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Reply

To the Editor:

We read with great interest the correspondence from Liccardi et al,¹ which adds valuable information to the review on allergy to furry animals recently published in the journal.² Liccardi et al used molecular allergy diagnostics on 741 subjects and found that sensitization to the lipocalins Equ c 1 (from horse) and Mus m 1 (from mouse) occurred only in those subjects who were also sensitized to cats and/or dogs. The authors suggest that allergic sensitization to cats and/or dogs might be a risk factor for sensitization to horse and mouse.

Applying a similar approach, using an experimental research ISAC prototype (Thermo Fisher Scientific, Uppsala, Sweden) containing 111 allergen components,³ we explored the pattern of sensitization to inhalant allergens in a cohort of school-age children (n = 92) with controlled persistent or severe uncontrolled asthma. We found that 60 children (63%) were sensitized to inhalant allergens, including allergens from cats (Fel d 1, 2, 4) and dogs (Can f 1, 2, 3, 5), 14 children (15%) were sensitized to other inhalant allergens, but not allergens from cats and/or dogs, and 21 children (22%) were not sensitized to any inhalant allergen. Twenty-nine children were sensitized to Equ c 1, and all these were also sensitized to allergens from cats and/or dogs, and of these children 72% (21 of 29) were sensitized to both Equ c 1 and Fel d 4. Eight children were sensitized to Mus m 1, and 7 of these were sensitized to cats and/or dogs. All these 7 children were sensitized to Fel d 1, 6 were sensitized to Fel d 4, and 6 were sensitized to Equ c 1. Two patients were Equ c 1 negative and Mus m 1 positive.

In addition, we investigated 694 randomly selected children (age, 11-12 years) from a population-based study in Northern Sweden (The Obstructive Lung Disease in Northern Sweden [OLIN] longitudinal pediatric study) with sensitization to inhalant allergens. Using extract-based methods (Immunocap, Thermo Fisher Scientific), we found that sensitization toward horse occurred in 54% (106/196) of the children who were sensitized to both cats and dogs, in 41% (114 of 281) of those who were sensitized to either cat or dog, and in 10% (8 of 82) of the children without sensitization toward cats and/or dogs.

These Swedish results from *both* a highly selected population of children with persistent or severe asthma and from a

population-based study support the results provided by Liccardi et al to some extent. Sensitization to horse and/or mice seems to be associated with sensitization toward cats and/or dogs, and a likely explanation is cross-reactivity due to the homogeneity between the lipocalins from cat, dog, mouse, and horse. Amino acid identity between Equ c 1 and Fel d 4 is 67%, between Mus m 1 and Fel d 4 is 49%, between Equ c 1 and Can f 6 it is 57%, and between Mus m 1 and Can f 6 is 47%.⁴

However, it should be emphasized that both Liccardi et al's and our data are cross-sectional and it is currently not possible to state that sensitization to cats and/or dogs increases the risk of sensitization to horse and mouse. Furthermore, it is not clear whether this IgE-cross-reactivity is related to clinical symptoms. We have previously shown that IgE antibodies to some lipocalins are more common in severe childhood asthma,⁵ but clearly more studies are needed to clarify whether clinical symptoms are likely to arise upon exposure to horse or mice in this case.

The clinical relevance of low levels of IgE to Equ c 1 or Mus m 1 is also unknown. Low levels of IgE might not give rise to clinical symptoms, but could possibly, upon regular horse or mice contact, contribute to an amplification of the allergic response over time and lead to epitope spreading and ultimately to clinical symptoms.

We certainly do agree with Liccardi et al that more research is needed on the complex relationship between allergen exposure, the development of allergic sensitization, and allergic diseases. One example of the complexity of these processes was shown in a longitudinal analysis from the OLIN studies. In this study, exposure to cats at home protected against sensitization not only toward cats but also in general. Furthermore, the incidence data from OLIN demonstrate that sensitization to an increasing number of allergens is developed throughout childhood.⁶

With this in mind, it is our understanding that to answer the interesting research question posed by Liccardi et al, longitudinal population-based studies with repeated analysis of IgE antibodies and meticulous data on exposure are needed.

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