

Changes in IgE-mediated allergy to ubiquitous inhalants after removal from or diminution of exposure to the agent causing occupational asthma

L. PERFETTI, J. HÉBERT*, Y. LAPALME*, H. GHEZZO, D. GAUTRIN and J.-L. MALO

Department of Chest Medicine, Sacré-Coeur Hospital, Montreal, and *the Centre hospitalier de l'Université Laval, Québec, Canada

Summary

Background One possibility, among others, for explaining the persistence of asthma symptoms in occupational asthma (OA) after the cessation of exposure to the causal agents may be that subjects become sensitized to ubiquitous inhalants.

Objective The aim of this study was to evaluate the development or increase of IgE-mediated sensitization to ubiquitous allergens, both to high- and low-molecular-weight agents, in 100 subjects with OA after cessation of exposure.

Methods Subjects were evaluated on a first visit, at the time of diagnosis of OA, coinciding with the cessation or diminution of exposure to the causal agent, and on a second visit, 5.8 ± 3.3 years afterwards. At each visit, a history of ocular, nasal and asthmatic symptoms related to exposure to common allergens was obtained together with spirometry and assessment of bronchial responsiveness to methacholine. We analysed total IgE and specific IgE to *Dermatophagoides farinae*, *D. pteronyssinus*, birch, ragweed and timothy grass pollens, cat and dog danders, and *Alternaria*, using enzyme allergosorbent test (EAST) from blood samples taken on each visit.

Results Total IgE levels showed a tendency to diminish. No changes were found in the number of positive EAST (presence of detectable levels of specific IgE) or in the levels of specific IgE. Although significantly more symptoms of rhinoconjunctivitis and asthma in contact with house dust ($P < 0.05$) and pets ($P < 0.01$) were reported on the second visit than on the first, no significant changes in the frequency of symptomatic sensitized subjects were found.

Conclusion Subjects with OA are unlikely to develop IgE-dependent sensitization to common inhalants after removal from exposure to occupational agents.

Keywords: asthma, occupational asthma, IgE, radioallergosorbent test, occupational diseases

Clinical and Experimental Allergy, Vol. 28, pp. 66–73. Submitted 25 March 1997; revised 4 June 1997; accepted 24 July 1997.

Correspondence: Dr Jean-Luc Malo, Department of Chest Medicine, Sacré-Coeur Hospital, 5400 West Gouin, Montreal, Canada H4J 1C5.

J. L. Malo and D. Gautrin are research scholars with the Fonds de la Recherche en Santé du Québec and the Université de Montréal School of Medicine. Luca Perfetti is a research fellow, holder of a Government of Canada Award administered by the International Council for Canadian Studies. This study was partly funded by the Centre québécois d'excellence en santé respiratoire.

Introduction

Most subjects with occupational asthma (OA) still report symptoms of asthma and demonstrate non-specific bronchial hyperresponsiveness after cessation of exposure to the offending agent [1,2]. The factors that can affect the prognosis are not elucidated. It is known that the persistence of asthma after cessation of work is associated with a longer

duration of exposure before and after the onset on symptoms and with a more severe asthma as defined by the degree of airway obstruction and non-specific bronchial hyper-responsiveness at the time of diagnosis [1,2]. One possible explanation for the persistence of asthma may be that subjects with OA become sensitized to ubiquitous inhalants. We indeed observed that some patients with OA report the development of nasal, ocular and asthmatic symptoms related to exposure to pollens, pets and house dust after the cessation of exposure.

We therefore hypothesized that some subjects with OA may develop new or increased immunologic sensitization to ubiquitous allergens, as well as related symptoms. In these subjects, continuation of exposure to those allergens to which they have become sensitized, would contribute to the persistence of asthma symptoms after cessation of exposure to the occupational agent. We expected new or increased sensitization to occur mainly in the subgroup of subjects with OA due to high-molecular-weight substances, since the mechanism is IgE-dependent, but we did not exclude it in subjects with OA due to low-molecular-weight agents. The airway inflammatory changes may indeed contribute to the penetration of inhalants in the bronchial tree. The aim of this study was to evaluate the development or increase of IgE-mediated sensitization to ubiquitous allergens and of related ocular, nasal and asthmatic symptoms in 100 subjects with OA, both to high- and low-molecular-weight agents, after cessation of exposure.

Methods

Study design

This is a retrospective study in which every subject was evaluated on two separate visits. The first visit took place at the time of diagnosis of OA, which coincided with the cessation of exposure to the sensitizing agent. At this time, we administered a questionnaire on the history of ocular, nasal and asthmatic symptoms related to the exposure to common allergens. In addition, spirometry, bronchial provocation test with methacholine and skin-prick tests with ubiquitous inhalants were performed, blood was taken and serum frozen at -20°C . The same procedures were performed at the second visit, which took place at a distance of 5.8 ± 3.3 years after the first (minimum period of 2 years). Analysis of specific and total IgE in the sera collected on the two visits was performed at that time.

Subjects

Letters with an invitation to participate in the study were sent to patients with a diagnosis of OA, randomly selected from the files of our Center. Two hundred and forty-two

letters were sent: 100 patients agreed to take part in this study, 44 letters were returned due to change of address and two due to deaths of the patients, 11 subjects refused, and 85 did not answer.

Of the 100 patients with OA included, 26 were women and 74 were men. At the first visit, their age was $42.8.8 \pm 12.4$ years, the duration of exposure to the agent causing OA, 12.5 ± 11.5 years, and the duration of symptoms, 3.2 ± 3.3 years. Sixteen patients were smokers and 39 ex-smokers. The diagnosis of OA was confirmed by specific inhalation challenges in 95 (86 in the laboratory and nine in the workplace) and in the remaining five, by suggestive patterns of peak expiratory flow monitoring. OA was due to LMW agents in 60 cases (isocyanates in 38 of them) and to HMW agents in 36 cases (flour in 16 of them). In four cases, it was impossible to identify the sensitizing agent even though the asthma was clearly related to the workplace. All subjects gave written consent for this study. The protocol was accepted by the ethics committee of Sacré-Coeur Hospital.

Questionnaire

The questionnaire was administered by the treating physician at the first visit. A trained technician administered a standardized questionnaire at the second [3]. The two questionnaires addressed the presence of conjunctivitis, rhinitis, and asthma symptoms, either triggered by contact with cats, dogs or house dust (sweeping and vacuuming) or occurring in summer time, in situations of presumed high exposure to grass pollens (e.g. caused by mowing or walking on a freshly-cut lawn). Also included were questions on the presence of pets in the house and the duration of exposure to them, in order to estimate past and current exposure indexes.

Skin testing

Skin tests were performed by the prick method [4] on the forearm, using common inhalant extracts: mixed tree pollens, mixed grass pollens and ragweed pollens, *Alternaria tenuis*, *Aspergillus*, *Dermatophagoides farinae* and *D. pteronyssinus*, cat and dog danders, mixed feathers (Miles Inc., Elkhart, USA). Histamine phosphate (1%) was used as a positive control and diluent (glycerinated 0.9% saline solution) as negative control. After 15 min, the longest and orthogonal erythema diameter were measured, the mean diameter being derived. Skin-prick tests with a battery of common inhalants were performed on both visits. However, due to the fact that the allergens were not standardized and were probably not of the same antigenicity on both occasions, the results of these tests were used only to determine the number of subjects with atopy. Atopy, defined as the

Table 1. Baseline characteristics of participants and non-participants

	Participants			Non-participants		
	High-molecular weight (n = 36)	Low-molecular weight (n = 60)	All (n = 100)	High-molecular weight (n = 50)	Low-molecular weight (n = 87)	All (n = 142)
Sex (M/F)	23/13	48/12	74/26	36/14	72/15	112/30
Age (years)	40 ± 13	44 ± 11	43 ± 12*	34 ± 10	42 ± 13	39 ± 13*
Atopy (yes/no)	25*	23*	50	40	30	73
Smoking habits (S/ES/NS)	7/15/14	8/24/28	15/40/45	19/12/19	20/36/31	40/51/51
Duration of exposure (years)	12.8 ± 12.2	12.1 ± 11.1	12.4 ± 11.5*	9.2 ± 8.3	9.8 ± 10	9.4 ± 9.3*
Duration of symptoms (years)	4.3 ± 3.9	2.7 ± 2.9	3.2 ± 3.3	3.6 ± 3.5	3.2 ± 3.8	3.3 ± 3.6
FEV ₁ (% pred)	89 ± 20	93 ± 17	92 ± 18	91 ± 17	92 ± 20	91 ± 18
PC ₂₀ (mg/mL)						
< 0.25	5	4	10	5	10	15
0.25 – 1.0	12	14	27	10	23	34
>1.0 – 16.0	16	32	50	25	42	71
> 16	3	7	10	8	11	19

The molecular size of the responsible agent could not be determined in nine cases (four participants and five non-participants). See text for definition of atopy. PC₂₀ was not assessed in all subjects (missing values). * = $P < 0.05$.

presence of at least one immediate skin reaction to common inhalants at the first visit, was present in 50 patients.

Analysis of specific IgE

The following allergens were tested: *D. farinae*, *D. pteronyssinus*, birch, ragweed, timothy grass (*Phleum pratensis*) pollens, cat and dog danders and *A. tenuis*. The analysis of specific IgE was performed by means of an enzymatic allergosorbent test (EAST) (Kallestad Allercoat EAST Conjugate Pack-Sanofi Diagnostics Pasteur, INC- Chaska MN, USA) according to the manufacturer's recommendations. Briefly, test serum (50 µL) was incubated with allergen-coated paper disks for 3 h at room temperature. After washes, 100 µL of alkaline phosphatase-labelled anti-IgE antiserum was added for 18–24 h at room temperature. The disks were washed and incubated for 1 h at 37 °C with the substrate working solution (para-nitrophenyl phosphate) for developing the colorimetric reaction. After adding the stopping solution (1.0 M tri-basic potassium phosphate), absorbance values were measured at 405 nm in a microplate reader. Atopy, defined as the presence of detectable levels of specific IgE towards at least one tested allergen, was present in 49 patients at the first visit.

Analysis of total IgE

Disposable flexible polyvinylchloride microtiter plates were coated overnight at 4 °C with 100 ng/well of anti-human IgE

monoclonal antibody. The plates were washed and then saturated with 10% horse serum in TBS-tween for 1 h at 37 °C. Diluted serum samples and diluted IgE standards were added to the well in triplicate and allowed to react for 3 h at 37 °C. The plates were washed and then incubated overnight at 4 °C with 200 000 cpm of ¹²⁵I- labelled goat polyclonal antibody anti-human IgE. After washes radioactivity of individual wells are counted in a multigamma counter (Wallack-LKB, Finland). In non-atopic adult healthy subjects, IgE levels assayed with this method range from 12 to 144 IU/mL.

Respiratory function and bronchial responsiveness assessment

Spirometry was performed according to the guidelines of the American Thoracic Society [5]. Bronchial responsiveness to methacholine was assessed using a standardized procedure with the Wright's nebulizer (output = 0.14 mL/min) at tidal volume breathing for 2 min [6].

Handling of data

Specific IgE Levels of specific IgE were expressed as AllercoatTM EAST Units (AEU/mL) with a detection threshold of 0.009 AEU/mL. For the statistical analysis, data were categorized for each allergen as dichotomous variables: undetectable levels, detectable levels. We chose this low threshold, including as positive the subjects with

Table 2. Results of specific and total IgE assessments on the two visits

	First visit				Second visit			
	<i>n</i> tested patients	<i>n</i> positive/ <i>n</i> total	(%)	median (Q ₁ -Q ₃)	<i>n</i> positive/ <i>n</i> total	(%)	median (Q ₁ -Q ₃)	<i>P</i>
Positive EAST								
All	100	95/800	(12%)		83/800	(10%)		NS
HMW	36	47/288	(14%)		46/288	(14%)		NS
LMW	60	39/480	(8%)		29/480	(6%)		NS
Presence of atopy according to EAST								
All	100	49/100	(49%)		38/100	(38%)		0.05 < <i>P</i> < 0.01
HMW	36	21/36	(58%)		19/36	(53%)		NS
LMW	60	25/60	(41%)		17/60	(29%)		0.05 < <i>P</i> < 0.01
Total IgE levels (IU/mL)								
All	100			176 (38–489)			106 (23–437)	0.05 < <i>P</i> < 0.01
HMW	36			439 (137–609)			323 (63–497)	NS
LMW	60			86 (32–275)			73 (19–272)	NS

Positive EAST: number of positive Enzyme-Allergosorbent tests. Presence of atopy if at least one positive EAST. Distinction of subjects with occupational asthma to high- (HMW) and low-molecular-weight agents.

NS, no significant difference shown by McNemar test.

low levels of specific IgE, in order to make the test more sensitive. Furthermore, to compare the degree of EAST positivity, data were categorized in five classes (0–4), according to the information provided by the manufacturer.

Total IgE Total IgE levels, expressed as IU/mL were log transformed in order to approach a close-to-normal distribution of the variable.

Questionnaire Reported symptoms related to exposure to ubiquitous allergens were analysed as categorical variables. This was done separately for each allergen distinguishing four possibilities: no symptoms, rhinoconjunctivitis, asthma, or asthma with rhinoconjunctivitis. For the statistical analysis, data were generated for each allergen as dichotomous variables: no symptoms, rhinoconjunctivitis and/or asthma.

Statistical analysis

The McNemar test was used to evaluate the changes in the categorical dichotomic variables (presence-absence of symptoms, undetectable-detectable levels of specific IgE). A non-parametric test for paired data (Wilcoxon) was used to compare the levels of total IgE, which did not approach the normal distribution even after log transformation, and to compare the degree of EAST positivity, expressed in

classes. Non-parametric correlation between variations of PC₂₀ and total IgE were expressed as Spearman's ρ .

Statistical analysis was performed by means of the SPSS statistical software package (Chicago, IL, USA). A *P*-value ≤ 0.05 was considered significant.

Results

Subjects

Table 1 gives the characteristics of participants and non participants with OA due to HMW and LMW agents. After the diagnosis, 92 subjects were no longer exposed, while the remaining eight reported occasional or reduced levels of exposure (wearing a mask or respirator) for a mean duration of 3.6 ± 2.4 years. Overall, the duration of the period free of exposure was 5.4 ± 3.3 years. None of the subjects underwent hyposensitization treatments between the two visits. Only one subject had received a specific immunotherapy, in this case with grass pollens for 14 years, and it had been terminated 3 years before the first visit. Whereas duration of exposure was higher in participants than in non-participants, the other parameters were not significantly different. Atopy was more frequent in HMW- than in LMW-participants.

Specific IgE analysis

Table 2 gives the results of specific IgE on the two visits

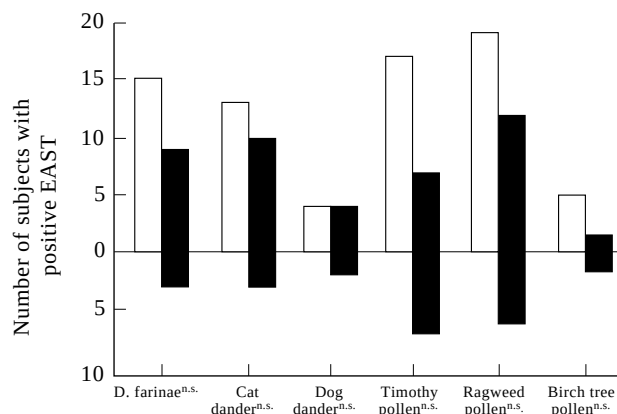


Fig. 1. The horizontal line separates subjects who lost or maintained sensitizations to the relevant allergen from the first to the second visit (above the line) from those who gained sensitizations (under the line). NS, not statistically significant. □, Subjects with positive results to the relative allergenic source at the first visit. ■, Subjects with positive results to the relative allergenic source at the second visit.

whereas Fig. 1 shows the changes in specific IgE-sensitization, expressed as positive or negative EAST, to the main allergens in all the subjects. Results of the EAST with *Alternaria* and *D. pteronyssinus*, that were not reported in the figure, did not show any significant difference, the number of positive tests passing from 17 to 13 and from 5 to 4 respectively. The total numbers of positive EAST at the first and second visits were compared, both in general and in the subgroups of OA to HMW and LMW agents. We found no change in the number of positive EAST in the overall group and in the subgroups; there was even a tendency to a

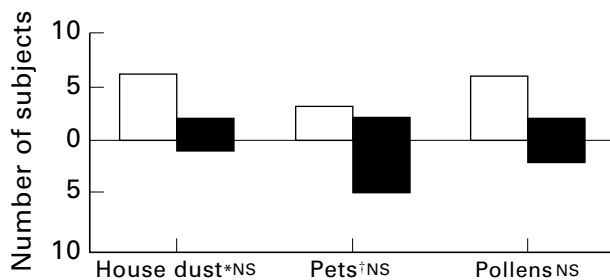


Fig. 2. Above the horizontal line are the subjects who lost or maintained symptoms from the first to the second visit and who showed at the same visit the presence of relevant specific IgE. Under the line are those subjects who presented both symptoms and relevant specific IgE only at the second visit. * $P < 0.05$ and $^{\dagger}P < 0.01$ (according to the McNemar test). n.s. = not statistically significant. □, Subjects reporting symptoms to the relative allergenic source and showing specific IgE at the first visit. ■, Subjects reporting symptoms to the relative allergenic source and showing specific IgE at the second visit.

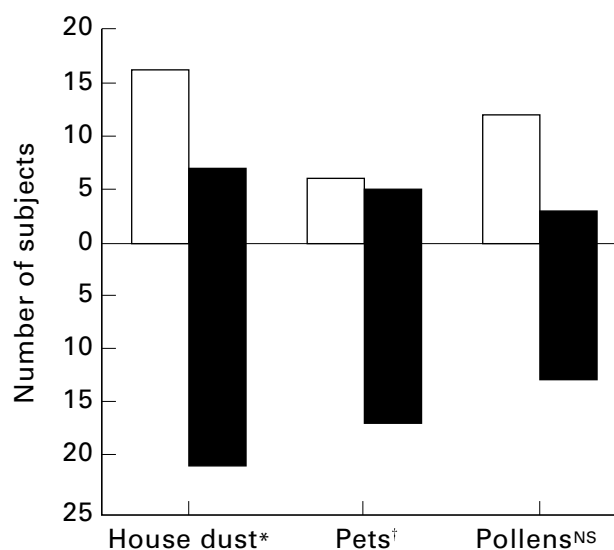


Fig. 3. The horizontal line separates subjects who lost or maintained symptoms due to the relevant allergen from the first to the second visit (above the line) from those who gained symptoms (under the line). * $P < 0.05$ and $^{\dagger}P < 0.01$ (according to the McNemar test). NS, not statistically significant. □, Subjects reporting symptoms to the relative allergenic source at the first visit. ■, Subjects reporting symptoms to the relative allergenic source at the second visit.

decrease in the LMW subgroup. The levels of specific IgE, expressed as EAST classes, did not change either after considering the results for each allergen separately or in general (not illustrated). In a subgroup of patients ($n = 25$) in whom asthma symptoms had started less than one year before the first visit, similar figures were obtained, with the total number of positive EAST going from 26 to 25 between visit one and visit two.

Total IgE

Table 2 shows the results of total serum IgE levels, both in general and in the subgroups according to the molecular weight of the responsible occupational agents. Total IgE levels showed a tendency to diminish. The variations of total IgE levels showed a significant inverse correlation with variations of PC20, both in the total group ($\rho = -0.24$; $P = .04$) and in the HMW subgroup ($\rho = -0.47$; $P = 0.01$), but not in the LMW subgroup ($\rho = -0.15$; $P = 0.37$).

Relationship between reported symptoms and immunological findings Figure 2 illustrates the changes (loss or gain of individuals) from the first to the second visit in the number of subjects reporting specific symptoms and showing at the same time detectable levels of specific IgE to the relevant allergen. The comparison with Fig. 3, which shows that significantly more symptoms of rhinoconjunctivitis and

asthma due to house dust and pets were reported on the second visit than on the first (irrespective from their immunologic finding), illustrates that evidence of specific sensitization was found in a small proportion of subjects reporting specific symptoms at the same visit only. No significant changes in the frequency of symptomatic sensitized subjects were found.

Hyperresponsiveness to methacholine ($PC_{20} < 8 \text{ mg/mL}$) tended to be more frequent at the second visit in the group of subjects with symptoms due to house dust but not sensitized to house dust mites as compared with the non-sensitized, non-symptomatic group (13/17 vs 28/51; $0.1 > P > 0.05$).

Discussion

The reasons for the persistence of asthma symptoms and airway inflammation in subjects with OA despite removal from exposure are not well elucidated. The majority of subjects who develop OA do not have asthma before they enter workplaces that cause the asthma. There are several possible explanations for the persistence of asthma: (1) some patients may continue to be exposed to the offending agent, or to cross-reacting substances, in their everyday environment even after they have quit their jobs; (2) once asthma, initially caused by occupational agents, has developed, viral infections, which have been shown to lead to airway inflammation [7], may partly be responsible for the persistence of hyperresponsiveness and symptoms; (3) some subjects with OA may be genetically predisposed to the development and perpetuation of asthma, regardless of the initial (starting) event [8]; (4) some subjects with pre-existing and clinically silent sensitizations to common aeroallergens would show bronchoconstriction and asthma symptoms when exposed to the relevant allergens once they have developed non-specific bronchial hyperresponsiveness; and (5) some subjects, especially atopics, could develop new sensitizations or increase pre-existing immunological sensitization, after the onset of asthma symptoms, favoured by increased permeability of airway epithelium and by the particular inflammatory milieu [9].

Our study's goal was to test the latter hypothesis and evaluate the incidence of new or increased sensitization and related symptoms to common aeroallergens in subjects with OA 5.8 years after cessation of exposure to the causal agent. We showed no evidence of IgE-mediated new or increased sensitization to common aeroallergens. The number of subjects showing the disappearance of specific IgE nearly equalled the number of subjects showing the appearance of specific IgE. The appearance of specific IgE in some subjects could, however, be clinically relevant. In our population of 100 subjects, 49 of whom were atopic (according to presence of specific IgE in the serum), we

observed the development of 22 new sensitizations occurring in 19 different subjects over a 5.8-year-interval. To assess the possible significance of the changes, it would be necessary to compare rates of sensitization with a matched control population without OA in a prospective study design. We believe that this may be considered a likely event in a general population. It has, in fact, recently been shown that in a population of children, 4% develop new sensitization to common aeroallergen over a 2-year period [10]. More interesting was the development of eight new sensitizations in six subjects (three with OA to HMW and three to LMW) who, at the first visit, showed no evidence of atopy either from personal or familial history or from skin test or specific IgE results, and whose total IgE levels were in the normal range (14–122 IU/mL). Based on this small group of subjects, it is tempting to say that it is the development of OA that triggers new sensitizations to common aeroallergens to which subjects had presumably already been exposed for long time. However, as discussed above, in the case of atopic subjects, we cannot exclude the possibility that a similar incidence of new sensitizations could be observed in a comparable non-atopic adult population. It should also be mentioned that in all but one subject these immunological sensitizations were clinically silent.

We observed a tendency to a decrease of total IgE in the group of all subjects with OA, with diminution of IgE levels in both subgroups exposed to LMW and HMW agents. Interestingly, the reduction of total IgE levels significantly correlated with that of bronchial reactivity to methacholine. The subgroup with OA to HMW but not to LMW agents contributed to the correlation. In Type I immediate hypersensitivity, which underlies OA to HMW agents, both eosinophil inflammation, known to be associated with bronchial hyperresponsiveness to methacholine [11], and total IgE synthesis are highly influenced by the degree of Th2 cell activation [12]. Thus, in this subgroup, the decrease of total IgE levels is probably the epiphenomenon of the diminution of bronchial inflammation that follows cessation of exposure to the causal agent and that is reflected by the reduced bronchial responsiveness to methacholine. The other possible explanation is that the level of total IgE diminishes with age.

When matching questionnaire and specific IgE results at each visit, the majority of subjects with detectable levels of specific IgE reported no specific symptoms. At the same time, the majority of subjects reporting symptoms in situations of potential allergenic exposure, showed no detectable levels of specific IgE. When considering ubiquitous aeroallergens acting through an IgE-mediated mechanism, one frequently finds immunologic sensitization, as assessed by specific IgE or by skin tests, without report of specific clinical manifestations. Sensitization does not necessarily imply clinical manifestations. Among sensitized subjects,

the low proportion of those reporting symptoms that we found in our study reflects a common phenomenon. Moreover, while the relation between degree of specific skin reactivity and specific bronchial responsiveness has been well documented (i.e., airway responsiveness to allergen is usually predicted by skin threshold to allergen [13]), the clinical relevance of *in vitro* IgE antibody tests has not been conclusively established, although a recent study indicated a threshold of IgE-specific levels defining clinical manifestation [14]. We can hypothesize that, having defined as sensitized all subjects with detectable levels of specific IgE, in some sensitized patients of our population, specific IgE levels were too low to be compatible with the clinical expression of the allergic sensitization.

The other finding, i.e., the presence of clinical manifestations upon contact with an allergenic source without evidence of immunological sensitization, has different explanations. First, we cannot exclude that, due to the known relatively low sensitivity of specific IgE analysis in detecting sensitization when compared to skin test (both by RAST and EIA) [15], some of the subjects reporting symptoms without showing specific IgE are indeed sensitized. Second, we also considered the possibility that reported symptoms may have been elicited through non-allergic mechanisms. In most patients with OA, non-specific bronchial hyperresponsiveness persists after cessation of exposure even after several years. Therefore, symptoms may still be triggered by potentially irritating stimuli. Both house cleaning and lawn mowing could easily induce nasal and ocular irritative symptoms in the general population and bronchial symptoms through non-specific bronchial hyperresponsiveness, particularly in subjects still showing a moderate degree of non-specific bronchial hyperresponsiveness [16]. Third, other factors, such as the inevitably modest degree of accuracy (positive and negative predictive values) of questions in predicting atopic sensitization to airborne allergens, should also be considered. In fact, the relationship between exposure to an allergenic source and the occurrence of related symptoms is not always evident. Unequivocal identification of the responsible agent, if any, is best achieved in a situation such as specific inhalation challenges. Finally, the questionnaire used for both visits was not similar, the first being openly addressed by a physician and the second being a standardized questionnaire administered by a technician, the first of which may have contributed to under reporting and the latter to over-reporting. Subjects may have become more aware of their symptoms between the two visits.

The participation rate was relatively low (100/242, 41%) but we do not think that this could have caused a significant bias. Indeed, the non-participants were similar to participants in terms of the variables which are relevant for predisposing to IgE-mediated sensitization (atopy) and for

causing permanent asthma (severity of asthma at the time of diagnosis, duration of symptoms before removal, airway caliber and responsiveness). In our study, we were able to rule out the possibility that symptoms reportedly due to house dust could be related to pet sensitization, since among subjects reporting symptoms due to house dust, only two were sensitized to pets, and neither had at that moment, or had had, any pets in the house. We were also able to exclude the possibility that sensitization to *Alternaria*, which grows on grass and whose spores are found at high concentration after lawn mowing [17], may have accounted for unexplained symptoms reported after lawn mowing, since the only two symptomatic subjects sensitized to *Alternaria* were also sensitized to grass pollens.

In conclusion, in general, sensitization to common aero-allergens does not represent a major factor in determining the persistence of asthma symptoms in OA after the cessation of exposure. Prospective studies are needed to test the other hypothesis presented in the first paragraph of the discussion above, addressing the factors that might determine the persistence of asthma symptoms and bronchial hyperresponsiveness.

Acknowledgements

The authors wish to thank Lori Schubert for reviewing the manuscript.

References

- 1 Chan-Yeung M, Malo JL. Natural history of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI., eds. *Asthma in the workplace*. New York: Marcel Dekker Inc 1993; 299–322.
- 2 Chan-Yeung M, Malo JL. Occupational asthma. *N Engl J Med* 1995; 333:107–12.
- 3 Burney PGJ, Laitinen LA, Perdrizet S et al. Validity and repeatability of the IUATLD (1984) bronchial symptoms questionnaire: an international comparison. *Eur Respir J* 1989; 2:940–5.
- 4 Pepys J. Types of allergic reaction. *Clin Allergy* 1973; 3:491–509.
- 5 American Thoracic Society. Standardization of spirometry-1987 Update. *Am Rev Respir Dis* 1987; 136:1285–307.
- 6 Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clinical Allergy* 1977; 7:235–43.
- 7 Bardin PG, Johnston SL, Pattemore PK. Viruses as precipitants of asthma symptoms II. Physiology and mechanisms. *Clin Exper Allergy* 1992; 22:809–22.
- 8 Cookson WOCM, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; 10:1292–5.
- 9 Bradley BL, Azzawi M, Jacobson M et al. Eosinophil,

- T-lymphocytes, mast cells, neutrophils, and macrophages in bronchial biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness. *J Allergy Clin Immunol* 1991; 88:661–74.
- 10 Johnston SL, Clough JB, Pattemore PK, Smith S, Holgate ST. Longitudinal changes in skin-prick test reactivity over 2 years in a population of schoolchildren with respiratory symptoms. *Clin Exp Allergy* 1992; 22:948–57.
- 11 Chetta A, Foresi A, Donno M et al. Bronchial responsiveness to distilled water and methacholine and its relationship to inflammation and remodeling of the airways in asthma. *Am J Respir Crit Care Med* 1996; 153:910–7.
- 12 Mosmann TR, Coffman RL. Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; 7:145–73.
- 13 Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis* 1987; 135:264–7.
- 14 Pastorello EA, Incorvaia C, Ortolani C et al. Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens. *J Allergy Clin Immunol* 1995; 96:580–7.
- 15 Bernstein IL. Proceedings of the task force on guidelines for standardizing old and new technologies used for the diagnosis and treatment of allergic diseases. *J Allergy Clin Immunol* 1988; 82:487–526.
- 16 Dolovich J, Hargreave FE. The asthma syndrome: inciters, inducers, and host characteristics. *Thorax* 1981; 36:641–4.
- 17 Gautrin D, Vandenplas O, DeWitte JD et al. Allergenic exposure, IgE-mediated sensitization and related symptoms in lawn cutters. *J Allergy Clin Immunol* 1994; 93:437–45.