

Immunotherapy with partially purified and standardized animal dander extracts

I. Clinical results from a double-blind study on patients with animal dander asthma

B. Sundin, M.D.,* G. Lilja, M.D., V. Graff-Lonnevig, M.D.,**
G. Hedlin, M.D.,* H. Heilborn, M.D.,*** K. Norrlind, M.D.,***
K-O Pegelow, M.D.,* and H. Löwenstein, Ph.D.**** Huddinge, Sweden**

Forty-one patients (21 adults and 20 children) with cat dander- or dog dander-induced asthma were selected for immunotherapy with standardized and partially purified cat- or dog-dander extracts by use of a double-blind protocol. Based on sex, age, clinical history, results of bronchial challenge, and crossed radioimmuno-electrophoresis studies, the patients were stratified in matched pairs, and the treatment alternatives were distributed randomly among the pairs. Twenty-two patients treated with allergen (15 with cat allergen and seven with dog allergen) and 17 patients receiving placebo therapy completed the first year of treatment. In the cat allergen-treated group, the bronchial sensitivity toward cat and histamine decreased ($p < 0.001$ and $p < 0.05$, respectively). Measured by bronchial challenge, the cat allergen-treated patients could tolerate 11 times more allergen at the end than at the start of the study, and they also demonstrated a tendency toward less pronounced symptoms after exposure to cat and dog allergens. No significant changes were observed in the dog allergen treated- or placebo-treated groups. The adverse effects in general were negligible except for some systemic side effects during rush hyposensitization, especially among the children, but these were mild and responded promptly to treatment. (J ALLERGY CLIN IMMUNOL 77:478-87, 1986.)

Animal danders play an important role as airborne allergens in allergic diseases. The overall prevalence of allergy to furred animals in an unselected group of Swedish school children has been estimated at 5.3%, and among children with asthma from the same population, 57%.¹ Allergy toward dog dander, defined as the observation of a positive SPT, has been found among 14% of unselected adolescents in Finland.² These figures are in agreement with those of Rudolph³ who recently reported an increasing tendency for sensitization to furred animals.

The keeping of furred pets is widespread in modern western communities, and thus, direct and indirect contact with animal danders cannot be avoided. In Sweden 50% of all youngsters have a furred animal at home,¹ and there is a growing interest in horseback

Abbreviations used

HEP: Histamine equivalent prick
CRIE: Crossed radioimmuno-electrophoresis
PEF: Peak expiratory flow
PC₂₀: 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

riding among school children.⁴ The occurrence of animal dander in house dust is frequent,⁵ and Vanto and Koivikko⁶ have demonstrated that 40% of children with asthma in Finland demonstrate a positive SPT with dog dander, although they have no direct contact with this animal.

The treatment of choice for most patients allergic to animal danders is to avoid contact with furred animals. Among those patients for whom avoidance of animal contact and pharmacologic therapy is insuffi-

From the *Huddinge, **Sachs, and ***Danderyd University Hospitals, Stockholm, Sweden, and the ****Protein Laboratory, University of Copenhagen, Copenhagen, Denmark.

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Reprint requests: Bo Sundin, M.D., Section of Allergology, Department of Medicine, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

cient, immunotherapy may be an alternative. However, immunotherapy with animal-dander extract has not previously been well studied. Earlier studies⁷⁻⁹ were performed without control groups and with extracts that were not standardized in any relevant way. Thus, the efficacy of immunotherapy with animal-dander has been questioned. As a result of the demand for reliably standardized extracts¹⁰ and with a growth in knowledge concerning the relevant allergens in different animal danders,¹¹⁻¹³ it is now possible to produce well-characterized and standardized animal-dander extracts. With the use of such characterized and standardized animal extracts for hyposensitization, Taylor et al.¹⁴ and Ohman et al.¹⁵ have demonstrated a reduction in the specific bronchial sensitivity in children with asthma.

The purpose of this investigation was to study the clinical and immunologic effects of immunotherapy by use of a standardized cat- or dog-dander extract (Alutard SQ; ALK, Copenhagen, Denmark) relative to placebo in patients with cat dander- or dog dander-induced asthma. In vitro results will be presented elsewhere.^{16, 17}

MATERIAL AND METHODS

Subjects

Forty-five patients, 22 children and 23 adults, with animal dander-induced bronchial asthma were selected for this study. Their asthma was considered to be mild-moderate, and most of the patients managed with only a β_2 -agonist. All patients were considered to be in need of further treatment, since they were frequently exposed to cat or dog dander, either in the working environment or in the homes of relatives or friends and suffered from asthma at exposure. None of the patients kept a furred animal at home. All were outpatients at allergologic departments of two pediatric and two medical clinics in Stockholm. A further criterion for inclusion in the study was a positive reaction after bronchial challenge with cat- or dog-allergen extract and a scoring system based on allergic history, SPT, and RAST results. A minimum score of 4 was required (Table I).

After the allocation (which is described below) but before the start of immunotherapy, four patients, two children and two adults, declined to participate in the study. This left 41 patients, 20 children and 21 adults, for the study.

Informed consent for participation in the study was given by all patients and parents, and the study was approved by the Committee of Ethics at the Karolinska Institutet.

Extracts

Partially purified, standardized allergenic extracts of cat or dog dander were used. According to the manufacturer (ALK, Copenhagen, Denmark) the extracts were prepared from danders excluding nonallergenic material and all molecules with a molecular weight <10,000. The extracts were standardized relative to an internal standard¹⁸ by a combi-

TABLE I. Parameters used for scoring

Score	History	Skin index (SI)*	RAST (classes)
0	Negative	<0.5	0 to 1
1	Doubtful	≥ 0.5 to <1.0	2
2	Positive	≥ 1.0	3 to 4

*SI = $\frac{D_{\text{Ex}} \times d_{\text{Ex}}}{D_{\text{Hist}} \times d_{\text{Hist}}}$ where the Ds are the largest diameter of the wheal and the ds the largest diameter perpendicular to the former with extract (Ex) or histamine dihydrochloride, 1 mg/ml (Hist), for the skin prick tests.

nation of three independent methods. Quantitative immunoelectrophoretic methods were used for quantitation of the content of the major allergens, as well as for checking the content of other potential allergens. RAST inhibition was used as a measure of the total allergenic activity and skin prick testing on a number (>10) of selected patients clinically allergic toward the allergens in question served as a control of the biologic activities. Since the biologic activity of SPT (HEP value, see explanation below)¹⁰ of the internal standards is known from skin prick testing on a larger number (>30) of clinically allergic individuals, the HEP value of the extracts could be calculated.^{10, 12, 13, 18} The extracts used for treatment (either a water-soluble extract, Aquagen SQ, or an aluminium hydroxide-adsorbed extract, Alutard SQ), for skin prick testing (dissolved in 50% glycerol, Soluprick SQ), for bronchial provocation tests (water-soluble extract, Aquagen SQ), for in vitro investigations, e.g., RAST, level of IgG antibodies (IgG RAST, IgG4 RAST, protein A from *Staphylococcus aureus* method), CRIE, level of precipitating antibodies, and dust analyses (a water-soluble extract, Aquagen SQ) were all identical in composition and from the same batch. The activities of the extracts were, according to the manufacturer, given in arbitrary SQ units, and a detailed antigenic analysis of the extracts will be reported elsewhere.¹⁷ One SQ unit of cat dander extract contained 43 pg of Ag No. 4 (cat Ag 1) and 468 pg of Ag No. 3 (cat albumin) anticipating 1 μg of cat Ag 1 to be equal to 1 Ohman unit.¹⁵ One SQ unit of dog-dander extract contained 760 pg of Ag No. 2 (dog albumin).¹⁷ The biologic activities of SPT were 2×10^{-5} HEP per SQ unit and 10^{-5} HEP per SQ unit for the cat and dog extracts, respectively.

Placebo extracts stimulating Alutard SQ cat or dog extract were composed of 0.01 mg of histamine hydrochloride, 0.4 mg of human serum albumin (Kabi, Stockholm, Sweden), and 0.04% (w/v) aluminium hydroxide, Alhydrogel (Suprefos, Copenhagen, Denmark). Serial dilutions of this extract were used for treatment of the placebo-treated group patients.

The HEP value is a measure of the biologic activity of the extract. One HEP equals the activity of an allergen extract for which the geometric mean wheal reaction of a number of patients (>30) allergic to the allergen in question is equivalent to that of histamine dihydrochloride (1 mg/ml).¹⁰



FIG. 1. Study design. CIE, crossed immunoelectrophoresis with intermediate gel.

Dosage

The immunotherapy of the adults was carried out with Alutard SQ extracts with weekly injections starting at a dose of 30 SQ units. The dose was then increased stepwise to an ideal maximum dose of 100,000 SQ units. The injections were administered every fourth week after the individual maximum dose was reached, which was considered as the maintenance dose.

Rush hyposensitization with the children was started with water-soluble extracts (Aquagen SQ). The starting level was 0.1 SQ units, and the dose was increased stepwise to an ideal maximum dose of 80,000 SQ units. The children received initially 5 to 7 injections every day, but at the higher concentrations the number of injections was only 2 to 3 daily. After reaching the individual maximum dose, there was a change from water-soluble extracts to depot extracts (Alutard SQ). These were administered as outpatient treatment at increasing weekly intervals until a frequency of one injection every fourth week was attained.

SPTs

SPTs were performed as titrations by use of allergen concentrations of 0.1, 0.3, 1.0, 3, and 10 HEP. The procedure is described in detail elsewhere.¹⁶

ACT

The specific bronchial sensitivity was measured with the use of inhalation of cat- or dog-dander extract (Aquagen SQ). The allergen was inhaled from a demand-type nebulizer (deVilbiss [deVilbiss Co., Somerset, Pa.] No. 40, nominal particle size 0.3 to 2 μ m, 0.16 ml/min) driven by an air pump. One milliliter of the test solution was inhaled in 5 to 6 minutes. The challenge was started with saline inhalation (9 mg/ml) followed by inhalation of allergen at a concentration of 10^{-3} HEP. The allergen concentration was then increased by factors of 10 up to a maximum concentration of 10 HEP per milliliter. The PEF was measured 5 and 15 minutes after inhalation with a Wrights peak flow

meter, and the interval between different concentration steps was 15 minutes. The allergen concentration eliciting a 20% reduction of peak flow compared to the value after saline inhalation was denoted PC₂₀ allergen.

HCTs

The unspecific bronchial sensitivity was measured by an HCT according to the method of Cockcroft et al.¹⁹ 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 maximal histamine concentration used was 32 mg/ml. The interval between 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 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 the concentration causing PC₂₀ and was obtained from the log dose-response curve by linear interpolation of the last two points.

In vitro tests

Analyses for IgG antibodies (IgG RAST, IgG4 RAST, protein A from *Staphylococcus aureus* method) and RAST, were performed and are described in detail elsewhere.¹⁶

Study design and allocation

The study was designed as double-blind with parallel groups. During the running-in period of 6 months before the start of immunotherapy, the patients were characterized with respect to SPT, ACT, HCT, level of IgG-blocking antibodies, RAST, CRIE, and level of precipitating antibodies.

Analyses of dust from the patients' homes were also made. Since most animal dander-allergic patients react to both dog and cat dander, the patients were asked to choose which animal they considered to be the most relevant in their case. The allergen extract used was then selected in accordance with this choice. Based on sex, age, clinical history, and the results of bronchial challenge and IgE specificities in cat and dog CRIE, the patients were stratified in matched pairs, and the two treatment alternatives, active or placebo treatment, were allocated randomly within the pairs.

After the running-in period, SPT was repeated immediately before starting the hyposensitization and after 3, 6, and 12 months of treatment. ACT, HCT, and RAST were performed after 9 and 12 months of treatment. CRIE as well as analyses for dust and for levels of IgG antibodies and precipitating antibodies were repeated at the end of the observation period (Fig. 1).

Global assessments

After 1 year of treatment, before the code was broken, global assessment was made both by the patient and the investigator by use of a questionnaire as well as information obtained from the patient's individual record.

The global assessment also included an evaluation of the patient's tolerance toward the immunotherapy and registered side effects.

Statistical methods

The Student's *t* test was used when differences in baseline peak flow were tested. A nonparametric test (Wilcoxon matched-pair, rank-sum test) and the Student's *t* test were used when differences were tested between allergen- and placebo-treated groups with respect to specific and unspecific bronchial sensitivity after 9 and 12 months of treatment. The PC₂₀ allergen and PC₂₀ histamine values were transformed logarithmically before calculation. The nonparametric Spearman rank correlation test was used when changes were compared in specific bronchial sensitivity with changes in allergen-specific IgG.

RESULTS

Patients

When the code was broken after 12 months of treatment, 22 patients were found to belong to the allergen-treated group (15, cat allergen-treated and seven, dog allergen-treated), and 17 patients belonged to the placebo-treated group. The reason for this inequality in the numbers of patients was that the allocation was made several months before the treatment began, and all four patients that declined to participate in the study belonged to the placebo-treated group. An additional two patients dropped out during treatment as a result of side effects. The allergen- and placebo-treated groups appeared to be quite similar in regards to sex, age, duration of asthma, concomitant allergies, and

TABLE II. Demographic data, concomitant allergies, and medication

	Allergen treatment	Placebo treatment
Children/adults	12/11	8/10
M/F	10/13	8/10
Age (yr) M $\pm$ SD	22.0 $\pm$ 12.0	21.0 $\pm$ 11.0
Range	8.5 to 47.0	8.0 to 40.0
Duration of asthma (yr) M $\pm$ SD	8.7 $\pm$ 5.6	12.2 $\pm$ 8.3
Range	2.5 to 20.0	1.0 to 34.0
Smokers	3	3
Associated allergic diseases		
Rhinoconjunctivitis	15	16
Urticaria	1	4
Atopic eczema	2	4
Clinical allergy		
Cat	6	6
Dog	4	1
Cat plus dog	13	11
Mite	0	0
Molds	1	0
Pollen	5	4
Medication		
β_2 -agonists and/or disodium cromoglycate	12	10
β_2 -agonists and/or theophyllin	9	7
β_2 -agonists and/or theophyllin and topical steroids	2	1

previous medication, indicating that the treatment allocation was satisfactory (Table II).

Dosage

After 1 year of treatment, the total dose of cat or dog allergen (SQ units) and the individual absolute doses of cat Ag 1, cat albumin, and dog albumin administered were about the same for children as for adults (Table III) in spite of the initial treatment differences. However, there was considerable individual variation in both groups, possibly reflecting differences in sensitivity toward cat and dog allergens.

Baseline values for PEF

The baseline peak flow values before the HCTs and ACTs were rather constant in both the placebo- and allergen-treated group. The mean variation coefficient

TABLE III. Total amount of allergen administered during the first year of immunotherapy

		SQ units	Cat albumin	Cat Ag 1	Dog albumin
		Mean*	(μ g) Mean $\pm$ SD	(μ g) Mean $\pm$ SD	(μ g) Mean ; SD
Cat	Children n = 8	1,000,000 (500,000 to 1,340,000)	469 $\pm$ 125 (236 to 583)	43 $\pm$ 11 (22 to 58)	—
	Adults n = 7	925,000 (300,000 to 1,500,000)	433 $\pm$ 221 (140 to 705)	40 $\pm$ 20 (13 to 65)	—
Dog	Children n = 4	1,070,000 (500,000 to 1,340,000)	—	—	912 $\pm$ 127 (726 to 1,008)
	Adults n = 3	980,000 (300,000 to 1,500,000)	—	—	849 $\pm$ 198 (687 to 1,069)

*Range listed in parentheses.

for the placebo-treated group was 7.2%, and 7.7% for the allergen-treated group. (Mean percent of predicted was 85.3% and 88.5%, respectively.) In both groups the children demonstrated a larger variability than the adults (placebo-treated group: children, 11.7%, adults 3.6%, with mean percent of predicted 79.2% and 89.5%, respectively; allergen-treated group: children, 8.8%, adults 6.5%, with mean percent predicted 88.1% and 89.5%, respectively). There was no significant difference between the allergen- and placebo-treated group with regard to the baseline peak flow values in any of the six inhalation tests.

ACTs

A PC₂₀ for allergen could be measured in 19/22 allergen-treated and 16/18 placebo-treated patients after 0, 9, or 12 months of treatment. In the case of three allergen- and two placebo-treated patients, a PC₂₀ could not be established caused by subjective symptoms as cough and dyspnea. In the cat allergen-treated group, the patients could tolerate five times more allergen after 9 months and 11 times more allergen after 12 months of treatment than at the start of hyposensitization. The corresponding figures for the dog allergen-treated patients were five and three times more. Individual values are illustrated in Fig. 2. Children and adults behaved in the same way. For the 15 cat allergen-treated patients, the log HEP PC₂₀ mean and SEM were, at 0 months, -1.47 and 0.21, respectively; at 9 months, -0.86 and 0.25; and at 12 months, -0.48 and 0.28, respectively. The change was significant at 9 months ($p < 0.01$) and 12 months ($p < 0.001$). This was, however, not the case in the dog allergen-treated group in which mean and SEM were, at 0 months, -1.46 and 0.31; at 9 months, -0.86 and 0.18; and at 12 months, -1.11 and 0.39, respectively. In the placebo-treated group there was

no change in the bronchial tolerance to allergen during the study (Fig. 3). Comparison of the two treatment groups (allergen and placebo) revealed no difference in the PC₂₀ before treatment, but after both 9 and 12 months, the difference was statistically significant ($p < 0.05$).

HCTs

A PC₂₀ could be established in 20/22 allergen-treated and 14/18 placebo-treated patients. In the cat allergen-treated group, there was an increase in the mean histamine PC₂₀ during the course of hyposensitization (0 months, 0.72 mg/ml; 9 months, 1.07 mg/ml; and 12 months, 1.48 mg/ml). After 12 months this increase was statistically significant ($p < 0.05$) both for children and adults. No change in PC₂₀ in the dog allergen-treated group was observed. Individual values are illustrated in Fig. 4. In the placebo-treated group, no changes in PC₂₀ could be found after 9 or 12 months of treatment (Fig. 5), and there was no difference between children and adults.

Patients' subjective assessment

After 12 months of immunotherapy, the patients' subjective assessment of the efficacy of the two treatment alternatives demonstrated that when the cat allergen-treated patients were exposed to cat, 9/15 experienced a reduction in severity of symptoms, whereas 6/15 remained unchanged. For the dog allergen-treated group, 4/7 had decreased symptoms and 3/7 remained unchanged after dog exposure. In the placebo-treated group, 5/17 had decreased symptoms on cat/dog exposure; 11 remained unchanged, and one patient reported an increase in severity of symptoms (Fig. 6). The patients were also asked about their asthmatic symptoms, provoked by non-allergenic factors such as cold, smoke, or physical

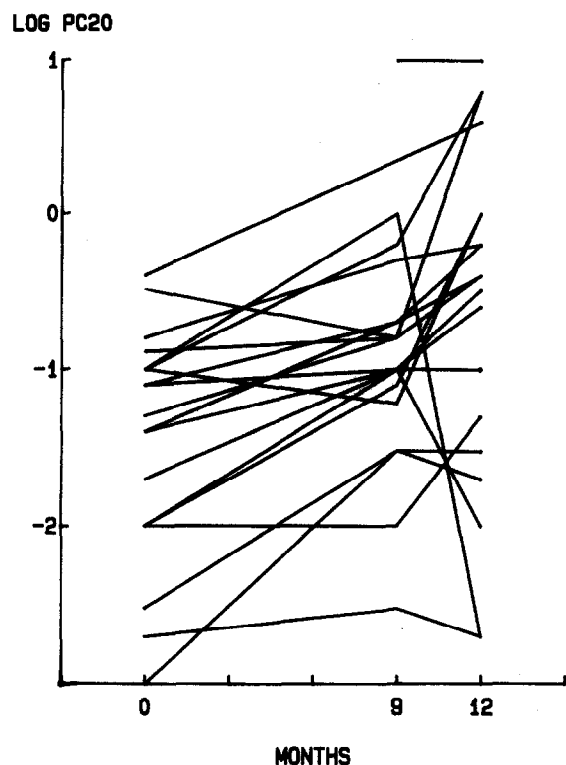


FIG. 2. Change in log PC₂₀ for allergen in the allergen-treated group.

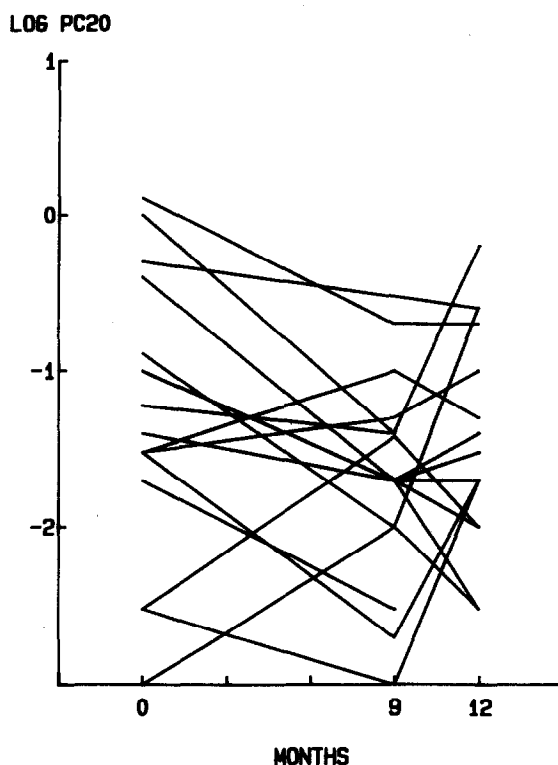


FIG. 3. Change in log PC₂₀ for allergen in the placebo-treated group.

activity. Fourteen patients, all allergen treated, reported less symptoms, whereas 25 of 39 patients reported no change in the severity of asthmatic symptoms of this type.

Side effects

Children. The children were treated initially by rush hyposensitization with aqueous extracts. In the allergen-treated group there were no side effects at lower dosages (<1000 SQ units) (Table IV). At higher doses, however, a number of local and systemic side effects were experienced, leading to changes in the planned dose schedule. Allergen doses of >10,000 SQ units elicited rise to SSE in all 12 children. These side effects were mild and responded promptly to treatment. After changing to depot extracts and administering maintenance doses, no SSE and only a few LSE were experienced. In the placebo-treated group five SSE were observed at higher histamine concentrations.

Adults. In the allergen-treated group four SSE and one LSE were observed, notably at doses exceeding 10,000 SQ units. No changes in the dose schedule were necessary. The number and distribution of side effects were the same in the placebo-treated group

(Table IV). Two patients in the adult group stopped the immunotherapy because of SSE, one in the placebo-treated group caused by recurrent urticaria and one in the allergen-treated group as a result of repeated attacks of pharyngeal angioedema some hours after the injections.

DISCUSSION

Immunotherapy is one of the alternatives available in the treatment of allergic asthma. However, the efficacy of immunotherapy is under debate, and during the previous decade, the efficacy has been argued to reflect the biologic activity of the allergen extracts.¹⁰ Thus, in pollen allergy the use of standardized and partially purified pollen extracts has been demonstrated to result in better protection than the use of crude extracts.²⁰⁻²² The same has been found with the use of venom extracts compared to whole body extracts in insect-sting allergy.²³⁻²⁵ In this study we used cat- and dog-dander extracts standardized by means of quantitative immunoelectrophoretic methods, RAST inhibition, and biologic activities assessed by skin tests on known allergic patients.

Patients selected for immunotherapy must fulfill strict criteria.²⁶ Thus, the selection of patients in this

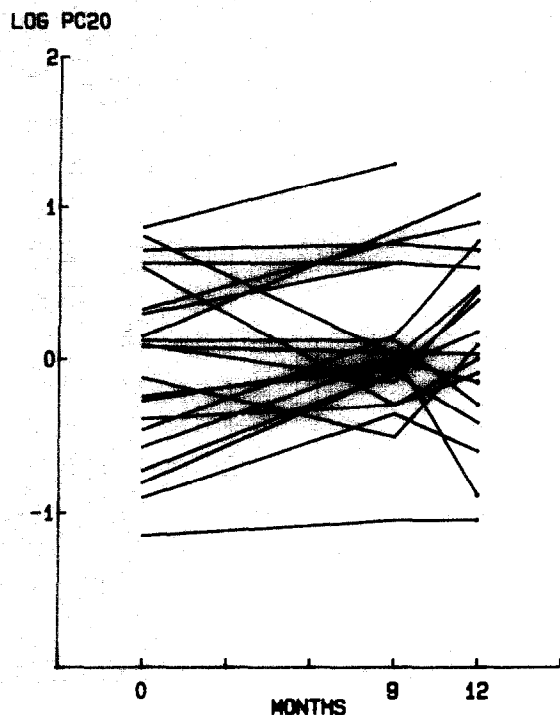


FIG. 4. Change in log PC₂₀ for histamine in the allergen-treated group.

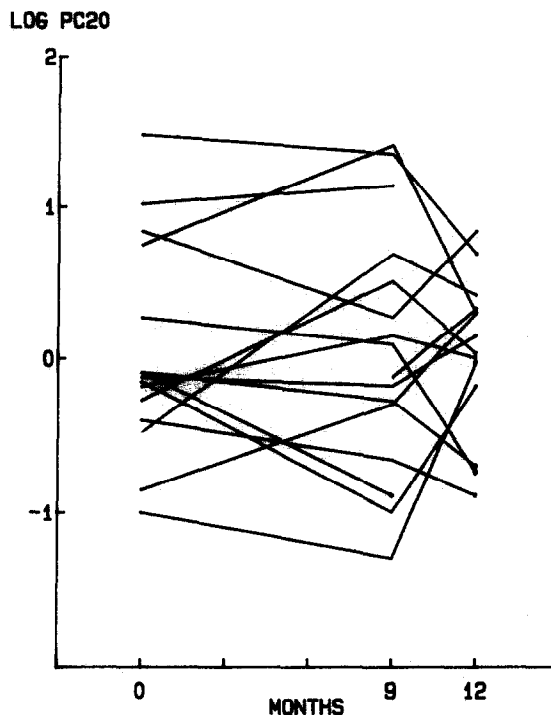


FIG. 5. Change in log PC₂₀ for histamine in the placebo-treated group.

study was dependent partly on a positive history of severe asthmatic symptoms on contact with cats and/or dogs and partly on positive bronchial challenge results. On the basis of these criteria, the cat-allergic patients ($n = 28$) were dominant among both children and adults. The distribution of cat and dog allergy among our patients is in agreement with the common observation that cats are more likely to cause allergic symptoms among atopics, especially among atopic children.^{3, 27-29} The reason for this is not known, but it has been speculated that the greater allergenicity of cats than of dogs might be a result of more intimate exposure to cats and/or that cat emanation in itself might be more allergenic than that of dogs.²⁹

The patients were matched not only according to sex, age, and specific and unspecific bronchial sensitivity but also according to the CRIE results. This made it possible to characterize each patient with respect to the presence of specific IgE as well to the IgG response to cat and dog major allergens during immunotherapy. The advantage of the use of CRIE analyses before and during immunotherapy to evaluate the efficacy of the hyposensitization has been demonstrated during immunotherapy against pollen allergy.³⁰ The changes in CRIE results, demonstrating clearly that no new allergies appeared as a result of the specific immunotherapy, are discussed in detail elsewhere.¹⁷

The dose schedules for children and adults were

slightly different, as described previously. The children were hospitalized and treated by rush hyposensitization with aqueous extracts, and after reaching maintenance dose, there was a change to depot extracts. Rush hyposensitization is widely used in treating children in Scandinavia and is often chosen from a social and practical point of view. The adults were treated as outpatients with weekly injections of depot extracts until the maintenance dose was reached. In spite of these methodological differences in the initial phase of hyposensitization, the mean total amount of allergen administered expressed in SQ units was almost the same for children and adults (children, 1,070,000, and adults, 980,000). Our patients received a mean of 16 μ g of cat Ag 1 (range 3.6 to 30) and 187 μ g of cat albumin (range 39 to 326) during the first 16 weeks of treatment, whereas the patients of Ohman et al.¹⁵ received a mean of 10.9 μ g of cat Ag 1 (range 0.24 to 24.8) and 277 μ g of cat albumin (range 6.1 to 630) within the same period. These figures are quite comparable.

The basal PEF values measured before all challenges remained constant through the study. For some patients the basal PEF values were occasionally lower than 80% of the predicted value but did not change systematically with time in either group. Furthermore, there was no significant difference between the two groups.

There was a significant increase in bronchial tol-

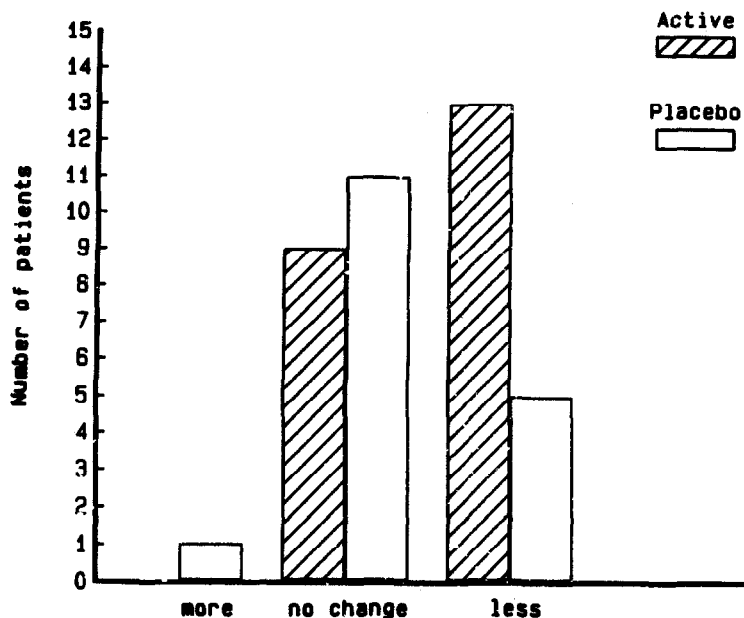


FIG. 6. Patients' subjective evaluation of their asthmatic symptoms provoked by cat or dog. Change after 12 months of immunotherapy.

erance toward cat allergen in the cat allergen-treated group after both 9 and 12 months of treatment, and these results are consistent with those of other authors.^{14, 15} The cat allergen-treated group could tolerate 11 times more allergen after 12 months of treatment than before hyposensitization began. This increase in bronchial tolerance appears to be of clinical importance and was related to the patients' subjective assessment. This is in accordance with findings of other authors.¹⁵ No significant change in bronchial tolerance for dog allergen was observed in the dog allergen-treated patients. In the placebo-treated group no change in bronchial tolerance for allergen could be observed.

Unspecific bronchial hypersensitivity is of importance in bronchial asthma and correlates well with the severity of the asthma.³¹ The immunologic reactivity of the bronchi is also dependent on their degree of biochemical reactivity, i.e., their sensitivity to liberated mediators. Several studies have demonstrated that there is a significant correlation between the bronchial sensitivity to allergen and the sensitivity to histamine.^{32, 33} A relatively small dose of inhaled allergen is needed to provoke asthma in a patient with high unspecific hypersensitivity and vice versa. After exposure to allergen, the unspecific bronchial sensitivity may increase.^{34, 35}

It is often found that subjects with asthma allergic to cat or dog and who keep a furred animal at home are unaware of the origin of the asthmatic symptoms, since the early phase of the allergic reaction is often misinterpreted. The patient believes that his asthma is

triggered by unspecific irritating factors such as cold air or cigarette smoke.³⁶

The present study has demonstrated a reduction in the unspecific bronchial sensitivity in the cat allergen-treated group after 12 months of treatment. The dog allergen-treated group was probably too small to reveal any statistically significant differences. Other studies^{14, 15} have failed to demonstrate a change in the unspecific bronchial sensitivity during the course of hyposensitization to cat dander. The reasons for this are unexplained, but it may be attributable to factors such as a short treatment time or choice of too small a patient group for reliable statistical analysis.

The frequency of SSE was in general low with the highest frequency experienced among the children during rush hyposensitization with aqueous extracts, and these occurred in the dose interval of 10,000 to 100,000 SQ units. However, these SSE were mild and responded promptly to treatment (Table IV). On changing to depot extracts, no SSE were experienced among the children. The adults received exclusively aluminum-absorbed depot extracts, and only four of 11 patients (36%) experienced SSE throughout the study. On the basis of hyposensitization studies with aluminium hydroxide-adsorbed grass-pollen extract³⁷ and/or grass-pollen extract conjugated to sodium alginate,³⁸ the incidence of SSE among adults during the first year of treatment has been reported to be 33%, which is quite consistent with our results.

The observed difference in the number of SSE during the initial phase of immunotherapy among the children compared to the adults is regarded as being

TABLE IV. Number of patients demonstrating side effects in connection with allergen injections

Allergen dose interval (SQ units)	SSE		LSE	
	Allergen therapy	Placebo therapy	Allergen therapy	Placebo therapy
Children during rush hyposensitization	n = 12	n = 8	n = 12	n = 8
0.1 to 1	—	—	—	—
1 to 10	—	—	—	—
10 to 100	—	—	—	—
100 to 1,000	—	—	—	—
1,000 to 10,000	3	1	1	—
10,000 to 100,000	12	4	1	—
Adults during dose increase and during maintenance treatment with depot extract.	n = 10	n = 10	n = 10	n = 10
10 to 100	1	1	—	—
100 to 1,000	—	—	—	—
1,000 to 10,000	—	—	—	—
10,000 to 100,000	3	3	1	1

SSE = symptoms of asthma, urticaria, and angioedema; LSE = local redness and edema of an intensity leading to decreased or unchanged allergen dose at the following injection.

a result of the more intensive treatment among the children and is consistent with other studies with aqueous purified cat-pelt extracts.^{14, 15} By contrast, no SSE were observed with the use of a standardized aluminium hydroxide-adsorbed dog-dander extract administered weekly to dog-allergic children.³⁹ Several authors report a high frequency of SSE when aqueous extracts are used compared to aluminium hydroxide-adsorbed extracts.⁴⁰⁻⁴² Thus, it might be advisable not to continue the immunotherapy with aqueous extracts beyond an allergen dose of 10,000 SQ units during rush hyposensitization. Beyond this level aluminium hydroxide-adsorbed depot extracts should be used.

In the placebo group some SSE were observed and were presumably provoked by the histamine content of the placebo solution. The histamine concentration in the placebo extract appeared to be adequate, since neither the patients nor the investigator could predict who had received placebo or allergen injections. Thus, the study was completed in a double-blind manner.

Analysis of dust from the patients' homes revealed no significant differences between the allergen- and placebo-treated groups with respect to the content of dog or cat antigens. Thus, the differences in specific and unspecific bronchial sensitivity in the two groups are not likely to have been caused by different levels of exposure.

In a concurrent study¹⁶ we have been able to conclude that the specific immunotherapy with the dander extracts elicited increased specific IgG levels and decreased skin reactivity, although these changes did not correlate with the increased bronchial tolerance toward allergen for the individual patient. Furthermore, in another concurrent study¹⁷ we have demonstrated

that the greatest contribution to reduction in the patients' allergen-specific IgE was a reduction in those IgE specificities directed against the major allergens and that no new allergies appeared as a result of the treatment.

In conclusion we found that both the specific and unspecific bronchial sensitivity decreased in patients with cat-dander asthma after treatment with standardized and partially purified cat-dander extract. We believe that this is an effect of the hyposensitization therapy and that the favorable effect on the unspecific sensitivity is probably secondary to the increased tolerance for cat dander. In patients with dog-dander asthma, treatment with dog dander produced a slight, although it was not significant, increase of the bronchial tolerance. In the placebo-treated group no changes in specific or unspecific sensitivity were observed. Although the extracts used are potent, their adverse effects are negligible when they are handled properly.

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