

Seasonal Variability of Non-Specific Bronchial Responsiveness in Asthmatic Patients with Allergy to House Dust Mites

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ABSTRACT

The aim of the study was to assess the seasonal variability of non-specific bronchial responsiveness to methacholine in allergic asthma. One hundred sixty-five patients (83 male and 82 female) entered the study: 86 subjects (group A) with allergy exclusively to mites and 79 (group B) with concomitant allergy to pollens, e.g., "Graminae" and "Parietaria." Inclusion criteria were the absence of sensitization to other allergens, no smoking habit, withdrawal from steroids, bronchodilators, sodium cromoglycate, and antihistamines for at least four weeks before enrollment, FEV1 > 70% of the predicted value, and absence of other respiratory diseases and of upper and lower respiratory tract infections for at least one month before the methacholine challenge. None of the patients had been previously treated with specific immunotherapy. Subjects of each group (A and B) underwent methacholine challenge at first visit and were divided into four subgroups according to the period when the challenge was performed. Subgroups A1 and B1 performed the challenge in December, January, and February; subgroups A2 and B2 in March, April, and May; subgroups A3 and B3 in June, July, and August; subgroups A4 and B4 in September, October, and November. PD20 values were expressed

as the natural logs of the cumulative dose of methacholine causing at least a 20% fall in FEV1. Statistical analysis was carried out using multiple group analysis and Student's t-test. Results showed that the highest non-specific bronchial responsiveness was observed in autumn ($\ln PC20 = 4.54 \pm 1.51$) in patients allergic to mites only (group A), and in summer ($\ln PC20 = 4.72 \pm 2.11$) in those of group B. Multiple group analysis showed statistical significant differences between subgroups within each group (group A, $p = 0.039$; group B, $p < 0.001$). In patients allergic exclusively to house dust mites (group A), multiple comparisons and Student's t-test showed statistically significant differences between non-specific bronchial responsiveness (NSBR) assessed in autumn and those of other seasons (winter, $p = 0.002$; spring, $p < 0.001$; summer, $p = 0.082$). These results confirm that the level of allergen exposure may influence NSBR. Mite-allergic patients showed an increase of NSBR in autumn, possibly as a consequence of higher indoor mite concentration. However, mite- and grass-allergic patients had wider variations of NSBR, possibly reflecting changes in seasonal pollen concentration. (Allergy and Asthma Proc 22:5–9, 2001)

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Indoor allergen exposure, particularly to house dust mites in Europe, is considered to be an important risk factor for the development of asthma and other allergic diseases.^{1,2}

Preventive measures, which allow a 95% reduction in the mite allergen exposure, may result in the resolution of respiratory symptoms and the improvement of non-specific bronchial responsiveness.³ However, there are some patients allergic to house dust mites who improve in their asthmatic symptoms after prolonged periods away from

allergen exposure, but they do not exhibit significant changes in non-specific bronchial responsiveness (NSBR).³

Domestic mite growth is determined mainly by availability of food sources, temperature, and air humidity.⁴ Relative humidity represents undoubtedly the most important factor for the well-being and multiplication of domestic mites, which thrive at values of relative humidity ranging between 70 and 90%.⁵ Domestic mites usually dry up at values below 55%, while they can be overwhelmed by the rapid growth of molds and bacteria if the relative humidity of the ambient air is higher than 90%.^{4,6} Air humidity may be considered the principal cause of the seasonal variation of house dust mite growth in geographic areas with a temperate climate. The growth of the house dust mite population rises and decreases, respectively, in late summer and winter.⁴ Climatic influences may well be thought as the main determining factor of the domestic mite levels in homes.

The aim of this study was to evaluate if the non-specific bronchial responsiveness of asthmatic patients with allergy to house dust mites had seasonal changes, likely related to the natural variation of the allergen concentration in the reservoir within homes.

PATIENTS AND METHODS

Between March 1993 and September 1997, non-specific bronchial responsiveness to methacholine was assessed in 165 patients (83 male; 82 female) with a clinical history indicative of asthma and in non-smokers.

Criteria for the study inclusion were: specific allergy to *Dermatophagoides pteronyssinus* with or without concomitant specific allergy to grass pollen ("Graminae" and "Parietaria") defined by positive skin-prick test (wheal diameter > 3 mm), confirmed by serum IgE assays (Pharmacia, Uppsala, Sweden); FEV1 > 70% of the predicted value; absence of other respiratory diseases; absence of upper and lower respiratory tract infections for at least a month before the methacholine challenge; withdrawal from eventual therapy with steroids, bronchodilators, sodium cromoglycate, and antihistamines for at least four weeks before the methacholine challenge. None of the patients was treated with specific immunotherapy.

A detailed allergological screening by skin-prick test for inhalants (Bayer, Munich, Germany) ruled out sensitization to other pollen, animal dander, and molds. The latter included *Alternaria tenuis*, *Aspergillus niger* and *fumigatus*, *Botrytis cinerea*, *Cladosporium herbarium*, *Curvularia*, *Fusarium*, *Helminthosporium*, *Mucor racemosus*, *Penicillium notatum*, *Pullularia*, *Rhizopus*, and *Trichophyton*.

Non-specific bronchial responsiveness was assessed using methacholine (Lofarma, Italy), as freeze-dried vials with buffer salt, from which 0.2% (2 mg/ml)–1% (10 mg/dl) isoosmolar solutions were simply obtained by adding 3 ml of water. After a baseline spirometry, patients inhaled buffered saline vehicle solution (8 doses) repeating spirometry at 90 and 180 s. Then methacholine doses were delivered

with a dosimeter (Mefar MB3); 45 μ l of each Mch concentration (from 3 μ g to 3200 μ g) were inhaled for 5 s during each of 5 breaths from FRC to TLC without breath-holding, until the cumulative dose of 3200 μ g was reached or at least a 20% fall in FEV1 had occurred. Lung function was measured 60 s after each dose.⁷

Values of PC20 were expressed as the natural logs (ln) of the cumulative dose of methacholine causing at least a 20% fall in FEV1.

Patients were divided into two groups: group A of 86 subjects with specific allergy exclusively to *Dermatophagoides pteronyssinus* and group B of 79 subjects with specific allergy to *Dermatophagoides pteronyssinus* and grass pollen (30 to "Graminae," 16 to "Parietaria," 33 to both grass pollens). Subjects of each group (A and B) underwent methacholine challenge at the first visit and were divided into four subgroups according to the period when the challenge was performed: subgroup 1 (A1 and B1) in December, January, and February (winter); subgroup 2 (A2 and B2) in March, April, and May (spring); subgroup 3 (A3 and B3) in June, July, and August (summer); subgroup 4 (A4 and B4) in September, October, and November (autumn). PD20 values (ln) between different subgroups within each group were analyzed using the multiple group analysis (ANOVA) and then compared individually using the Student's *t*-test.

RESULTS

Demographic details of each subgroup are shown in Table I. Baseline FEV1 and ln PD20 values expressed as mean $\pm$ SD for each subgroup are shown in Table II.

In group A the highest non-specific bronchial responsiveness was observed in autumn (subgroup A4), followed by

TABLE I
Demographic Details of Patients Included in the Study

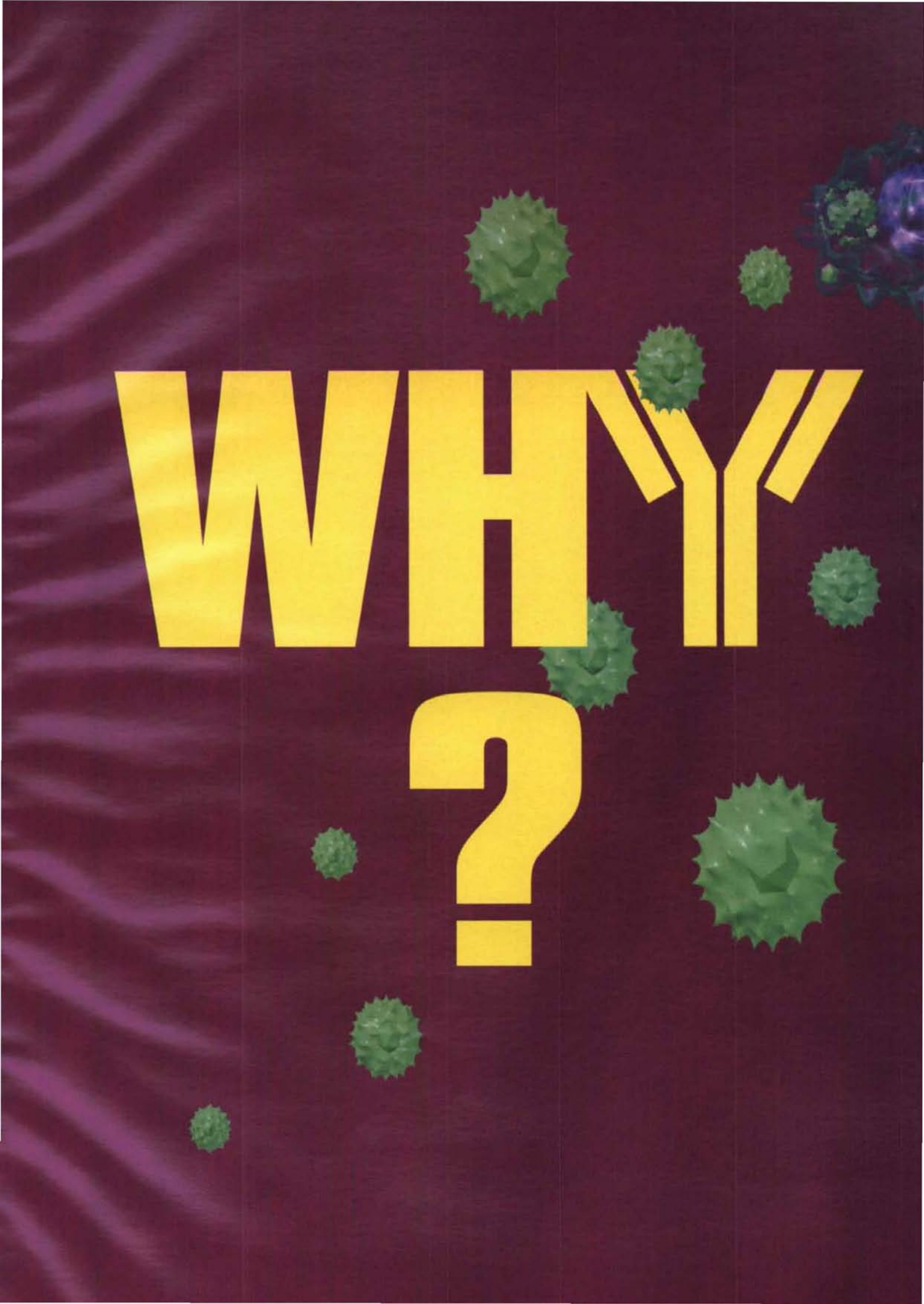
Group	Number	Sex		Age (M $\pm$ SD)
		M	F	
A	86	43	43	22.7 $\pm$ 12.7
A1*	33	15	18	23.9 $\pm$ 11
A2*	13	8	5	26.8 $\pm$ 15.2
A3*	14	8	6	23.5 $\pm$ 15.6
A4*	26	12	14	18.8 $\pm$ 11.3
B	79	40	39	20.3 $\pm$ 10
B1*	23	14	9	17.1 $\pm$ 7.1
B2*	19	9	10	25.2 $\pm$ 10.8
B3*	12	7	5	20.2 $\pm$ 10.6
B4*	25	10	15	19.6 $\pm$ 10.6

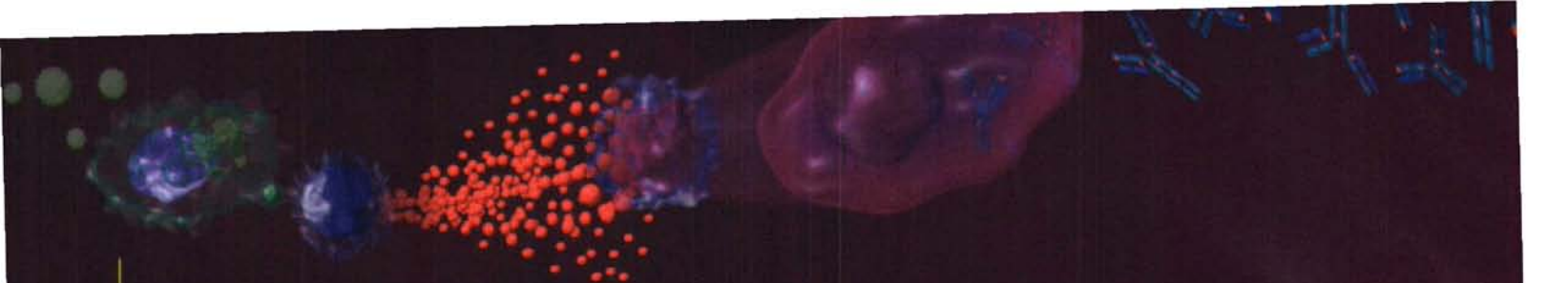
A, Patients allergic only to mites.

B, Patients allergic to mites and grass.

*Subgroups of patients reported according to periods of methacholine responsiveness assessment: 1, winter; 2, spring; 3, summer; 4, autumn.

WHY?





When it comes to asthma, why is control so often elusive?

While the pathophysiology of asthma is multifactorial—there are important links to the allergic cascade...

- Viral respiratory infections, oxidant pollutants and exposure to antigens are all associated with airway hyperresponsiveness, a hallmark of asthma¹
- Allergen-induced inflammatory responses of the respiratory system, mediated by IgE, are pivotal in many forms of asthma²
- IgE triggers the release of inflammatory mediators critical to early- and late-phase reactions of asthma and allergic rhinitis³

IgE—early and central in the allergic cascade

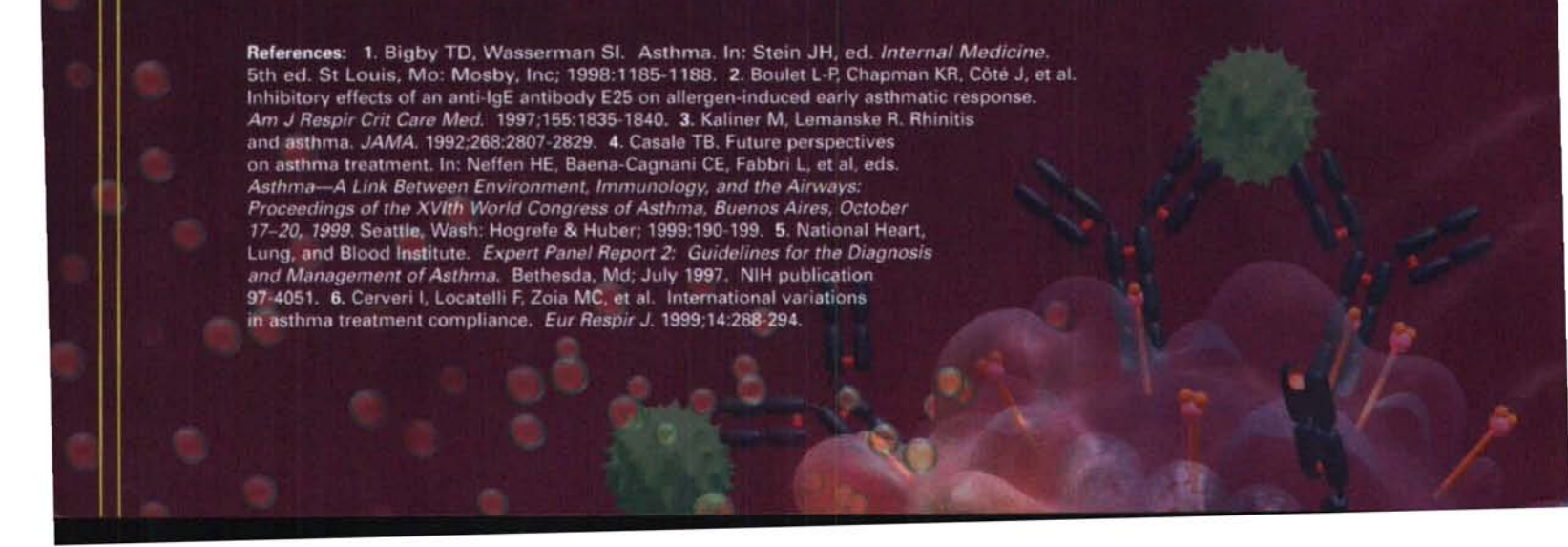
- IgE drives the events leading to the allergic cascade by initiating the inflammatory process³
- IgE binding to high-affinity receptors on mast cells and basophils helps set up response to future allergen exposure³
- IgE influences and is influenced by cytokine modulators,⁴ important components of the allergic cascade

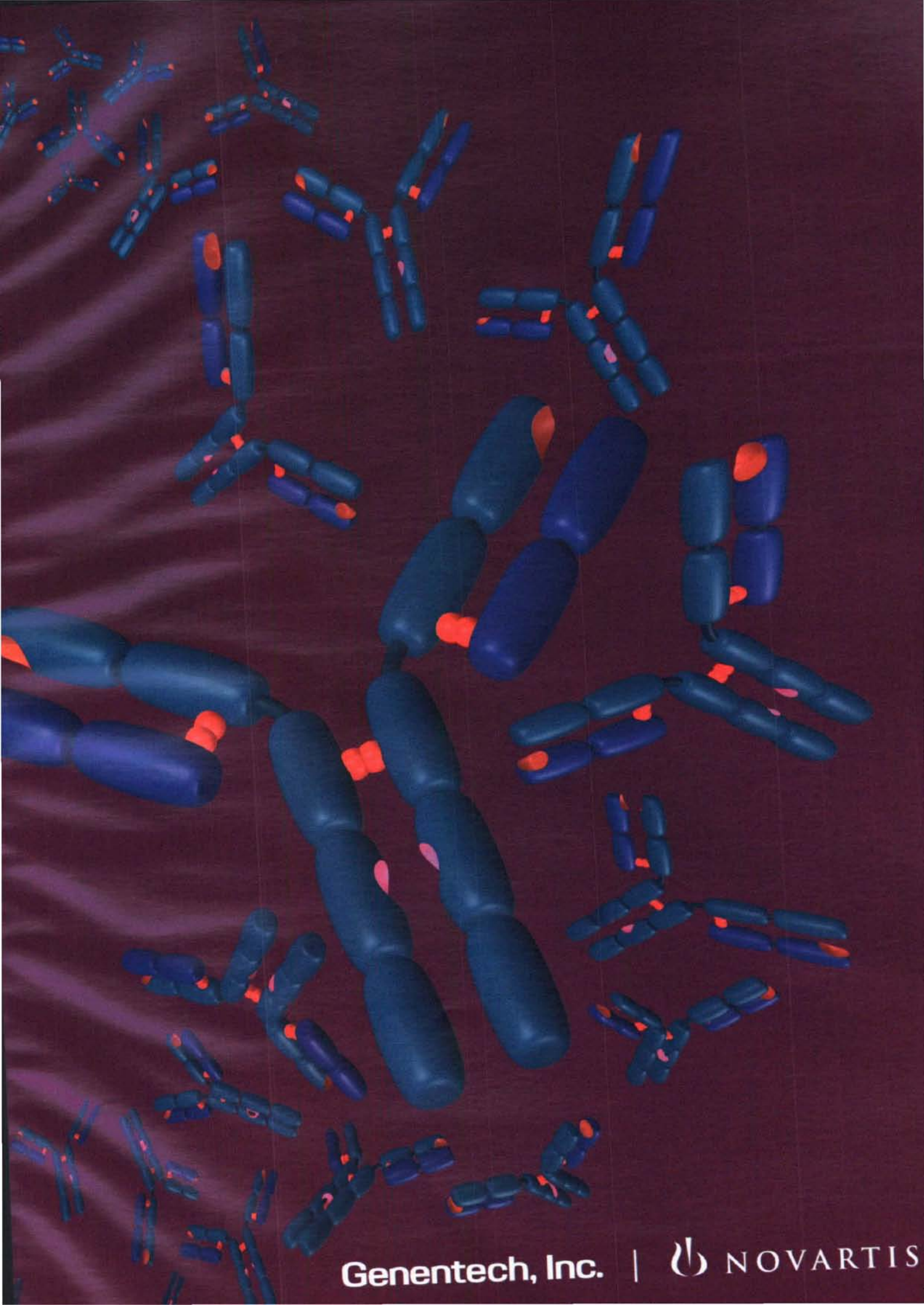
Strategies for the future

Greater understanding of IgE affords new insights—new hope...

- IgE blockers—targeting IgE—may soon afford exciting potential strategies⁴
- Cytokine modulating agents may provide different treatment options by interfering with signaling activities⁴
- Trigger avoidance and patient education and compliance with current treatment options will continue to figure prominently in enhancing asthma control^{5, 6}

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WHY?

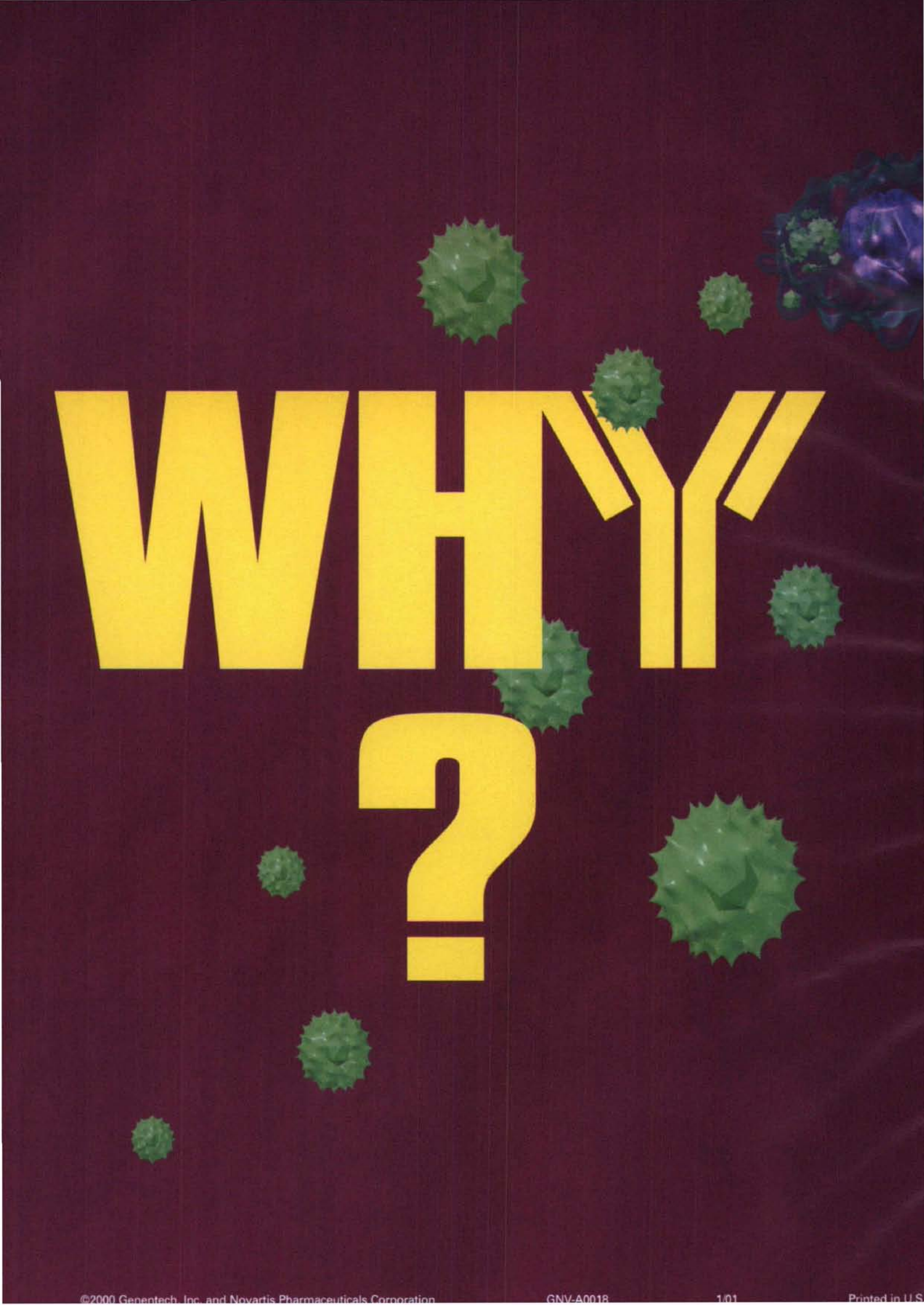


TABLE II

Baseline FEV1, Specific Sensitization, and Bronchial Responsiveness to Methacholine (Natural Logarithm PD20 FEV1) of Patients Included in the Study

Groups	FEV1 Baseline (M ± DS)	Sensitization			PD20 nat. log Methacholine
		Der	Gram	Par	
All pts	96.6 ± 10.7				
A	98.8 ± 12.1	86	0	0	
A1*	90.9 ± 9.6	33	0	0	6.10 ± 2.04
A2*	99.8 ± 11.2	13	0	0	6.74 ± 2.23
A3*	99.8 ± 11.2	14	0	0	5.44 ± 1.54
A4*	94.9 ± 7.8	26	0	0	4.54 ± 1.51
B	95.7 ± 11	79	63	49	
B1*	95.7 ± 10.4	23	17	16	6.58 ± 2.07
B2*	93.4 ± 9.1	19	14	14	5.26 ± 1.62
B3*	99.1 ± 11.1	12	12	6	4.72 ± 2.11
B4*	95.9 ± 12.8	25	20	13	5.43 ± 1.41

Multiple group analysis (ANOVA) group A: $p = 0.039$; group B: $p < 0.001$; Der: Dermatophagoides pteronissinus; Gram: pollen of "Graminae"; Par: pollen of "Parietaria Officinalis"; A: group of patients allergic only to mites; B: group of patients allergic also to pollen.

*Subgroups of patients reported according to periods of methacholine responsiveness assessment: 1, winter; 2, spring; 3, summer; 4, autumn.

those in summer (subgroup A3), winter (subgroup A1), and spring (subgroup A2) (Fig. 1). The multiple group analysis (ANOVA) showed significant mean differences between subgroups ($p = 0.039$). Statistically significant differences were also obtained when subgroup A4 (autumn) was compared to A1 (winter) ($p = 0.002$) and A2 (spring) ($p < 0.001$). Subgroup A3 (summer) showed slightly statistically significant differences when compared to A2 (spring) ($p = 0.088$) and A4 (autumn) ($p = 0.082$).

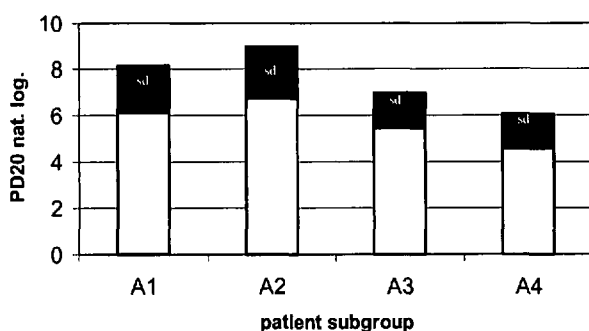


Figure 1. Mean values of the cumulative doses of methacholine, expressed as natural logarithms, in subgroups of patients allergic to mites, according to the period of methacholine responsiveness assessment (A1, winter; A2, spring; A3, summer; A4, autumn). A4 versus A1: $p = 0.002$; A3 versus A2: $p = 0.088$; A4 versus A2: $p < 0.001$; A3 versus A4: $p = 0.082$.

In group B the highest non-specific bronchial responsiveness was observed in summer (subgroup B3), followed by those in spring (subgroup B2) and autumn (subgroup B4). The non-specific bronchial responsiveness observed in winter (subgroup B1) was much lower (Fig. 2). The multiple group analysis (ANOVA) showed significant mean differences between subgroups ($p < 0.001$). When subgroups were compared individually, statistically significant differences existed only between subgroup B1 (winter) and each of the other subgroups, respectively B2 (spring) ($p = 0.029$), B3 (summer) ($p = 0.017$), and B4 (autumn) ($p = 0.028$).

DISCUSSION

Several studies underline the importance of early exposure to house dust mites for sensitization,⁸⁻¹⁰ while little is known on the level of exposure necessary to trigger symptoms in sensitized subjects.¹¹ Some data suggest that exposure to 2 µg Der p I per gram of dust leads to an increased risk of sensitization.⁸ The amount of allergen exposure necessary to trigger an asthmatic response in sensitized subjects is extremely variable, but for most of them 10 µg Der p I per gram of dust is sufficient to increase the bronchial responsiveness and provoke respiratory symptoms.^{2,3,12}

Several authors claim that bronchial hyperresponsiveness is the consequence of the inflammatory process and reflects the severity of the disease.⁸ There is a relationship between the onset of late phase reaction after a specific bronchial challenge and the sustained increase in bronchial responsiveness.¹³ The pivotal role of inflammation in the determination of bronchial hyperresponsiveness has been reported by many authors.^{14,15} The grade of bronchial hyperresponsiveness has been shown to be related to the frequency of symptoms and use of bronchodilators.^{14,16}

In genetically susceptible individuals, a critical level of allergen exposure may induce sensitization and further exposure may cause a chronic bronchial inflammation causing

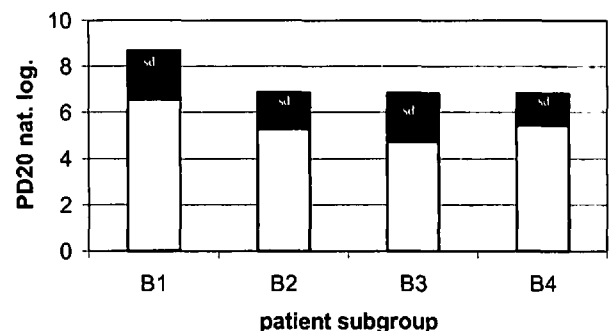


Figure 2. Mean values of the cumulative doses of methacholine, expressed as natural logarithms, in subgroups of patients allergic to mites and pollens, according to the period of methacholine responsiveness assessment (B1, winter; B2, spring; B3, summer; B4, autumn). B1 versus B2: $p = 0.029$; B1 versus B4: $p = 0.028$; B1 versus B3: $p < 0.017$.

bronchial hyperresponsiveness and the onset of symptoms.¹⁷

However, several confounding factors may affect interpretation of results leading to this model. An asthmatic attack in a sensitized individual can be triggered not only by the specific allergen, but also by non-specific factors such as ozone, passive smoking, cold air, SO₂, and rhinoviruses, especially in young patients.

The difficulty of assessing house dust mite airborne concentration has led to the majority of studies using dust concentrations of mite allergens as an indicator of potential exposure.¹⁸ The concentration of Der p I per gram of dust does not always correlate with airborne levels of allergen potentially respirable. However, a correlation between allergen dust concentration and severity of asthmatic symptoms has been described in patients allergic to house dust mites.¹⁹

The seasonal variation of house dust mite airborne concentration is less relevant than that of grass pollen, especially in the geographic areas whose climate is not affected by significant fluctuations of air humidity during the year.^{20–22} However, an increase in severity and frequency of asthmatic symptoms in patients with an allergy to house dust mites is always observed during the months with the highest air humidity (autumn in temperate climates).

Changes in bronchial responsiveness of house dust mite-allergic subjects are described in relation to the seasonal differences in allergen exposure.⁸ It was recently shown that the non-specific bronchial responsiveness of patients allergic to house dust mites increased in autumn, when the highest allergen concentration was estimated in the reservoir of house dust mites; Der p I concentration increased in parallel to the highest air humidity observed in that period.²³ The increase of bronchial responsiveness was also accompanied by a rising number of blood eosinophils in the same period, supporting the possibility that eosinophilic inflammation may be involved in the bronchial hyperresponsiveness.²³ Other studies did not confirm these data, probably because they were carried out in geographic areas with very high air humidity all year round, so that the seasonal changes of allergen concentration in the house dust mite reservoir are usually not significant.²⁴

Our results show the seasonal variability of non-specific bronchial responsiveness of house dust mite-allergic patients. In the group of patients allergic only to house dust mites (group A), we observed the highest levels of non-specific bronchial responsiveness in September–November (A4) and the lowest in March–May (A2). Statistically significant differences were found when PD₂₀ values of the autumn subgroup were compared with those of other seasons (Student's *t*-test and ANOVA).

Different results were found in patients sensitized not only to house dust mites but also to grass pollen, as wider changes of bronchial responsiveness are due to the seasonal variation of grass pollen airborne concentration.

The continuous allergen exposure in sensitized individuals plays a pivotal role in maintaining the bronchial chronic inflammation. Presumably bronchial responsiveness is affected by the level of exposure, which is strictly dependent on the allergen concentration in the reservoir within homes. Preventive measures aimed at lowering house dust mite allergen levels should be carried out, as it has been shown that bronchial hyperresponsiveness of allergic patients may improve.²⁵ The efficacy of the current methods (mechanical, physical, and chemical) to reduce house dust mite infestation is certainly influenced by climatic conditions, particularly air humidity. Therefore, specific measures to decrease humidity level in homes should be utilized to reduce the house dust mite concentration.

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