

A New Approach to Environmental Control Trials



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The article by Ahmed et al¹ in this issue describes a secondary analysis of data from a randomized clinical trial that has been published previously.² The original trial was carefully done, and the resulting database is quite complete. It included 361 asthmatic children who were allergic to mouse allergen, and who had high levels of mouse allergen in their home. They were randomized to a treatment group with aggressive mouse allergen abatement using integrated pest management plus education, or to a control group that received education alone. In the intent to treat analysis, both treatment and control groups saw similar reductions in household mouse allergen; 47% of the treatment group and 40% of the control group saw mouse allergen in settled dust reduced below 0.5 mcg/g, a level previously shown to be a threshold for disease activity in asthmatic patients.³ Asthma disease activity was improved about the same in both groups. This apparently negative result, with little difference seen in the treatment and control groups, is disappointingly similar to earlier indoor environmental control trials.^{4,5}

In their original paper, Matsui et al² also reported a different analysis, one that produced interesting and important findings. They sorted their data by changes in indoor allergen exposure rather than treatment and control. Sorting by level of allergen reduction meant that families who had reduced mouse allergen to safe levels, whether in the treatment or control group, were compared with those who had not successfully reduced exposure. The results were striking. For example, every 50% reduction in allergen was associated with a 4% reduction in disease activity over the year. “An individual experiencing a 90% reduction in bedroom floor dust mouse allergen levels was estimated to have 14.1 fewer symptom days ($P < .001$) ... and 0.8 fewer acute visits ($P < .001$) per year compared with baseline.”

The mouse allergen abatement trial should be considered in historical perspective. Clinical trials of environmental avoidance have been hobbled by study designs that usually lead both treatment and control groups to reduce indoor exposure. Current ethical standards require that participants be informed of potential hazards involved in the proposed research. No one would argue that this is appropriate for randomized placebo-controlled clinical

trials of drug treatments. The dilemma in environmental research is that you are proposing that exposure to something in their home (ie, chemical, pollutant, allergen) is the hazard, and that the research will test the effect of reducing this hazard. Given this understanding, who would choose to be in a control group whose children will continue to be exposed? And who would not try the proposed beneficial treatment on their own, especially if is directed at indoor pests? Environmental avoidance involves changes in behavior sustained over a long period, so creating a valid control group under these conditions is almost impossible. This issue has received much greater attention and concern since 2000, when a Maryland Appeals Court ruled that participants in a home-based lead abatement trial could sue the investigators for the risk to their children. The implications for home-based environmental research of this decision are discussed in several references.^{6,7} In the mouse allergen trial, it is likely that education given to the control group, or the knowledge that they were participating in a trial of a potentially helpful therapy, encouraged many families to try allergen control measures on their own. This makes it difficult to test a hypothesis that reducing exposure in the home to allergens to which you are sensitized improves asthma control.

In their current paper, Ahmed et al¹ sort their data in yet another way, by atopic status, categorizing asthmatic children as highly atopic (≥ 6 positive prick skin tests) or less atopic. This time they found that highly atopic children saw no improvement in asthma during the year, whereas less atopic children did improve. The authors suggest that children with multiple sensitivities might not improve because exposure to other important allergens did not decrease. Another possibility is suggested by a recent report from a conference considering the many European birth cohort studies; they concluded that asthmatic children defined as highly atopic are a distinct subgroup,⁸ one that is more likely to have a positive family history, higher levels of total and specific IgE, and whose asthma is usually more severe, higher levels of total and specific IgE, and less improvement with age when followed prospectively. By examining multiply sensitized (more than 6 positive skin tests), they may have also selected for the most severe and intractable asthmatics.

Although *post hoc* analysis is frowned upon in clinical trial methodology, given the frustrating changes in control groups seen in many trials of environmental control, it seems a valid approach, provided it is included in the original trial protocol. It would be interesting to repeat this analysis using databases from other environmental intervention trials to see if these findings can be confirmed. A better understanding of the determinants and best practices for avoidance of indoor allergens may result.

The authors comment that the level of mouse-specific IgE did not affect the outcome of the trial. This seems counterintuitive, and I hope that this point will be examined and described in more detail in subsequent publications. In general, anyone with a positive prick skin test (greater than 3-mm net wheal diameter)

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or a level of IgE to cat allergen greater than 0.8 radioallergosorbent test units will respond to a controlled cat environment with an acute asthmatic response.⁹ Perhaps the comparison would be confounded by the finding that highly atopic individuals are likely to have higher levels of both specific and total IgE. This might be resolved by examining the relationship in the less atopic group, provided there is an adequate sample size.

The paper is encouraging in a practical way. Perhaps environmental control does make sense after all, and perhaps education alone is as successful as more elaborate and expensive methods. I would also disagree with the authors' conclusion that no clinical characteristic clearly identified a subgroup that should be targeted. Treatment is only indicated in children with a positive prick test to mouse allergen who are exposed to mouse allergen in their homes. It also appears that highly atopic asthmatics, who may also be the most intractable, should not be expected to respond as well. Perhaps in these children, educational efforts would be better spent on medication treatment and adherence.

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