

The allergic paradox: A key to progress in primary prevention of asthma

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Key words: Asthma, allergen avoidance

There is a high burden of disease caused by asthma in many countries. This burden is attributable to its prevalence in persons of all ages^{1,2} and its effect on individuals and society. Although therapy is effective in improving disease control, there is no available treatment that can reproducibly induce disease remission. Hence interventions that can prevent the onset of the disease in the first place are keenly sought.

Most of the trials of interventions for the primary prevention of asthma and allergic disease have focused on a window of opportunity in very early life³⁻⁵ and therefore have enrolled infants at or before birth. The rationale for this is 2-fold. First, the incidence of asthma is highest in childhood,^{6,7} and primary prevention needs to start before most cases occur. Second, there is some evidence that the immunologic events linked to asthma, in particular the polarization of T-cell cytokine responses to allergen, are still relatively plastic in the first 18 months to 3 years of life.⁸ It remains unknown whether this plasticity is associated with a greater amenability to modification by environmental or other interventions during this time.

There are several hypotheses for the cause of asthma, and in fact, a range of environmental exposures can lead to manifestations of this heterogeneous disease. Nevertheless, allergen avoidance, specifically house dust mite allergen avoidance, has been the main focus of interventions to prevent asthma.⁹⁻¹³ The primary reason for this is the strong association between asthma or its physiologic hallmark airway hyperresponsiveness and sensitization to allergens.¹⁴ Furthermore, it is well established that the physiologic and pathologic features of asthma in human subjects can be induced or exacerbated by exposure to allergens.¹⁵ Perhaps the best model in adults for the role of exposure and sensitization to environmental allergens in the development of asthma is occupational asthma.¹⁶ The allergen model for prevention of asthma has much to recommend it.

Lodge et al,¹⁷ in this issue of the *Journal*, have reinforced the importance of early allergic sensitization as a harbinger for the development of asthma. In common with previous investigators, they have shown that children who are allergic to house dust mite have an increased risk of having wheeze in later childhood,

irrespective of whether they have wheeze at the time their allergic status is assessed. However, the present study extends this finding in 2 important respects.

First, the authors show that the prognostic significance of sensitization to house dust mite is evident at age 2 years and is strongest in those who are sensitized to this allergen at age 1 and 2 years. This finding emphasizes the importance of the events leading to sensitization at this early age in the evolution of asthma. Second, they demonstrate that this occurs irrespective of whether there is accompanying sensitization to other ingested or inhaled allergens and that sensitization to these other allergens does not have prognostic significance for later wheeze. At least in the environment in which this study was conducted, there is something special about house dust mite sensitization,¹⁸ even at this early age.

The study is not without limitations, as the authors acknowledge. The subjects were all studied in a single city. It is unclear how generalizable these findings are to other environments, particularly those relating to the specific importance of house dust mite allergy. Certainly, house dust mite sensitization has been shown to be an important predictor of the development of asthma in many other environments, as described by Kuehr et al,¹⁹ but in cold climates cat allergen sensitization seems to be a more important predictor,²⁰ as does cockroach allergen in coastal northern US cities, such as New York.²¹ The other limitation of this study was the lack of power to properly exclude sensitization to other allergens as independent predictors of subsequent wheeze. CIs around estimates for monosensitization to other allergens were wide, and the authors have not undertaken a global multivariate analysis to assess the independent effects of sensitization to specific allergens, presumably because of problems with collinearity.

Despite these limitations, the message from the article is clear. Sensitization to house dust mite is common, it occurs early in life, and, at this early age, it is a powerful predictor of subsequent wheezing illness at age 12 years.

It is for the reasons cited above and reinforced by these new findings that house dust mite allergen avoidance has had a leading role in most trials of primary prevention interventions. However, despite the strong rationale, allergen avoidance interventions have not generally been successful in preventing either sensitization or asthma. Even rigorous and apparently effective attempts at removing house dust mite allergen from the environment have not resulted in a reduction in house dust mite sensitization. Indeed, there has been evidence of an early increase in sensitization²² or eczema²³ in some studies. At the present time, the promise of allergen avoidance in early life as a means of preventing the onset of asthma has not been realized.

We appear to have an allergic paradox: evidence of the importance of house dust mite allergen in various components of asthma but empiric evidence that practical avoidance measures

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Disclosure of potential conflict of interest: G. B. Marks has received research support from the National Health and Medical Research Council of Australia.

Received for publication August 24, 2011; accepted for publication August 25, 2011.

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J Allergy Clin Immunol 2011;128:789-90.

0091-6749/\$36.00

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doi:10.1016/j.jaci.2011.08.020

do not prevent the disease. The resolution of this paradox is likely to hold an important key to our understanding of this disease and how to prevent it. This author cannot resolve it, but there are several potential lines of enquiry.

Improved understanding of exposure-response relationships might be a good starting point. There is some evidence that these might be nonlinear.²⁴ It is possible that there is an ideal level of house dust mite allergen exposure to minimize the risk of asthma and that current regimens are missing this mark, leaving either too much or too little in the infant's environment. Coexposures are likely to be important. Is it possible that interventions to remove allergen from the environment are also removing protective factors? Perhaps the observed nonlinear exposure-response relationships are attributable to the overlay of these 2 effects: reduction in allergen exposure and coincident removal of protective factors.

Finally, the heterogeneous nature of the entity we are trying to prevent might be part of the problem. It is plausible that the allergen avoidance works to prevent some forms of asthma but not others. We do not yet fully understand the heterogeneity of this disease. Latent class analysis²⁵ and other statistical techniques, together with more comprehensive phenotyping and genotyping information, might help to unravel this heterogeneity and identify particular types of asthma that can be prevented by allergen avoidance interventions.

I look forward to a time when we can confidently advise concerned parents how to prevent their child from having asthma. It seems we still have a long way to go.

REFERENCES

- Lai CKW, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476-83.
- James AL, Knuiman MW, Divitini ML, Hui J, Hunter M, Palmer LJ, et al. Changes in the prevalence of asthma in adults since 1966: the Busselton health study. *Eur Respir J* 2010;35:273-8.
- Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113:650-6.
- Holt P, Macaubas C. Development of long term tolerance versus sensitisation to environmental allergens during the perinatal period. *Curr Opin Immunol* 1997;9:782-7.
- Holt P, O'Keefe P, Holt B, Upham J, Baron-Hay M, Suphioglu C, et al. T-cell "priming" against environmental allergens in human neonates: sequential deletion of food antigen reactivity during infancy with concomitant expansion of responses to ubiquitous inhalant allergens. *Pediatr Allergy Immunol* 1995;6:85-90.
- Matricardi PM, Illi S, Gruber C, Keil T, Nickel R, Wahn U, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32:585-92.
- Wijga A, Tabak C, Postma DS, Kerkhof M, Wieringa MH, Hoekstra MO, et al. Sex differences in asthma during the first 8 years of life: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. *J Allergy Clin Immunol* 2011;127:275-7.
- Weber-Chrysochoou C, Crisafulli D, Kemp A, Britton W, Marks GB. Changes in dust mite-specific cytokine responses during the first 8 years of life: relation to clinical and allergic outcomes at the age of 8 years. *Allergy* 2009;64:45.
- Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116:49-55.
- Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307-13.
- Marks GB, Toelle B, Ng K, Almqvist C, Webb K, Tovey E, et al. Eight year outcomes of HDM avoidance and diet fatty acid interventions in a high risk birth cohort: the childhood asthma prevention study. *Eur Respir J* 2008;32:359s.
- Custovic A, Simpson B, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low allergen environment can be achieved and maintained during pregnancy and early life. *J Allergy Clin Immunol* 2000;105:252-8.
- Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17:329-36.
- Peat J, Salome C, Woolcock A. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990;85:65-74.
- Pin I, Freitag AP, O'Byrne PM, Girgis-Gabardo A, Watson RM, Dolovich J, et al. Changes in the cellular profile of induced sputum after allergen-induced asthmatic responses. *Am Rev Respir Dis* 1992;145:1265-9.
- Malo JL, Chan-Yeung M. Occupational asthma. *J Allergy Clin Immunol* 2001;108:317-28.
- Lodge CJ, Lowe AJ, Gurrin LC, Hill DJ, Hosking CSK, Rida U, et al. House dust mite sensitization in toddlers predicts current wheeze at 12 years. *J Allergy Clin Immunol* 2011;128:782-8.
- Woolcock A, Peat J, Mellis C, Leeder S. House dust mite atopy is important in childhood asthma but ryegrass atopy is not. *Am Rev Respir Dis* 1992;145:A662.
- Kuehr J, Frischer T, Meinert R, Barth R, Schraub S, Urbanek R, et al. Sensitization to mite allergens is a risk factor for early and late onset of asthma and for persistence of asthmatic signs in children. *J Allergy Clin Immunol* 1995;95:655-62.
- Korppi M, Hyvarinen M, Kotaniemi-Syrjanen A, Piippo-Savolainen E, Reijonen T. Early exposure and sensitization to cat and dog: different effects on asthma risk after wheezing in infancy. *Pediatr Allergy Immunol* 2008;19:696-701.
- Olmedo O, Goldstein IF, Acosta L, Divjan A, Rundle AG, Chew GL, et al. Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City. *J Allergy Clin Immunol* 2011;128:284-92, e7.
- Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170:433-9.
- Marks GB, Mirshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006;118:53-61.
- Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. *J Allergy Clin Immunol* 2008;122:114-8, e5.
- Siroux V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J* 2011;38:310-7.