

Immunotherapy with cat- and dog-dander extracts

IV. Effects of 2 years of treatment

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Thirty-five patients (20 children and 15 adults) with animal-dander asthma completed 2 years of immunotherapy with partly purified and standardized cat- or dog-dander extracts. The first year of the study was performed double-blind with a placebo-treated control group. These 15 patients were transferred to active treatment for a second year. All patients were followed by use of the skin prick test (SPT), allergen and histamine bronchial challenges, and tests for allergen-specific IgE, IgG1, and IgG4 levels. In the group treated with active extracts for 2 years (group A), the previously reported decrease in bronchial responsiveness to cat extract ($p < 0.001$) and histamine ($p < 0.01$) was even more pronounced after the second year. After 1 year of active treatment in the original placebo group (group B), a significant decrease in the bronchial responsiveness to cat extract was noted ($p < 0.001$). The responsiveness to histamine was decreased only in the patients treated with cat-dander extracts ($p < 0.05$). A significant decrease in the SPT ($p < 0.001$) and an increase in the allergen-specific IgE ($p < 0.001$) and IgG4 ($p < 0.001$) was also noted in patients (group B) treated with cat-dander extracts. The side effects in the two groups (A and B) were negligible, except for some systemic side effects, especially among the children during the initial phase of immunotherapy. The symptoms were mild and responded promptly to treatment. The fact that the clinical and immunologic changes after 1 year of active treatment are the same in the B group as in the A group suggest that the matching and randomization procedures were adequate and that the previously reported successful treatment in the A group was achieved by hyposensitization and was not a chance finding. This conclusion is further supported by the fact that the second year of treatment in the A group resulted in an even more pronounced tolerance to histamine and allergen. (*J ALLERGY CLIN IMMUNOL* 1989;83:37-44.)

The introduction of characterized and standardized animal-dander allergen preparations¹ has made it possible to use immunotherapy successfully in patients with animal-dander asthma. The beneficial effects of short-term immunotherapy with these preparations in cat- and dog-dander asthma have been demonstrated in several studies during the last few years.²⁻⁶ However, no studies on the long-term effects of immunotherapy with standardized animal-dander extracts have been published.

In this study we report the results of 2 years of

Abbreviations used

HEP:	Histamine equivalent prick
CRIE:	Crossed radioimmuno-electrophoresis
PEF:	Peak expiratory flow
PC ₂₀ :	Provocation concentration of allergen or histamine causing a 20% decrease in PEF rate
HCT:	Histamine challenge test
ACT:	Allergen challenge test
SPT:	Skin prick test
SSE:	Systemic side effects
LSE:	Local side effects
SQ:	Arbitrary unit for a biologically standardized, partially purified allergen extract

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treatment with a standardized cat/dog-dander allergen preparation in patients with animal-dander asthma. The study was performed double blind placebo controlled during the first year. The patients in the

TABLE I. Demographic data in the two treatment groups (A group, allergen treatment for 2 years; B group, placebo treatment 1 year and allergen treatment 1 year)

	A group	B group
Duration of treatment (mo)	24	12
Children/adults	12/8	8/7
M/F	10/10	8/7
Age (yr) range	8.4-47.0	7.8-35.7

placebo-treated group were then transferred to active treatment during the second year.

PATIENTS AND METHODS

Forty-five patients (20 children and 25 adults) with cat and/or dog asthma were selected for immunotherapy with standardized cat/dog-dander extract. The study was performed double blind in the first year with matched pairs stratified with respect to sex, age, clinical history, and the results of bronchial challenge and IgE specificities in cat/dog CRIE. The two treatment alternatives (see below) were randomly allocated within the pairs. During the randomization and during the first year of treatment, six patients dropped out of the study, leaving 39 patients for final evaluation. When the code was broken after 12 months of treatment, 22 patients were found to belong to the allergen-treated group (15 cat-allergen and seven dog-allergen treated) and 17 patients to the placebo-treated group (12 cat-allergic, placebo treated and five dog-allergic, placebo treated).

Demographic data concerning the original patients and the results of the first year of treatment have been published elsewhere.⁵

Patients who received allergen (A group) during the first year were offered a further 2 years of treatment. During the second year, two patients, both adults (one treated with cat-dander extracts and one treated with dog-dander extracts), did not continue their immunotherapy (for personal reasons) and were considered as dropouts.

The 17 patients who received placebo (B group) during the first year were offered to be transferred to allergen treatment for 3 years. Two patients, both adults and cat-allergic, chose not to continue and are also considered as dropouts.

This left 35 patients (20 children and 15 adults) to be evaluated 2 years after the beginning of the study. Demographic data are presented in Table I.

The two treatment groups (A group, allergen for 2 years; B group, placebo for 1 year and allergen for 1 year) were characterized before the start of the immunotherapy and after 12 and 24 months with respect to SPT, ACT, HCT, allergen-specific IgE (CRIE and RAST), and allergen-specific IgG1 and IgG4.

Extracts

Partly purified, that is, excluding non-IgE-binding components, and standardized allergenic extracts of cat and dog dander were used. The extracts used for treatment, SPT, bronchial challenge, and for in vitro investigations were all identical in composition and from the same batch, as previously described.^{5,7} The contents of *Fel d* I (former cat Ag 4 or cat Ag 1) and Ag 3 (cat albumin) in the cat-dander extract were 43 and 468 pg per SQ unit, respectively, assuming 1 µg cat Ag 1 to be equal to 1 Ohman et al.³ unit. The content of Ag 2 (dog albumin) in the dog-dander extracts was 760 pg per SQ unit.^{5,7}

Placebo extracts containing various concentrations of histamine (Kabi Vitrum, Stockholm, Sweden) simulating Alutard SQ (ALK, Copenhagen, Denmark) cat or dog extracts were used during the first year of treatment in the B group. The compositions of the placebo extracts have been described elsewhere.⁵

Dosage

Immunotherapy in adults was carried out with aluminum hydroxide-adsorbed extracts (Alutard SQ) with weekly injection starting at a dose of 30 SQ units. The dose was then increased stepwise to an ideal maximum dose of 100,000 SQ units. When the individual maximum dose was reached, it was considered to be the maintenance dose and administered every fourth week.

The children were hospitalized for 1 to 2 weeks when they were treated with rush hyposensitization with water-soluble extracts, Aquagen SQ (ALK, Copenhagen, Denmark). The initial dose was 0.1 SQ unit, which was increased stepwise to an ideal maximum dose of 80,000 SQ units. The children initially received five to seven injections daily, but at higher concentrations the number of injections was reduced to two to three daily. After the individual maximum dose was reached, depot extracts (Alutard SQ) were administered in the outpatient ward once a week. When the maintenance dose was reached, the injections were administered every fourth week.

The patients (adults and children) in the A group continued to receive a maintenance dose every fourth week, while the patients (adults and children) in the B group were switched to allergen after the first year. They then received their injections according to the dose regimens described earlier.

SPT

SPTs were performed with titrations, with allergen concentrations of 0.1, 0.3, 1, 3, and 10 HEP. All patients were tested before starting immunotherapy and again after 12 and 24 months. Histamine hydrochloride (1 mg/ml) and the allergen diluent served as positive and negative controls, respectively. A wheal of at least 2 mm was regarded as a positive reaction. A mean wheal diameter was calculated with the mean of the largest diameter and the largest perpendicular diameter. The tests were performed single with both cat- and dog-dander extracts at each time. The same trained nurses performed all the tests throughout the study.

ACT

The specific bronchial responsiveness was measured by use of inhalations of cat- and dog-dander extract (Aquagen SQ). The allergens were inhaled from a demand-type nebulizer (DeVilbiss No. 40 [DeVilbiss Co., Somerset, Pa.], nominal particle size 0.3 to 2 μm , 0.16 ml of solution per minute), driven by an air pump. One milliliter of the test solution was inhaled during 5 to 6 minutes. The challenge, starting with saline inhalation (9 mg/ml), was followed by the inhalation of the allergen at a concentration of 10^{-3} HEP per milliliter. The allergen concentration was then increased tenfold at each challenge dose up to a maximum concentration of 10 HEP per milliliter. PEF was measured 5 and 15 minutes after inhalation with a Wright peakflow meter, and the interval between the various concentration steps was 15 minutes. The allergen PC₂₀ was obtained from the log dose-response curve by linear interpolation of the last two points.

All challenges were performed at the same time of the day.

HCT

The nonspecific bronchial sensitivity was measured by HCT according to the method of Cockcroft et al.⁸ The histamine aerosol was inhaled from the same type of nebulizer (DeVilbiss No. 40) as described above. The challenge was started with saline inhalation (9 mg/ml), after which the histamine aerosol (histamine hydrochloride) was inhaled (in 10 normal breaths) in increasing concentrations, starting with a concentration of 0.0625 mg/ml. The maximum histamine concentration used was 32 mg/ml. The interval between the inhalation of each successive histamine concentration was approximately 5 minutes, and the histamine concentration was doubled each time. PEF was measured immediately and again 5 minutes after each inhalation. The best of three PEF measurements was used in the calculation. Histamine challenge was continued until PEF had been reduced by at least 20% relative to the value after saline inhalation or until the subject experienced discomfort, such as coughing or dyspnea. The result was expressed as PC₂₀. The histamine challenge was always performed at least 1 week before the allergen challenge and at the same time of day.

In vitro tests

Specific IgE- and IgG-levels. Serum-specific IgE was measured by RAST technique, as described in an earlier article.⁶

Serum-specific IgG1 and IgG4 levels were all simultaneously measured by performing a radioimmunoassay similar to the RAST technique and with the patients' immunoglobulin fractions obtained as previously described.⁶ The anti-IgG1 and anti-IgG4 were gifts from Dako, Copenhagen, Denmark, and were raised in rabbits with the relevant human myeloma immunoglobulin fractions. The antibodies were labeled by the chloramine-T method. All the antibodies used were demonstrated to be subclass specific.

TABLE II. Doses (in micrograms) of the antigens administered to the two study groups

	A group	B group
<i>Fel d 1</i>		
First year		
N	15	12
Mean $\pm$ SD	42 $\pm$ 16	—
Range	13 – 65	—
Second year		
N	14	10
Mean $\pm$ SD	32 $\pm$ 13	27 $\pm$ 14
Range	8 – 52	1.2 – 49
Cat albumin		
First year		
N	15	12
Mean $\pm$ SD	452 $\pm$ 170	—
Range	140 – 705	—
Second year		
N	14	10
Mean $\pm$ SD	347 $\pm$ 139	300 $\pm$ 157
Range	80 – 561	13 – 537
Dog albumin		
First year		
N	7	5
Mean $\pm$ SD	885 $\pm$ 149	—
Range	686 – 1068	—
Second year		
N	6	5
Mean $\pm$ SD	613 $\pm$ 68	697 $\pm$ 70
Range	527 – 698	621 – 783

N, Number of patients.

The data in the children and adults are considered together in their respective groups.

All analyses were performed in duplicate, and the mean values were used. Errors in the analysis for the individual allergen extracts range from 10% to 20% relative deviation. The results were listed as percent of total activity added in the radioimmunoassays.

Statistical methods. All values were log transformed before calculations. The Student's *t* test for paired samples was used for testing changes in dosages, SPT, ACT, HCT, IgE, and IgG levels within the groups and for two samples for testing changes in the same parameters between the groups. When changes in specific and nonspecific bronchial sensitivity were compared with changes in SPT, RAST, and IgG subclasses, the nonparametric Spearman rank correlation test was used.

RESULTS

Dosage

There were no significant differences between adults and children regarding the total doses of cat- and dog-dander extracts administered during the first

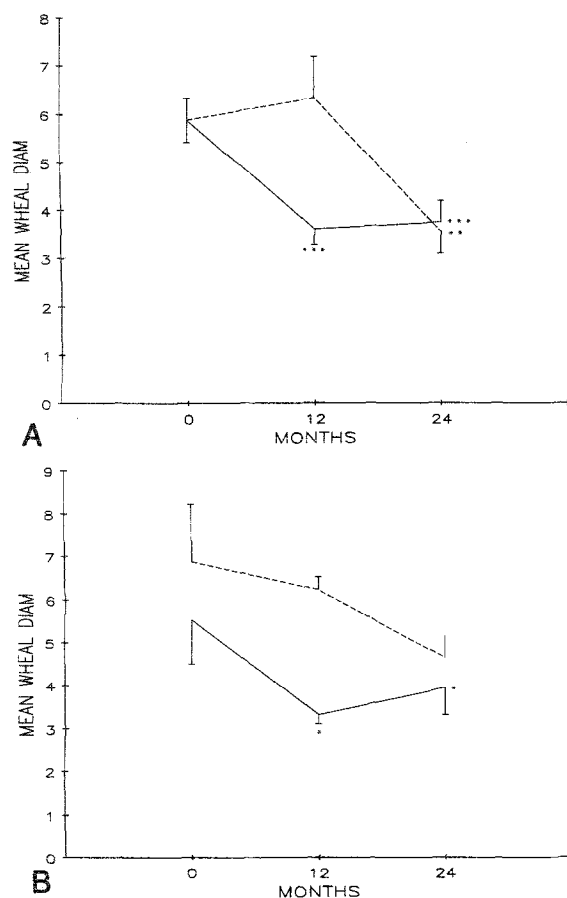


FIG. 1. A, Wheal diameter in the A group (unbroken line) and the B group (interrupted line) with cat allergen (3 HEP). Mean $\pm$ SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. **B,** Wheal diameter in SPT in the A group (unbroken line) and the B group (interrupted line) with dog allergen (3 HEP). Mean $\pm$ SEM. * $p < 0.05$.

and second years of treatment. Consequently, the data in the adults and the children in the different study groups were considered together.

The doses of the antigens (*Fel d* I, cat albumin, and dog albumin) administered to the A group (adults and children) and B group (adults and children) are presented in Table II.

In the A group, less allergen was administered during the second treatment year (cat, $p < 0.05$; dog, $p < 0.05$). The doses of cat-and dog-dander allergen in the B group were also lower than in the first year in the A group.

SPTs

The decrease in mean wheal diameters for patients treated with cat dander extract in the A group after the first year ($p < 0.001$) remained unchanged after

TABLE III. Allergen challenge (cat or dog) in the A and B groups after 0, 12, and 24 months of immunotherapy

Mo of treatment	Allergen challenge	
	Cat	Dog
A group		
0	0.03 $\pm$ 1.62	0.03 $\pm$ 2.04
12	0.33 $\pm$ 1.91***	0.08 $\pm$ 2.45
24	0.93 $\pm$ 1.7***	0.2 $\pm$ 1.35*
B group		
0	0.09 $\pm$ 1.55	0.02 $\pm$ 2.95
12	0.04 $\pm$ 1.55	0.03 $\pm$ 2.51
24	0.35 $\pm$ 1.48***	0.19 $\pm$ 3.3

Presented as log PC₂₀ allergen (HEP); mean $\pm$ SEM.

* $p < 0.05$ compared to pretreatment values.

** $p < 0.01$ compared to pretreatment values.

*** $p < 0.001$ compared to pretreatment values.

2 years of treatment. The results of SPT with an allergen concentration of 3 HEP are illustrated in Fig. 1, A. In the B group, there was no change in SPT the first year (placebo-treatment year), but after 1 year of treatment with cat-dander extract, the changes were the same as in the A group ($p < 0.01$). The slight decrease in mean wheal diameters in patients treated with dog-dander extract in the A group after 1 year of treatment persisted after the second year with no significant change (Fig. 1, B). In the B group, there was also a slight but not statistically significant decrease in SPT after 1 year of active treatment with dog-dander extracts.

Baseline values for PEF

Baseline peak flow rates before the histamine and allergen challenges remained constant throughout the study in both groups. (In the A group, the mean value was 87.2% of predicted, and in the B-group, the mean value was 89% of predicted). There was no significant difference between the allergen- and placebo-treated groups with respect to baseline pulmonary function in any of the six challenges (allergen and histamine after 0, 12, and 24 months of treatment).

ACTs

PC₂₀ in the patients treated with cat-allergen in group A increased significantly after 12 and 24 months of treatment ($p < 0.001$; Table III). These patients tolerated 11 times more cat allergens after 12 months and 31 times more allergen after 24 months of treatment than at the start. In the dog-allergen treated pa-

TABLE IV. Histamine challenge in the A and B groups after 0, 12, and 24 months of immunotherapy

Mo of treatment	Histamine challenge	
	Cat-allergen treated	Dog-allergen treated
A group		
0	0.72 ± 1.38	1.58 ± 1.66
12	1.48 ± 1.45**	1.66 ± 1.82
24	2.57 ± 1.51**	1.9 ± 1.38
B group		
0	1.91 ± 1.55	1.12 ± 1.51
12	1.26 ± 1.41	1.1 ± 1.38
24	2.19 ± 1.66*	1.12 ± 1.55

Presented as log PC₂₀ histamine (milligrams per milliliter); mean ± SEM.

**p* < 0.05 compared to pretreatment values.

***p* < 0.01 compared to pretreatment values.

****p* < 0.001 compared to pretreatment values.

tients in group A, there was an increasing, although it was not statistically significant, tolerance after 12 months of treatment. After 2 years of treatment, there was a further increase in tolerance (*p* < 0.05). In the B group, no changes were observed at the end of the placebo-treatment year, but when the patients were transferred to active treatment, the tolerance increased but only significantly in cat-allergen treated patients (*p* < 0.001).

A comparison of the two cat-allergen treated groups (allergen and placebo) revealed no differences in PC₂₀ before treatment, but after 12 months, the difference was statistically significant (*p* < 0.05). However, after the treatment was changed to allergen in the B group, no difference between the two groups was observed. Comparison of the two dog-allergen treated groups, however, revealed no significant differences.

HCTs

After 12 months, the cat-allergen treated patients in group A increased their tolerance for histamine (*p* < 0.01), and this increase was even more pronounced at 24 months, although the change was not statistically significant between 12 and 24 months (Table IV). In the dog-allergen treated patients in group A, there was a slight, but not significant, increase in tolerance at 12 and 24 months. The B group did not change during the placebo-treatment year. However, when the treatment was changed to allergen,

TABLE V. Specific IgE levels to cat and dog allergen expressed as percent of total activity in the two treatment groups after 0, 12, and 24 months of immunotherapy

Mo of treatment	IgE levels	
	Cat-allergen treated	Dog-allergen treated
A group		
0	7.32 ± 1.11	9.69 ± 2.13
12	10.5 ± 1.42**	9.4 ± 1.5
24	11.1 ± 2.24**	13.1 ± 2.68
B group		
0	5.85 ± 0.97	12.4 ± 1.47
12	6.4 ± 1.52	11.0 ± 2.89
24	22.7 ± 2.65***	22.8 ± 2.83***

Mean ± SEM.

**p* < 0.05 compared to pretreatment values.

***p* < 0.01 compared to pretreatment values.

****p* < 0.001 compared to pretreatment values.

the cat-allergen treated group increased their tolerance to histamine (*p* < 0.05). No changes occurred in the dog-allergen treated group.

Specific IgE levels

In the cat-allergen treated group, specific IgE levels to cat allergen increased after 1 year of treatment (*p* < 0.01), and there was a further slight increase after 2 years of treatment (Table V). In the dog-allergen treated group, there was also a slight, although it was not statistically significant, increase after 2 years of treatment. In the B group, there was no change in specific IgE levels for cat or dog allergen during the first year, but when the treatment was changed to allergen, the concentration of specific IgE increased significantly in both the cat-allergen and the dog-allergen treated groups (*p* < 0.001).

Specific IgG levels

IgG4 levels increased in the A group during the first year, and after 12 months the levels were significantly increased (cat, *p* < 0.001; dog, *p* < 0.01; Table VI). During the second year the IgG4 levels further increased. In the B group the IgG4 levels increased (*p* < 0.001) when placebo was changed to allergen treatment in both cat- and dog-allergen treated patients.

The cat-allergen treated patients in the A group demonstrated no increase in IgG1 levels during the first year, but after 24 months of treatment, the levels

TABLE VI. IgG1 and IgG4 levels to cat and dog allergen in the two treatment groups after 0, 12, and 24 months of immunotherapy

Mo of treatment	Cat-allergen treated	Dog-allergen treated
IgG1		
A group		
0	19.1 ± 2.36	28.46 ± 3.96
12	18.7 ± 2.83	32.26 ± 4.03**
24	29.7 ± 1.06***	28.67 ± 2.44
B group		
0	17.1 ± 3.01	33.2 ± 1.26
12	17.1 ± 2.99	31.48 ± 0.67
24	30.28 ± 0.9***	26.9 ± 1.41
IgG4		
A group		
0	14.1 ± 3.3	31.0 ± 3.02
12	24.3 ± 5.5***	42.7 ± 3.83**
24	48.4 ± 1.4***	49.8 ± 1.99**
B group		
0	15.8 ± 3.98	31.9 ± 5.16
12	14.6 ± 3.51	38.48 ± 2.61
24	34.5 ± 4.44***	44.0 ± 4.44***

Percent of total activity added in the radioimmuno assay; mean ± SEM.

* $p < 0.05$

** $p < 0.01$ compared to pretreatment values.

*** $p < 0.001$ compared to pretreatment values.

were significantly increased ($p < 0.001$). A similar change was observed in the B group.

In the dog-allergen treated groups, only slight changes in specific IgG1 occurred.

Correlation between in vitro and in vivo results

No correlations were found between the outcome of bronchial challenges and the results of the SPT, RAST, and IgG subclasses.

Side effects

Children. During rush hyposensitization, there were no SSE (bronchial asthma or urticaria) at lower doses (<1000 SQ). However, all the children developed mild SSE in the dose range of 1,000 to 10,000 SQ (Table VII). During maintenance therapy, there were a few SSE (predominantly cat-allergen treated patients) with doses of 1,000 to 100,000 SQ.

Two children, one in the A group and one in the B group, reacted repeatedly to cat-allergen treatment in the 1,000 to 10,000 SQ dose range and were unable to reach the 10,000 to 100,000 SQ dose range.

No local LSE (induration >3 cm) were observed during rush hyposensitization. Two children (one in the A and B group, respectively) developed LSE during maintenance therapy with cat extracts at doses between 10,000 to 100,000 SQ.

The number of SSE during rush hyposensitization was 44 (a total of 575 injections, 7.7%), and during maintenance treatment, 20 (a total of 400 injections, 5%). The corresponding values of LSE among the children during maintenance treatment was 0.7% (three of 400 injections).

Adults. LSE and SSE were rare in both groups. SSEs were mild, they responded promptly to treatment, and they did not interfere with the dose schedules (Table VII).

In the B group, one patient reacted during cat-allergen treatment with SSE and LSE at 100 to 1000 SQ and was unable to reach a higher concentration (Table VII).

The frequency of SSE with active extracts during dose increase and maintenance treatment in adults was 4% (18 of 443 injections). The frequency of LSE was only 0.5% (two of 411 injections).

DISCUSSION

In earlier studies^{5,6} we reported a decrease in bronchial responsiveness to cat allergen and histamine, a reduced skin sensitivity, and favorable subjective and objective changes in well-being after 1 year of treatment. The aim of the present study was to determine whether the beneficial effects on bronchial responsiveness to allergen and histamine after the first year of allergen treatment were maintained during a second year of immunotherapy. Moreover, by evaluating the in vitro and in vivo parameters in the B group when placebo was changed to allergen, it should be possible to confirm further both the effect of treatment and the reliability of the matching procedure.

The matching procedure, including CRIE,⁹ appeared to be adequate, since the patients in the B group during allergen treatment responded like the A group to the in vivo and the in vitro parameters. This will be discussed later. CRIE appears to be of great value in matching patients for immunotherapy studies, since individual IgE specificities can be studied in detail.¹⁰ It is also a useful tool for determining whether new IgE specificities appear during treatment.⁷ This was not the case in any of the patients in this study (to be published).

The dose schedules for the children and the adults were slightly different, as described previously. However, the allergen doses administered to the children and the adults were of the same magnitude during the first 2 years. The specified differences in allergen

TABLE VII. Number of patients demonstrating SSE in connection with allergen injections

Allergen dose range (SQ units)	A group		B group			
	Allergen therapy		Placebo therapy	Allergen therapy		
	Cat	Dog		Cat	Dog	
	N = 8	N = 4	N = 8	N = 6	N = 2	
Children during rush hyposensitization						
0.1-1,000	—	—	—	—	—	
10,00-10,000	3	—	1	2	1	
10,000-10,0000	8	4	4	4	2	
Children during maintenance treatment with depot extract						
1,000-10,000	1	—	—	1	—	
10,000-100,000	2	—	—	1	—	
Adults during dose increase and during maintenance treatment with depot extract						
	N = 7	N = 3	N = 9	N = 4	N = 3	
10-100	1	—	1	—	—	
100-1,000	—	—	—	1	—	
1,000-10,000	—	—	—	—	—	
10,000-100,000	3	—	3	1	—	

doses in the A group during the first and second years of treatment are a consequence of the rush hyposensitization in the children at the start of the immunotherapy, since a clustered therapy schedule results in a higher total dose. In the B group, in spite of the clustered schedule, the total doses of cat and dog allergens were less than in group A during the first year. This may be a consequence of increased experience that leads to fewer injections and a decrease in the total dose.

SSEs occurred in all the children during rush hyposensitization with allergen extracts. During maintenance treatment, there were few SSEs both in children and adults. However, the SSEs were mild and responded promptly to treatment. Two children and one adult reacted repeatedly with SSEs at low doses, 100 to 10,000 SQ, and were unable to reach an ideal maintenance dose. This underlines the importance of individualization of the immunotherapy. Since the children in the B group during rush hyposensitization reacted like the children in the A group with SSEs at doses >10,000 SQ, this finding confirms that rush hyposensitization should be interrupted at doses >10,000 SQ. This was proposed in an earlier article.⁵

The occurrence of SSEs among all the patients, children and adults, during maintenance treatment was 3.9% (26 of 660 injections). This figure is somewhat lower than in other studies.^{11, 12}

The decreased bronchial responsiveness to allergen and histamine observed in both groups after treatment with cat allergen indicates a close relationship between specific and nonspecific bronchial responsiveness in

patients with asthma. It appears reasonable that the allergic inflammation of the bronchial mucosa also increases the sensitivity to histamine and naturally occurring nonspecific agents also reported by other investigators.¹³ In the same way, treatment of the inflammation, either directly by pharmacologic means or indirectly by allergen elimination¹⁴ or immunotherapy, will produce a favorable effect. In perennial asthma the strict avoidance of allergen exposure (i.e., to molds or mites) may be impossible and therefore the inflammatory reaction in the bronchi may remain unchanged. Immunotherapy may therefore even increase the nonspecific bronchial sensitivity that has been demonstrated in some studies.¹⁵

To influence the inflammatory reaction in the bronchi, it is possible that immunotherapy should be continued during a certain period of time. In this study the decrease in histamine sensitivity was noticed after 9 months of treatment, and a further reduction was observed as the treatment continued. In other studies, where a purified cat allergen was used for immunotherapy during 4 to 6 months, no effect on nonspecific sensitivity was noticed.^{2, 3}

Since no dogs or cats were allowed in the patients' homes and dust analyses demonstrated very low allergen contents,⁷ another explanation for the improvement in nonspecific sensitivity could quite simply be a lower exposure level. However, the elimination of allergen exposure could not have been the only reason for increased tolerance to histamine and allergen. In the placebo-treated group in which the allergen exposure was the same as in the active-treated group,

no changes were observed during the first placebo-treatment year, but when the treatment was changed to allergen, the decrease in allergen and histamine responsiveness was the same as in the active-treated group. Therefore, it appears reasonable to attribute the decrease in responsiveness to the immunotherapy, and furthermore, it is likely that a dose-response relationship develops as the treatment continues. The fact that the B group increased their tolerance also during active treatment indicates that the A and B groups had identical immunologic responses and that the matching procedure had been done in an adequate way.

In the patients treated with dog-dander extracts, there was a small increase in bronchial allergen tolerance after 1 and 2 years of treatment in the A and B groups, respectively. However, this increase did not appear to be of clinical importance. The histamine responsiveness did not change significantly nor did the skin sensitivity. Although the allergen doses, measured as SQ units, were about the same in patients treated with cat- and dog-dander extracts, the bronchial and skin sensitivity decreased less in the group treated with dog-dander extract. This may have been caused by a less potent dog extract. An observation in favor of this is that the patients treated with dog-dander extracts had a lower number of SSEs and LSE than those treated with cat-dander extracts. However, although the IgE and IgG levels changed during treatment with dog-dander extracts, this does not appear to be closely related to the skin and bronchial sensitivity. This finding is in agreement with a lack of correlation between the in vivo and in vitro parameters in the patients who were successfully treated with cat-dander extracts.

In conclusion, we found that immunotherapy with a partly purified and standardized cat-allergen extract reduced bronchial sensitivity to both allergen and non-specific stimuli. The effect of immunotherapy with dog-dander extracts was less convincing. Furthermore, the favorable effect noticed in our study and in other studies after short-term treatment appears to be even more pronounced when therapy with hyposensitization is extended to 2 years. Side effects were rare, they were usually mild, and they responded promptly to treatment.

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