Sputum Eosinophilia and Maximal Airway Narrowing in *Dermatophagoides pteronyssinus* Allergic Rhinitis Patients* Only Rhinitis or Rhinitis Plus Mild Asthma?

María J. Alvarez Puebla, MD, PhD; Rodolfo Castillo, MD, PhD; Agustín Rey, MD, PhD; Nancy Ortega, MD; Carlos Blanco, MD, PhD; and Teresa Carrillo, MD, PhD

**Study objective:** To study the existence of bronchial disease among rhinitis patients. To evaluate the laboratory test or set of tests (ie, symptoms, exposure, and sensitization to the allergen, and the provocative dose of methacholine [Mth] causing a 20% fall in FEV$_1$ [PD$_{20}$] and the maximal response plateau [MRP] to Mth) that best identifies a case of mild asthma.

**Design:** Cross-sectional analysis in 52 *Dermatophagoides pteronyssinus*-monosensitized patients who were consulting a physician for perennial rhinitis.

**Setting:** Allergy Department, Hospital Doctor Negrín, Las Palmas, Grand Canary Island, Spain.

**Interventions and measurements:** Patients filled out a standardized asthma symptom questionnaire, and underwent sputum induction and Mth challenge in which 40% falls in FEV$_1$ were attained. Dose-response curves were expressed in terms of both PD$_{20}$ values and the level of the MRP. *D pteronyssinus* allergen exposure was assessed in dust samples from patients’ beds.

**Results:** No difference between patients who positively responded to the questionnaire and those who did not was observed. Mth-PD$_{20}$ values were not detected in 13% of the patients reporting bronchial symptoms, and an MRP was not identified in 59% of the subjects who did not respond positively. A higher degree of allergen sensitization (ascertained from skin test results, and total and specific serum IgE levels) and higher degree of sputum eosinophilia were detected in subjects in whom an MRP had not been identified. The presence of sputum eosinophilia provided the best differentiation between those patients who presented with an MRP and those who did not.

**Conclusion:** The individual perception of bronchial symptoms is highly variable among perennial allergic rhinitis patients. The lack of a maximal airway-narrowing plateau is related to the presence of sputum eosinophilia, which might be useful in the detection of patients susceptible to anti-inflammatory therapy. Prospective studies evaluating whether these patients are more likely to develop symptomatic asthma in the future and if the early anti-inflammatory treatment prevents its development are needed.

**(CHEST 2002; 122:1560–1565)**

**Key words:** allergic rhinitis; bronchial hyperresponsiveness; eosinophils; maximal airway narrowing; maximal response plateau; methacholine; mild asthma; sputum

**Abbreviations:** AS$^-$ = asthma symptoms negative; AS$^+$ = asthma symptoms positive; BHR = bronchial hyperresponsiveness; BPT = bronchial provocation test; GM = geometric mean; IQR = interquartile range; MRP = maximal response plateau; MRP$^-$ = maximal response plateau not found; MRP$^+$ = maximal response plateau found; Mth = methacholine; PD$_{20}$ = provocative dose of a substance causing a 20% drop in FEV$_1$
both by patient \(^4\) and physician \(^5\) may be highly variable. Allergic asthma often is associated with rhinitis, which constitutes an independent risk factor for its development.\(^6\) Rhinitis symptoms can induce a higher degree of disability in the patient than mild bronchial symptoms,\(^7\) leading to serious underdiagnosis and, consequently, to the undertreatment of patients with mild asthma.\(^8\)

Epidemiologic studies have clearly demonstrated a close relationship between asthma and the exposure to the allergens of the house dust mite *Dermatophagoptes pteronyssinus*.\(^9,10\) In the present report, we have studied 52 recently diagnosed patients who were allergic to *D pteronyssinus* and who consulted physicians for symptoms of perennial rhinitis. Patients were grouped first according to their positive or negative responses to a standardized asthma symptom questionnaire, and second according to the whether a maximal response plateau (MRP) could be identified. A number of tests that are usually utilized to determine whether a maximal response plateau (MRP) could be attained.  A variability rate lower than 5% among basal and postdiluent FEV\(_1\) values was measured by spirometry 3 min following inhalation. A variability rate lower than 5% among basal and postdiluent FEV\(_1\) values was required to start the test. The challenge finished when a fall in FEV\(_1\) values ≥ 40% from the postdiluent value was achieved or when the highest Mth concentration was inhaled. Results were expressed in terms of the Mth-provocative dose of a substance (Mth) causing a 20% fall in FEV\(_1\) (PD\(_{20}\)) from baseline values. The level MRP, which was considered to be present if three or more of the highest doses of the agonist fall within a 5% response range, was obtained by averaging the data points on the plateau.

### Materials and Methods

#### Subjects and Study Design

We selected 52 nonsmoking *D pteronyssinus*-allergic patients who consecutively attended our department reporting noseasonal rhinitis. *D pteronyssinus* sensitization was established by means of positive skin-prick test results with a standardized extract (ALK-Abelló; Madrid, Spain) and detection of a specific IgE to this allergen in the context of a compatible clinical history. Subjects who had been sensitized to other perennial or seasonal allergens were excluded. Patients underwent clinical and physical evaluations and filled out a standardized asthma symptoms questionnaire. According to their responses to the questionnaire, they were matched in the asthma symptoms-positive (AS+) group or the asthma symptoms-negative (AS−) group.\(^11\) Mth-BPT, until FEV\(_1\) values fell by 40% from baseline, was performed, and blood and sputum samples were collected afterward. The exposure to the major allergen of *D pteronyssinus* (Der p 1) was assessed in dust samples from patients’ beds. During the 2 months before entry into the study, subjects had not presented with airways infections, and only short-acting β-agonist drugs used “as needed” were allowed. No antiallergy drugs were taken within 24 h before the BPT. The test finished when a fall in FEV\(_1\) values ≥ 40% from the postdiluent value was achieved or when the highest Mth concentration was inhaled. Results were expressed in terms of the Mth-provocative dose of a substance (Mth) causing a 20% fall in FEV\(_1\) (PD\(_{20}\)) from baseline values. The level MRP, which was considered to be present if three or more of the highest doses of the agonist fell within a 5% range, was obtained by averaging the data points on the plateau.

#### Methods

**Asthma Symptoms Questionnaire:** Patients completed a standardized asthma symptoms questionnaire for which the reproducibility and validity had been demonstrated.\(^11\) The frequency of presentation of 10 bronchial symptoms (ie, dyspnea during exercise, diurnal resting dyspnea, diurnal wheezing, diurnal cough, nocturnal wheezing, nocturnal dyspnea, nocturnal cough, sleep disturbance, fear because of asthma, and chest tightness) during the last month was scored as follows: 0, never; 1, on 1 day or a few days; 2, on several days; 3, on most days; and 4, every day. The total symptoms score ranged from 0 to 40 points.

**Collection of Dust Samples and Quantitation of Mite Allergens:** Dust collection was carried out as described.\(^12\) A portable vacuum cleaner provided with a prefiter (ALK-Abelló) that retains 74% of particles 0.3 to 0.5 μm in size, 81% of particles 0.5 to 1.0 μm in size, 95% of particles 1.0 to 10 μm in size, and 100% of larger particles\(^13\) was used. The layer of bedding below the lower sheet, the layer above the upper sheet, and inside the pillow case were vacuumed for 2 min per m\(^2\). The filter box then was removed and stored in a plastic bag at −20°C until further analysis could be conducted. The content of major mite allergen (Der p 1) was determined in duplicate by a commercial enzyme-linked immunosorbent assay based on monoclonal antibodies (ALK). Standard curves for these assays (1 to 200 ng allergen/mL) were routinely obtained from freeze-dried whole mite extracts that were titrated against purified allergens. Allergen concentrations were estimated from three independent experiments. The mean intra-assay coefficient of variation was < 3%, while the interassay coefficient of variation from control subjects tested with all the assays was < 15%. The detection limit of the assays was 1 ng/mL.

**Mth BPT:** Testing was performed according to international guidelines.\(^14,15\) Dilutions of Mth (Provocoline; Roche Laboratories; Nutley, NJ) at 0.125, 0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0, 50.0, 100.0, and 200.0 mg/mL in phosphate-buffered saline solution were made on the study day. Baseline spirometry was performed, and FEV\(_1\) values ≥ 75% of predicted normal values were required. The reference values of Crapo et al\(^16\) were used. Patients had not inhaled β-agonist drugs or ingested caffeine on the day of the test. Diluent (phosphate-buffered saline solution) and Mth at increasing concentrations were administered using a dosimeter (MEFAR srl; Borezzo, Italy) that had been programmed to deliver five inhalations of 1 s each, with 10 mL solution administered in each inhalation. FEV\(_1\) values were measured by spirometry 3 min following inhalation. A variability rate lower than 5% among basal and postdiluent FEV\(_1\) values was required to start the test. The challenge finished when a fall in FEV\(_1\) values ≥ 40% from the postdiluent value was achieved or when the highest Mth concentration was inhaled. Results were expressed in terms of the Mth-provocative dose of a substance (Mth) causing a 20% fall in FEV\(_1\) (PD\(_{20}\)) from baseline values. The level MRP, which was considered to be present if three or more of the highest doses of the agonist fell within a 5% range, was obtained by averaging the data points on the plateau.

**Sputum Induction:** Sputum samples were obtained by hypertonic saline solution inhalation, as has been described.\(^17\) Subjects were pretreated with four puffs of inhaled salbutamol. To avoid the contamination of the sample, patients rinsed their mouths and cleaned their noses before induction and, when possible, before expectoration. An ultrasonic nebulizer (Ultraneb 2000; De Vilbiss; Somerset, PA) was used to administer the saline solution at 5% for three periods of 10 min each. After each period, patients were asked to cough and expectorate into a sterile container, and, when possible, saliva was put into a different receptacle. The test finished when a macroscopically adequate sputum sample was obtained or when the three periods of inhalation had been completed.

The volume of the entire sputum sample was measured, and 3 mL of the sample was mixed with an equal volume of dithiothreitol (Sputasol; Unipath LTD; Basingstoke, Hampshire, Hampshire, England). A volume of 3 mL of the sample was mixed with an equal volume of dithiothreitol (Sputasol; Unipath LTD; Basingstoke, Hampshire, England).
UK) at 1:100 and was stirred at room temperature for 15 min. The mixture was filtered through one 0.45-μm filter (Millipore; Sommerset, PA) and was centrifuged at 1,500g for 10 min. The pellet was suspended in a 0.9% saline solution, was cytocentrifuged, and was stained either with Papanicoula or Giemsa stains for differential cell counts. The sample was considered to be adequate for analysis when macrophages could be visualized and squamous cell contamination was < 20%.15 The percentage counts of macrophages, eosinophils, neutrophils, mast cells, lymphocytes, and ciliated cells were made over a total count of 400 cells. A single person, blinded to the patients’ clinical conditions, performed the evaluation.

Soluble Markers in Serum: The concentrations of total specific IgE and 2.0 kilounits/L for total IgE concentrations were measured by fluoroenzyme immunosorbent assay (UNICAP; Pharmacia Diagnostics; Uppsala, Sweden). The limits of detection for the assays were 0.35 kilounits/L for bent assay (UNICAP; Pharmacia Diagnostics; Uppsala, Sweden).

Statistical Analysis

Statistical analysis of the data was performed using a statistics program (SPSS for Windows, version 8.0; SPSS; Chicago, IL). Descriptive statistics summarized the demographic and clinical features of the patients. Results were expressed as the median and interquartile range (IQR). Mth-PD20 values were log-transformed for analysis, and the results were expressed in terms of the geometric mean (GM). Differences between groups were analyzed by the Mann-Whitney U test, and correlation between variables was determined using the Spearman rank correlation coefficient. We used a model of multiple linear regression in which the variables that differed between groups were sequentially entered and applied to the dependent variable until a model in which no more variables were eligible for entry or removal was arrived at. The value of F was the criterion for entering variables (F < 0.05) or removing variables (F > 0.1). A p value of < 0.05 was considered to be significant.

RESULTS

First Criterion of Grouping: Response to the Asthma Symptom Questionnaire

The 52 mite rhinitis patients were matched according to their positive (n = 30) or negative (n = 22) responses to the questionnaire (Table 1). Groups did not differ in age, sex, allergen sensitization, Der p 1 exposure, or baseline lung function. Sputum induction was safe in every patient. Adequate samples for analysis were obtained in 93% of the AS+ patients and in 68% of the AS− patients. No difference in sputum composition was detected between groups. The results of the Mth-BPT were positive (ie, the induced FEV1 falls ≥ 20%) in 26 of the AS+ patients (86%) and in 11 of the AS− patients (50%). An MRP was identified in 14 patients (47%) and 9 patients (41%), respectively. No differences between groups were detected in either Mth-PD20 values (GM, 2.63 vs 0.65 mg, respectively) or Mth-MRP values (median, 21% [IQR, 17 to 27] vs 10% [IQR, 9 to 30], respectively).

Second Criterion of Grouping: Identification of an MRP

Patients were grouped according to whether an MRP was found (MRP+; n = 23) and or was not found (MRP−; n = 29) [Table 2]. Asthma symptoms were reported by 16 of the MRP+ patients (69%) and by 14 of the MRP− patients (48%). When groups were compared, the magnitude of the skin test response, and the levels of total and D pteronyssinus-specific serum IgE were higher in the MRP− group. Adequate sputum samples were obtained in 14 patients (61%) from the MRP+ group and in every patient from the MRP− group. The MRP− group exhibited higher percentages of eosinophils and neutrophils, and lower numbers of ciliated cells in the sputum samples than did the MRP+ group. Mth-PD20 values, detected in eight patients (35%) from the MRP+ group and in every patient from the MRP− group, were lower (p < 0.001) in the former group (GM, 6.97 vs 0.14 mg, respectively).

Table 1—Data From the Patients Grouped According to Their Positive or Negative Responses to the Asthma Symptoms Questionnaire*

<table>
<thead>
<tr>
<th>Variables</th>
<th>AS+</th>
<th>AS−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma score, points</td>
<td>10 (4.25–15.75)</td>
<td>0</td>
</tr>
<tr>
<td>Age, yr</td>
<td>21 (18–24)</td>
<td>21 (16–31)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Skin-prick test, mm²</td>
<td>60 (36–68)</td>
<td>81 (35–130)</td>
</tr>
<tr>
<td>Total serum IgE, KU/L</td>
<td>438 (113–1495)</td>
<td>502 (162–1391)</td>
</tr>
<tr>
<td>D pteronyssinus serum IgE, KU/L</td>
<td>89 (32.2–100)</td>
<td>90 (66.5–98)</td>
</tr>
<tr>
<td>Der p 1 exposure, μg/g dust</td>
<td>8.83 (3.8–20.0)</td>
<td>16.35 (3.13–38.4)</td>
</tr>
<tr>
<td>Baseline FEV₁, %</td>
<td>90 (77.7–99.7)</td>
<td>90 (67–98)</td>
</tr>
<tr>
<td>Mth-PD20, mg</td>
<td>2.62</td>
<td>0.65</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>7.0 (3.0–11.7)</td>
<td>9.4 (4.0–20.5)</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>7.0 (1.8–13.2)</td>
<td>6.7 (2.3–17.0)</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>46.5 (20.0–68.0)</td>
<td>53.0 (30.0–60.0)</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>13.0 (4.0–26.0)</td>
<td>16.0 (8.5–30.5)</td>
</tr>
<tr>
<td>Ciliated cells</td>
<td>14.8 (9.5–30.5)</td>
<td>7.3 (3.0–20.0)</td>
</tr>
</tbody>
</table>

*Values given as median (IQR), unless otherwise indicated.
†Values given as GM.
### Table 2—Data From the Patients Grouped According to the Identification of an MRP*

<table>
<thead>
<tr>
<th>Variables</th>
<th>MRP+</th>
<th>MRP−</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma score, points</td>
<td>8 (1–12.7)</td>
<td>10 (2.5–16.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>20 (17–22)</td>
<td>21 (18–25)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>65</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Skin-prick test, mm²</td>
<td>56 (28–84)</td>
<td>102 (65–151)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total serum IgE, KU/L</td>
<td>237.5 (113–492)</td>
<td>640 (313–1379)</td>
<td>0.021</td>
</tr>
<tr>
<td>Der p 1 exposure, µg/g dust</td>
<td>14.1 (3.3–23.2)</td>
<td>13.9 (4.3–41.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline FEV₁, %</td>
<td>94 (89–100)</td>
<td>91 (78–100)</td>
<td>NS</td>
</tr>
<tr>
<td>Mth-PD₂₀, µmol</td>
<td>6.97</td>
<td>0.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>4.4 (3.0–8.7)</td>
<td>15.0 (12.2–19.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>5 (1.5–14.7)</td>
<td>7.5 (5.5–14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>52.5 (34.2–63.7)</td>
<td>55.0 (22.0–69.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>8.0 (1.5–20)</td>
<td>21.0 (10.5–25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ciliated cells</td>
<td>22.0 (10.0–30.5)</td>
<td>6.2 (2.2–14.0)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Values given as median (IQR), unless otherwise indicated. NS = not significant.
†Mann-Whitney U test.
‡Values given as GM.

### Correlation and Linear Regression Study

When the whole sample of patients was analyzed, the number of sputum eosinophils correlated both with total serum IgE levels (p = 0.003; r = 0.50) and Mth-PD₂₀ values (p = 0.035; r = −0.45). Mth-PD₂₀ values correlated with the skin test area (p < 0.001; r = −0.53) and showed a trend toward correlation with the percentage of neutrophils in the sputum (p = 0.059; r = −0.34).

A linear regression test was performed by the step-wise entering of the variables that had differed between groups (ie, skin test; total and D pteronyssinus-specific IgE levels, and the numbers of eosinophils, neutrophils, and ciliated cells) and was applied to the dependent variable (ie, presentation or not of an MRP). Only sputum eosinophilia contributed to the identification of an MRP (β = 0.463; p = 0.030).

### Discussion

Allergic asthma and rhinitis are related disorders that frequently are associated and show a parallel development. Although less frequently than in patients with asthma, the lower airways of rhinitis patients exhibit eosinophilic infiltration and increased sensitivity to bronchoconstricting agonists, suggesting that both diseases are manifestations of the same disorder. Some authors have documented the benefits of the early detection and onset of inhaled steroid therapy in patients with mild asthma. However, these patients often exhibit normal baseline lung function test results and, given the low sensitivities of the biochemical tests, diagnosis of their conditions depends mainly on clinical data (ie, recurrent attacks of cough, chest tightness, dyspnea, and wheezing). The individual perception of airway-narrowing episodes is highly variable, leading to the misdiagnosis of asthma, implying long-term and unnecessary drug therapy, or, alternatively, leading to the underdiagnosis and consequent undertreatment of asthma.

In this study, we classified a group of mite-allergic patients who consulted physicians for perennial rhinitis on the basis of their positive or negative responses to a validated asthma symptom questionnaire. No different allergen exposure, sensitization, or sputum composition was detected between patients reporting asthma symptoms and those who did not. BHR, often expressed in terms of sensitivity (ie, PD₂₀ values), is a cardinal feature of asthma that also has been described among some rhinitis patients. The values for Mth-PD₂₀ notably overlap between rhinitis and asthma, and thereby, a positive response to Mth is not diagnostic of asthma, but a negative response among patients currently exposed to the allergen rules out the diagnosis of the disease.

We evaluated subjects who were sensitized to and currently exposed to the perennial indoor allergen D pteronyssinus and observed no different sensitivity to Mth between those reporting bronchial symptoms and those who did not. More importantly, Mth-PD₂₀ values were not detected in 14% of the subjects reporting recent bronchial symptoms, which brings into question the diagnosis of asthma in these subjects.

BHR is a complex functional disorder of the airways that is defined by dose-response curves that provide different information. The shift of the curve to the left indicates increased sensitivity and structurally correlates with a loss of integrity of the respiratory epithelium. The severity of the re-
sponse, reflected by the shape of the curve, is evaluated in terms of the dose-response curve slope and the MRP.\textsuperscript{22} Bronchial response is secondary to both the reduction in the forces that limit airway narrowing and the increase in airway wall thickness.\textsuperscript{24,25} The inflammatory infiltrate and the edema of the submucosa as well as the deposition of collagen in the epithelial subbasement membrane increase the thickness of the bronchial wall and enhance the response to the agonist. The MRP, the point at which the inhalation of increasing concentrations of stimulus induces no further airflow limitation, is presumably the major pathophysiologic abnormality in asthma patients since its absence or detection in high degrees of airway narrowing puts subjects at risk from serious disease.\textsuperscript{26} The plateau level also has a higher capacity than bronchial sensitivity to discriminate asthma from rhinitis.\textsuperscript{27} In our study, a plateau level was not identified in more than half of the patients, and, strikingly, 44% of them did not report bronchial symptoms.

Bronchial challenge tests that employ high concentrations of an agonist to measure the maximal degree of airway narrowing are far from practical for routine clinical purposes due to the large falls in \textit{FEV}\textsubscript{1} values that are induced and because they are extremely time-consuming. Therefore, we evaluated whether any other index could differentiate those patients who lacked an MRP from the remainder of rhinitis patients. Allergen sensitization (\textit{ie}, skin test results, and total and \textit{D pteronyssinus-specific IgE levels}) was higher among patients in whom no MRP was identified, suggesting a more intense systemic immunologic response to the allergen. Higher numbers of eosinophils and a trend toward higher numbers of neutrophils in sputum also were observed among patients without MRPs. In patients with severe asthma, sputum eosinophilia has been reported to be an independent factor for persistent airflow limitation.\textsuperscript{28} Eosinophils are a major source of transforming growth factor-\(\beta\),\textsuperscript{29} a cytokine that is implied in the development of fibrosis within asthmatic airways.\textsuperscript{30} Bronchial biopsy specimens from patients with severe asthma in whom eosinophilia persisted despite steroid therapy exhibited increased concentrations of transforming growth factor-\(\beta\) coincident with a thicker subbasement membrane.\textsuperscript{31} These data suggest a close relationship between eosinophilic inflammation and the structural changes in the airways that, at least in part, are responsible for the increased bronchial response. In this study, the presence of eosinophilia in sputum and the level of the MRP correlated in allergic rhinitis patients.\textsuperscript{17} Our results showed that, even among subjects consulting physicians for rhinitis symptoms, sputum eosinophilia was the only factor correlated with the lack of MRP, which supports the role for eosinophils in the initiation of the bronchial structural changes that lead to a higher degree of airway narrowing.

When using immunocytochemistry techniques,\textsuperscript{32,33} asthma patients exhibit higher numbers of epithelial cells in sputum than do nonasthmatic patients. The weak reproducibility of the sputum epithelial cells counts when standard optical microscopy is utilized\textsuperscript{33} might explain the fact that in our study their numbers were strikingly higher in the patients in whom an MRP was detected, and also were higher than those described by other authors.\textsuperscript{32,33}

In summary, there is not a clear differentiation between allergic rhinitis alone and allergic rhinitis plus mild asthma. A degree of eosinophilic bronchial inflammation that relates to the increase or lack of increase in the level of the maximal airway narrowing plateau is detected even in some rhinitis patients who do not report asthma symptoms. Our results are preliminary findings that are in no way sufficient to predict whether these rhinitis patients without asthma symptoms and with normal lung function will develop symptomatic asthma in the future. However, given the close relationship between bronchial eosinophilia, airway fibrotic changes, and the lack of an MRP, long-term anti-inflammatory treatment in these patients might be considered. Prospective studies are needed to evaluate whether such treatment, based on the presence of sputum eosinophilia, might prevent the development of symptomatic asthma.

ACKNOWLEDGMENT: The authors thank Ms. Theresa Hetherington for her review of the English language of this manuscript.

REFERENCES

3 Haahlet T. The long-term influence of therapeutic interventions in asthma with emphasis on inhaled steroids and early disease. Clin Exp Allerg 1998; 8:133–140