

Management of Allergy to Animal Danders

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ABSTRACT

Allergy to furred animals is an extremely important clinical problem. We review current data on animal allergens and animal dander sensitivities and attempt to provide a rational approach to their control. Environmental control measures are stressed as the first line of therapy, and the role of immunotherapy is discussed. Throughout, we refer primarily to cats and dogs, both because they are the most common animals in our lives and because they have been the most extensively studied. However, most of what is said will be applicable to other animal allergens.

INTRODUCTION

SENSITIVITY TO ANIMAL ALLERGENS is extremely common. Surveys have found that 5%–10% of the general population and 15%–30% of allergic populations have positive skin tests to cats and dogs.^(1–3) Positive skin tests to cats are about twice as common as to dogs. In laboratory facilities, the prevalence of allergic skin tests and symptoms to laboratory animals ranges between 15% and 30%. Rats are the most commonly implicated, then rabbits and guinea pigs.^(4–6)

One of the reasons furred animals are such common causes of allergic disease is that humans insist on close contact with them. Currently, over half of all homes in the United States house at least one cat or dog, with a total pet population of over 100 million. In addition, cat and dog allergens have been found in household dust from almost every home sampled,⁽⁷⁾ and most commercially available “house dust” extracts contain measurable concentrations of cat allergen.⁽⁸⁾ Rodents, including guinea pigs, hamsters, rabbits, rats, and mice, are also commonly kept as pets in the home, as well as in schools and even pediatric hospitals. Animal danders are potential occupational sensitizers for veterinarians and for the nearly 100,000 laboratory workers who work with animals in the United States.

The clinical manifestations of animal allergy range from isolated cutaneous lesions to typical rhinoconjunctivitis to severe, life-threatening asthma. Cutaneous lesions are most commonly contact urticaria but also may include an intensely pruritic maculopapular rash on the face, neck, and upper trunk associated with respiratory symptoms during airborne exposure. Some patients report that respiratory symptoms occur immediately on exposure, but during controlled challenges with naturally occurring allergen, both upper and lower respiratory symptoms, as well as mast cell mediator concentrations in nasal lavage fluid, rarely become

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significant before 15–30 min of exposure.^(9–11) Under circumstances when allergen levels are low or where sensitivity is trivial, symptoms may not appear until there have been several days of cumulative exposure.

THE ALLERGENS

Several major animal allergens have now been defined (Table 1). Overall, they are typical of most allergens, i.e., acidic glycoproteins with molecular weights of 15–30,000 kD. In most cases, these allergens are found in secretions. For instance, *Fel d I*, the major allergen of the domestic cat, is produced in cat saliva and in sebaceous glands of cat skin.^(12,13) In dogs, major allergens have been identified in saliva, dander, and possibly urine.^(14,15) In rats and mice, urine is the most important source of allergen, and in rabbits and guinea pigs, allergens are located in both saliva and urine.^(6,16)

It is presumed that secretions containing allergen dry on fur, bedding, and other objects and then become airborne when these reservoirs are disturbed. For example, with rat allergen, airborne concentrations are 10–100 times higher when bedding is disturbed or when the animals are handled than during quiet activity.⁽⁹⁾ Airborne cat and rat allergens have been best studied and have been demonstrated to be associated with particles that range in size from less than 1 μm to larger than 20 μm , with a significant proportion on particles less than 5 μm .^(17–20) The exact proportion on these very small particles is not entirely clear, however. Studies from our laboratory indicate that they comprise less than 15% of total cat allergen,⁽²⁰⁾ although others have reported that this number may approach 50% in some homes.⁽¹⁸⁾

The physical nature of the allergens is important for several reasons. Particles of this size (<5 μm) tend to remain airborne for hours after they are produced, whereas larger particles typical of pollen and dust mite allergens settle to the ground within minutes.^(18,19) The distinct nature of particles bearing animal allergen is important in the design of environmental control measures to reduce allergen exposure. The particles are sticky and adhere to walls, clothing, and other surfaces.⁽²¹⁾ As a consequence, the allergens are virtually ubiquitous and are widely distributed even in homes that have never had pets.⁽⁷⁾ Finally, the wide distribution of particle sizes includes many that are capable of reaching the lower airways in significant quantities.⁽²²⁾

DIAGNOSIS OF ANIMAL ALLERGY

As with all allergens, the diagnosis of animal allergy should always begin with a careful history. In some instances, such as the individual who had acute symptoms with every visit to a home with a cat, the history may be so clear as to be virtually diagnostic. In other instances, however, such as the individual who owns a cat and experiences chronic, low-grade symptoms, the history may be very difficult to interpret, especially if the patient is found to be allergic to multiple allergens. An element of denial can lead to distorted historical information, particularly when it comes to a beloved family pet.

TABLE 1. MAJOR ANIMAL ALLERGENS

<i>Animal</i>	<i>Name</i>	<i>Source</i>
Cat	<i>Fel d I</i>	Saliva, pelt
Dog	Multiple allergens	Saliva, pelt
Rat	<i>Rat n I + II</i>	Urine
Mouse	<i>Mus m I</i>	Urine
Guinea pig	Multiple allergens	Saliva, urine
Rabbit	Multiple allergens	Saliva, urine
Gerbil	Multiple allergens	Pelt, serum
Hamster	Multiple allergens	Pelt
Horse	<i>Equ c I, II, III</i>	Pelt
Cow	<i>Bos d I, II, III</i>	Pelt

MANAGEMENT OF ALLERGY TO ANIMAL DANDERS

The next step in the diagnosis of animal allergy involves the demonstration of allergen-specific IgE either by skin tests or by in vitro methods, such as RAST. Although both false positive and false negative tests certainly occur, we have found that individuals with a negative puncture skin test to rat allergen are very unlikely to have a positive challenge test and that most with a positive puncture skin test will react in a 1 h challenge, albeit in a highly variable manner.⁽²³⁾

The potential limitations of both skin tests and RASTs lie in the quality of the allergen extracts being used. For cat, extracts standardized for *Fel d I* content are now available that ensure reasonable sensitivity and specificity. Even these extracts are not perfect, however, in that an occasional individual may be sensitive to cat because of IgE production toward another cat protein, such as serum albumin. These individuals might be missed using the extract standardized for *Fel d I* and might test positive to a less pure cat pelt extract.

The situation for dog and most other animals is even less clear. For dog, at least two and possibly as many as six major allergens may exist.⁽¹⁴⁾ Breed-specific allergens also have been suggested.⁽¹⁵⁾ Similar difficulties may be encountered with each of the animals for which multiple major allergens exist. Thus, although most animal-allergic individuals will be identified with the use of commercially available extracts, occasional false negative reactions will certainly be encountered.

The combination of a careful history and tests for specific IgE will diagnose animal allergy accurately in most individuals. Unfortunately, however, some individuals will deny that a pet is causing their symptoms even with a suggestive history and markedly positive allergy test. These situations can be approached by two means, challenge studies or trials of avoidance. Challenge studies, which can be performed by either bronchial, nasal, or conjunctival provocation, have been shown to correlate with skin test and RAST results.⁽²⁴⁾ These procedures and the more recently described environmental challenge studies with naturally generated allergen particles⁽⁹⁻¹¹⁾ should be viewed as research procedures that will provide important experimental support for clinical diagnostic tests but are not as yet available for routine clinical use. Trials of avoidance are, therefore, more commonly recommended. These may be accomplished by carefully observing symptoms during an extended vacation or trial period of pet removal. It is critical to note, however, that the pet must be out of the home for at least 4–6 months before allergen levels will be sufficiently reduced in most instances and that in some homes even this may not be long enough (Fig. 1).⁽²⁵⁾

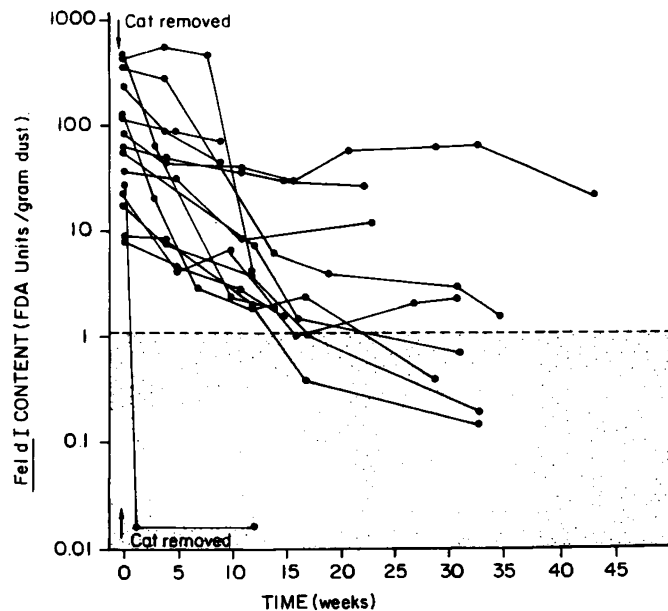


FIG. 1. The decline in *Fel d I* in household dust samples after cat removal. (From Wood RA, Chapman MD, Adkinson NF, et al. *J Allergy Clin Immunol* 1989;83:730.)

TREATMENT OF ANIMAL ALLERGY

Once a convincing diagnosis of animal allergy has been made, several therapeutic options are available. Avoidance is always the preferred treatment, but it may not be possible in all situations. Medications generally are the second line of treatment and usually are effective. Immunotherapy should be considered the last line of treatment in most situations.

Whenever possible, avoidance is the treatment of choice for all animal allergy. This approach is clearly the most effective and may provide substantial relief without the use of medication or immunotherapy. Unfortunately, however, many problems may be encountered with it in both the home and the workplace. In the home, the patient or the family often will refuse to give up the offending pet. If symptoms are mild, this may be a reasonable decision when considering the importance of the pet to the family. If this choice is made, it may be helpful to take some preventative measures to limit exposure. When symptoms are more severe, however, compromises may no longer be appropriate, and the physician's recommendations should clearly reflect that sentiment. We firmly believe that the refusal to remove a pet from the home of a child with severe asthma and documented sensitivity to that pet is tantamount to child abuse.

If a pet is removed from a home, aggressive cleaning measures should be instituted to reduce the residual allergen content as rapidly as possible. In most homes, it will take 4–6 months to reduce allergen levels in settled dust to a level found in homes that never housed a pet (Fig. 1), which in the vast majority of individuals should be clinically insignificant.⁽²⁵⁾ The process can be accelerated, however, by removing the major reservoirs for the allergen, particularly carpets and upholstered furniture, and by increasing ventilation (i.e., increasing outside air exchange by opening windows or furnace intake vents). Thus, it might be reasonable to try to reduce the allergen content of a bedroom or family room more rapidly by taking these aggressive measures. Unfortunately, in our limited study, it did not appear that steam cleaning or more frequent vacuuming accelerated the rate of cat allergen removal.⁽²⁵⁾ Further, we have identified several homes in which cat allergen levels remained persistently elevated in spite of cat removal and routine cleaning.

Some degree of avoidance may be possible without completely removing the pet from the home. It may be possible to reduce the allergen content in a particular room or area of a home by limiting the pet's access to that area, removing carpets and upholstered furniture, and increasing ventilation. For cats, it has been shown that allergen levels may be reduced by bathing the animal frequently, approximately once a week.^(26,27) It has yet to be determined whether washing is helpful for dog allergen. Room air cleaners, particularly those using HEPA or electrostatic filters, may help in this situation. This may be particularly true for cat allergen (and any other allergen carried on relatively small particles) because the airborne allergen will tend to remain suspended for longer periods of time and, therefore, be available for air filtration. The true impact of these measures on allergen levels and patient symptoms awaits further study.

For laboratory animal workers, veterinarians, and others with significant occupational exposure to animals, substantial avoidance may be impossible without changing professions. Employers may attempt to decrease the frequency of sensitization by excluding atopic workers, but the available data are not strong enough to justify this step. It may be warranted, however, to warn prospective employees who are atopic that working with animals carries an increased risk of sensitization and that protective measures should be considered. Allergen levels can best be reduced by containing the source production. In the case of a laboratory, this can be accomplished by housing rodents in Microisolator caging and by using laminar flow cleaning facilities and laminar flow operating tables. In a veterinary practice, such equipment is not affordable, but it may be helpful to ensure high ventilation rates (at least 10 room volume changes per hour with no recirculation) and to wear protective clothing, gloves, and masks.

When avoidance is not possible or can be only partially accomplished, medications may be needed to alleviate the allergic symptoms induced by animal exposure. The medications are identical to those used for other inhalant allergens. Thus, antihistamines and topical cromolyn sodium or corticosteroids can be used for nasal and ocular symptoms and cromolyn, beta-agonists, corticosteroids, or theophylline might be needed to control asthmatic symptoms. Individuals who can predict their animal exposure should be instructed to premedicate themselves before exposure. Cromolyn may be particularly effective in this regard, although beta-agonists and antihistamines also are generally effective.

IMMUNOTHERAPY WITH ANIMAL DANDERS

Several important trials on animal dander immunotherapy have been performed. In this section, we review the details of some of these trials and provide further recommendations regarding patient selection for this mode of treatment.

Dr. John Ohman and colleagues published the first two controlled studies on animal dander immunotherapy. Both studies examined immunotherapy in adults with cat-induced asthma. The first study, published in 1978, evaluated 10 individuals in a double-blind placebo-controlled trial using a standardized cat pelt extract.⁽²⁸⁾ Subjects were treated for 3–4 months and received cumulative doses of 1.7–4.7 mg of *Fel d I*. Systemic reactions occurred in 3 of the 5 treated patients. At the conclusion of the study, those subjects who had received active treatment were found to have a reduction in both skin and bronchial reactivity to cat pelt extract. No change in nonspecific bronchial reactivity was detected.

The second controlled study was published in 1984.⁽²⁹⁾ It also used a double-blind design and a standardized cat extract. A total of 17 subjects (9 active, 8 placebo) completed the 4 month protocol and received a cumulative dose of *Fel d I* of 0.24–24.8 units (1 µg said to equal approximately 0.04 units, thus cumulative doses from 6 to 620 µg). This study also demonstrated reduced skin and bronchial reactivity. In addition, subjects were exposed to cats in a natural setting and were found to have delayed ocular and pulmonary responses. Systemic reactions were again common, with a total of 10 such reactions occurring in 4 individuals.

The first published report on dog immunotherapy also appeared in 1984.⁽³⁰⁾ In this study, 27 children with asthma and dog sensitivity were enrolled in a 12 month double-blind placebo-controlled protocol. Doses were increased on a weekly basis until significant side effects occurred or until a maximal dose of 100,000 SQ units was achieved. Doses were then given at 6 week intervals. Eleven of the 15 subjects in the active group reached the maximum dose. The other 4 had large local reactions and had to be maintained on doses ranging from 8000 to 50,000 SQ units. No systemic reactions occurred. Results of this study demonstrated a significant decrease in conjunctival reactivity and a trend toward reduced bronchial reactivity to dog allergen in the treated group. Of note, half of the subjects in each group reported that their symptoms on dog exposure were significantly reduced.

The next major study on animal dander immunotherapy examined both cat- and dog-sensitive individuals.^(31–33) In the initial study, 41 patients (21 adults and 20 children) with cat-induced or dog-induced asthma were treated with standardized cat and dog extracts. Thirty-nine patients, of whom 22 were on active therapy (15 cat, 7 dog) completed 1 year of therapy. Adults were given increasing doses on a weekly basis until a dose of 100,000 SQ units was attained, at which time they were given injections every 4 weeks. Children were treated using a rush hyposensitization protocol in which they were hospitalized for 1–2 weeks and given 5–7 injections per day. They were increased to a maintenance dose of 80,000 SQ units and then also treated every 4 weeks. For both cat and dog, the mean cumulative dose of allergen at the end of 1 year of treatment was about 1,000,000 SQ units. There was, however, a significant range in dose in individual patients (300,000–1,500,000 for both cat and dog). For cat, the cumulative dose of *Fel d I* was also calculated and found to range from 13 to 65 µg (1 SQ unit equals 43 pg *Fel d I*). Side effects in this protocol were described as minimal, although all children experienced at least mild systemic side effects during rush hyposensitization (total 7.7% of injections), and 4% of all injections in the actively treated adults resulted in systemic side effects.

The subjects in this study were extensively evaluated with regard to a variety of clinical and immunologic parameters. In the cat allergen-treated group, bronchial sensitivity to both cat and histamine decreased significantly. In fact, the cat-treated patients could tolerate approximately 11 times more allergen by bronchial inhalation at the end than at the start of the study. In the dog-treated patients, no change in either specific (dog) or nonspecific bronchial reactivity was detected. For both groups, there was a tendency toward fewer subjective symptoms on uncontrolled animal exposure, although once again, many placebo-treated patients (5 of 17) also reported reduced symptoms.

Another controlled trial of cat immunotherapy was published by Van Metre et al. in 1988.⁽³⁴⁾ In this trial, 22 patients with cat-induced asthma were treated for 1 year with a standardized cat extract or placebo in a double-blind protocol. Maintenance doses ranged from 0.32 to 4.56 units of *Fel d I*, with cumulative doses

ranging from 3.6 to 115.8 units (median 46.2 units, 1 unit stated to equal 4.6 μg , thus, cumulative doses 16.6–532 μg). Extensive evaluations were undertaken, and significant changes were demonstrated between the active and placebo groups in bronchial challenge (cat extract PD_{20}) and skin reactivity to cat extract.⁽³⁵⁾ With regard to the bronchial provocation, treated subjects required a median of 2.8 times more allergen to elicit a 20% fall after treatment as compared to pretreatment challenges. Most subjects also underwent a natural cat exposure, and although there was a trend toward decreased response, the results were not statistically significant. Overall, the therapy was well tolerated, with only 2 systemic reactions in the 339 active injections that were given.

SUMMARY OF IMMUNOTHERAPY STUDIES

As summarized in Table 2, nine studies on animal dander immunotherapy have been reported since 1978.^(28–40) Five of these studies, with a total of 115 subjects, were blinded. Three of these studied cat immunotherapy, one studied dog, and one studied both cat and dog. Asthmatic subjects were used in each of these trials, and it should be noted that no studies have evaluated patients with rhinitis induced by animal danders. Although the data are still somewhat limited, several conclusions can be drawn from the available data.

First, there is general agreement that immunotherapy for both cat and dog is efficacious. Reactivity as determined by skin tests, inhalation challenge, and conjunctival challenge was reduced by immunotherapy in most studies. The reduction in allergen bronchial challenge sensitivity may be as little as 2.8-fold⁽³⁴⁾ or as great as 11-fold.⁽³³⁾ This difference might be of practical significance, as 3-fold changes would probably mean very little to an individual who lives with a cat, whereas a 10-fold change might provide some protection. Based on our knowledge of allergen levels in homes, however, even that change might not provide significant protection for patients living in homes with pets. For example, although we believe that levels of cat allergen in settled dust above 2000 ng/g may be associated with symptoms, levels of cat allergen in homes with cats are usually above 50,000 ng/g and commonly reach 200,000 ng/g.⁽⁸⁾ Thus, patients living with pets may live too far above the threshold of response to benefit significantly from immunotherapy. Unfortunately, although several studies have suggested symptomatic improvement on animal exposure, few have adequately studied this parameter, particularly in patients living with pets. Furthermore, in the two studies that used a controlled exposure to live cats, one showed no improvement after immunotherapy,⁽³⁴⁾ and the other showed only a modest delay in the onset of symptoms.⁽²⁹⁾ We believe, based on the available data, that immunotherapy is most likely to be successful in individuals with intermittent exposure and that it cannot be recommended as a routine for individuals who live with a cat or dog.

Second, although some data regarding allergen doses can be taken from these studies (Table 2), the results are somewhat confusing and do not provide an adequate answer as to the doses that might be most efficacious. In the studies in which *Fel d I* was measured, maximum cumulative doses ranged from 64.5 μg to 4.7 mg, apparently with similar efficacy. Maintenance doses ranged widely and are even more confusing. For example, Van Metre et al.⁽³⁴⁾ strived to reach a maintenance dose of 4.56 FDA units (21 μg), Bacur et al.⁽³⁹⁾ used a peak dose of 100,000 biologic units (said to contain 200 μg of *Fel d I*), and Taylor et al.⁽²⁸⁾ used a dose of 800 μg . For the studies using SQ units, 1 SQ unit was said to contain 43 pg of *Fel d I*, so that maintenance doses of 100,000 SQ units would be expected to contain only 4.3 μg .⁽³³⁾ Bertelson et al. suggested that doses of 100,000 SQ units for either cat or dog were likely to be efficacious (5 of 6 subjects), whereas doses less than 80,000 SQ units were effective in only 2 of 8 subjects.⁽⁴⁰⁾ Finally, it should be noted that these doses would be difficult to attain with many commercially available extracts.

Third, conclusions can be drawn as to the safety of animal dander immunotherapy. The studies suggest that systemic reactions with such therapy are common, especially with cat. This is likely due to the fact that more potent cat extracts, standardized for *Fel d I*, are available for use. We would, therefore, recommend that animal dander immunotherapy be undertaken with caution and that it not be used lightly. It clearly should not be added to an extract unless there are strong indications to do so. Reaction rates such as these may even make immunotherapy impractical in some situations.

TABLE 2. STUDIES ON ANIMAL DANDER IMMUNOTHERAPY

Year	Ref	Animal studied	Duration	No. of subjects	Design	Ages	Maintenance dose ^a	Cumulative dose	Symptoms	Bronchial challenge	Skin reactivity	Nonspecific reactivity
1978	28	Cat	3-4 months	10	DBPC ^b	24-43	800 µg	1.7-4.7 mg	—	Improved	Decreased	No change
1984	29	Cat	4 months	17	DBPC	22-48	4.9 units (122 µg)	0.24-24.8 U (6-620 µg)	Improved	Improved	Decreased	No change
1984, 1986	30, 36	Dog	1 year	27	DBPC	5-18	—	—	—	No change (CI)	Decreased	—
1986	31-33	Cat/dog	1 year	39	DBPC	8-47	100,000 SQ U (4.3 µg)	300,000-1,500,000 U (12.9-64.5 µg)	No change	Cat: Improved Dog: No change	Decreased	Cat: Decreased Dog: No change
1989	37	Cat/dog	2 years	35	Open	8-47	—	—	No change	Improved (cat and dog)	Decreased	Cat: Decreased Dog: Decreased
1988	38	Cat/dog	3 months	13	Open	19-40	—	0.8-9.07 U (20-227 µg)	—	Cat: No change Dog: Improved	Decreased	No change
1988, 1989	34, 35	Cat	1 year	22	DBPC	21-52	4.56 units (21 µg)	3.6-115.8 U (16.6-533 µg)	No change	Improved	Decreased	No change
1989	39	Cat/dog	1 year	17	Open	16-56	100,000 BU	—	Improved	Not done (CI)	Decreased	—
1989	40	Cat/dog	9 months	14	Open	7-15	100,000 SQ U	—	—	Improved	Decreased	—

^a Doses are provided in the units used in each reference. Whenever possible, doses have been converted to the actual quantity of Fel d I, using conversion data provided in that reference.

^b DBPC, double-blind, placebo controlled; CI, Conjunctival—improved.

Finally, immunotherapy should be considered for animal allergy in certain clinical situations. As described, the benefits of immunotherapy in animal allergy are significant but not dramatic. Thus, although it is likely to be very helpful for the individual with intermittent exposure, we would conclude that it is not likely to prove helpful for most patients who want to continue to live with a pet to which they are highly sensitive. Immunotherapy has its greatest appeal to that group of occasionally exposed individuals who suffer significant symptoms in the presence of optimal pharmacotherapy or to those with unavoidable social or occupational contact with a pet or other animal.

DISCUSSION

The treatment of animal dander sensitivity relies on reducing allergen exposure whenever possible and the use of medications and immunotherapy when necessary. Although we would like to think that removing an animal from a home should be a relatively simple matter, virtually all families respond to this recommendation with some degree of emotion. Further, even if a patient is able to avoid animal exposure at home, pets are so common that some degree of exposure outside the home is inevitable. Medications usually will be effective in these situations, and if not, immunotherapy may provide added relief and should be considered.

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