

Immunotherapy with cat- and dog-dander extracts

V. Effects of 3 years of treatment

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The effect of a 3-year course of cat or dog immunotherapy (IT) was evaluated in 32 patients with a history of asthma on exposure to cat or dog. Twenty-one subjects (14 children and seven adults) received cat IT and 11 subjects (six children and five adults) received dog IT. Bronchial challenges with allergen and histamine were performed once a year. Specific IgE, IgG1, and IgG4 were measured, and skin prick tests were done in connection with the challenges. Allergen sensitivity decreased significantly in both treated groups ($p < 0.001$ and $p < 0.05$ in the cat-allergen and dog-allergen treated groups, respectively). Bronchial hyperreactivity measured by the provocative concentration of histamine causing a 20% decrease in peak expiratory flow in the cat-allergen treated patients ($p < 0.001$) but not in the dog-allergen treated patients. Skin sensitivity decreased in both groups ($p < 0.01$ and $p < 0.05$), whereas specific IgE increased initially but dropped to the pretreatment level during the second year. Specific IgG1 and IgG4 increased during the first and second year in the cat-allergen treated group ($p < 0.01$ and $p < 0.001$), whereas only IgG4 increased in the dog-allergen treated group ($p < 0.01$). Five cat-allergen treated children and one of the adults who completed 3 years of therapy had mild systemic reactions. We conclude that cat IT ameliorated bronchial allergen sensitivity and bronchial hyperreactivity and resulted in an adequate antibody response. Dog IT was less efficacious but led to attenuation of bronchial allergen sensitivity. (J ALLERGY CLIN IMMUNOL 1991;87:955-64.)

Animal dander is a common cause of allergy in adults and children with asthma. Furred pets are abundant. About 60% of families with schoolchildren in Sweden have one or more furred pets.¹ Complete avoidance of exposure to animal dander is thus virtually impossible to achieve. Cats and dogs are major causes of allergy to animal dander. The primary measure to take, when allergy is present, should be elimination of the offending animal or any furred pet in the home of the patient. It is, however, often difficult to avoid temporary contacts or indirect exposure to cat and/or dog dander. IT, together with pharmacotherapy, could therefore be an adequate combination for treatment of allergic patients. In short-term studies of cat IT by Taylor et al.² and Ohman et al.³ beneficial effects on bronchial allergen sensitivity have been ob-

Abbreviations used

HEP:	Histamine-equivalent prick
Cum dose:	Cumulative dose of allergen received during 3 years
SPT:	Skin prick test
ACT:	Allergen challenge test
HCT:	Histamine challenge test
PC ₂₀ :	Provocative concentration of allergen (HEP) or histamine (milligrams per milliliter) causing a 20% decrease of peak expiratory flow
SSE:	Systemic side effects
IT:	Immunotherapy
BHR:	Bronchial hyperreactivity
Ab:	Antibody
PEF:	Peak expiratory flow

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served. Another study by Van Metre et al.⁴ has further established that cat IT ameliorates symptoms of asthma after exposure to cats.⁴ In a previous article on the present study, we have demonstrated decreasing bronchial and skin sensitivity to cat allergen after 1 year of cat IT.^{5,6} We have also reported attenuation

TABLE I. Demographic data in the two groups that completed 3 years of therapy and in the dropouts

	Allergen-treated groups		Dropouts
	Cat	Dog	
No.	21	11	8
Children/adults	14/7	6/5	0/8
Age range (yr)	9-47	11-36	18-48

of bronchial sensitivity to dog allergen in dog IT-treated patients after 2 years of treatment.⁷ BHR measured by repeated histamine challenges decreased in our cat-allergen treated patients after only 1 year of therapy. No effect on BHR was observed in the other previously mentioned cat-IT studies.²⁻⁴ We now report the results of 3 years of IT with cat and dog extracts focusing in particular on the effect on BHR.

MATERIAL AND METHODS

Of the initially 40 patients who started receiving therapy, 21 cat-allergen treated (14 children and seven adults) and 11 dog-allergen treated subjects (six children and five adults) completed 3 years of therapy. Demographic data of these 32 subjects and the eight dropouts are presented in Table I.

Of patients who left the study, one cat-allergen treated adult developed laryngeal edema after the first injection at the maintenance level and withdrew. Three adults declined a second year of therapy. One of the adults was a dog IT-treated woman who developed recurrent asthma after several of the injections; the other two adults belonged to the placebo-treated group and thus did not receive any active treatment. Four patients left the study during the second year of treatment, two of these patients because of SSEs. Both adults were treated with the cat extract. One adult had four systemic reactions, including one with urticaria asthma and transient hypotension, the other adult had a single asthmatic reaction. Thus, three adults in the cat-allergen treated group and one adult in the dog-allergen treated group left the study because of occurrence of systemic reactions. All eight adults who withdrew from the study had histories of asthma and pharmacotherapy comparable to those patients who remained in the study. Likewise, pretreatment skin sensitivity and bronchial sensitivity to allergen and histamine were not significantly different in the dropouts, which is illustrated for the cat-allergen treated group in Table II.

The study design was double-blind and placebo-controlled the first year. The results have been published elsewhere.^{5,6,8} During the second year, the placebo-treated group was administered active extracts, and the initially active-treated patients continued their therapy for a second year. The results from the second year of the study have also been published.⁷ Finally, 21 subjects completed 3 years

of treatment with cat extract and 11 subjects received dog extract for 3 years. All subjects were evaluated by allergen bronchial challenge, histamine bronchial challenge, specific IgE, IgG1, and IgG4, and SPT titrations once a year. All tests were performed by the same nurses at the same time of the year through the 3-year-long study. The results of the initial placebo-treated and active-treated groups are considered together.

Extracts

Partly purified standardized extracts of cat and dog dander from ALK (Hørsholm, Denmark) were used for treatment, bronchial challenge, SPT, and Ab measurements, as previously described.⁸ The content of *Fel d 1* and cat albumin in the cat extract was 4.3 and 46.8 µg/ml. The content of dog albumin in the dog extract was 76.0 µg/ml. One milliliter of each extract contains 100,000 SQ units. The biologic activity of the extracts was expressed in HEP units,⁹ 1 SQ unit being equal to 2×10^{-3} HEP and 10^{-3} HEP for the cat and dog extracts, respectively (Table III). Depot extracts were aluminium hydroxide-adsorbed (Alutard SQ).

Dosage

Aluminium hydroxide-adsorbed extracts (Alutard SQ) were used throughout the study for the adults. The children started therapy by rush hyposensitization with water-soluble extracts (Aquagen SQ), and they were transferred to depot extracts when they had reached the maintenance-dose level. The build-up dose of the depot extracts was administered once a week and the individual maximum dose, ideally 100,000 SQ units, that is, 4.3 µg of *Fel d 1* or 76 µg of dog albumin, was administered every fourth week.

SPT

SPTs were performed with a titration procedure including five half-log dilution of the extracts (0.1, 0.3, 1, 3, and 10 HEP). Histamine hydrochloride (1 mg/ml) and the diluent were used for positive and negative control, respectively. A mean wheal diameter was calculated by measuring the largest diameter, determining its orthogonal perpendicular, and dividing the sum by two.

ACT

Bronchial sensitivity to cat and dog in the respective patients was measured by inhalation of cat- or dog-dander

TABLE II. Skin sensitivity (millimeter), PC₂₀ allergen (HEP), and PC₂₀ histamine (milligram per milliliter) before treatment in the cat-allergen treated group (mean ± SEM)

	Dropouts	Completed	
No.	6	21	
SPT (mm)	6.6 ± 1.0	6.2 ± 0.4	NS
ACT (PC ₂₀) HEP	0.42 ± 0.23	0.56 ± 0.4	NS
HCT (PC ₂₀) mg/ml	4.8 ± 2.0	1.5 ± 0.4	NS

NS, No significant difference between the groups.
Six subjects left the study during the first and second year; statistics by Mann-Whitney U test.

TABLE III. Extract description per milliliter

	SQ units	HEP	Antigen (μg)
Cat	100,000	2	4.3 (<i>Fel d I</i>)
Dog	100,000	1	76.0 (dog albumin)

extracts from a demand-type nebulizer (DeVilbiss No. 40, DeVilbiss Co., Somerset, Pa.) driven by an air pump. The challenge started with inhalation of saline and was then continued by tenfold stepwise-increasing doses of allergen every 15 minutes. One milliliter of the respective allergen dilutions was inhaled during 5 to 6 minutes, and PEF was recorded 5 and 15 minutes after each challenge dose. The starting dose was 10⁻³ HEP for both the cat and dog extract. The maximum dose was 10 HEP for both extracts. The challenge was stopped when PEF decreased by 20% or more compared to the postsaline PEF recording. PC₂₀ was calculated from the dose-response curve. All challenges were performed at the same time of the day.

HCT

BHR was evaluated by means of HCT according to the method described by Cockcroft et al.¹⁰ After inhalation of saline, histamine hydrochloride was administered by a DeVilbiss nebulizer in doubling concentrations, starting with 0.06 mg/ml. The maximum concentration used was 32 mg/ml. Each inhalation was administered for 30 seconds, and there were 5 minutes between the different concentrations. PEF was measured immediately after the inhalation was completed and then after 5 minutes. The challenge was stopped when PEF had dropped 20% or more compared to PEF after the saline inhalation. The result was expressed as PC₂₀. The histamine challenge was performed a week before the ACT.

Specific IgE and IgG levels

Serum-specific IgE was measured by performing a radioimmunoassay similar to the RAST technique and with

TABLE IV. Cum doses (in micrograms) of *Fel d I* and dog albumin administered after 3 years of therapy

	Allergen-treated group	
	Cat	Dog
Cum dose (μg)		
Mean	103.8	2142
± SEM	± 6.9	± 94
Range	16.5-158.6	1596-2645
Children		
Mean	97.9	2013
Adults		
Mean	114.0	2296

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 Abs were labeled by the chloramine-T method. All Abs used were demonstrated to be subclass specific. 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 expressed as percent of total activity added in the radioimmunoassays.

Statistics

Wilcoxon paired sign-rank test was used to evaluate changes related to therapy, and Spearman's rank correlation was used to test for association between variables.

RESULTS
Dosage

After 3 years, the cumulative dose of *Fel d I* ranged from 16.5 to 158.6 μg; mean 103.8 μg. The children received slightly less, mean, 97.9 μg, than the adults, mean, 114 μg. The difference was not significant (Table IV). Three children and one adult did not reach the targeted maintenance dose (4.3 μg of *Fel d I*), three of these patients because of SSE and the third child because of repeated local reactions. The maintenance doses in these four subjects were 0.35, 0.43, 1.7, and 3.4 μg of *Fel d I*. In the dog-allergen treated group, the mean cumulative dose after 3 years of treatment was 2142 μg of dog albumin, ranging from 1596 to 2645 μg. The six children received mean 2013 μg, and the five adults who completed the 3-year course of therapy received mean 2296 μg, which was significantly more than the children (*p* < 0.05) (Table IV). All but one child received the expected maintenance dose, 76 μg of dog albumin. The child had

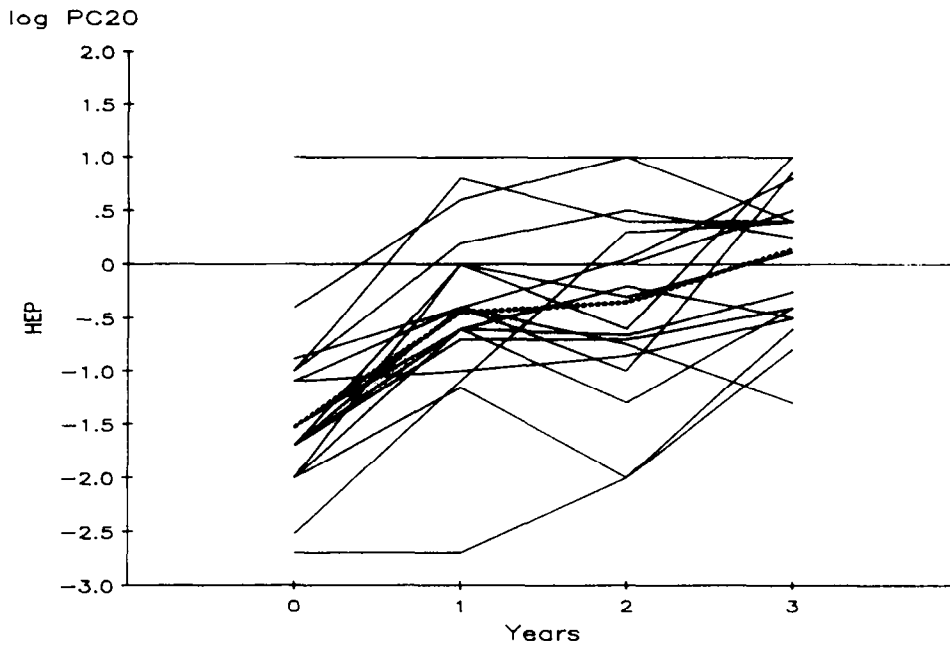


FIG. 1. Cat-allergen treated subjects; bronchial challenges with cat extract before therapy and after 1, 2, and 3 years of treatment. Data are expressed as log PC₂₀ (HEP units). Medians are indicated.

TABLE V. Number of subjects with SSEs during treatment with depot extracts

Dose level (SQ)	Allergen-treated groups			
	Cat		Dog	
	Children	Adults	Children	Adults
100	—	—	—	—
1,000	1*	—	—	—
10,000	1*	1†	—	1*†
100,000	3	2 + 1† + 1*†	—	—

*Recurrent SSE.

†Adults who withdrew before the study was completed.

a couple of large local reactions and had to stop the build up at a dose of 53 µg.

SSEs

As reported previously, SSEs were common initially in the children when they were treated with water-soluble extracts; 19 of 20 children had one or two SSEs.⁵ All children were transferred to depot extracts, when they reached their maintenance dose, that decreased the incidence of SSE considerably. The total number of patients who had SSE during treatment with depot extracts, including patients who withdrew, are presented in Table V. Five cat-allergen treated children had SSEs, occurring in three children at the 100,000

SQ dose level. Three of the children had one episode of mild urticaria and/or asthma; the fourth child had four episodes of mild asthma that affected the dose schedule and resulted in a cum dose that was about half the expected dose. The fifth child had recurrent SSEs, mainly asthma, at the 10,000 and 100,000 SQ level and received a cum dose of 16.5 µg of *Fel d 1*. Two adults who completed 3 years of therapy each had a single episode of asthma. SSEs in four of the adults who left the study have been described in MATERIAL AND METHODS. There were no hospitalizations caused by SSE throughout the study. All subjects responded promptly to treatment with inhalation of a β₂-agonist when asthma was the main symptom and/or antihistamines and epinephrine when urticaria occurred.

SPT

Skin sensitivity measured by the mean wheal diameter induced by 10 HEP extracts decreased during the first year of treatment from mean 6.2 to 3.6 mm in the cat-allergen treated group ($p < 0.01$) and from 5.9 to 4.2 mm in the dog-allergen treated group ($p < 0.05$). No further decrease was observed in either group during the rest of the treatment.

ACTs

Bronchial sensitivity to cat dander decreased continuously during the treatment. In the cat-allergen

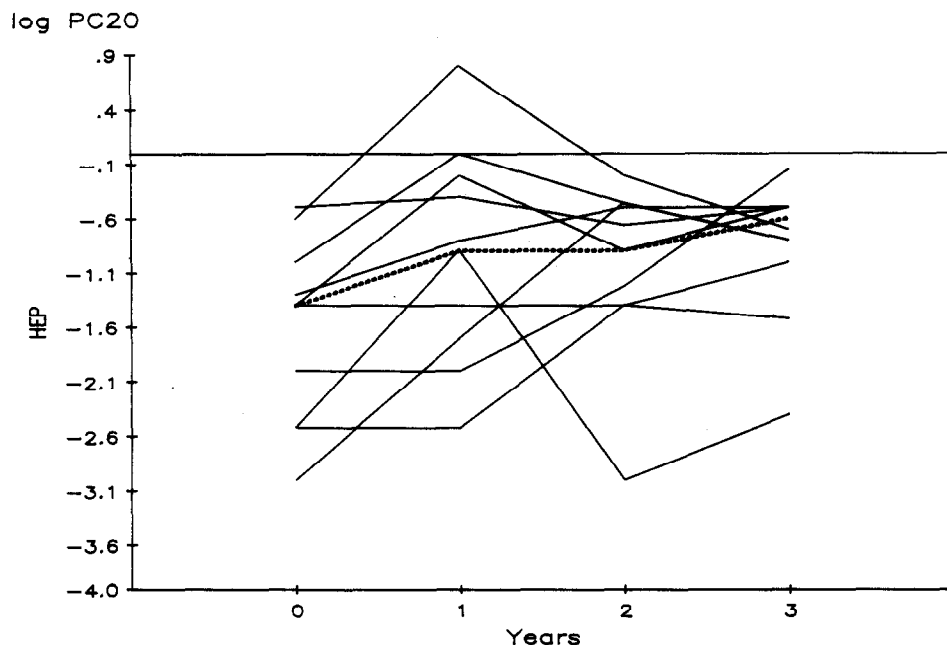


FIG. 2. Dog-allergen treated subjects; bronchial challenges with dog extract before therapy and after 1, 2, and 3 years of treatment. Data are expressed as log PC₂₀ (HEP units). Medians are indicated.

treated group, PC₂₀ subsequently increased from mean 0.56 HEP before therapy to mean 1.3, 1.9, and 2.7 after 1, 2, and 3 years of therapy ($p < 0.001$ for all subjects compared to PC₂₀ before therapy). The decrease from the second year of treatment to the end of the study was also significant ($p < 0.05$), whereas the change during the third year was not significant. The individual data (log transformed) are illustrated in Fig. 1.

In the dog-allergen treated group, there was also a significant decrease of bronchial sensitivity to allergen, although it was not as pronounced as in the cat-allergen treated group. Mean PC₂₀ was 0.08 HEP before therapy and 0.80, 0.20, and 0.28 after 1, 2, and 3 years of therapy. There was a significant change during the first year ($p < 0.05$). There was no significant change during the second and third year of treatment. A significant difference from before therapy remained at the end of the study ($p < 0.05$). The high mean PC₂₀ after the first year was explained by one subject who had a dramatic increase of PC₂₀ from 0.04 to 0.63 HEP. His PC₂₀ then decreased during the second and third year. The individual data of the 10 subjects who completed the final challenges are presented in Fig. 2.

HCTs

BHR decreased in the cat-allergen treated group throughout the study. PC₂₀ increased from mean 1.5

mg/ml before therapy to mean 4.3 mg/ml after the first year ($p < 0.01$) and to mean 9.0 and 15.3 mg/ml after the second and third year ($p < 0.001$ for both years compared to before therapy). The change during the second year was also significant ($p < 0.05$), whereas the increase of PC₂₀ during the last year was not significant. In 11 subjects, PC₂₀ was >8 mg/ml at the end of the study. None had a PC₂₀ ≥ 8 mg/ml before the treatment started. The individual data (log transformed) are presented in Fig. 3.

In the dog-allergen treated group, there was no significant change of PC₂₀. Individual data are presented in Fig. 4. There was a correlation between the changes of bronchial sensitivity to allergen and histamine after 3 years ($r = 0.47$ and $p < 0.01$; $r = 0.70$ and $p < 0.01$ in the cat-allergen and dog-allergen treated groups, respectively).

Ab levels

Specific IgE levels. Cat-specific IgE levels increased during the first year of treatment ($p < 0.01$), declined during the second year ($p < 0.01$), and remained unchanged during the third year. At the end of the study, the specific IgE levels did not significantly differ from levels obtained before the study started (Table VI).

Dog-specific IgE levels demonstrated a similar pattern, increased during the first year ($p < 0.05$) and decreased during the third year. There was no significant difference between the dog-specific IgE levels

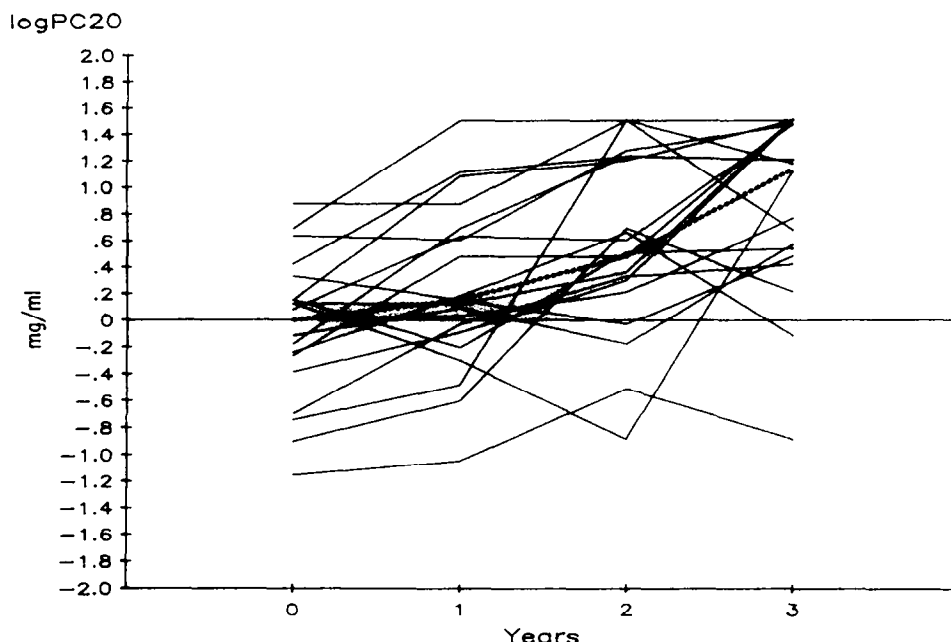


FIG. 3. Cat-allergen treated subjects; histamine bronchial challenges before therapy and after 1, 2, and 3 years of treatment. Data are expressed as log PC₂₀ (milligrams per milliliter). Medians are indicated.

TABLE VI. Specific IgE levels to cat and dog allergen, expressed as percent of total activity (mean $\pm$ SEM)

Years of treatment	IgE levels	
	Allergen-treated groups	
	Cat	Dog
0	7.1 $\pm$ 1.0	10.2 $\pm$ 1.7
1	15.0* $\pm$ 1.9	15.0† $\pm$ 2.4
2	9.8‡ $\pm$ 1.5	14.3† $\pm$ 2.1
3	8.3 $\pm$ 1.5	12.0 $\pm$ 2.0

* $p < 0.001$ compared to pretreatment levels.

† $p < 0.05$ compared to pretreatment levels.

‡ $p < 0.01$ change during the second year.

before the treatment was started and at the end of the study (Table VI).

Specific IgG levels. (Table VII) Cat-specific IgG1 increased during the first and second year of therapy ($p < 0.01$ and $p < 0.001$) but did not change further during the third year. Cat-specific IgG4 rose from mean 15.8% (of total activity) to mean 28.7% during the first year ($p < 0.001$) and to 46.4% during the second year ($p < 0.001$). There was a decrease in most subjects during the third year to mean 39.9% ($p < 0.01$). Dog-specific IgG4 increased during the first and second year ($p < 0.01$ for both) and did not change further during the third year.

There was no significant correlation between the increase of IgG4 and the decrease of bronchial sensitivity in the cat-allergen treated group ($r = 0.16$; $p > 0.05$). There was no significant correlation between the increase of IgG4 and the cumulative dose of *Fel d 1* or the change of PC₂₀ histamine. The rise of cat-specific IgG4 during the first year did not relate to the final result of the treatment, measured as change of bronchial sensitivity to allergen or by subjective evaluation of specific or nonspecific symptoms (by chi-square analysis).

Patients' subjective assessment (Figs. 5 and 6)

Fifteen of the 21 patients who completed 3 years of *cat-allergen therapy* reported little or no symptoms when they were exposed to cats at the end of the study. The remaining six patients had not noted any change of their cat sensitivity, two of these subjects had obtained the two lowest cum doses (16.5 and 47.6 μ g of *Fel d 1*) because of repeated SSEs. Symptoms of BHR, when they were exposed to cold air, smoke, or exercise, had decreased in nine subjects and increased in one subject. In the *dog-allergen treated* group, five of 11 subjects had less symptoms when they were exposed to dogs, whereas the other subjects had not noted any change. Symptoms of BHR had decreased in three and increased in one subject.

There was no significant relation between symptoms at exposure to cat or dog and the magnitude of the decrease of allergen bronchial sensitivity; neither

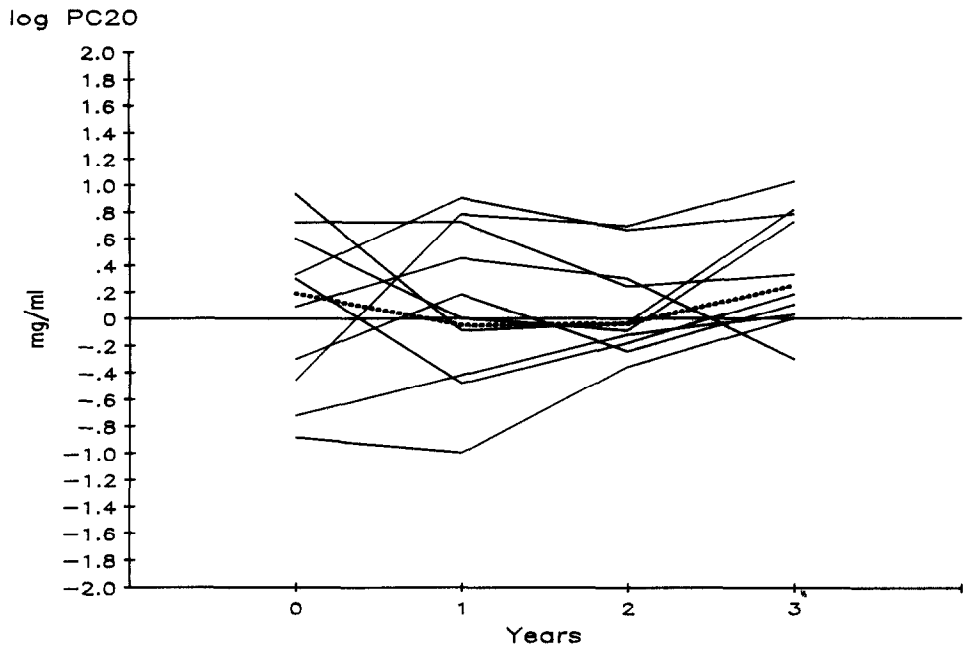


FIG. 4. Dog-allergen treated subjects; histamine bronchial challenges before therapy and after 1, 2, and 3 years of treatment. Data are expressed as log PC₂₀ (milligrams per milliliter). Medians are indicated.

TABLE VII. Cat- and dog-specific IgG1 and IgG4 levels during 3 years of therapy (mean $\pm$ SEM)

Years of treatment	Allergen-treated groups			
	Cat		Dog	
	IgG1	IgG4	IgG1	IgG4
0	21.0 $\pm$ 1.7	15.8 $\pm$ 2.8	31.9 $\pm$ 0.7	34.3 $\pm$ 2.2
1	23.9* $\pm$ 2.1	28.7* $\pm$ 4.2	33.9 $\pm$ 1.6	45.1† $\pm$ 2.2
2	29.1* $\pm$ 1.2	46.4* $\pm$ 1.8	29.9 $\pm$ 1.5	49.2† $\pm$ 1.8
3	28.7* $\pm$ 1.2	39.9*‡ $\pm$ 1.8	34.6 $\pm$ 0.8	48.1† $\pm$ 2.7

* $p < 0.001$ compared to pretreatment levels.
† $p < 0.01$ compared to pretreatment levels.
‡ $p < 0.01$ decreases during the third year.

was there any significant relation between BHR symptoms and the magnitude of the decrease of bronchial sensitivity to histamine in either group (by chi-square test).

DISCUSSION

The beneficial effect of IT with a cat-dander extract in patients with cat asthma has been further established by this study. By now a number of controlled studies have been published that have confirmed that IT with purified and standardized cat extracts is a successful treatment in cat-allergic patients with asthma.^{2-5, 11, 12}

After completion of the 3-year treatment period, we found that the most pronounced effects of the therapy

occurred during the first year. In the cat-allergen treated group, specific and nonspecific bronchial sensitivity decreased, IgE increased, as did specific IgG1 and IgG4, and skin sensitivity decreased. The effects during the second and third year were less remarkable, although nonspecific bronchial sensitivity decreased further and specific IgG1 and IgG4 continued to rise during the second year. There was a difference between the cat-allergen and dog-allergen treated groups. The effects of the therapy were less pronounced in the dog-allergen treated group. There was no significant attenuation of BHR, and dog-specific IgG1 did not rise during the treatment. Furthermore, SSEs were rare in the dog-allergen treated group; only one subject had SSE, albeit recurrent SSE. Our results

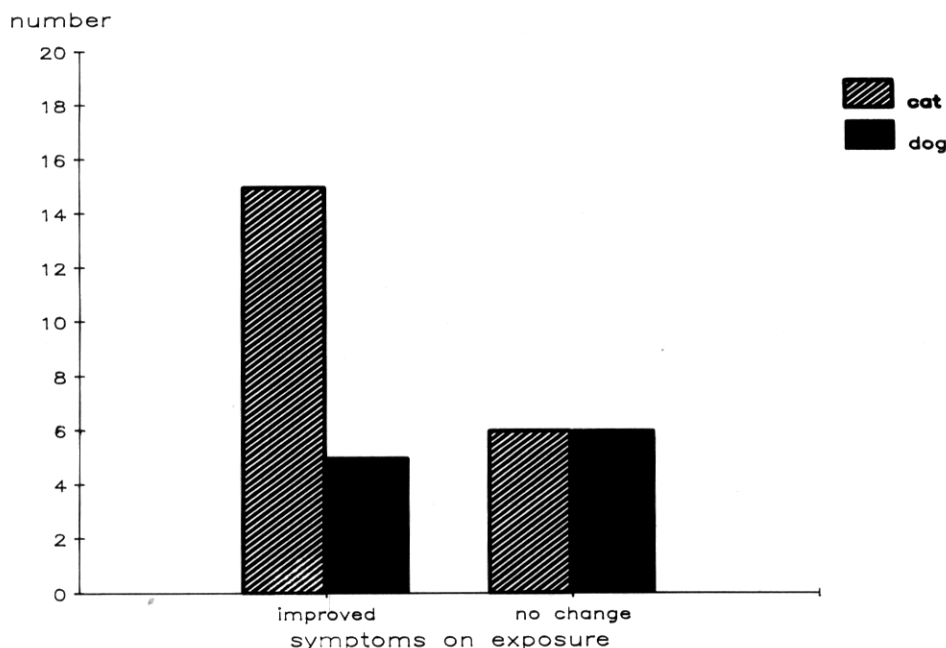


FIG. 5. Patients' subjective evaluation of change of symptoms on exposure to cat or dog in the respective treatment groups after 3 years of therapy.

are comparable with results of another dog-allergen IT study by Valovirta et al.¹³ with the same extract. The dog extract was half as potent as the cat extract measured by HEP units; thus, the dog-allergen treated subjects received a less biologically active extract than the cat-allergen treated subjects, which could have had some significance for the better effect of the cat-allergen therapy. Another question that arises from this discrepancy of efficacy is if the difference could be explained by the dog not having a major allergen of the same dominance as the *Fel d I* in the cat. A third possibility would be that there is some kind of difference between cat and dog allergy per se. A combined allergy to cat and dog was reported in more than half of the subjects in our study; still most of these subjects considered cat allergy to be the dominant allergy.⁵ It thus appears as if cat allergy usually causes more symptoms than dog allergy in subjects who have a combined sensitivity. An observation that was also made by Murray et al.¹⁴

The amelioration of symptoms on natural exposure to cats was convincing, although it did not appear to be closely related to the change of bronchial sensitivity expressed as PC₂₀. The reason might be that the global evaluation made by the participants in this study was too crude. There were no recorded daily symptom scores or PEF measurements during any part of the study. Had these measurements been made, they might have improved the relationship between objective and subjective assessments of efficacy. It could also be argued that a bronchial ACT might not reflect

the severity of clinical symptoms. Van Metre et al.¹⁵ has, however, demonstrated bronchial challenge to be well correlated to natural exposure; therefore, although the correlation is not linear, ACT is a reasonably accurate measurement of the severity of the allergy. However, there can be a discrepancy between symptoms and the challenge result in some patients. There was not a direct relation between the cum dose of *Fel d I* and the decrease of the bronchial cat sensitivity either. This finding could be exemplified by the patient who received the lowest cum dose (16.5 µg of *Fel d I*) and whose bronchial sensitivity to cat antigen decreased more than 100-fold; she still did not report less symptoms on exposure to cats. In contrast, the patient who received the highest cum dose (158.6 µg of *Fel d I*) was one of two patients whose cat sensitivity on bronchial challenge increased in spite of decreased symptoms on exposure to cats.

Furthermore, it is unlikely that the natural history of animal-dander allergy was an important factor in the decrease of bronchial allergen sensitivity, first, because the studies of the natural history of animal-dander allergy demonstrate a low remission rate,^{14, 16} and, second, because the decreased sensitivity was only found in the active-treated patients during the first placebo-controlled year of the study. Third, there was no patient who had more symptoms on exposure to cat or dog after therapy.

The optimal dose in a single patient is difficult to decide. A maintenance dose that had to be kept below the optimal dose (4.3 µg of *Fel d I* or 76 µg of dog

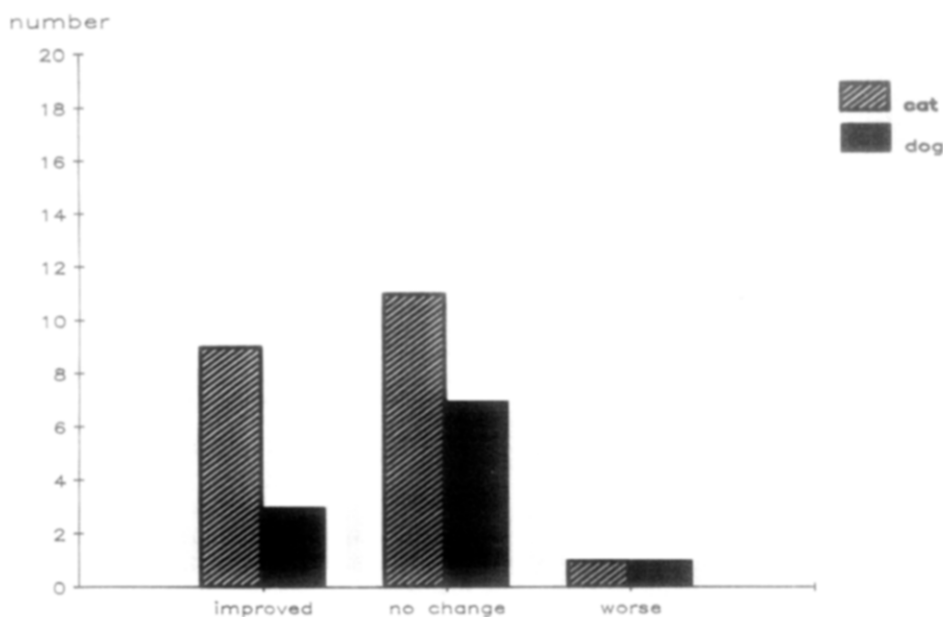


FIG. 6. Patients subjective evaluation of change of severity of symptoms induced by cold air, smoke, or exercise after 3 years of therapy.

albumin) still brought about an effective treatment. In four of the five patients who received cum doses <90 μg of *Fel d 1*, bronchial cat sensitivity decreased more than tenfold. To determine the optimal dose in each patient, the occurrence of side effects has to serve as a guide. In this study, most side effects were observed at doses near or at the maintenance level. Although SSEs were fairly common, all but one SSE were mild and could be effectively and promptly treated. In the other cat-IT studies, a similar or higher incidence of systemic reactions has been reported.^{2,4} We thus consider both cat and dog IT with depot extracts to be safe for treatment provided maintenance dose is adjusted to the particular patient. Rush hyposensitization with water-soluble extracts, as in the children, resulted in an unacceptable high incidence of SSEs.

Ab levels during the treatment confirmed previous observations of an initial rise of IgE followed by a decline to pretreatment levels. IgG1 and IgG4 increased for 2 years and then declined slightly during the third year. The hypothesis of Djurup and Malling¹⁷ that the higher the increase of IgG4 the greater the risk of treatment failure was not confirmed since there was no such correlation.

This study has demonstrated decreasing BHR during the course of therapy, which has not been observed in any other cat-IT study of patients with asthma.^{2,4} In a study of birch-pollen allergic patients with rhinitis and increased BHR, Rak et al.¹⁸ reported less hyperreactivity during the birch-pollen season in a group of patients treated with IT compared to a placebo-treated group. In contrast, increased BHR

was observed by Murray et al.¹⁹ in dust mite-treated children. The difference might be that cat exposure has been rare and probably voluntarily avoided by our subjects, whereas dust mite-allergic subjects cannot avoid the allergen. In the other mentioned cat-IT studies, cats were not always removed, or contacts with cats were not avoided^{2,4}; as in dust mite studies, continuous exposure might therefore explain the failure to achieve efficacy against BHR. Our patients did not have any furred pets when they were recruited. Removal of pets could therefore not explain the change of bronchial sensitivity to animal dander or histamine. To confirm that the homes of the patients were free from animal dander, dust samples were obtained and analyzed for cat and dog dander before the study was started. The dust samples were also analyzed for dust mite, and no home was found to be infested with dust mite.²⁰ It is also important to note that patients who participated in our study were SPT negative to dust mite and, with one exception, to molds. Thus, the effect of BHR might be good if continuous exposure of the offending allergen can be avoided during treatment, as in our cat-allergic subjects and off season in the birch-pollen treated patients.

Another possible reason for the improvement of BHR could have been changes of the pharmacotherapy regimen. No patient was, however, started on topical steroids or sodium cromoglycate during the study; thus, the improvement could not be attributed to introduction of anti-inflammatory treatment.

Children are known often to outgrow asthma, but

it is still not clear if allergies become less important as a cause of symptoms as they grow older. It is possible that part of the improvement could be explained by spontaneous remission of asthma. We did not have a nontreated control group during the second and third year, and we therefore cannot be certain that the whole effect can be attributed to the treatment. There are, however, some strong indications that the treatment did affect BHR. First, like bronchial allergen sensitivity, bronchial histamine sensitivity decreased most and only in the active-treated patients during the first placebo-controlled year of therapy.⁵ Second, the initially placebo-treated patients had a comparable decrease of histamine sensitivity during their first year of active therapy.⁷ Third, there was a similar proportion of subjects who were very much improved among the children and the adults who completed 3 years of therapy. In studies of the natural history of asthma, about 20% of the subjects with mild to moderate asthma have been reported to deteriorate during adolescence.²¹ One study of the natural history of BHR has demonstrated a high degree of variability in the response to methacholine in both directions,²² whereas, in our study, 19 of 21 patients had an attenuation of their airway response to histamine. According to the previous studies, a variability demonstrating both an increased and a decreased histamine sensitivity would have been expected if the natural history had been of major importance. Finally, this group of subjects with mild to moderate asthma without perennial allergies to dust mite or molds might have a disease severity and allergy pattern that is particularly suited for IT. It could be suggested that they might have managed quite well on pharmacologic treatment in combination with avoidance of cats and/or dogs. Complete avoidance was, however, not possible to achieve in most subjects, and some subjects had symptoms on indirect exposure. A question that still remains to be answered is why the dog-allergen treatment was less effective than the cat-allergen treatment.

In conclusion, we have demonstrated IT with a dog extract to have beneficial effects in patients with mild to moderate asthma. We have also found treatment with a cat extract to be very successful with effects on allergen sensitivity and BHR. These effects could have altered the course of the disease favorably in both children and adults.

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