

EDITORIAL

Clinical & Experimental Allergy

The long-term protective effects of domestic animals in the home

This editorial discusses the findings of the paper in this issue by Wegeienka et al [12] pp. 979–986.

E. A. Erwin, J. A. Woodfolk, E. Ronmark, M. Perzanowski and T. A. E. Platts-Mills

Asthma and Allergic Diseases Center, University of Virginia Health System, Charlottesville, VA, USA

In 1999, Hesselmar et al. [1], in Sweden, reported striking evidence that children raised in a house with a cat were less likely to become allergic to proteins in cat dander. The initial response to their report ranged from outright disbelief to the argument that this result must reflect a lower prevalence of cat ownership among allergic families [2]. Looking back, it is remarkable that this phenomenon had not been noticed earlier. For those of us who actually went back and examined our data, the apparent protective effect of cat ownership was strong [3–6]. More importantly, it was also true for dogs and in some studies for experimental animals [7–10]. The protective effect of domestic animal ownership has been seen in the United States, the United Kingdom, New Zealand, and also in studies in different parts of Sweden [3, 5–7]. In many of those studies, there was very little evidence that ‘allergic’ families selectively chose not to keep animals [5–7]. We reported on a cohort of children in New Zealand where 50% of the children with asthma had cats at home. Among the 50 children with asthma who lived in a home with a cat, there were 34 who had IgE antibodies to dust mite but were not sensitized to cats. Thus, there was a large proportion of allergic children who did not become allergic to cats as judged by the serum IgE antibodies, despite having very high exposure to cat allergens [6].

Among the early papers was one on a birth cohort in Detroit that reported a stronger protective effect with more than one animal in the home, and also an apparent beneficial effect of animal ownership on lung function [11]. In that cohort, detailed questionnaires provided no

evidence that families with an allergic parent had chosen not to keep animals [11]. In the present issue, Wegeienka et al. [12], report results on the same Detroit cohort at the age of 18 years. The results provide some of the clearest evidence to date that there is a critical age at which exposure to animals can have a protective effect. Specifically, they argue that the animal exposure needs to occur in the first year of life [12]. Few of the other studies have enough variability in ownership to come to a conclusion about the effects of early exposure. If all the families with animals in a cohort keep animals consistently for the first 5 years, it is not possible to answer which of those years is the most important. In the current report, Wegeienka and colleagues also show that the long-term effect of early cat ownership is greater than that with dog, and that the phenomenon appears to be allergen-specific.

Mechanisms of tolerance to domestic animals

The resulting question now is how exposure at such an early age can have this profound and lasting effect? Of course, what we really need to know is, what is the mechanism of tolerance? When tolerance to cats was first described, many authors assumed that it would be comparable with the effect of farm animals, which appears to be dependant on an early exposure to endotoxin or environmental microorganisms [13, 14]. Indeed, Ownby et al. argued strongly that the effect was likely to be due to increased endotoxin exposure [11]. At that time, it was assumed that high exposure to endotoxin would shift the immune response towards a Th1 response and that the effect was likely to be non-specific. Many observations now argue against that view.

Firstly, in many studies, measurements of endotoxin have not been higher in homes with domestic animals as compared with homes without pets [15–18].

Secondly, the effect of cat ownership appears in most studies, including the one reported in this issue, to be cat specific. As we have already mentioned, children living in

Correspondence:

Thomas A. E. Platts-Mills, MD, PhD, FRS, Allergy Division, PO Box 801355, University of Virginia Health System, Charlottesville, VA 22908 1355, USA.

E-mail: tap2z@virginia.edu

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a house with a cat can produce high levels of IgE to mite while remaining 'tolerant' to the cat. A shift toward a Th1 type response would be expected to diminish allergic sensitization in a non-specific manner, rather than selectively influencing sensitization to specific allergens.

Thirdly, the isotype of the IgG antibodies to Fel d 1 in non-allergic children does not support a shift to Th1. The quantities of IgG4 antibodies to Fel d 1 in sera from non-allergic children who have IgG antibodies are consistently similar to the quantities found in allergic children [3, 7]. Given that the antibody class switch to IgG4 is fully dependant on IL-4, this observation is more in keeping with a variation in the Th2 response, as opposed to a Th1 response, *per se* [3, 10].

Finally, detailed studies of T cell responses to Fel d 1 and peptides from Fel d 1 do not show a response that is restricted to Th1 cytokines. Although IFN- γ is a feature of the cytokine response in almost all individuals, the response also includes IL-10 and IL-5. Production of IL-10 is a feature of the T cell response to Fel d 1 in the following three groups of subjects: (i) allergic, (ii) those with IgG but no IgE antibodies and (iii) 'non-responders' who have no detectable serum antibodies to Fel d 1. This suggests that T cell control mechanisms operate to suppress the titre of IgE antibodies and enhance the production of IgG4 antibodies in both allergic and 'cat-tolerant' individuals [19]. Furthermore, a role for IL-10 in suppressing antibody production in non-responders cannot be excluded.

Reversibility of tolerance to domestic animals

An important question in understanding the mechanisms of 'tolerance' is whether this state is fixed or can reverse with decreased exposure [20]. There have been persistent anecdotal reports about students who go away from home to college and then experience symptoms around their cat on returning home. In Boston, this was named the 'Thanksgiving' effect. The implication is that some forms of tolerance could reverse within a few months, i.e. between September and November. The limitation of those reports is that the students were not followed prospectively, and it is not known whether the students

did or did not have positive skin tests to cat (or serum IgE antibodies) before they left home. We believe there are at least four different groups of students who are living in a house with a cat: (Table 1).

- (i) Allergic subjects who are aware of symptoms and have positive skin tests and IgE antibodies.
- (ii) Subjects who are not aware of symptoms related to cats but who nonetheless have positive skin tests with generally low titre IgE antibodies.
- (iii) Subjects without positive skin tests or IgE antibodies to cat who have measurable or high IgG antibodies to Fel d 1 and also are not aware of symptoms.
- (iv) Non-responders who have negative skin tests as well as no detectable serum IgE or IgG antibodies specific for cat allergens.

Recent data from a 2-year prospective study at the University of Virginia suggests that the students who develop more symptoms are likely to be of the second group and that immunologically tolerant students without IgE antibodies do not become allergic within this time period (E. Erwin, H. James, J. Roper, J. Woodfolk, and T. Platts-Mills, unpublished data).

Exposure and dosing for tolerance to domestic animals

The positive evidence from the Detroit group that the first year of life is the critical or at least the optimal period for exposure to an animal, and that the effect of cat exposure appears to be specific raises further questions about the possible mechanisms. Current estimates of high exposure to cat suggest that 20–50 times more allergen is inhaled as compared with mite allergen [21, 22]. In addition, we assume that a large part of the estimated 1 μ g of cat allergen inhaled per day is swallowed. On this basis, daily exposure to cat, or dog, allergens is not far different from the doses used for sublingual 'desensitization' [23, 24]. Thus the argument could be made that some children living in a house with a cat have sufficient oral exposure in the first year of life to establish a form of tolerance that strongly inhibits the risk of subsequent sensitization nasally or through the skin. If so, this may relate to the evidence that oral exposure to peanut at an early age can prevent sensitization through the skin [25].

Table 1. The complexity of 'cat allergy' and tolerance

Phenotypes	Antibodies	Symptoms	T cell cytokines
Sensitized			
(i) Allergic	IgE and IgG ($\pm$ IgG4)	Rhinitis, conjunctivitis, asthma, and AD [‡]	↓ IFN- γ , IL-10, ↑ IL-5
(ii) Sensitized but not symptomatic	Low IgE and IgG ($\pm$ IgG4)	None (or minimal)	
Tolerant (modified Th2)	IgG ($\pm$ IgG4) but no IgE	None	IFN- γ , ↑ IL-10*
Non-responders	No IgE or IgG	None	↑ IFN- γ , IL-10

*IL-10 increased in DR7⁺ individuals.

[‡]AD; atopic dermatitis

In conclusion, there are still many questions regarding the mechanism of tolerance. However, some details are becoming clear. It seems increasingly likely that tolerance can be allergen specific (qualitatively and quantitatively), and that high environmental exposure is necessary to

induce tolerance, that exposure in the first year of life is critical, and that tolerance does not easily 'reverse' to a sensitized state. Understanding these issues is important in interpreting symptoms and particularly in relation to advice about reducing exposure to animal allergens.

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