthmatics who had never smoked comparison of the FEV_1 with the data of Knudson *et al* and with that of a local healthy population gave identical results, while the decline of FEV_1 with age found by Knudson *et al* and Burrows *et al* was similar to that observed in four other studies.[21–24]

Methods of estimating the severity of previous asthma are necessarily imprecise because they depend largely on subjective criteria and on the weighting applied to these criteria by the investigators. Nevertheless, in this study the factors used to quantitate severity, except for loss of time from work, bore a consistent relationship to the highest FEV_1 during treatment and were internally consistent with the patients' assessment of the severity of their asthma.

Some support for the suggestion that asthma alone can cause irreversible airflow obstruction comes from previous studies of airway function during remission from asthma even though these were not designed to examine this question.[4 5 7 25] Loren *et al* reported three children with severe asthma and an irreversible component of airflow obstruction despite intensive treatment with bronchodilators and prednisolone.[10]

Factors which may contribute to the development of irreversible airflow obstruction include cigarette smoking and respiratory illness in childhood.[26] Our results in lifelong non-smokers and in those whose asthma started after the age of 15 years showed that the development of irreversible obstruction in asthma is not dependent on smoking or on a childhood onset of asthma. Furthermore, neither these factors nor chronic cough and sputum appear to influence the degree of airflow obstruction.

The observation that the women in this study had a significantly greater decline of FEV_1 with age than men, but no difference in the severity of asthma as a function of age or duration of disease, suggests a possible sex related difference in the degree of irreversible obstruction that is independent of the severity of asthma. The strong relationship between the degree of airflow obstruction and the duration and severity of asthma, which together accounted for 37% of the variability in FEV_1 %P, suggests that chronic poorly controlled asthma causes irreversible narrowing of airways and raises the possibility that improved control of asthma may prevent irreversible obstruction. The findings therefore provide some support for recent suggestions that one of the aims of treatment in chronic asthma should be to maintain airway function as near normal as practicable.[27] The extent to which the conclusions of our study apply to the general population of patients with asthma cannot be stated. There is, however, a high incidence of airflow obstruction in non-hospital patients with asthma;[6 28] if persistent asthma can cause irreversible obstruction then the implications are general.

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