

Immunotherapy for cat asthma

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In 22 patients with cat asthma who were highly sensitive to cat, we compared, double-blind, the effects of immunotherapy with cat-hair and dander extract (11 patients) with effects of placebo (11 patients). Patients were matched by the dose of the cat extract expressed in Food and Drug Administration (FDA) units of Fel d I (previously called cat allergen 1) required for end point reaction in intradermal skin test end point titration (STEPT), for in vitro leukocyte histamine release (LHR), and for the dose of cat extract producing a 20% fall in FEV₁ (cat-extract PD₂₀) in bronchoprovocation test. Patients were matched also for bronchoprovocation dose of methacholine producing a 20% fall in FEV₁ (methacholine PD₂₀). Patients were randomly assigned to one of two treatment groups. During immunotherapy, doses were increased to maintenance dose of 4.56 FDA units of Fel d I, or, if this were less, to the highest tolerated dose. Systemic reactions to cat-extract immunotherapy were mild and infrequent. Before and during immunotherapy, we measured (in FDA units of Fel d I) cat-extract PD₂₀, cat-extract intradermal STEPT, cat-extract in vitro LHR, serum levels of cat IgG and cat IgE, and methacholine PD₂₀. After they had received 1 year of immunotherapy, patients receiving cat extract, in comparison to patients receiving placebo, had decreased cat-extract PD₂₀ ($p < 0.01$), diminished responses to cat-extract intradermal STEPT ($p < 0.025$), increased IgE antibodies toward cat extract ($p < 0.01$), increased IgG antibodies toward cat extract, Fel d I, and cat albumin ($p < 0.001$), but no significant change in cat-extract in vitro LHR or in methacholine PD₂₀. We conclude that cat-extract immunotherapy was well tolerated, significantly decreased skin and bronchial responses to cat extract, and significantly increased IgE antibodies to cat extract and IgG antibodies to cat extract, Fel d I, and cat albumin. (J ALLERGY CLIN IMMUNOL 1988;82:1055-68.)

Cat asthma is a common condition that produces considerable morbidity.¹⁻⁴ Although cat avoidance in theory provides adequate treatment, it may be difficult or impractical to implement for at least two reasons. First, many people keep cats. For example, it has been estimated that 31% of the homes in the USA contain one or more cats.⁵ Second, significant quantities of

cat allergen have been demonstrated in dust collected from houses in which cats were not kept, or, at least, were alleged to be absent.⁶ Therefore, immunotherapy with cat allergenic extract is frequently used in an attempt to reduce symptoms of asthma caused by casual exposure to cats.¹⁻⁴ Consequently, it is important to have reliable information on the safety and effectiveness of this immunotherapy.

Currently available, reliable information comes from the published results of three separate, randomized, placebo-controlled, double-blind trials.^{1-3, 7-9} These trials have involved, collectively, 29 actively treated and 25 placebo-treated patients with cat asthma. Immunotherapy with cat extract produced multiple, statistically significant effects in comparison to placebo. Systemic reactions occurred one or more times in 18* of the 29 patients who received cat

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Supported in part by National Institutes of Health Grants RO1-AI 18374 and AI 08270, Outpatient Clinical Research Center Grant RR 00722, gifts from Allergologisk Laboratories, Copenhagen, Denmark. Computational assistance was received from CLINFO, sponsored by National Institutes of Health Grant 5MOIR35-2 0.

Received for publication Feb. 19, 1988.

Accepted for publication May 28, 1988.

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*One or more systemic reactions in three of five patients receiving cat extract,¹ in four of nine patients receiving cat extract,² and in 16 of 22 patients, of whom 15 received cat extract and seven received dog extract.³

Abbreviations used

<i>Fel d I</i> :	Name assigned by the International Union of Immunological Societies Subcommittee on Allergen Nomenclature for the cat (<i>Felis domesticus</i>) allergen, previously called cat allergen 1 ¹⁰
FDA unit:	Arbitrary unit (about 4.5 µg ²⁵) for measurements of <i>Fel d I</i> introduced by Anderson and Baer ¹¹ of the USA Food and Drug Administration
HSA-saline:	Normal saline with 0.03% human serum albumin preserved with 0.4% phenol
STEPT:	Skin test end point titration
LHR:	Leukocyte histamine release
Cat-extract PD ₂₀ :	Bronchoprovocation dose of cat extract that produces a 20% fall in FEV ₁
Methacholine PD ₂₀ :	Bronchoprovocation dose of methacholine that produces a 20% fall in FEV ₁
Cat-room exposure PD ₂₀ :	Dose of cat allergen inspired from cat-room air that produces a 20% fall in FEV ₁
r _s :	Spearman rank-correlation coefficient
pt:	Patient

extract¹⁻³ and were associated with rapid dose buildup and high peak doses. Other significant effects included decreases in bronchial reaction to inhalation challenge with cat extract,¹⁻³ delay in onset of eye and pulmonary symptoms during exposure in a room containing living cats,² decrease in cutaneous reaction to prick test with cat extract,^{1,2,8} increase in IgG antibodies to cat antigens, including *Fel d I*,^{2,7-9} and an initial rise in anticat IgE levels followed by a fall toward pretreatment levels.^{8,9} The effects of immunotherapy on non-specific bronchial reactivity differed in the three studies. One study reported significant decreases in responses to histamine bronchoprovocation³; the other two studies reported no significant changes in responses to histamine bronchoprovocation¹ and to methacholine bronchoprovocation,² respectively. However, the cat-hair and dander extract used for immunotherapy in the study³ that reported reduction in reactivity differed from the cat-pelt extract used in the studies^{1,2} that reported no change.

Our purpose was to provide more data on the safety and effectiveness of immunotherapy with cat extract for cat asthma. We have attempted to reduce the fre-

TABLE I. Patients' characteristics at the time of onset of immunotherapy

Characteristic	Treatment group	
	Cat extract	Placebo
Total No. patients	11	11
M	5	5
F	6	6
Age (yr)		
21-30	4	4
31-40	3	5
41-50	3	1
51-52	1	1
Previous immunotherapy	5 1952*	4 1953-68*
	1965	1959
	1969-71	1962-63
	1969-76	1979
	1975 (cat†)	

* Year(s) in which previous immunotherapy was administered.

† The one patient known to have received cat-extract immunotherapy previously.

quency of systemic reactions by using a dose buildup process that was slower than that used in the three previous studies.¹⁻³ We have studied the effects of immunotherapy on the results of cat-extract bronchoprovocation tests, skin tests, and in vitro LHR, on IgG antibodies toward whole cat extract, toward *Fel d I*, and toward cat albumin, on IgE antibodies toward cat extract, and on nonspecific bronchial reactivity. We have developed methods for measuring cat-room exposure PD₂₀.

METHODS**Patients**

We have treated 22 patients who had a history of asthma after exposure to cat. Their ages and sex are presented in Table I. No patient was pregnant at the onset of immunotherapy. Nine of the 22 patients had been immunized with allergenic extracts in the past (Table I), but only one patient was known to have received cat extract. None had received immunotherapy within 5 years before the onset of the present study. All patients met the following criteria: a history of repeated episodes of asthma after natural exposure to cats, a 2+ reaction to intradermal skin test to cat extract at a concentration containing no more than 4.56×10^{-4} (0.000456) FDA units per milliliter of *Fel d I*, in vitro LHR by cat extract, significant levels of IgE antibody toward cat extract, a 20% drop in FEV₁ from exposure to a room containing living cats, and also from bronchoprovocation with cat extract.

The patients were recruited by news media release, from The Johns Hopkins Allergy Clinics, and the practices of the participating physicians.

TABLE II. Treatment schedule

Dose	Concentration	ml	Dose	Concentration	ml
1	1:1000	0.1	11	1:10	0.2
2		0.2	12		0.3
3		0.35	13		0.45
4		0.7	14		0.7
5	1:100	0.1	15	CONC*	0.1
6		0.2	16		0.15
7		0.35	17		0.2
8		0.7	18		0.3
9	1:10	0.1	19		0.45
			20		0.7
10		0.15	21		1.0

*Concentrated solution of cat extract contained 4.56 FDA units of *Fel d I* per milliliter. Concentrated solution of placebo contained 0.275 mg of histamine phosphate per milliliter. Dilutions were made with HSA-saline.

Cat extract and placebo

Cat allergenic extract ALK 1209/229452 was supplied by Allergologisk Laboratories, Copenhagen, Denmark. Permission for use of this extract in this study was granted by U.S. Food and Drug Administration BB-IND 1770. This extract was prepared by extracting hair and dander obtained from overtly healthy cats. It was distributed in vials, each containing 2 million SQ units of freeze-dried extract. When the contents of one vial were reconstituted with 20 ml of diluent, the resulting solution contained 4.56 FDA units (about 21 μg^{25}) of *Fel d I* and 9.0 μg of cat albumin per milliliter. The manufacturer had demonstrated by crossed radioimmuno-electrophoresis that the extract contained *Fel d I*, cat albumin (Ag 2), and epithelial allergens, which have been designated Ag 3, Ag 11, Ag 12, and Ag 13, according to Danish Allergen Standardization 76 for cat hair and dander.¹² This extract was used for immunotherapy and for those diagnostic tests that required cat extract.

In this study we used a placebo solution that was indistinguishable in color from the cat extract. The concentrated placebo solution was prepared by diluting histamine phosphate injection, United States Pharmacopeia, 2.75 mg/ml, 1 ml in 9 ml of HSA-saline. Tenfold dilutions with HSA-saline were prepared to provide a graduated increase in local reactions caused by histamine.

Freeze-dried cat extract was stored at about -10°C ; diluted solutions were stored at about 4°C . Fresh dilutions of cat extract and placebo were made at intervals of about 1 month.

Initial screening evaluation

Initial evaluation of prospective patients began with history and physical examination. Thereafter, intradermal STEPT with cat extract was accomplished according to the method of Norman et al.¹³ Serial tenfold dilutions of reconstituted cat extract were applied to the skin of the patient's back. Testing was carried through dilutions weak enough to elicit a negative or trace reaction. Disposable 1.0 ml tuberculin syringes with 26-gauge needles were used to

inject 0.05 ml of the extract dilutions intradermally. The result was read 15 minutes after application of the test. The perimeter of the zone of erythema and the perimeter of the wheal produced by each intradermal skin test were outlined with a ballpoint pen with black ink. Hypoallergenic micro-pore surgical tape (3M No. 1535, 3M Medical-Surgical Division, St. Paul, Minn.) was applied to the tracing to take off the results of the test. The tape was mounted on white paper and produced a permanent record of the perimeter of the wheal and of the erythema. The largest diameter of the wheal and the orthogonal diameter (that diameter perpendicular to the midpoint of the largest diameter of the wheal²⁴) were measured, and the arithmetic mean of these two values was taken as the diameter of the wheal. The mean diameter of the zone of erythema was calculated in a similar fashion from the measurements of its largest diameter and of its orthogonal diameter. The end point was the equivalent dose of *Fel d I* in FDA units that was contained within 0.05 ml of the most dilute solution required to produce a 2+ skin reaction (wheal diameter, ≥ 10 mm; erythema diameter, 20 to 30 mm). Where successive tenfold dilutions produced a 0 to 1+ reaction (wheal diameter, < 10 mm; erythema diameter, < 20 mm) followed by a 3+ or greater reaction (wheal diameter, ≥ 10 mm; erythema diameter, > 30 mm), the end point was the dose halfway between the log dose for 1+ reaction and the log dose for 3+ or greater reaction. Patients were admitted to the study who had a 2+ reaction to a dilution equal to or less concentrated than a 1:10,000 dilution of an extract containing 4.56 FDA units per milliliter of *Fel d I*.

To calculate more precisely the dose of extract that produced a definable end point in the intradermal test, we measured the dose required to produce a zone of skin erythema with a mean diameter of 20 mm by a modification of the method described by Turkeltaub et al.²⁴ The mean erythema diameter was plotted as a function of the log dose of cat extract (in FDA units of *Fel d I* equivalents) for the two successive tenfold dilutions of cat extract that produced erythema diameters of < 20 mm and of

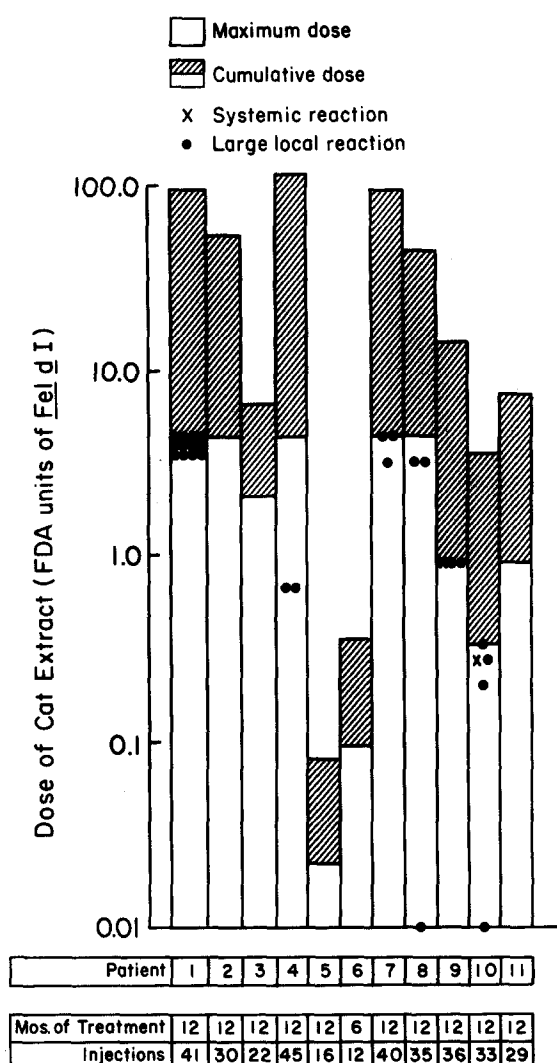


FIG. 1. The maximum single dose and the cumulative dose of cat extract administered to each patient during the first year of immunotherapy. Also illustrated is the dose at which each large local reaction and each systemic reaction occurred, the number of months during the year in which treatment was administered, and the number of injections administered.

>20 mm, respectively, and the dose was calculated that produced a zone of erythema with a mean diameter of 20 mm.

Comprehensive initial evaluation

Patients meeting the criteria for entry into the study described above were further evaluated. Hematocrit, total and differential white blood cell counts, and urinalysis were performed.

Allergy skin testing with seasonal and perennial inhalant allergens was accomplished by methods routinely used in The Johns Hopkins Allergy Clinics.

In vitro LHR by cat extract was done by a method that used micromodification of the release phase according to

the method of May et al.¹⁴ and the automated measurement of histamine according to the technique of Siraganian.¹⁵

Serum levels of anticat IgE toward cat extract were measured by an agarose-based RAST,¹⁶ and total IgE levels were measured by a noncompetitive radioimmunosorbent test, as described previously.¹⁶ Serum levels of anticat IgG toward cat extract were measured by *Staphylococcus aureus* protein A solid-phase radioimmunoassay with the same allergosorbent as for the RAST.¹⁷ The cat allergosorbent used for both the IgE and IgG determinations was prepared from the cat extract used for the study.

Specific IgG and IgE antibodies toward highly purified *Fel d I* and cat albumin were measured by a double-antibody radioimmunoassay⁷ with the *Fel d I* preparation reported previously⁴ and a cat-albumin preparation kindly supplied by Dr. John Ohman.⁷ IgE antibody levels were measured only on pretreatment sera because of probable interference in the IgE determination from the high IgG antibody levels found in most posttreatment sera. The antibody levels toward both purified cat allergens are expressed in arbitrary units per milliliter where 1 unit is about 1 ng. These units were carefully calibrated against units used in a previous study⁷ to ensure comparability between studies.

Bronchoprovocation with cat extract was performed, as described previously.⁴ Increasing concentrations were administered until a 20% or greater fall in FEV₁ was observed and methacholine PD₂₀ could be calculated.

Bronchoprovocation with methacholine was administered, as previously described.⁴ Increasing concentrations were administered until methacholine PD₂₀ or greater was observed and could be calculated.

Cat-room exposure was accomplished by methods previously reported.⁴ Exposure was continued for a maximum of 2 hours. It was stopped when the patient experienced a 20% or greater fall in FEV₁ so that cat-room exposure PD₂₀ (in *Fel d I* equivalents) could be calculated. In those circumstances in which the patient experienced less than cat-room exposure PD₂₀ during the 2-hour exposure period, the cat-room exposure PD₂₀ could not be calculated.

Treatment

Patients were divided into two matched groups; each group ultimately contained 11 patients. Matching of the groups was based on sensitivity to the study cat extract as determined by intradermal STEPT, in vitro LHR, and cat-extract PD₂₀, and on nonspecific bronchial reactivity, as measured by methacholine PD₂₀. Patients were entered into immunotherapy in cohorts containing four to six patients. By random selection, one group received cat extract and the other group received placebo at intervals of about 1 week, according to the schedule of injections presented in Table II. After dose No. 21 was achieved, this dose was continued as a maintenance dose at intervals of about 2 weeks until the patient had had a year or more of treatment. If local or systemic reactions prevented reaching dose no. 21, the highest tolerated dose was administered as a maintenance dose.

Blinding was accomplished by methods previously described.¹⁸ Briefly, the personnel was divided into an injecting and an evaluating team. The injecting team decided doses in full knowledge of the patient's treatment and responses but did not evaluate the patient's response to treatment. The evaluating team carried out all patient contacts except the actual injections but remained blind to the treatment. The patients did not know what treatment they were receiving.

Observations

Patients kept a daily record of asthmatic symptoms and medications taken.^{19, 20} During the initial series of injections of rising doses of extract and the subsequent course of maintenance injections, we obtained a physician record of symptoms and physical findings pertaining to asthma and a measurement of peak expiratory flow²⁰ each time the patient attended the clinic.

Intradermal STEPT, in vitro LHR, cat-extract PD₂₀, and methacholine PD₂₀ were measured before immunotherapy and at about 6-month intervals thereafter. Serum levels of IgG and IgE antibodies toward the whole cat extract were measured before immunotherapy and at about 3-week intervals during the dose buildup phase of immunotherapy and at about 3-month intervals thereafter. IgG antibody levels toward *Fel d I* and toward cat albumin were measured before immunotherapy and at about 6-month intervals thereafter in the patients treated with cat extract. In placebo-treated patients, they were measured before treatment and after about 1 year of treatment, or after about 6 months of treatment in patients treated for less than 1 year. IgE antibodies toward *Fel d I* and toward cat albumin were measured before immunotherapy.

The technique for measuring responses to the room containing living cats⁴ was not developed until five patients (cat extract-treated group patients 2, 7, and 8; placebo-treated group patients 3 and 5) had received immunotherapy for 1 year and six patients (cat extract-treated group patients 3, 4, and 5; placebo-treated group patients 2, 4, and 7) had received immunotherapy for 6 months. Therefore, only 11 patients (cat extract-treated group patients 1, 6, 9, 10, and 11; placebo-treated group patients 1, 6, 8, 9, 10, and 11) had measurements of these responses made before treatment and, for the duration of treatment, at about 6-month intervals thereafter. The other patients had their first measurements about 6 months after onset of treatment (six patients) or about 1 year after the onset of treatment (five patients) (see Fig. 8).

Analysis of data

Data from placebo-treated and cat extract-treated patients were compared by the nonparametric Mann-Whitney U test²¹ or the Wilcoxon ranked-sums test.²² The r_s was used to measure the significance of the correlations between the results of various tests used in the same patient.²¹ Data reduction and statistical testing were performed with the CLINFO computer system provided by the National Institutes of Health Division of Research Resources to The Johns Hopkins University School of Medicine.

TABLE III. Large local reactions and systemic reactions during the first year of immunotherapy with cat extract

	No.
Subjects	11
Injections	339
Large local reactions	
Reactors	6
Reactions	26
Reactions per 100 injections	7.7
Systemic reactions	
Reactors	2
Reactions	2
Reactions per 100 injections	0.6

RESULTS

Matching of patient groups

The patient group that received cat extract and the group that received placebo were matched so that they were not significantly different with reference to pre-treatment measurements of responses to cat-extract intradermal STEPT and in vitro LHR tests, measurements of cat-extract PD₂₀ and methacholine PD₂₀, serum levels of IgG and IgE antibodies toward whole cat extract, *Fel d I*, and cat albumin (see Figs. 2 to 7).

Dosage achieved (Fig. 1)

During the first year of immunotherapy with cat extract, five of the 11 patients achieved the target maximum dose of 4.56 FDA units of *Fel d I* equivalents, and four other patients achieved maximum doses of 2.05, 0.91, 0.91, and 0.32 FDA units of *Fel d I*, respectively. These nine patients received a total of 22 to 45 (median 35) injections and cumulative doses of 3.6 to 115.8 (median 46.2) FDA units of *Fel d I* equivalents during a time period of 12 months. They were considered to have received adequate treatment with cat extract. Two other patients received much lower doses and were considered to have received inadequate treatment with cat extract. One patient (No. 5) came in for injections at very irregular intervals, and during the first 12 months of immunotherapy, had only 16 injections and achieved a maximum dose of 0.02 and a cumulative dose of 0.08 FDA units of *Fel d I*. The other patient (No. 6) dropped out of the trial after 6 months of therapy at a time when she had received 12 injections and had achieved a maximum dose of 0.09 and a cumulative dose of 0.36 FDA units of *Fel d I*.

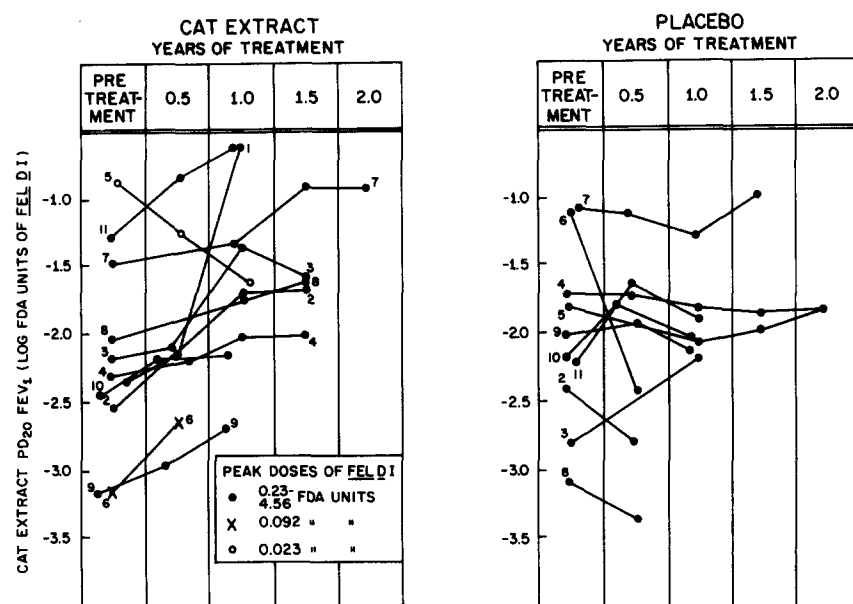


FIG. 2. Cat-extract PD₂₀ in log FDA units of *Fel d I* before treatment and at 6-month intervals for the duration of treatment.

Untoward reactions

The reactions that occurred during the first year of immunotherapy in the patients that received cat extract are listed in Table III. Two subjects each had one mild systemic reaction that required treatment with antihistamines. The systemic reaction rate was 0.6 reactions per 100 injections. Twenty-six large local reactions (induration >5 cm in diameter) occurred in the 11 patients, a reaction rate of 7.7 per 100 injections. Twelve of these reactions (46% of the total) were observed in one patient. Five subjects had neither systemic nor large local reactions. The doses at which systemic and large local reactions occurred are presented in Fig. 1.

Treatment and control groups

For the purpose of data analysis, the patients were divided into a treatment group and a control group. The treatment group contained the nine patients who were considered to have achieved adequate maintenance doses of cat extract between 0.23* and 4.56 FDA units (about 1 to 21 μg^{25}) of *Fel d I*. The control group contained the 11 patients who received placebo and the two patients who were considered to have achieved inadequate maintenance doses of cat extract of 0.023 and 0.092 FDA units (about 0.1 to 0.5 μg^{25}) of *Fel d I*, respectively. The responses of the two

patients who received inadequate doses of cat extract are differentiated from responses of the nine patients who received adequate doses in the figures that report the data (Figs. 2 to 8). Treatment and control groups demonstrated no significant differences with reference to pretreatment measurements of cat-extract PD₂₀ (Fig. 2), cat-extract intradermal STEPT (Fig. 3), methacholine PD₂₀ (see Fig. 5), IgG antibody levels toward whole cat extract, *Fel d I*, and cat albumin (see Fig. 6), IgE antibody levels toward whole cat extract (see Fig. 7), *Fel d I*, cat and cat albumin, and in vitro LHR by whole cat extract (Fig. 4). The responses of the nine patients in the treatment group were also compared to the responses of the 11 patients who received placebo (placebo-treated group).

Responses of patients to cat-extract bronchoprovocation (Fig. 2)

After 6 months of immunotherapy, the patients in the treatment group had a small but not yet significant increase in cat-extract PD₂₀ in comparison to the patients in the control group and to patients of the placebo-treated group. Comparison of the ratios of the values of these measurements at 6 months to the values of measurements obtained before treatment in patients in the treatment group and the control group revealed a median ratio of 1.45 in the treatment group (range, 1.15 to 3.24) and a median ratio of 0.95 (range, 0.045 to 3.16) in the control group ($p = 0.1$). Comparison of the same ratios in the patients in the treatment group to these ratios in patients in the placebo-treated group

*Patient No. 10 had large local or systemic reactions to doses containing 0.32 and 0.27 FDA units of *Fel d I* (Fig. 1) and therefore was maintained at a dose containing 0.23 FDA units of *Fel d I*.

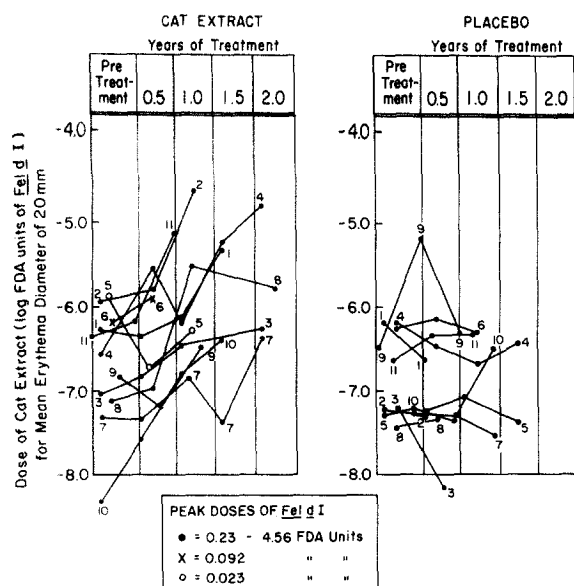


FIG. 3. Intradermal doses of cat extract in log FDA units of *Fel d I* required to produce a zone of skin erythema with a mean diameter of 20 mm before treatment and at 6-month intervals for the duration of treatment.

(median, 0.95; range, 0.045 to 3.16) revealed a similar trend ($p < 0.1 > 0.05$).

After 1 year of immunotherapy, the patients in the treatment group had a larger and by now significant increase in cat-extract PD₂₀ in comparison to patients in the placebo-treated group. Comparison of the ratios of the values of the measurements at 1 year to the values of the measurements obtained before treatment in patients in the treatment and control groups revealed a median ratio of 2.8 (range, 1.2 to 46.8) in the treatment group and a median ratio of 0.80 (range, 0.15 to 3.8) in the control group ($p < 0.01$). Comparison of the same ratios in the patients in the treatment group to these ratios in patients in the placebo-treated group (median, 0.83; range, 0.55 to 3.8) also revealed a significant difference ($p < 0.01$).

Responses of patients to cat-extract intradermal STEPT (Fig. 3)

After 1 year of immunotherapy (but not after 6 months of immunotherapy), the patients in the treatment group, in comparison to patients in the control group, had a significant increase in the intradermal STEPT dose of cat extract required to produce a zone of skin erythema with a mean diameter of 20 mm. Comparison of the ratios of the values of these measurements at 1 year to the values obtained before treatment in patients in the treatment and control groups revealed a median ratio of 3.98 (range, 1.4 to 58.9) in the treatment group and a median ratio of 1.16 (range, 0.31 to 5.2) in the control group ($p < 0.01$). Comparison of the same ratios in patients in the treat-

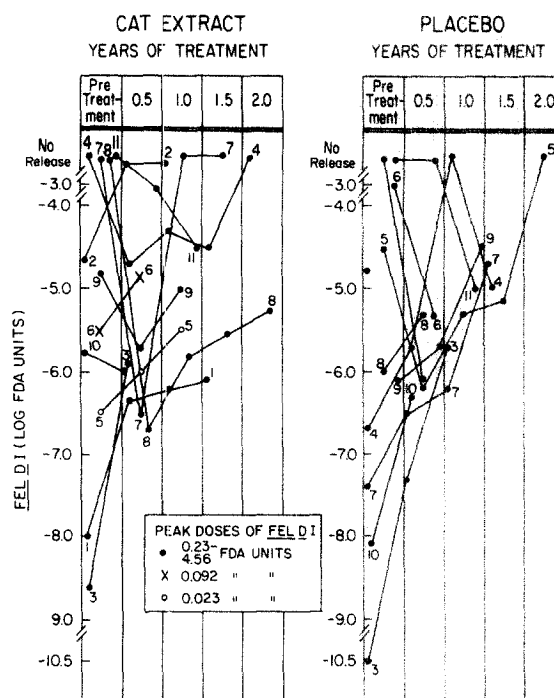


FIG. 4. The quantity of cat extract in log FDA units of *Fel d I* required to produce 50% in vitro LHR before treatment and at 6-month intervals for the duration of therapy.

ment group to these ratios in patients in the placebo-treated group (median, 1.51; range, 0.31 to 5.2) revealed a similar significant difference ($p < 0.01$).

Responses of patients to in vitro LHR tests (Fig. 4)

After 1 year of immunotherapy, there was no significant difference between the patients in the treatment group and those in the control group with regard to responses to in vitro LHR tests, as measured by the doses of cat extract, expressed in FDA units of *Fel d I*, required for 50% in vitro LHR. Comparison of the ratios of the values of these measurements at 1 year to the values of measurements made before treatment in patients in the treatment and control groups revealed a median ratio of 0.76 (range, 0.0000016 to 47,863) in the treatment group and a median ratio of 15.1 (range, 0.00001 to 5,011,812) in the control group ($p = 0.159$). The wide variability of the values of the measurements was noteworthy and was observed both within the groups of patients and in most individual patients.

Responses of patients to methacholine bronchoprovocation (Fig. 5)

After 1 year of immunotherapy, there was no significant difference between the patients in the treatment group and patients in the control group with reference to responses to methacholine bronchoprov-

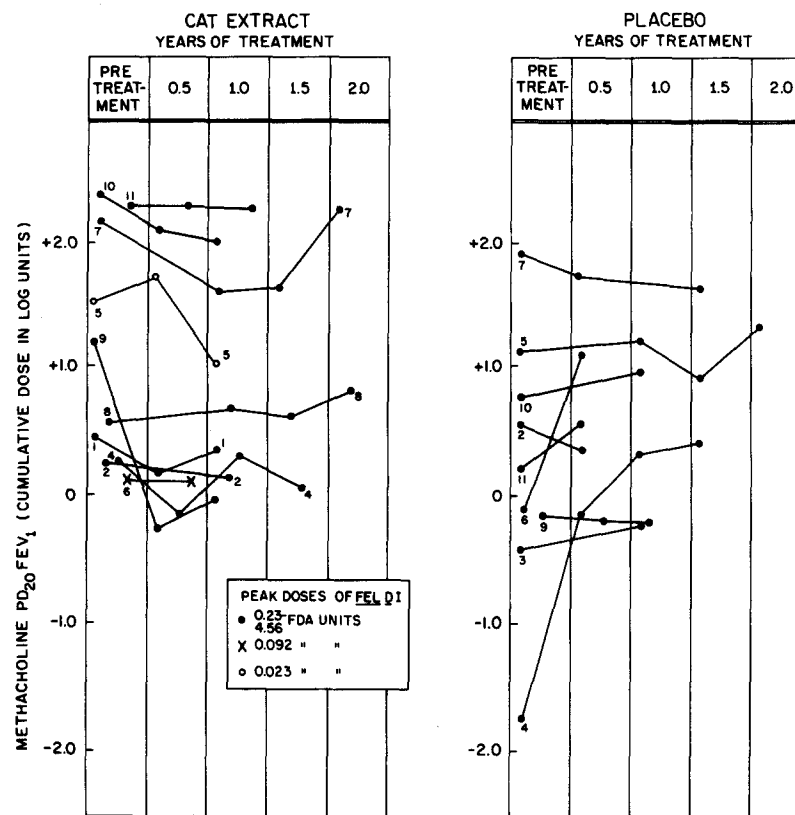


FIG. 5. Methacholine PD₂₀ in log units before treatment and at 6-month intervals for the duration of treatment.

ocation. Comparison of the ratios of the values of methacholine PD₂₀ measurements at 1 year to the values of measurements made before treatment in patients in the treatment and control groups revealed a median ratio of 0.76 (range, 0.28 to 1.3) in the treatment group and a median ratio of 1.32 (range, 0.33 to 125.9) in the control group ($p = 0.18$).

Anticat IgG antibody levels (Fig. 6)

Toward whole cat extract. After both 6 months and 1 year of immunotherapy, the patients in the treatment group, in comparison to patients in the control group, had a significant increase in IgG antibody toward whole cat extract (Fig. 6). Comparison of the ratios of the values of these measurements at 6 months to the values obtained before treatment in patients in the treatment and control groups revealed a median ratio of 1.60 (range, 1.09 to 2.47) in the treatment group and a median ratio of 0.94 (range, 0.52 to 1.49) in the control group ($p < 0.001$). Comparison of the ratios of the values of these measurements at 1 year to the values obtained before treatment in patients in the treatment and control groups revealed a median ratio of 3.93 (range, 1.77 to 30.7) in the treatment group and a median ratio of 1.1 (range, 0.36 to 2.14) in the control group ($p < 0.001$).

Comparison of the same ratios in the patients in the treatment group to these ratios in patients in the placebo-treated group (6-month median, 0.94; range, 0.52 to 1.49; 6-month median, 1.1; range, 0.36 to 2.14) revealed similar highly significant differences ($p = 0.0025$). After 1 year of immunotherapy, these antibody levels tended to plateau.

Toward Fel d I. After 1 year of immunotherapy, the patients in the treatment group, in comparison to patients in the control group, had a significant increase in IgG antibody toward *Fel d I* (Fig. 6). Comparison of the ratios of the values of these measurements at 1 year to the values obtained before treatment in patients in the treatment and control groups revealed a median ratio of 13.5 (range, 4.75 to 33.1) in the treatment group and a median ratio of 0.9 (range, 0.53 to 2.77) in the control group ($p < 0.001$). Comparison of the same ratios in patients in the treatment group to these ratios in patients in the placebo-treated group (median, 0.9; range, 0.53 to 2.77) revealed similar highly significant differences ($p < 0.001$).

Toward cat albumin. After 1 year of immunotherapy, the patients in the treatment group, in comparison to patients in the control group, had a significant increase in IgG antibody toward cat albumin (Fig. 6). Comparison of the ratios of the values of these mea-

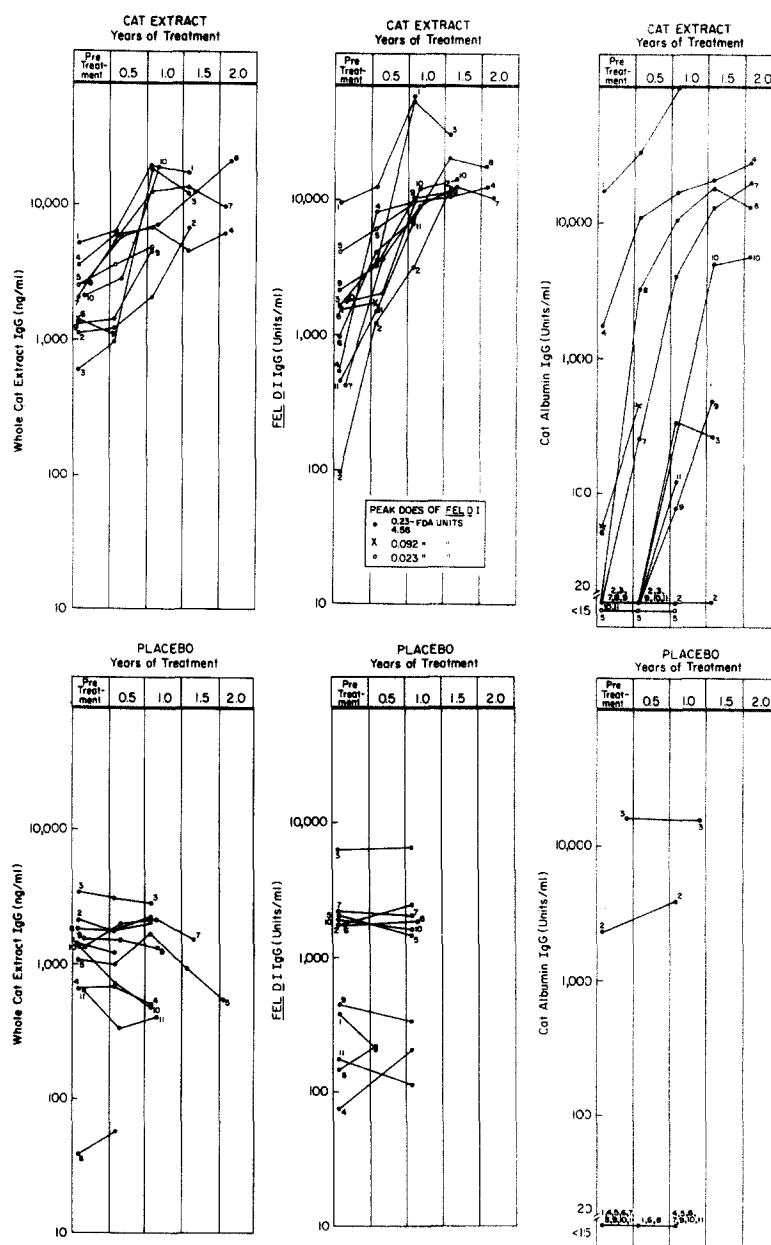


FIG. 6. Serum levels of IgG antibody toward whole cat extract in nanograms per milliliter toward *Fel d I* in units per milliliter, and toward cat albumin in units per milliliter before treatment and at 6-month intervals for the duration of treatment, except for levels toward *Fel d I* and toward cat albumin in placebo-treated patients, which were made only after 1 year of treatment or after 6 months of treatment in these patients treated for less than 1 year.

measurements at 1 year to the values obtained before treatment in patients in the treatment and control groups revealed a median ratio of 9.91 (range, 1 to 743) in the treatment group and a median ratio of 1.0 (range, 0.94 to 1.67) in the control group ($p < 0.001$). Comparison of the same ratios in patients in the treatment group to these ratios in patients in the placebo-treated group (median, 1.0; range, 0.94 to 1.67) revealed similar highly significant differences ($p < 0.001$). Although each of the nine patients in the treatment group had an increase in IgG antibodies toward both

whole cat extract and *fel d I*, eight of these nine patients had an increase in IgG antibody toward cat albumin and one did not.

Anticat IgE antibody levels (Fig. 7)

Toward whole cat extract. Most of the patients who received cat extract had a modest rise in serum level of IgE antibody toward whole cat extract, followed by a fall to levels near or slightly below the pretreatment levels. Most patients who received placebo demonstrated little change in IgE levels. After both 6

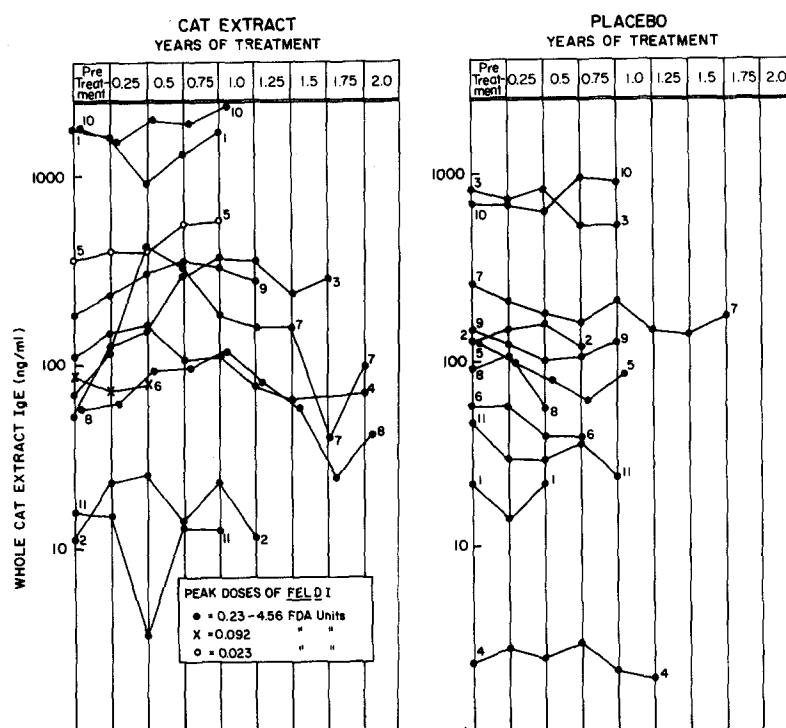


FIG. 7. Serum levels of IgE antibody toward whole cat extract in nanograms per milliliter before treatment and at 3-month intervals for the duration of treatment.

months and 1 year of immunotherapy, the patients in the treatment group, in comparison to patients in the control group, had a significant increase in IgE antibodies toward whole cat extract. Comparison of the ratios of the values of these measurements at 6 months to those obtained before treatment in patients in the treatment and control groups revealed a median ratio of 1.59 (range, 0.22 to 6.04) in the treatment group and a median ratio of 0.89 (range, 0.64 to 1.24) in the control group ($p = 0.025$). Comparison of the ratios of the values of these measurements at 1 year to values obtained before treatment in the treatment and control groups revealed a median ratio of 1.77 (range, 0.8 to 7.01) in the treatment group and a median ratio of 0.83 (range, 0.51 to 1.64) in the control group ($p < 0.01$). Comparison of the same ratios in the patients in the treatment group to these ratios in patients in the placebo-treated group (6-month median, 0.68; range, 0.64 to 1.24; 1-year median, 0.8; range, 0.51 to 1.27) revealed similar significant differences (6 months, $p = 0.025$; 1 year, $p < 0.01$).

Toward Fel d I. All patients with IgE antibody toward whole cat extract before immunotherapy had detectable serum levels of IgE antibody toward Fel d I. These levels in units per milliliter were the following for cat-extract treated patients: 4 (pt 11), 5 (pt 6), 7 (pt 8), 9 (pt 2), 11 (pt 3), 17 (pt 7), 18 (pt 4),

19 (pt 9), 30 (pt 5), 53 (pt 10), and 57 (pt 1). For placebo-treated patients, levels were 5 (pt 4), 6 (pts 5 and 8), 9 (pt 11), 10 (pt 6), 12 (pt 1), 19 (pt 7), 27 (pt 9), and 45 (pts 2, 3, and 10). For each patient, there was significant rank correlation between the levels of IgE antibody toward whole cat extract and levels toward Fel d I ($r_s = 0.81$; $p < 0.01$).

Toward cat albumin. Only three of the 22 patients had detectable serum levels of IgE antibody toward cat albumin before treatment. The serum level in units per milliliter was 26 in cat extract-treated patient 1, and levels were 9 and 54, respectively, in placebo-treated patients 2 and 3.

Responses of patients to deliberate natural exposure to cats (Fig. 8)

Not every patient had measurements before treatment and after 6 months of immunotherapy because the method was not developed until the first cohort of five patients had been treated for 1 year and the second cohort of six patients had been treated for 6 months. Furthermore, there are multiple instances (Fig. 8, open circles) in which exposure to cat allergen in the cat room was not sufficient to produce a 20% fall in FEV₁. Nevertheless, the data demonstrate a trend for all adequately treated patients to require a greater dose to respond, whereas of 11 patients receiving placebo, four required a greater exposure and two required less.

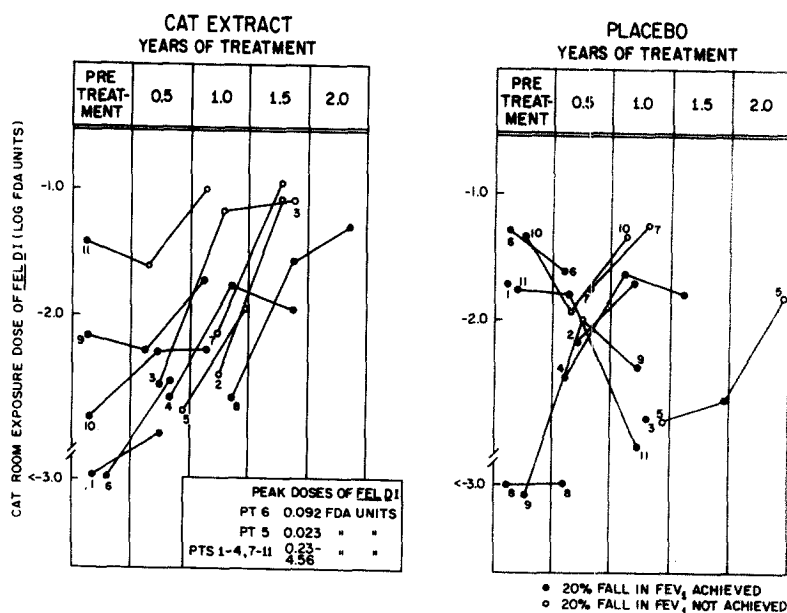


FIG. 8. The cat-exposure dose of *Fel d 1* in log FDA units in the cat room. Those doses that produced a 20% fall in FEV₁ in 2 hours or less time are illustrated by *closed circles*; those doses that did not produce a 20% fall in FEV₁ are illustrated by *open circles*. In those circumstances in which the technique was available for use (see text), the measurements were made in each patient before treatment and at 6-month intervals for the duration of treatment.

There is difficulty with statistical analysis of the data because of the problems mentioned above.

DISCUSSION

After 1 year of immunotherapy, our treated patients had decreased sensitivity to the effects of broncho-provocation with cat extract. The ratio between the value of cat-extract PD₂₀ at this time to the value before treatment was larger in patients in the treatment group (median ratio, 2.8) than in patients in the control group (median ratio, 0.8). This difference in ratios was highly significant ($p < 0.01$), albeit relatively small. Our favorable results confirm those of previous trials.¹⁻³ Thus, decreased bronchial sensitivity to cat extract in immunized patients has now been demonstrated by somewhat different but comparable methods in four different trials that have used a total of 38 immunized patients and 38 control patients. The decrease in sensitivity to cat-extract bronchoprovocation probably means that the patients also had a significant decrease in sensitivity to natural exposure to cats, because we have demonstrated previously that specific measurements of sensitivity by exposure to cat (cat-room exposure PD₂₀) were significantly correlated with the results cat-extract PD₂₀ when the measurements were made on the same patient at approximately the same time.⁴

After 1 year of immunotherapy, our treated patients also had decreased sensitivity to intradermal skin tests

with cat extract. The ratio of the intradermal STEPT dose of cat extract required to produce skin erythema with a mean diameter of 20 mm after 1 year of treatment to the same dose before treatment was significantly larger ($p < 0.025$) in patients in the treatment group (median ratio, 3.0) than in patients in the control group (median ratio, 1.16). This finding of decreased skin sensitivity to cat extract in treated patients is demonstrated for the first time by use of the intradermal test but is comparable to the decrease in skin sensitivity to prick test with cat extract demonstrated in the three previous trials.¹⁻³ We have made a comparison of the results of intradermal tests and of prick tests in our patients with three different end points for the prick tests and two different end points for the intradermal test and have demonstrated significant decrease in skin sensitivity to cat extract after 1 year of immunotherapy by all five methods ($p < 0.025$ to < 0.01). These results will be reported in detail elsewhere.

We found no significant differences between the patients in the treatment group and patients in the control group with regard to their responses to in vitro LHR tests. These findings agree with findings previously reported by our group for adult patients with ragweed-pollen hay fever treated with ragweed-pollen extract.^{18, 23} However, the wide inpatient variability and interpatient variability of the results of the in vitro LHR tests with cat extract differed from the more

restricted variability noted with in vitro LHR tests with ragweed extract.^{18, 23} The reason for these differences is not apparent.

In our patients, immunotherapy with cat extract produced no change in sensitivity to inhaled methacholine. These findings are in agreement with those of two previous trials that reported insignificant changes in responses to methacholine bronchoprovocation² and to histamine bronchoprovocation,¹ respectively. Our findings disagree with findings of a third study that reported significant decreases in response to histamine bronchoprovocation.³ The reason for these differences is not entirely clear. The patients in the Scandinavian study who had a decrease in nonspecific bronchial reactivity³ had no cats or other furred animals at home.⁹ Patients in the present study and in the other two U.S. studies^{1, 2} had variable exposure to cat at home. It has been postulated that the increase in nonspecific bronchial reactivity in patients with asthma is a consequence of bronchial inflammation caused by the allergic reaction of the bronchi to chronic continuing exposure to specific allergens.²⁶⁻²⁹ Thus, patients with a higher level of chronic exposure to cats might demonstrate less decrease in nonspecific bronchial reactivity after effective immunotherapy with cat extract than patients with a lower level of exposure. Furthermore, it may require treatment with all significant allergens (rather than a single one) to achieve a change in nonspecific reactivity.

Immunotherapy with cat extract in doses between 0.23 and 4.56 FDA units (about 1 to 21 μg^{25}) of *Fel d I* was associated with large and highly significant increases in serum levels of IgG antibody to whole cat extract, similar to increases demonstrated in the three previous trials.^{2, 8, 9} As previously demonstrated by one of our group for sera obtained from one⁷ of the three previous trials, these increases in specific IgG antibody have always included significant increases in antibody to *Fel d I*, and frequently (observed in eight of nine patients in this study and in 13 of 16 patients in the previous study⁷) have also included increases in IgG antibodies to cat albumin.

Immunotherapy with cat extract in doses between 0.23 and 4.56 FDA units (circa 1 to 21 μg^{25}) of *Fel d I* was usually associated with an increase in serum levels of IgE antibody to whole cat extract. In comparison to patients in the control group, patients in the treatment group had significant increases in serum levels of this specific IgE antibody after treatment for 6 months ($p = 0.025$) and for 1 year ($p < 0.01$). The increase after 1 year of treatment occurred at a time when bronchial sensitivity to cat extract and skin sensitivity to cat extract were both significantly decreased. Evidently, the decreased bronchial and

skin sensitivity to cat extract observed in these patients is not due to decrease in serum levels of IgE antibody toward cat extract. Ultimately, in most patients followed long enough, the serum levels of IgE antibody toward whole cat extract fell to levels near or lower than the levels before immunotherapy. These findings are similar to findings previously reported by the Scandinavian group.⁸

Before immunotherapy, all patients had IgE antibody toward whole cat extract and toward *Fel d I*. There was significant correlation ($r_s = 0.81$; $p < 0.01$) between the serum levels of IgE toward whole cat extract and levels toward *Fel d I*. This finding supports the previous findings that *Fel d I* is the major allergen in whole cat extract.^{2-4, 7-11}

Our patients had less frequent systemic reactions to immunotherapy (one reaction each in two of the 11 patients) than the patients reported in the three previous trials (one or more reactions in 18 of the 29 patients; see footnote page 1055). We attribute this decrease in frequency of systemic reactions to a slower buildup in dose than that used in two of the previous trials^{2, 3} and to both a slower buildup in dose and a lower peak dose than that used in the third previous trial.¹ However, it is important to emphasize that despite considerable caution in advancing doses, a few systemic reactions occurred in our patients receiving cat extract. These systemic reactions were similar in type but occurred less frequently than reactions observed in our studies of immunotherapy with ragweed-pollen extract administered by comparable schedules (cat, 0.6 systemic reactions per 100 injections; ragweed, 3.2 systemic reactions per 100 injections).^{18, 23}

We conclude that immunotherapy with cat-hair and dander extract is as safe as immunotherapy with ragweed-pollen extract when comparable dose buildup schedules and maintenance doses are used.

More data are needed on the effects of immunotherapy with cat extract on the responses of patients to natural exposure to cats. It appears desirable that the technique used in this trial for measuring cat-room exposure PD_{20} should be modified to deliver, in 30 minutes, about tenfold more cat allergen than that delivered in 2 hours by the technique used in the present study. Such an increment would elicit, in about 30 minutes of exposure in the cat room, a dose of about 0.23 FDA units (-0.64 log FDA units) of *Fel d I*, a dose of cat allergen equivalent to the peak cumulative doses provided by our bronchoprovocation technique at the present time. These doses should permit attaining a 20% fall in FEV_1 with all or most natural exposures to cats and thus generate data on decreased sensitivity to natural exposure to cat comparable to the data on decreased sensitivity to bronchoprovocation with cat extract. It would then be pos-

sible to measure cat-room exposure PD_{20} before treatment and at 6-month intervals for the duration of treatment.

This study demonstrated that our patients who received adequate doses of cat extract for 1 year had a highly significant decrease in both bronchial and skin sensitivity to cat allergen. However, it is important to recognize that this decrease in sensitivity is limited; it is not a complete loss of sensitivity. The median decrease in both bronchial and skin sensitivity is about threefold. A less than complete reduction in sensitivity can only provide protection against cat-allergen exposure that is less than the newly raised level of tolerance. How often the amount of cat allergen in the natural environment will exceed the protection afforded by immunotherapy needs further study. Optimal control of cat asthma will probably require a combination of reduction in cat-allergen exposure and immunotherapy with cat allergenic extract, supplemented by bronchodilators on occasions when asthma breaks through these preventive measures. What exposure elicits late-phase reactions has not been studied here, nor has the effect of immunotherapy on such reactions been investigated.

REFERENCES

1. Taylor WW, Ohman JL, Lowell FC. Immunotherapy in cat-induced asthma: double-blind trial with evaluation of bronchial responses to cat allergen and histamine. *J ALLERGY CLIN IMMUNOL* 1978;61:283-7.
2. Ohman JL, Findlay SR, Leiterman M. Immunotherapy in cat-induced asthma: double-blind trial with evaluation of in vivo and in vitro responses. *J ALLERGY CLIN IMMUNOL* 1984;74:230-9.
3. Sundin B, Lilja G, Graff-Lonnevig V, Hedlin G, Heilborn H, Norrlind K, Pegelow KO, Løwenstein H. Immunotherapy with partially purified and standardized animal dander extract. I. Clinical results of a double-blind study on patients with animal-dander asthma. *J ALLERGY CLIN IMMUNOL* 1986;77:478-87.
4. Van Metre TE, Marsh DG, Adkinson NF, Fish JE, Kagey-Sobotka A, Norman PS, Radden EB, Rosenberg GL. Dose of cat (*Felis domesticus*) allergen I (*Fel d I*) that induces asthma. *J ALLERGY CLIN IMMUNOL* 1986;78:62-75.
5. The veterinary services market. *J Am Vet Med Assoc* 1983;183:841.
6. Wood RA, Eggleston PA, Lind P, Ingemann L, Schwartz B, Graveson S, Terry D, Wheeler B, Adkinson NF. Antigenic analysis of house dust samples. *Am Rev Respir Dis* 1988;137:358-63.
7. Ohman JL, Marsh DG, Goldman M. Antibody responses following immunotherapy with cat pelt extract. *J ALLERGY CLIN IMMUNOL* 1982;69:320-6.
8. Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Sundin B, Løwenstein H. Immunotherapy with cat- and dog-dander extracts. II. In vivo and in vitro immunologic effects observed in a 1-year double-blind placebo study. *J ALLERGY CLIN IMMUNOL* 1986;77:488-96.
9. Løwenstein H, Graff-Lonnevig V, Hedlin G, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Sundin B. Immunotherapy with cat- and dog-dander extracts. III. Allergen-specific immunoglobulin responses in a 1-year double-blind placebo study. *J ALLERGY CLIN IMMUNOL* 1986;77:497-505.
10. Marsh DG, Goodfriend L, King TP, Løwenstein H, Platts-Mills TAE. Allergen nomenclature. *J ALLERGY CLIN IMMUNOL* 1987;80:639-45.
11. Anderson MC, Baer H. Allergenic active components of cat-allergen extracts. *J Immunol* 1981;127:972-5.
12. Løwenstein H. Physicochemical and immunochemical methods for the control of potency and quality of allergenic extracts. In: Brede HD, Göing H, eds. *Regulatory control and standardization of allergenic extracts*. Stuttgart: Gustav Fischer Verlag, 1980:75.
13. Norman PS, Lichtenstein LM, Ishizaka K. Diagnostic tests in ragweed hay fever: a comparison of direct skin tests, IgE antibody measurements, and basophil histamine release. *J ALLERGY CLIN IMMUNOL* 1973;52:210-24.
14. May DC, Lyman M, Alberto R, Cheng J. Procedures for immunochemical study of histamine release from leukocytes with small volumes of blood. *J ALLERGY CLIN IMMUNOL* 1970;46:12-28.
15. Siraganian RP. An automated continuous-flow system for the extraction and fluorometric analysis of histamine. *Anal Biochem* 1974;57:383-94.
16. Adkinson NF Jr. Measurement of total serum immunoglobulin E and allergen-specific immunoglobulin E antibody. In: Rose M, Freidman H, eds. *Manual of clinical immunology*. Washington, D.C.: American Society of Microbiology, 1976.
17. Hamilton RG, Sobotka AK, Adkinson NF Jr. Solid phase radioimmunoassay for quantitation of antigen-specific IgG in human sera with ^{125}I protein A from *Staphylococcus aureus*. *J Immunol* 1979;122:1073-9.
18. Van Metre TE Jr, Adkinson NF, Amodio FJ, Lichtenstein LM, Mardiney MR, Norman PS, Rosenberg GL, Sobotka AK, Valentine MD. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. *J ALLERGY CLIN IMMUNOL* 1980;66:500-13.
19. Van Metre TE Jr, Anderson AS, Barnard JH, Bernstein IL, Chafee FH, Crawford LV, Wittig HJ. A controlled study of the effects on manifestations of chronic asthma of a rigid elimination diet based on Rowe's cereal-free diet. 1, 2, 3. *J ALLERGY* 1968;41:195-208.
20. Bruce CA, Norman PS, Rosenthal RR, Lichtenstein LM. The role of ragweed pollen in autumnal asthma. *J ALLERGY CLIN IMMUNOL* 1977;59:449-59.
21. Siegel S. *Nonparametric statistics for the behavioral sciences*. New York: McGraw-Hill, 1956.
22. Lindgren BW. *Statistical theory*. 2nd ed. London: MacMillan Co., 1968:437-8.
23. Van Metre TE Jr, Adkinson NF, Amodio FJ, Kagey-Sobotka A, Lichtenstein LM, Mardiney MR, Norman PS, Rosenberg GL. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J ALLERGY CLIN IMMUNOL* 1982;69:181-93.
24. Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman PS. A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J ALLERGY CLIN IMMUNOL* 1982;70:343-52.
25. Chapman MD, Aalberse RC, Brown MJ, Platts-Mills TAE. Monoclonal antibodies to the major feline allergen *Fel d I*. II. Single step affinity purification of *Fel d I*, N-terminal sequence analysis, and development of a sensitive two-site immunoassay to assess *Fel d I* exposure (Table III). *J Immunol* 1988;140:812-8.
26. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE.

- Allergen-induced increase in nonallergic bronchial reactivity. Clin Allergy 1977;7:503-13.
27. Cartier A, Thomson NC, Frith PA, Roberts R, Hargreave FE. Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. J ALLERGY CLIN IMMUNOL 1982;70:170-77.
 28. Boulet L-P, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. J ALLERGY CLIN IMMUNOL 1983;71:399-406.
 29. Cockcroft DW, Murdock KY, Kirby J, Hargreave FE. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. Am Rev Respir Dis 1987;135:264-7.

Lack of subsensitivity to terfenadine during long-term terfenadine treatment

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Eleven healthy male volunteers ingested terfenadine, 60 mg, every 12 hours for 56 days. Compliance was monitored strictly throughout the study. Before the first terfenadine dose on day 0, and 12 hours after the evening terfenadine dose every seventh day and on randomly selected "unscheduled" days, wheal-and-flare areas were measured after intradermal injections of 0.01 ml of histamine phosphate (1.0 mg/ml and 0.1 mg/ml). On days 0, 28, and 56, six volunteers had skin tests hourly for 12 hours after the morning terfenadine dose. On all study days, serum terfenadine metabolite I concentrations were measured each time histamine skin tests were performed. On days 7, 14, 21, 28, 35, 42, 49, and 56, the mean areas of the histamine-induced wheals did not differ significantly from each other but were significantly decreased compared to the mean wheal area on day 0 ($p < 0.01$). On these days, the mean areas of the histamine-induced flares also did not differ significantly from each other but remained significantly suppressed compared to the mean flare areas on day 0 ($p < 0.01$). Wheal-and-flare suppression was noted in all unscheduled histamine skin tests performed 12 hours after the evening terfenadine dose. In the subgroup of volunteers who had hourly tests, on day 0, the mean wheal-and-flare areas were significantly suppressed from 2 to 12 hours after the dose, with maximal wheal suppression occurring at 5 hours ($p < 0.05$) and maximal flare suppression occurring from 3 to 9 hours ($p < 0.01$). On day 28 in the subgroup, the mean wheal area was significantly larger 12 hours after the dose than before the dose or at any other time ($p < 0.01$), but the mean flare areas did not differ significantly at any time ($p = 0.01$). On day 56 in the subgroup, the mean wheal areas did not differ significantly from before the dose to 12 hours after the dose, nor did the mean flare areas differ significantly at any time ($p = 0.01$). The mean serum concentration of terfenadine metabolite I 12 hours after the evening dose did not differ significantly on days 7, 14, 21, 28, 35, 42, 49, and 56 ($p = 0.01$). Unscheduled serum terfenadine metabolite I concentrations measured 12 hours after the dose provided additional confirmation of compliance. In the subgroup, the mean serum elimination half-life value and the mean area under the serum concentration versus time curve of terfenadine metabolite I did not differ significantly on day 0, day 28, or day 56 ($p = 0.01$). We conclude that subsensitivity to the antihistaminic effect of terfenadine did not develop during 56 days in compliant subjects, as evidenced by continued suppression of the histamine-induced wheals and flares. Also, the pharmacokinetics of terfenadine metabolite I remained unchanged after 56 days of terfenadine treatment. (J ALLERGY CLIN IMMUNOL 1988;82:1068-75.)

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Supported by Merrell Dow Pharmaceuticals (Canada) Inc., Richmond Hill, Ontario, Canada, and Schering-Plough Corp., Kenilworth, N.J.

Received for publication Feb. 25, 1988.

Accepted for publication May 28, 1988.

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Patients who receive a first-generation H_1 -receptor antagonist regularly for weeks or months often appear to develop subsensitivity to the drug.¹⁻⁶ Subsensitivity may be manifest as diminished efficacy in relieving symptoms; that is, a larger dose of the H_1 -receptor antagonist is required to elicit an antihistaminic effect of similar magnitude to the effect produced by the initial H_1 receptor-antagonist dose at the onset of treat-