

REDUCTION OF BRONCHIAL HYPERREACTIVITY DURING PROLONGED ALLERGEN AVOIDANCE

THOMAS A. E. PLATTS-MILLS EUAN R. TOVEY
E. BRUCE MITCHELL HELEN MOSZORO
PAULINE NOCK SUSAN R. WILKINS

*Clinical Research Centre, Northwick Park Hospital,
Watford Road, Harrow HA1 3UJ*

Summary To study the long-term effects of avoiding domestic allergens, nine asthmatic patients who were allergic to dust mites lived in hospital rooms for two months or more. In all patients symptoms and early morning peak flows improved. In seven patients anti-asthma treatment could be reduced and it was possible to carry out repeated bronchial provocation with histamine. Five of these patients showed a progressive eightfold or greater increase in the concentration of histamine necessary to provoke a 30% fall in forced expiratory volume in one second (PD₃₀). The increase in PD₃₀ in the seven patients during their period of living in hospital was highly significant. Avoidance of important allergens seems not only to result in clinical remissions but in many cases may also reduce bronchial hyperreactivity.

Introduction

BRONCHIAL hyperreactivity is present in almost all asthmatic patients and can be demonstrated by provocation with small quantities of nebulised histamine or methacholine chloride. Non-specific factors such as exercise, emotion, tobacco smoke, and cold air may precipitate attacks of bronchospasm in patients with bronchial hyperreactivity.¹⁻³ In addition, nocturnal falls in catecholamine production may lead to nocturnal bronchospasm in patients whose bronchi are hyperreactive.^{4,5} Most young asthmatic patients are allergic⁶ and acute bronchospasm can occur after either natural exposure to allergens or provocation with nebulised allergen extract.⁷ However, the importance of allergens in perennial asthma is not clear.² One possibility that could explain the very strong association between allergy and

asthma is that allergens as well as triggering acute episodes of bronchospasm are a cause of bronchial hyperreactivity.^{8,9} Patients in whom asthma develops in association with hay fever have been shown to lose their sensitivity to histamine after the pollen season.^{10,11} Furthermore, asthmatic children who stayed in a sanatorium in Davos for one year showed progressive reductions in bronchial hyperreactivity.¹²

In England the house-dust mite *Dermatophagoides pteronyssinus* is the most important allergen associated with asthma.^{6,13} Complete avoidance of this allergen in houses is difficult because it is present in carpets, furniture, and clothing as well as in bedding.^{14,15} We have studied the long-term effects of avoiding dust-mite allergens by allowing nine asthmatic patients to live in "dust free" hospital rooms, while being free to go to work, shopping, &c.

Material and Methods

Patients

We investigated patients with asthma who were sensitive to inhalant allergens including *D. pteronyssinus* as demonstrated by strongly positive prick skin tests, and who were willing to use a hospital room as their bedroom/living room for a long time. All nine patients had had asthma for more than one year and all except one required continuous medical treatment. Five of the patients had originally presented as emergencies with severe bronchospasm, whereas the remaining four were referred for advice on management of their asthma.

Conditions of Admission

Patients stayed either in a filtered-air room or in an ordinary hospital side room. They were allowed to leave the hospital but were required not to visit any domestic houses and not to be in contact with animals. Three patients who were skin-test-positive to grass pollen were studied outside the grass-pollen season. In patient 5, history and skin tests indicated an allergy to laboratory animals. She also had positive skin tests to cat dander and *D. pteronyssinus*. This patient worked in an environment away from laboratory animals for the period of the study.

Bronchial Provocation with Histamine

Peak expiratory flow rate was recorded three times daily. Inhalation challenge was performed only when peak flow was >70%

of the predicted values with less than 20% diurnal variation, and patients could perform repeated forced expiration without bronchospasm developing. Challenge was carried out with saline and/or histamine acid phosphate diluted in phosphate-buffered saline pH 7.4, by means of a modification of the technique of Hargreave.⁸ Salbutamol was withdrawn for at least 8 h before histamine provocation. Solutions were nebulised in an Acorn nebuliser (Medic-aid Ltd., Chichester) with oxygen at a flow rate of 8 litres/min. Patients were allowed to breathe the nebulised histamine normally for 2 min. Forced expiratory volume in one second (FEV₁) was recorded before and on three occasions after the inhalation. The concentration of histamine causing a 30% fall in FEV₁ at 10 s, 30 s, or 2 min after inhalation was taken as the end point (PD₃₀ histamine).

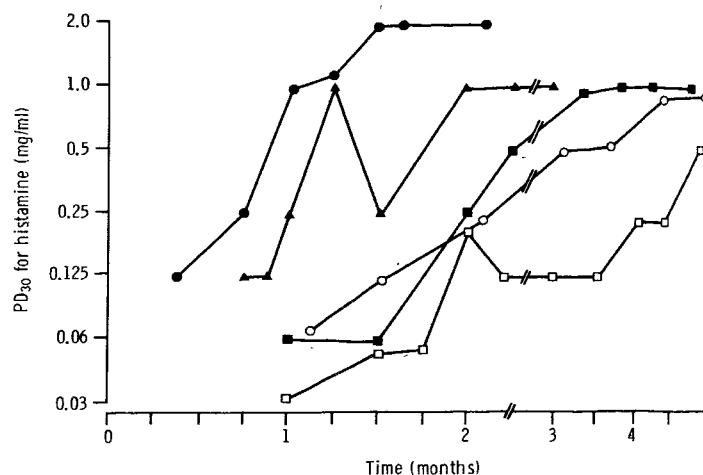
Measurement of IgE, Specific Antibodies, and Dust Mite Allergen

Total IgE concentrations were measured by double-antibody inhibition radioimmunoassay (RIA). Specific IgG and IgE antibodies to the dust mite allergen, antigen P₁, were measured by antigen binding RIA.¹⁶ Antigen P₁ in dust samples from hospital rooms and the patients' houses was measured by double-antibody RIA.¹⁵ Dust samples were also examined for mite bodies and the species were determined. In eight houses the dominant species was *D. pteronyssinus*, while in the ninth the dominant species was *Euroglyphus maynei*. Only occasional mites were found in the hospital and these were all *D. pteronyssinus*.

Results

Nine patients were admitted to the ward and their peak flows were measured 3 times daily. Eight patients showed diurnal variation in peak flow and in each case the early morning values improved within two weeks. As the patients improved, their treatment, which had been maintained at pre-admission levels, was gradually reduced. By the end of the study two patients were entirely off treatment, five were on a low-dose of salbutamol only, and two patients remained on a reduced dose of inhaled steroid. Although dust mite allergen was detected in the hospital rooms, concentrations (mean 240 ng antigen P₁/g of dust) were on average <2% of those found in dust from the patients' houses (mean 13600 ng antigen P₁/g of dust). In keeping with the levels found in hospital dust, allergen was not detected in hospital air.¹⁵ Thus, accommodation in conditions that largely avoided exposure to dust mite and other domestic allergens was accompanied by consistent improvement in symptoms and allowed large reductions of medical treatment.

On admission only three of the patients could carry out repeated forced expiration. However, by the end of one month, seven of the patients were able to tolerate bronchial provocation with histamine, and initial provocation tests indicated that they all had bronchial hyperreactivity (PD₃₀ 0.03–0.125 mg histamine/ml). Two patients, although they had improved clinically, were unable to undergo repeated provocation studies; when tested they showed PD₃₀ of 0.03 and 0.06 mg histamine/ml. Five of the patients progressively improved over a period of six weeks to four months, showing an eight-fold or greater increase in PD₃₀ (see accompanying figure). For the seven patients who had repeated bronchial provocation, the change in PD₃₀ was highly significant. Over the period when these changes were occurring there was no significant increase in FEV₁ (table I). For these patients early morning peak flow values improved markedly between admission and the first provocation, with little change subsequently (table II). None was receiving inhaled steroid or disodium cromoglycate ('Spinhaler') at the end of the study. Serum IgE and specific antibodies to antigen P₁ were



Time course of changes in bronchial reactivity to histamine in five patients showing eight-fold or greater increase in PD₃₀.

Time is given in months after admission. Normal range for PD₃₀ histamine in our laboratory is 2.0 to >8.0 mg/ml.

measured before and during the study. The maximum fall in total IgE was 40% with a mean fall of 18.7%, while the maximum fall in specific antibodies to antigen P₁ was 26% and the mean falls were 15.6% for IgE ab and 8% for IgG ab. There was no correlation between changes in PD₃₀ histamine and changes in total IgE or specific IgE antibodies.

TABLE I—RELATION BETWEEN FEV₁* AND BRONCHIAL REACTIVITY TO HISTAMINE DURING PROLONGED ADMISSIONS

Patient	Age	Sex	PD ₃₀ histamine (mg/ml)							Predicted FEV ₁ †
			0.03	0.06	0.125	0.25	0.5	1.0	2.0	
1‡§	35	F	2.7 ^a 3.1							3.0
2‡§	27	M	5.1.....4.8							4.5
3§	20	M	5.3.....5.3							4.6
4‡§	18	M	2.85.....3.0							3.8
5‡§	27	F	3.5.....3.3							3.1
6	22	M	3.4.....3.2							3.9
7‡	18	F	3.0.....2.9							2.95

*Values shown for each patient are the FEV₁ in litres before first bronchial provocation and the FEV₁ before final provocation with histamine, values at intervening provocations did not vary by more than ±10% of mean of two values shown.

†Predicted values for FEV₁ from J. E. Cotes. Lung function, 4th ed. Oxford: Blackwell, 1979.

‡Patients who were unfit for provocation testing at start of study.

§PD₃₀ values for these patients increased significantly with time ($p < 0.005$) (Kendall's rank correlation coefficient). Combined p value for seven patients was < 0.001 (R. A. Fisher, Statistical methods, Edinburgh: Oliver and Boyd, 1944).

Discussion

Our results confirm that many chronic asthmatic patients who are allergic to dust will improve if they live away from their houses,¹⁷ and in most cases it was possible markedly to reduce their treatment. In addition, we demonstrated that in five out of nine cases there was pronounced reduction in bronchial reactivity to histamine. We believe that reduced allergen exposure allowed these progressive changes in hyperreactivity. If so, what is the mechanism? Hyperreactivity may be purely a secondary consequence of bronchospasm and allergens may contribute because they cause bronchospasm. Persistent bronchospasm might well lead to changes in nervous or muscular patterns in the lung which appear as hyperreactivity. Hargreave et al. have reported that increased non-specific hyperreactivity can occur after bronchial provocation with allergen extract,⁸ however, this phenomenon has not been reported after

TABLE II—CHANGES IN INHALED TREATMENT AND MORNING PEAK EXPIRATORY FLOW RATE

Patient	Time	Beclomethasone (µg)	DSCG (mg)	Salbutamol (µg)	Peak flow* (l/min)
1	Admission†	300	..	800	248
	1st provocation	..	..	200	336
	Final provocation	..	..	100‡	356
2	Admission	..	160	800	303
	1st provocation	..	80	400	575
	Final provocation	..	..	..	480
3	Admission	..	80	200	452
	1st provocation	..	40	100	570
	Final provocation	..	..	100‡	605
4	Admission	300	..	400	236
	1st provocation	200	..	200	425
	Final provocation	..	..	100‡	460
5	Admission	300	..	600	290
	1st provocation	300	..	600	450
	Final provocation	..	..	..	445
6	Admission	..	..	100	390
	1st provocation	..	..	100	430
	Final provocation	..	..	100‡	442
7	Admission	200	..	400	230
	1st provocation	200	..	400	416
	Final provocation	..	..	400	380

*Peak flow values are mean of early morning results for 3 days, after admission and, before provocations.

†Also on sustained release aminophylline, 100 mg three times/day at admission.

‡Doses not taken every day.

repeated histamine challenge. Provocation with nebulised allergen extract is entirely different from natural exposure to pollen grains or dust mite faecal particles. Natural exposure represents at most a few hundred large particles inhaled per day. Mite faecal particles which are on average 20 µm in diameter contain about 0.1 ng antigen P₁.¹⁸ By contrast, bronchial provocation is carried out with many millions of droplets about 2 µm in diameter with an allergen content of $\leq 1 \times 10^{-6}$ ng allergen. Thus, although the total quantity of allergen inhaled during a 2 min provocation may be high relative to natural exposure, the quantity contained in each droplet is very small.¹⁵ It seems possible that a few large allergen particles entering the lung might cumulatively contribute to bronchial reactivity, although the patient was unaware of increased bronchospasm at the time of inhalation. The response of the lungs to allergen may be comparable with late reactions seen after bronchial provocation,^{7,19} but it seems more likely that local high concentrations of allergen would induce a cellular response with a longer time course.^{20,21}

Most previous reports on bronchial hyperreactivity suggest that this phenomenon, which is relatively constant, can be exacerbated by virus infections,²² but is an underlying property of the asthmatic lung.^{1,2} Previous reports of a reduction in reactivity have two features in common; firstly in each case reduction has taken many weeks or months, and secondly it has only been seen under conditions that include almost complete avoidance of relevant allergens.⁹⁻¹² To complete the argument, we would need to expose the patients to house dust in hospital and demonstrate a return of bronchial reactivity. However, the problems of setting up a dusty room in hospital and keeping patients in for even longer periods are formidable. Two of our patients, despite remaining clinically well, showed little change in bronchial

reactivity. This observation may reflect lack of time, or continued exposure to a relevant allergen, or may support the view that in some cases non-specific irritability once established becomes very difficult to reverse.⁹ Four of the patients shown in the figure were available for repeat study 3 months or more after returning home. Two patients remained well and off treatment, one still had a PD₃₀ of 2.0 while in the other PD₃₀ had been reduced from 1.0 to 0.5. The two other patients have remained well controlled but required treatment during May, June, and July possibly because of exposure to grass pollen. One was on beclomethasone 300 µg/day and his PD₃₀ had fallen from 0.5 to 0.25 while the other was taking inhaled disodium cromoglycate 16 mg/day and his PD₃₀ (off treatment) had fallen from 1.0 to 0.125 mg histamine/ml.

Several other factors might have contributed to reduced reactivity in our patients. These include the emotional effects of admission, increased exercise, and reductions in treatment. Some of the patients did undergo increased exercise as they felt better. Both inhaled disodium cromoglycate and inhaled steroids have been reported to reduce bronchial reactivity. However, all the patients who showed reductions in reactivity had been off steroids and disodium cromoglycate for at least 3 weeks before the end of the study, so these were unlikely to contribute to our findings. However, the possibility remains that repeated inhalations of β-adrenergic agonists such as salbutamol could contribute to or prevent reversal of hyperreactivity.

Bronchial provocation with histamine or methacholine is an index of the ease with which bronchospasm can be provoked in a patient's lung; generally this correlates well with other measurements of non-specific reactivity.²³ In patients with normal or near normal FEV₁, the histamine PD₃₀ seems to be a good guide to the severity of their asthma. All of our patients showed improvement both clinically and in peak flow values during the early part of the study. The patients who showed increases in PD₃₀ continued to improve subjectively, in particular none of them had any acute episodes of breathlessness during the final six weeks of the study and all five reported increased exercise tolerance. Routine bedroom cleaning may improve symptoms,²⁴ but usually does not lead to major reductions in dust mites or dust mite allergens.^{14,25} We believe that adequate cleaning would require removal or treatment of carpets and soft furniture throughout the house as well as removal of soft toys. Our results imply that if houses were changed sufficiently to achieve allergen levels comparable to those found in hospital rooms that many patients would have a reduction not only in symptoms triggered by house dust but also in those symptoms that are secondary to bronchial hyperreactivity.

We thank Dr J. Milledge, Dr Jean Morris, Dr A. M. Denman, and Dr A. D. B. Webster for referring patients for the study, Dr D. Altman (CRC) for statistical advice, and the staff of Darwin and Galen wards. The Asthma Research Council supported this study and Bencard supplied *D. pteronyssinus* culture.

Correspondence should be addressed to T. A. E. P.-M., Division of Immunology, Clinical Research Centre, Watford Road, Harrow HA1 3JU.

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ORCHIDECTOMY ALONE IN TESTICULAR STAGE I NON-SEMINOMATOUS GERM-CELL TUMOURS

M. J. PECKHAM
J. E. HUSBAND

A. BARRETT
W. F. HENDRY

*Institute of Cancer Research,
and Royal Marsden Hospital, Sutton, Surrey*

Summary 53 patients with clinical stage I non-seminomatous germ-cell testicular tumours were entered into a prospective study to receive no treatment other than orchidectomy until unequivocal clinical evidence of metastases was established. Of this group, 9 men (17%) have relapsed, 8 within six months of orchidectomy. All 9 are alive and disease-free after chemotherapy. The relapse rate was higher in patients with malignant teratoma undifferentiated (embryonal carcinoma) primary tumours than in those with malignant teratoma intermediate (teratocarcinoma); 42.8 and 3.4%, respectively. The results were compared with those from 157 men treated by orchidectomy and radiotherapy for stage I disease. In this group, 49 patients (25.8%) relapsed and 85% of relapses occurred within one year of orchidectomy. The tempo of relapse was identical for embryonal carcinoma and teratocarcinoma. Of 32 patients in whom serum markers were measured before orchidectomy, 24 (75%) had raised levels of alphafetoprotein and/or beta human chorionic gonadotropin. These preliminary results imply that routine lymphadenectomy or lymph node irradiation in clinical stage I testicular non-seminoma may be unjustifiable.

Introduction

HITHERTO, patients with stage I non-seminomatous germ-cell testicular tumours (NSGCTT) have been treated by orchidectomy and radical node dissection or radiotherapy. Either form of treatment, employed with immediate or deferred chemotherapy, cures all but a few patients.¹⁻⁴ The proportion of patients curable by orchidectomy alone is unknown although one data analysis suggests that this may be as high as 60–80%.⁵ Furthermore, the accuracy of clinical staging has improved with the advent of computerised

tomographic (CT) scanning.⁶ Recent studies have led to a better understanding of prognostic factors in stage I disease, including histology,⁴ post-orchidectomy changes in serum marker levels, and spermatic cord involvement by tumour.^{4,7}

With these developments it seemed probable that the relapse rate in stage I patients treated by orchidectomy alone would be low and, if so, the value of lymph node surgery or radiotherapy would be questionable. The advent of effective chemotherapy has made a study of the curative potential of orchidectomy possible since the probability of cure in patients with limited volume metastases is high. In order to investigate this we abandoned lymph node irradiation in 1979 in favour of a policy of close surveillance after orchidectomy.

Patients and methods

Staging included chest radiography, lymphography, intravenous urography, CT scanning of thorax and abdomen, ultrasonic scanning of liver and retroperitoneum, measurement of serum alphafetoprotein (AFP) and beta human chorionic gonadotropin (hCG) levels, and liver function tests. Pre-orchidectomy AFP and hCG levels were obtained whenever possible.

Histology of the primary tumour was reviewed in all cases and classified as malignant teratoma undifferentiated (MTU) (embryonal carcinoma); malignant teratoma intermediate (MTI) (teratocarcinoma); malignant teratoma trophoblastic (MTT); teratoma differentiated (TD); or yolk sac carcinoma (YS). Seminoma components were noted but did not modify the classification. Seminoma associated with a raised serum AFP level (Sem AFP+) was regarded as a non-seminomatous germ-cell tumour.

According to the staging classification used at the Royal Marsden Hospital⁸ our patients fit into the following categories:

- I—no clinical evidence of metastasis; serum markers negative at time of orchidectomy or reverting to normal after removal of the primary tumour.
- Im—no clinical evidence of metastasis; persistently raised serum marker(s) after orchidectomy.
- IIA—abdominal node involvement, metastases <2 cm diameter.
- IIB—abdominal node involvement, metastases 2–5 cm diameter.
- IIIB—infra and supradiaphragmatic node involvement; abdominal node status as for IIB.
- IVAL₁—abdominal status as for IIA; <3 pulmonary metastases.
- IVAL₂—abdominal node status as for IIA; multiple lung metastases, none exceeding 2 cm in diameter.

T. A. E. PLATTS-MILLS AND OTHERS: REFERENCES—continued

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