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Animal danders

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The domestication of wild animals has played a large role in the development of human civilization [1]. Dogs were domesticated for hunting and protection, and the reasons for domesticating cats are less obvious. By the 18th century, it is probable that most of the population had been exposed to a wide range of animals since early childhood. In some current farming communities, children routinely are exposed to farm animals in the first 2 years of life [2,3]. In most modern cities, the only animals that are common in houses are cats and dogs, and many children become allergic to proteins found in cat or dog dander [4–6]. There is consistent evidence that sensitization to cat allergen is associated strongly with allergic rhinitis and asthma [6–8].

Since the cat allergen Fel d 1 first was purified by Ohman and colleagues, it has been used to estimate the potency of cat extracts and to measure the quantity of cat allergen in dust samples and in air [9]. The assumption is that one allergen can act as an index of exposure. This theory is true if the allergen represents a major proportion (ie, $\geq 40\%$) of the allergen coming from that source, or if the allergen has a consistent relationship to other allergens in the extract. Fel d 1 seems to represent a large proportion (possibly as high as 65%) of the allergenic activity in cat extract. The use of Fel d 1 to measure exposure or to study immune responses to cat allergens has not been questioned. For other allergens, such as Can f 1, Rat n 1, and Mus m 1, the evidence is less complete (Table 1). When examining the biology of immune responses to allergens, it may be relevant to consider the proteins that are inhaled together [10–12].

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Table 1

Comparison of animal dander allergen with other airborne allergens

Source	Airborne particles		Allergen		Sequence homology (possible function)
	Origin	Size	Abbreviation	MW(kD)	
Dust mite (<i>D pteronyssinus</i>)	Feces	10–40 μ m	Der p 1 Der p 2	25 13	Cysteine protease (epididymal protein)
German cockroach (<i>Blattella germanica</i>)	Frass, saliva	>5 μ m	Bla g 2 Bla g 5	36 23	Aspartic protease GST
Grass	Pollen	30 μ m	Lol p 1	29	Cysteine proteinase
Domestic animals					
Cat (<i>Felis domesticus</i>)	Dander particles	2–15 μ m	Fel d 1	36	(Uteroglobulin)
Dog (<i>Canis familiaris</i>)	Dander	2–15 μ m	Can f 1	21	Lipocalin
Rodents					
Mouse (<i>Mus musculus</i>)	Urine	2–20 μ m	Mus m 1	22	MUP
Rat (<i>Rattus norvegicus</i>)	Urine	2–20 μ m	Rat n 1	19	Lipocalin (Pheromone binding)
Farm animals					
Cattle (<i>Bos domesticus</i>)	Skin	—	Bos d 2	20	Lipocalin
Horse (<i>Equus caballus</i>)	Salivary gland	—	Equ c 1	25	Lipocalin

Abbreviations: MUP, mouse urinary protein; MW, molecular weight.

Data from <http://www.allergen.org>.

After the purification of Fel d 1, it became possible to make monoclonal antibodies and to develop two-site immunometric ELISAs [13]. These assays have enabled the establishment of several important facts:

- Dust from houses with a cat has high concentrations of allergen (up to 1 mg/g of dust).
- Cat allergen is distributed widely and may be present at up to 50 μ g/g in schools, public buildings, and homes without a cat [14–16].
- Cat allergen is airborne continuously in homes with a cat (ie, for many hours after disturbance or with minimal domestic disturbance).
- Fel d 1, which previously was believed to be a salivary protein, predominantly is produced in the skin of cats.

Many of the same observations apply to dogs, whose allergens are produced in the skin, are airborne without disturbance, and become widely distributed beyond homes with a dog [17,18]. For other animals, the information is much less complete. Mice and rats (especially older male rats) produce large quantities of lipocalins, proteins of the pheromone type, in urine (ie 1 mg/mL). These allergens

are not attached to a particle, but instead become airborne after urine dries on bedding particles, dander, or other dust particles [12]. Interestingly, some of the measures designed to protect the animals from infection in an animal house may make the situation worse for allergic individuals. This is because the airflow is directed across the cages and toward the animal handlers.

Allergens from farm animals, such as cattle (Bos d 2) and horses (Equ c 1), also belong to the lipocalin family of proteins. These proteins bind and transport small hydrophobic molecules. They share 20% to 25% sequence homology but contain three structurally conserved regions that preserve ligand binding and allow 50% cross-reactivity [19]. Bos d 2 has been isolated from cow skin, and Equ c 1 has been isolated from horse salivary gland. A recombinant Bos d 2 has been produced in *Escherichia coli* as a fusion protein with glutathione S transferase (GST) [20].

The definition of protein allergens has facilitated studies on the immune response to dander allergens. Skin tests and measurements of immunoglobulin E (IgE) antibody are carried out with crude extracts. Measurements of IgG antibody are carried out best with purified allergens. In vitro studies on T cells are done best with purified allergens or peptides that are synthesized using the amino acid sequence of the native molecule. Increasing evidence has shown that many children and adults who are exposed to cat allergen develop some form of tolerance.

Animals as a source of airborne allergens: proteins and particles

Although there are important questions about whether proteins differ in the ability to sensitize humans, it seems that any foreign protein that is inhaled persistently can become an allergen [21]. It is necessary to determine which proteins are produced by animals and how these proteins become airborne. Several different sources of allergen have been identified: urine (for rodents), feces (for mites), saliva (for cat and cockroach), and flakes of skin or other particles on the skin (for cat and dog). For each source, at least some allergens have been purified, cloned, and measured (Table 1). Knowing how proteins become airborne is essential to understanding the techniques that are used to control airborne animal allergens and to interpreting the immune response to these allergens.

Animal allergens generally do not have enzymic activity. Fel d 1, Can f 1, Rat n 1, and Mus m 1 have not been shown to have enzymic activity. The common features of these proteins are size, solubility in aqueous solution, and physical presence on particles that can become airborne. The saturated vapor pressure of molecules greater than 2000 Da (ie, all known allergens) is close to zero. This fact means that proteins can only be inhaled on a particle. For many allergens, the particle is an inherent feature of the plant or animal (eg, pollen grains, mite feces, fungal spores). Mouse and rat urine contains proteins that become airborne after drying onto particles, predominantly bedding [12]. Dander is the particles that come off the skin of cats or dogs; however, this term is not well defined. Its main constituent seems to be flakes of skin, which can be

visualized (Fig. 1A); however, the particles that carry cat allergen have been shown to be diverse (Fig. 1B) [10]. The physical properties of dander (ie, number of particles, shape, physical dimensions) cannot be defined accurately. The size of particles bearing cat allergens has been estimated using impaction devices and falling speeds. These techniques measure aerodynamic properties, not actual size. Flakes behave dramatically differently from spheres.

The quantities of airborne allergens are generally small (ie, 2–40 ng/m³) [10,22]. Analysis requires a sensitive assay and a technique for sampling large quantities of air (Table 2). Personal samplers can provide better information, but they are difficult to design. Tovey and colleagues developed a nasal sampler that can collect and identify allergen-containing particles [23,24]. The device is not

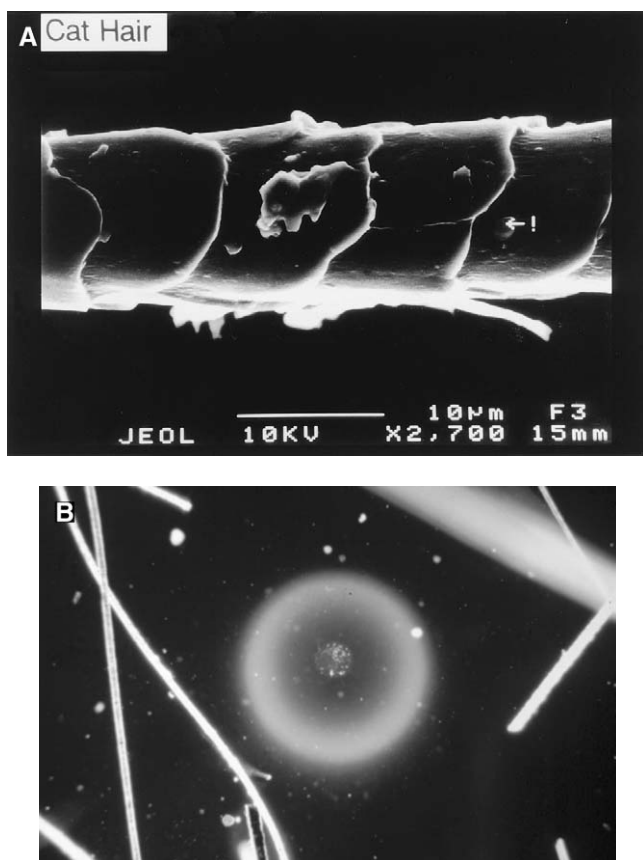


Fig. 1. (A) A scanning electron micrograph of a cat hair. A flattened dander flake is seen on the underside. (B) Particles of cat hair and dander impacted on agar containing rabbit anti-Fel d 1 polyclonal antiserum. The precipitation rings identify allergen on hairs and on other ill-defined particles. (Courtesy of L. Sieber and E. Tovey, Sydney University.)

Table 2
Devices for sampling airborne allergens

Device	Reference	Flow rate (m ³ /h) ^a	Features
Filter holder and pump			
Low volume ^b	[31]	3.0	Prolonged sampling necessary
High volume	[33]	10	Rapid analysis but noisy and can cause air disturbance
Cascade impactors			
Casella	[22,27]	1.1	Identification of particles
Anderson	[11]	1.7	Determination of particle size
Glass impingers	[22,28]	1.1	Decreased sensitivity because of liquid in reservoir but can determine size
Ion chargers ^c	[34]	60	Silent and easily sampled with little air disturbance and can run for 24 h

^a Room air cleaners generally use higher airflow (eg, Enviracare HEPA filters have flow rates of 300–600 ft³/min [600–1200 m³/h]).

^b Air Sentinel, (QuanTec-Air, Frankfurt, Germany).

^c Ionic Breeze Quadra (Sharper Image, San Francisco).

consistently well accepted, and it is difficult to quantitate the allergen in absolute units. Immunoassays for allergens initially were based on radio-labeled, purified proteins, but these assays have been replaced by two-site monoclonal, antibody-based ELISAs [13,25,26]. Each of these assays measures a single defined protein. Their results are only as good as the definition of the major allergen. In most cases that have been tested, the results with different allergens from the same source have been similar [27,28]. For Der p 1 and Der p 2 and for Bla g 1 and Bla g 2, the results for airborne allergens are similar [27–29]. The obvious implication is that different proteins that are derived from a given source are carried on the same particles. Thus it is assumed that the results obtained for specific animal allergens can be generalized to other proteins from the same source.

Techniques for airborne sampling can be divided into those that assess particle size (eg, impactors, impingers) and those that do not (eg, filters, ion-charging techniques). The behavior of particles after undergoing artificial disturbance can be used to derive aerodynamic properties (Tables 1,2). Information about airborne cat allergen comes from multiple techniques and many different laboratories. Cat allergen is airborne for long periods after disturbance, which in most houses means that it is airborne continuously [22,30–32]. It is airborne on particles that are small enough to remain airborne (ie, aerodynamic size of $\leq 3\text{-}\mu\text{m}$ diameter) [22,27,31–33]. The quantities of airborne allergen in a house with a cat can be measured using high- or low-volume pumps and a filter, cascade impactors, impingers, or an ion-charging device. The airborne quantities range from 5 to 50 ng/m³ without disturbance. These values can increase 10-fold during vacuum cleaning or domestic activity. Much of the allergen that becomes airborne during activity is on larger particles and falls rapidly. Exposure to cat allergen is on

particles ranging in size from approximately 1 to $\geq 10 \mu\text{m}$ in diameter. The quantity of allergen carried on these particles probably varies by 1000-fold (because the volume of a $10\text{-}\mu\text{m}$ sphere is 1000 times the volume of a $1\text{-}\mu\text{m}$ sphere). This variation in size may be important in influencing the site of deposition in the respiratory tract, and the difference in allergen quantity per particle may be relevant to the immune response.

Using an ion-charging device that collects particles silently onto steel plates, the authors measured 24-hour exposure in a series of houses with or without a cat [34]. The results suggest that daily exposure may be as high as $1 \mu\text{g Fel d 1/d}$. Even in undisturbed conditions or in a house without a cat, exposure may be 20 ng/d [34]. Comparable values have been reported for dog allergen in homes with a dog and for rat allergen in an animal-holding facility [12,17,33]. Estimates of daily exposure to mite or cockroach allergen generally have been lower ($0.2\text{--}5.0 \text{ ng/d}$). Using the ion-charging device in bedrooms or living rooms without artificial disturbance, the authors found little airborne Der p 1, Der f 1, or Bla g 2 [34].

Few studies address the quantity of airborne exposure to farm animals. Data from Nepal suggest a decreased risk for asthma (odds ratio, 0.4) for individuals living in a house with cattle [35]. In one study, airborne and floor dust samples were obtained from a stable and its vicinity to measure Equ c 1 [36]. The levels of allergen decreased with increasing distance from the stable; levels were below the level of detection within 40 m of the stable.

Exposure to airborne animal dander and the immune response to animal-derived allergens

Ishizaka argued that IgE antibodies were part of an immune response that included IgG and IgA antibodies [37]. In his study, he used ragweed antigens, and results with nonallergic individuals were negative. It was argued that the status of nonallergic subjects could be described as “non-responder” or “immune ignorance” [38]. It seemed that increasing exposure to pollens or dust mites would lead to a progressively higher number of individuals who develop allergy [21,39–41]. New evidence shows that the highest levels of cat allergen do not lead to higher prevalence of sensitization and that many children and young adults living in a house with a cat produce IgG antibody to Fel d 1 without becoming allergic and without an increased risk for asthma [42–46]. This antibody response has been described as a “modified T_H2 ” response, because the response includes IgG4 antibodies to Fel d 1 and the expression of the gene for IgG4 is dependent on interleukin 4 (IL-4) [44]. The prevalence of this type of tolerance is related strongly to exposure. Among children aged 10 to 13 years who live in a house with a cat, up to 50% may have this form of immunologic tolerance [45]. Preliminary evidence from New Zealand, the United Kingdom, and the United States suggest that this form of response is rare with dust mites [44,46]. This difference in the dose–response to cat and dust mite allergens is presented (Fig. 2). In this figure, exposure is presented as allergen inhaled per

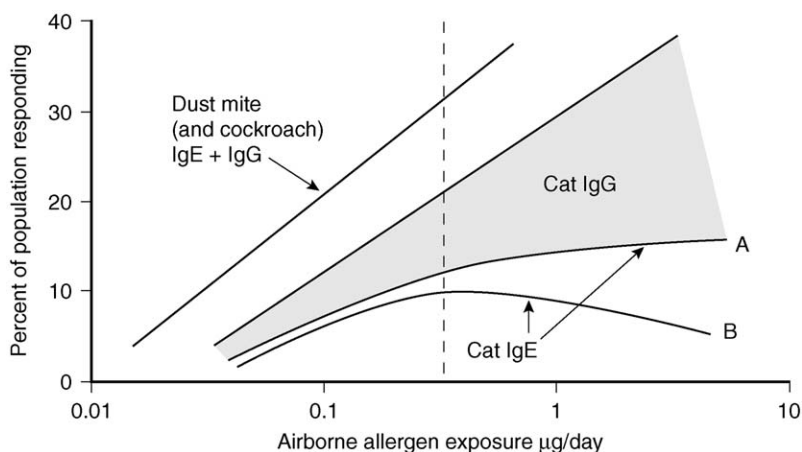


Fig. 2. The immune response to dust mite and cat. There is a direct response to dust mite exposure, and IgE production is accompanied by IgG production. At high levels of cat exposure, some individuals make IgG without IgE. Other individuals produce IgE and IgG (line A or B). The prevalence and titre of IgE to cat is not as high as prevalence and titre can be for mite.

day, on a scale ranging from 0.01 to 10 $\mu\text{g}/\text{d}$. These values are estimates based on measurements made with several different approaches. The authors would like to be able to define the probability of developing tolerance at different levels of exposure. Such a measurement would make it possible to interpret clinical results and would allow comparison with other allergens that can cause this response (ie, dog, rat). The authors would like to compare animal dander with exposure to mites and cockroaches. Estimates of airborne exposure to Der p 1 or Bla g 2 are dependent on a different set of assumptions and are not directly comparable.

Actual measurements of allergen inhaled into the nose or lungs during natural exposure are not possible. Tovey et al developed several different approaches, including an impaction device worn in the nostrils that samples the air inhaled and collects allergen particles on an agar-covered surface. This approach requires antisera, which accurately identifies the allergens on the particles but also requires visual examination to count the allergens. Quantitation is not easy, and the comparison of different allergens depends on too many assumptions. The next best approach is to have a 24-hour monitoring of the allergen that is airborne in a home. This method requires a volumetric sampler with minimal noise. Possible methods include a low-volume pump and filter running at approximately 3 m^3/h or an ion-charging device that creates airflow. The authors' results using the ion-charging device can be calculated as nanograms or micrograms of allergen inhaled per day. The estimates are the basis of the values in Fig. 2, suggesting that subjects in a house with a cat inhale 0.05 to 0.3 μg Fel d 1 per day. It is likely that exposure to dog or rat allergens is at similar levels. In houses without a cat, exposure can be as high as 0.01 to 0.10 $\mu\text{g}/\text{d}$. This level in houses without a cat is sufficient to sensitize genetically at-risk children. As mentioned

earlier, it is difficult to make comparable measurements for dust mite allergens; however, the actual quantities of Der p 1 found with 24-hour monitoring were less than 0.01 $\mu\text{g}/\text{d}$. The levels of inhaled allergen are much lower for dust mites than for cats: The authors believe that cat exposure in a house without a cat is 10 to 100 times greater than dust mite exposure. The most obvious explanation for the development of tolerance to cat allergens is high exposure.

Reducing exposure to animal allergens

Despite the complex relationship between exposure to animal dander allergens and sensitization (ie, production of IgE antibody), there is consistent evidence that sensitized individuals are at increased risk for asthma. In many studies, patients with cat allergies have increased risk for prevalent and incident asthma (range of odds ratios, 3–6) [7,45]. For rats and other rodents, sensitized individuals are also at increased risk for asthma [12]. There is a good case that symptomatic individuals who have positive skin test results or IgE antibodies should reduce their exposure to cats, dogs, small rodents, and animals used in experimental facilities. Over the last 5 years, exposure outside homes or in facilities where animals are not physically present has become an important issue. A large proportion of children who become sensitized do not live in a house with a cat, raising the question of whether avoidance measures should be recommended for houses without a cat or for schools. Implementing avoidance to prevent initial sensitization may not be possible, however. Because cat allergen is distributed widely in the environment, exposure prevention would involve controlling exposure in school, in the patient's home, and in homes with a cat that the patient may visit.

Because animal allergens can be measured easily in the air of homes with a cat, avoidance measures can be evaluated by monitoring airborne allergen or by measuring allergen (eg, Fel d 1, Can f 1) in dust samples. The measurement of allergen in dust is traditionally as micrograms of allergen per gram of dust; however, in many avoidance situations, there is a good case for measuring total dust recovered [41,47]. The measures that have been proposed and tested for reducing exposure to cat allergens can be listed under the following four headings.

Removal of the animal

Extensive studies by Wood and co-workers have established that the concentration of Fel d 1 in a home progressively decreases after the animal is removed [48]. If the carpets and furnishings remain in the house, it generally takes 6 to 12 weeks before cat allergen levels fall below 2 $\mu\text{g}/\text{g}$ of dust. With aggressive cleaning (eg, removing carpets, washing walls), the process can be accelerated [48]. It is up to the family to decide whether to keep the animal. Clinician should provide possible approaches to controlling allergen if the cat remains [49]. The

difficulty of achieving these measures usually persuades the family to consider finding another home for the animal.

Controlling reservoirs

Animal-derived allergens accumulate on any materials within the house. Although carpets and sofas are the worst offenders, allergens can also accumulate in drapes, clothing, and bedding. These reservoirs act as a continuous source of airborne allergens, even if they are only moderately disturbed. The quantity of cat allergen in a carpet may be as high as 100 mg of Fel d 1, whereas the quantity of airborne allergen is 10 to 20 ng/m³ [50]. In an average room, the carpet contains sufficient allergen to replace the allergen in the air many thousands of times. Installing polished floors, buying wooden or leather furniture, and replacing drapes is recommended. Bedding should be washed, and pillows and mattresses should be covered to prevent accumulation of allergens. Although these measures do not prevent allergen from landing on surfaces, they make cleaning to get rid of the allergen easier.

Treatment of the animal

Although multiple reports suggest that different types of cats and dogs cause different degrees of sensitization, the evidence is not clear, except that male cats and male rats produce more allergen than do their female counterparts. For male cats, neutering can reduce allergen; however, only a minority of families have non-neutered cats. Various chemicals have been recommended to reduce the production of allergen by animals, but the results have been unconvincing. Acepromazine was recommended because it reduced saliva production in cats, but the bulk of allergen comes from the skin [51]. The idea of washing cats came from two observations: the yield of allergen was found to decline with repeated washing of cats; and several patients reported that regular washing of the cat resulted in control of their symptoms. Initial experiments showed a dramatic decrease in allergen dispersal after weekly washing [49]. The results of subsequent experiments were variable; in some cases, little effect was found 1 week after washing, and allergen dispersal was reduced for only a few days [50,51]. Washing cats can remove milligram quantities of allergen from the cat [50], and long-term washing may decrease the quantity of allergen that accumulates in the house. In some cases, washing the cat regularly may enable allergic patients to keep their pets.

Use of air cleaners to reduce airborne animal dander

Personal or room air cleaners are popular. This popularity may reflect a desire to control air quality in one's own space or reflect a perceived benefit. Air cleaners remove a wide range of particles from the air, including tobacco smoke, candle smoke, perfumes, spores, pollen grains, and animal dander. It is not clear how much of the perceived benefit occurs because of removal of specific

allergens, removal of nonspecific irritants, or air movement. It is a mistake to assume that the benefits of air cleaning relate to particles or allergens that we can measure or that the benefits are restricted to allergic subjects.

For known allergens, two different problems have been identified. For allergens carried on large particles ($\geq 10 \mu\text{m}$ in diameter), which only become airborne during or after disturbance, air cleaners can only have a limited role in reducing allergen exposure [10,27]. For small particles, such as cat dander, operation of a cleaner may disturb the room air and make the situation worse. With a high-energy particulate air (HEPA) filter running at 300 ft³/min, the airflow blowing onto a carpet can disturb more allergen than the cleaner removes from the air [22]. In a house with high levels of cat allergen in carpets and sofas, the flux of allergen coming off surfaces overwhelms the cleaner [50]. In these cases, avoidance measures should address reservoirs before air cleaners are used. There is some debate about what flow of air through a cleaner is necessary to control allergen in a room. A cleaner that produces 600 m³/h cleans 18,000 ft³/h, equivalent to cleaning a 13x15x8-ft room at least 10 times per hour. A cleaner that produces 60 m³/h cleans the air in the room once per hour. The clinical efficacy of these procedures depends on: (1) the circulation of air in the room; (2) the flux of allergen coming off the walls; and (3) the number of hours that the cleaner is working. Given that high-volume cleaners can disturb allergen, it is not possible to define a clean air delivery rate that is needed to provide effective air cleaning.

Summary

Animals release proteins into their surroundings through secretions, as excretions, or as dander. The quantity of dander that is dispersed by cats, dogs, or humans is sufficient to supply food for dust mites and to supply easily measurable quantities of proteins in dust. Fel d 1, Can f 1, and human IgA or IgG can be found in microgram quantities in dust samples. Allergens also can accumulate from the urine of wild or pet rodents. For cats and dogs, the accumulation of dander particles is not related to the cleanliness of the animals. All animals, including humans, provide a fully adequate supply of organic material for bacterial growth in a carpet, provided conditions are sufficiently humid. The authors' preliminary results in Virginia do not find a significant difference in endotoxin between homes with or without animals. The likely explanation for the nonallergic IgG and IgG4 response to cat, dog, or rat allergens is high exposure to proteins from these animals.

If the highest levels of cat allergen in a home can result in immunologic tolerance, it is unlikely that primary avoidance would be successful at reducing exposure. The data showing that 80% of Swedish children with cat allergies never had lived with a cat imply that the concentrations of cat allergen in schools or in houses without a cat are sufficient to cause sensitization. Primary prevention would be possible only on a community basis, which is unlikely to occur [52].

Sensitization to cat, rat, dog, or mouse allergens consistently is associated with asthma. In symptomatic children with positive skin test results, there is a strong case for allergen avoidance and a clear need for controlled trials. Controlled trials of avoidance should include houses without cats and schools. Controlling exposure to cat allergens with the cat in situ requires aggressive measures, such as removing reservoirs, washing the cat, and air cleaning [49]. Many allergic or symptomatic children who live with a cat do not have positive skin test results or positive IgE antibodies to cats. Avoidance measures related to animals should be recommended only for individuals with positive skin test results. Increasing evidence shows that exposure to cats, dogs, rats, and other animals can induce a form of immunologic tolerance without causing allergic disease, and it is important to understand why this change occurs with dander allergens rather than with all allergens. The most probable explanations are related to the form and quantity of airborne allergens.

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