

EDITORIAL

Relevance of early or current pet ownership to the prevalence of allergic disease

Inhaled dust has the potential to cause disease either because it includes a substance that is inherently toxic to the lungs, or because the subject has made an immune response to a protein in the dust. The inflammatory effects of indoor allergens, such as those derived from dust mite or cat, have only been demonstrated among individuals who have made an immune response. Thus, the risk of asthma or rhinitis in epidemiological studies is restricted to skin test-positive individuals. Similarly, inflammatory effects in the lungs following bronchial challenge have only been demonstrated with individuals who are skin test-positive or have specific IgE ab in their serum. Since the immune response to foreign proteins is dependent on exposure, it is logical to assume that there will be a dose–response relationship. For dust mite the evidence strongly supports a positive direct relationship between mite allergen concentration in dust and sensitization to mite allergens [1–6]. A direct relationship between mite allergen exposure and asthma has also been seen in some studies but in most cases this was not very strong [1,4,7–9]. Evaluation of these relationships assumes that we know how to measure exposure and also that the response increases consistently with increased exposure, i.e. that the dose–response is linear. This latter point is very important because many arguments about the reasons for the increase in asthma assume that the dose–response is linear. In keeping with that, it is often argued that an increase in allergen in the homes or a change in the immune response would have a predictable effect on the prevalence of sensitization regardless of the nature of the allergen.

Reports that the presence of a pet in the home might decrease sensitization to animal-derived allergens were very interesting because they suggested that the shape of the dose–response was different, and they also raised the question of whether high exposure could induce an immune response that did not carry the risk of allergic disease [10–14]. If high-dose tolerance to animal allergens does occur, understanding the mechanism(s) could provide insight into the factors controlling the prevalence of allergic disease and also help define a target for immunological intervention. Reviewing the literature there are clearly many unanswered questions. We would like to draw attention to some of these:

- 1 If the presence of an animal in the home decreases the risk of sensitization to allergens from that animal, does it have any effect on sensitization to other allergens?
- 2 Can the presence of animals in a large proportion of the houses in a community decrease the population prevalence of sensitization to animal dander?
- 3 Is this phenomenon related to the age at which exposure occurs (e.g. first two years), and is the 'tolerance' to animal dander reversible?
- 4 Is there a measurable immune response to cat (or dog) allergen among children who live in a house with an animal, but are not allergic by skin test?

The paper published in this issue of the Journal illustrates the complexity of these questions very well [15]. The authors conclude that part of the apparent effect of pets is due to decisions made by allergic families to get rid of an animal or avoid having a cat or dog; thus, some of the decreased prevalence of cat sensitization could be due to selection. However, as they recognize, when previous pet owners are combined with current pet owners, the prevalence of sensitization in this group (i.e. 'pet ever') (8.3%) is lower than among those families which never had an animal (10.3%). Several things are clear in this study; keeping a cat out of the house was not protective; given the very high levels of allergen in houses with a cat, it is striking that there was no dose–response and that the overall prevalence of cat sensitization (i.e. 9.8%) was not very high.

The evidence that the presence of a cat in the house can decrease sensitization comes from several types of information. In cross-sectional studies the prevalence of sensitization to cat among subjects with the highest exposure is lower than among those with moderate exposure [6,10–13]. Within those studies and in case control studies it is possible to identify many atopic subjects with documented high exposure (i.e. presence of a cat in the house or $\geq 20 \mu\text{g}$ Fel d 1/g dust) who are not allergic to cats by skin test, IgE ab or symptoms. While there is only limited data on population prevalence, we would draw attention to data in the European Community Respiratory Health Survey (ECRHS) studies comparing Spain, Sweden and Australia/New Zealand (Table 1) [11]. In Australasia a very high proportion of families keep cats and yet cat sensitization was found in only 10% of the subjects compared to $\sim 30\%$ for dust mites [11,16]. Indeed, despite the number of cats in Australia and also the UK, dust mite sensitization and exposure consistently dominates the epidemiology of asthma [3,7,9,16]. Taken together the results suggest that the highest exposure to cat allergen does not increase the risk of sensitization as much as 'high' exposure to mite allergen does, and that in some populations high cat exposure may actually reduce sensitization.

Three lines of evidence argue against 'family choice' as an important cause of the phenomenon: Firstly, the data on population prevalence in Australia or the UK would not be expected since there is adequate cat allergen throughout the community to sensitize. Secondly, in Scandinavian studies the same phenomenon is seen among children with a family history of asthma; and thirdly, the finding of significant number of highly exposed atopic children who have made IgG ab to Fel d 1 without becoming allergic to cats.

In almost all studies there are a large number of atopic and non-atopic subjects who have not made IgE ab to cat allergens despite being exposed to quantities of cat allergen greater than those that we consider are necessary to sensitize. In an attempt to illustrate this, we have used estimates of airborne exposure based on previous and new sampling techniques (Fig. 1). In this

Table 1. Cat ownership and cat sensitization in three countries studied in European Community Respiratory Health Survey (ECRHS)

		Cat ownership %	Cat sensitization % IgE antibodies
Spain (n = 1380)	Albacete	5.3	2.7
	Barcelona	9.2	14
	Galdakao	11.1	2.9
	Huelva	3.7	2.9
	Oviedo	9.9	4.2
Sweden (n = 1501)	Goteborg	15.7	13.2
	Umea	20.1	14.1
	Uppsala	22.8	14.3
Australia/ New Zealand (n = 1224)	Christchurch	59.3	13.5
	Hawkes Bay	68.6	8.6
	Wellington	52.7	7.5
	Melbourne	35	10.5

Modified from Roost *et al.* J Allergy Clin Immunol 1999; 104: 941–7.

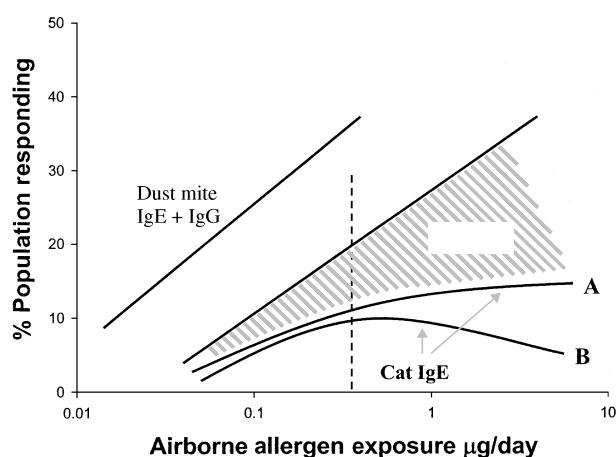


Fig. 1. The proposed model of exposure response relationship is based on data from multiple published and unpublished studies. The curve for sensitization to cat allergens is either flattened (A) or bell-shaped (B). The shaded area indicates the numbers of subjects who produce IgG to Fel d 1 without IgE ab. The dashed line indicates the lower limit for airborne exposure in a house with a cat.

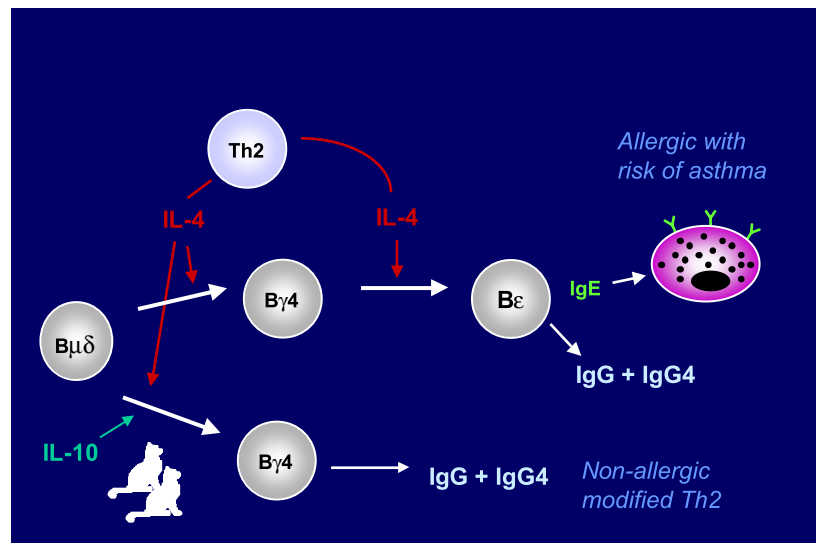
model the dose–response relationship between exposure to cat and sensitization to cat may be bell-shaped (B) or simply flattened (A). Whatever the true shape of the curve we predict that with high exposure there is a major discrepancy between the number of subjects who are allergic to mite and the number who become allergic to cat. We believe this is also true in the cohort reported by Dr Anyo and her colleagues because all studies from the Netherlands have reported mite sensitization at 20–30% [15].

Given the extensive speculation about events in early childhood influencing the immune response to inhalant allergens, it is not surprising that many groups have attempted to identify whether the effect of a pet in the home requires early exposure, or can occur later in life. In some published studies, early exposure to animals appears to be essential, but in other studies it appears that current exposure is more important [10,17]. The present paper based on questionnaires provides fairly strong evidence that the effect of the animal is not restricted to the first

two years. In the model we are proposing it is possible that a large proportion of individuals who become allergic to cats would never have lived in a house with a cat. Indeed, we are now aware of communities where as many as three-quarters of cat allergic subjects have never lived in a house with a cat [18]. By contrast, most of the individuals who are exposed to $\geq 20 \mu\text{g}$ Fel d 1, but are not sensitized, live in a house with a cat [14,18]. The relative proportion of individuals in each group is critically dependent on the shape of the sensitization curve (Fig. 1) and the proportion of families in the community that own a cat. Given what we know about passive transfer of cat allergen throughout a community (i.e. schools, other houses, clothing, etc.), it is not surprising that many children become sensitized to animal dander despite not owning a pet [19]. However, the size of this problem is astonishing. It now appears that in some communities the bulk of the clinical problem of cat allergy relates to families who do not own a cat.

A further issue raised by the epidemiological findings is whether different forms of immune response can be induced by high exposure to cat allergen. If, as has been proposed, the alternative to a Th2 response to inhalants is a Th1 response, then high exposure to pet allergen plus the associated endotoxin exposure might be expected to induce such a response [20,21]. The primary evidence for a Th1 response in non-allergic individuals has come from studies on T cell clones or proliferation of peripheral blood mononuclear cells (PBMCs) *in vitro* [1,22,23]. The evidence from clones can be very detailed but is based on a small number of clones. This is particularly true for cat-specific clones [24]. The PBMC data is also difficult to interpret because the patterns of cytokines produced by human lymphocytes are not as neatly delineated as they appear to be in experiments done with carefully selected strains of inbred mice [25]. In addition, *in vitro* responses can be influenced by the medium, the extract, the use of whole antigen compared to peptides and the density of cells in the culture [25–27]. We have argued in the past that most non-allergic individuals demonstrated immune ignorance, i.e. they have no skin tests, no serum antibodies, and poor or no *in vitro* T cell responses [28]. Most of these results that are quoted to support the concept of ‘Th1 to Th2 balance’ relate to mite allergen. Until recently there has only been limited data about the immune response to cat allergens in non-allergic individuals. However, it should be noted that there have been no reports that cat allergens can induce delayed hypersensitivity (DH) skin tests, although DH is one of the cardinal features of a Th1 response. Similarly, there are no reports of hypersensitivity pneumonitis or other chronic fibrotic lung disease associated with cat allergen exposure. Our results on a population-based cohort of 226 children identified 52 who had made an IgG ab response to Fel d 1 without becoming allergic, and we also reported that this response was very strongly associated with exposure [14]. Furthermore, we found that an equal proportion of the IgG ab in the non-allergic children and in the allergic children was of the IgG4 isotype [14]. A similar form of response, i.e. increasing IgG4 without IgE ab or with decreasing IgE, has been described before in relation to natural bee stings, immunotherapy with bee venom, immunotherapy to other allergens, exposure to rat urinary allergen among animal handlers, and the response to food allergens in childhood [29–32]. The significance of this response to cat allergens comes from evidence that the expression of the gene for IgG4 is IL-4-dependent and thus, is a feature of a Th2 response [33,34]

Fig. 2. The modified Th2 response occurring in children exposed to high levels of the major cat allergen, Fel d 1, is characterized by the presence of serum IgG and IgG4 antibodies in the absence of IgE. In the allergic response, antibody isotype switching to IgE (and IgG4) ab production is regulated by the Th2 cytokine, IL-4. The presence of IgE ab is a risk factor for development of asthma. In the modified Th2 (or tolerant) response, production of IgG4 and IgE ab is uncoupled, possibly by the regulatory cytokine IL-10, resulting in no serum IgE ab and no risk of asthma.



(Fig. 2). The exciting aspect of this 'modified Th2' response to cat allergen is that, for the first time, a form of immunological tolerance has been described in relation to one of the allergens associated with asthma in the general population. To date this form of high-dose tolerance has not been observed with dust mite or cockroach allergens. Thus, one could ask why the response occurs with cat allergen or why it doesn't occur with other allergens.

If the presence of a cat in the house decreases the risk of sensitization to cat allergens, it is possible that endotoxin coming from the cat contributes to the effect [35]. We could ask whether the mechanism of the effect of domestic animals is the same phenomenon as the decreased risk of sensitization among children in farming families. Von Mutius and her colleagues found that children who spent significant time in a milking shed during the first year of life had a markedly decreased risk of sensitization and asthma [35]. This may well be the same phenomenon that Charles Blackley reported in 1873! [36]. However, in the studies from southern Germany the effect was not allergen-specific and the presence of a cat did not influence the results. Clearly the presence of cows in a barn is a potent source of endotoxin and an animal in the home could also be a source of gram negative bacteria and thus of endotoxin. Recent studies on endotoxin levels in houses would support this interpretation of the data [37]. However, the levels of endotoxin reported in houses in the USA are generally much lower than those reported from the homes of farmers [37–40]. Again it is possible that endotoxin has a proinflammatory effect at low-dose but can suppress immune responses at high-dose. Given the ability of endotoxin to induce IL-10 production it seems possible that it could enhance the effects of high-dose cat allergen. It is certainly simplistic to assume that the primary effect of inhaled endotoxin is to enhance Th1 responses.

There are several possible explanations for the effects of cat exposure. The most obvious comes from estimates suggesting that the quantity of cat allergen inhaled is 10–100 times higher than for mite or cockroach allergens. The alternative explanation is that the major cat allergen, Fel d 1, does not have

significant enzymic activity. Perhaps less likely to be relevant is the fact that the smaller size of particles carrying cat allergen would allow penetration of allergen further into the lung and possible influence the immune response. Finally, it is possible that significant cat allergen is swallowed and that the heavy glycosylation of Fel d 1 influences the response in the gut.

In conclusion, the recent findings about cat allergens have many implications:

- A large proportion of cat-allergic children have never lived in a house with a pet; thus, in communities with a significant number of pets, passive exposure may be the primary cause of allergic diseases related to animals.
- Since the dose–response for cat is flat or bell-shaped, increasing exposure is not a convincing explanation of increased prevalence of cat sensitization or increased asthma.
- The fact that the children who make an IgG and IgG4 antibody response to Fel d 1 without IgE ab, have no associated risk of asthma argues strongly that it is the IgE antibody arm of the Th2 response that is responsible for the risk of asthma.
- The immune response identified in the non-allergic children has many features of a modified Th2 response (i.e. IgG4 ab without IgE ab) and very little evidence of a Th1 response (no DH or precipitating antibodies). Indeed, we would question whether the evidence for a Th1 response to inhaled allergens is convincing.
- This modified response is not seen with mite allergen and the really important question may be why mite (and cockroach) allergens do not induce this change.

References

- 1 Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chapman MD (Chairmen). Indoor allergens and asthma. Third International Workshop, Cuenca, Spain. *J Allergy Clin Immunol* 1997; 100:S1–S24.
- 2 Kuehr J, Frischer J, Meiner R. Mite exposure is a risk factor for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994; 94:44–52.

- 3 Peat JK, Tovey E, Toell BG et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153:141–6.
- 4 Charpin D, Birnbaum J, Haddi E et al. Altitude and allergy to house-dust mites. A paradigm of the influence of environmental exposure on allergic sensitization. *Am Revs Resp Dis* 1991; 143:983–6.
- 5 Lau S, Illi S, Sommerfield C et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Group. *Lancet* 2000; 356:1392–7.
- 6 Sporik R, Squillace SP, Ingram JM, Rakes G, Honsinger RW, Platts-Mills TAE. Mite, cat and cockroach exposure, allergen sensitization and asthma in children. *Thorax* 1999; 54:675–80.
- 7 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergens (Der p 1) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990; 323:502–7.
- 8 Squillace SP, Sporik RB, Rakes G et al. Sensitization to dust mites as a dominant risk factor for adolescent asthma. *AJRCCM* 1997; 156:1760–4.
- 9 Peat JK, Tovey E, Gray EJ, Mellis CM, Woolcock AJ. Asthma severity and morbidity in a population sample of Sydney schoolchildren: Part II-Importance of house dust mite allergens. *Aust NZ J Med* 1994; 24:270–6.
- 10 Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergen development? *Clin Exp Allergy* 1999; 29:611–7.
- 11 Roost HP, Kunzli N, Schindler C et al. Role of current and childhood exposure to cat and atopic sensitization. *J Allergy Clin Immunol* 1999; 104 (5):941–7.
- 12 Ronmark E, Jonsson E, Platts-Mills TAE et al. Incidence and remission of asthma in school children: Report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatrics* 2001; 107:E37.
- 13 Henrik AM, Holmen TL, Bjermer L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. *Resp Med* 2001; 95:122–9.
- 14 Platts-Mills TAE, Vaughan J, Squillace S, Woodfolk JA, Sporik R. Sensitisation, asthma and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; 357:752–6.
- 15 Anyo G, Brunekreef B, deMear G, Arts F, Janssen N, van Liet P. Early current and past pet ownership. *Clin Exp Allergy* 2002; 32:361–6.
- 16 Sears MR, Herson GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite, and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989; 19:419–24.
- 17 Ownby DR, Johnson CC, Peterson EL. Exposure to cats and dogs during the first year of life reduces atopy and improves lung function in boys. *Am J Resp Crit Care Med* 2001; 163:A722.
- 18 Ronmark E, Lundback B, Jonsson E, Platts-Mills TAE. Asthma, type-I allergy and related conditions in 7- and 8-year old children in Northern Sweden. *Resp Med* 1998; 92:316–24.
- 19 Ishikawa K, Iwasaki E, Baba M, Chapman MD. High prevalence of sensitization to cat allergen among Japanese children with asthma, living without cats. *Clin Exp Allergy* 1999; 29:754–61.
- 20 Cookson WO, Moffatt MF. Asthma: an epidemic in the absence of infection? *Science* 1997; 275:41–2.
- 21 Busse WW, Lemanske RF Jr. Asthma. *N Eng J Med* 2001; 344:350–62.
- 22 Wierenga EA, Snoek M, DeGroot C et al. Evidence for compartmentalization of functional subsets of CD4+ lymphocytes in atopic patients. *J Immunol* 1990; 144:4651–6.
- 23 Parronchi P, Macchia D, Piccinni MP et al. Allergen- and bacterial antigen-specific T-cell clones established from atopic donors show a different profile of cytokine production. *Proc Natl Acad Sci USA* 1991; 88:4538–42.
- 24 Van Neerven RJ, van de Pol MM, van Milligen FJ, Jansen HM, Aalberse RC, Kapsenberg ML. Characterization of cat dander-specific T lymphocytes from atopic patients. *J Immunol* 1994; 152:4203–10.
- 25 Woodfolk JA, Platts-Mills TAE. Diversity of the human allergen-specific T cell repertoire associated with distinct skin test reactions. DTH-associated major epitopes induce Th1- and Th2-dominated responses. *J Immunol* 2001; 167:5412–9.
- 26 Woodfolk JA, Sung SSJ, Benjamin DC, Lee JK, Platts-Mills TAE. Distinct human T cell repertoires mediate immediate and delayed-type hypersensitivity to the *Trichophyton* antigen, Tri r 2. *J Immunol* 2000; 165:4379–87.
- 27 Haselden BM, Syrigou E, Jones M et al. Asthma, rhinitis, other respiratory diseases. *J Allergy Clin Immunol* 2001; 108:349–56.
- 28 Rawle FC, Mitchell EB, Platts-Mills TAE. T cell responses to the major allergen from the house dust mite *Dermaphagoides pteronyssinus*, Antigen P1: comparison of patients with asthma, atopic dermatitis, and perennial rhinitis. *J Immunol* 1984; 133:195–201.
- 29 Aalberse RC, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. *J Immunol* 1983; 130:722–6.
- 30 Rowntree S, Cogswell JJ, Platts-Mills TAE, Mitchell EB. Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic disease. *Arch Dis Child* 1985; 60:727–35.
- 31 Muller UR, Adkiss AC, Fricker M et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in bee sting allergic patients. *J Allergy Clin Immunol* 1998; 101:747–54.
- 32 Doekes G, Preller L, Vermeulen R, Spithoven J, Heederik D. Humoral immune responses to pig urinary proteins and respiratory health of pig farmers. *J Agromedicine* 1997; 4:79–80.
- 33 Zhang K, Mills FC, Saxon A. Switch cycles from IL-4 directed epsilon class switching from human B lymphocytes. *J Immunol* 1994; 152:3427–35.
- 34 Agrest A, Vercelli D. Analysis of gamma-4 germ line transcription in human B cells. *Int Arch Allergy Immunol* 1999; 118:279–81.
- 35 Braun-Fahrlander C, Gassner M, Grize L et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999; 29:28–34.
- 36 Blackley CH. Experimental Researches on the Causes and Nature of Catarrhus Aestivus. London: Dawson's, 1959.
- 37 Gereda JE, Klennert MD, Price MR, Leung DY, Liu AH. Metropolitan home living conditions associated with indoor endotoxin levels. *J Allergy Clin Immunol* 2001; 107:790–6.
- 38 Gereda JE, Leung DYM, Thatayatikom A et al. Relation between house dust endotoxin exposure, type 1 T-cell development, and allergen sensitization in infants at high risk of asthma. *Lancet* 2000; 355:1680–3.
- 39 Reed CE, Milton DK. Endotoxin-stimulated innate immunity: a contributing factor for asthma. *J Allergy Clin Immunol* 2001; 108:157–66.
- 40 Von Mutius E, Braun-Fahrlander C, Schierl R et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; 30:1230–4.

T. A. E. PLATTS-MILLS, M. PERZANOWSKI,
J. A. WOODFOLK and B. LUNDBACK*
University of Virginia Health Systems
PO Box 801355, Charlottesville,
VA 22908, USA
E-mail: tap2z@virginia.edu
*Karolinska Institutet, Stockholm, Sweden

Erratum

Relevance of early or current pet ownership to the prevalence of allergic diseases

T. A. E. Platts-Mills, M. Perzanowski, J.A. Woodfolk and B. Lundback

Clin Exp Allergy 2002; 32: 335–8.

There was an error in Fig. 1 of this editorial. Part of the Figure was missing. The correct Figure is displayed below.

