bronchial hyperresponsiveness at inclusion and during follow-up; it is possible that this would not have been found in daily practice.

We agree that the definition of asthma is important, but we do not agree that our definition is well outside the boundaries of other asthma definitions. Like GINA 1998, published after the start of our study, we required repeated episodes of symptoms typical of asthma. In addition, we required a good response to treatment with β2 agonist; this is described in detail (p. 253). Peak-flow variations, lung function measurements, and medications are included in the study but were not reported in detail in our article. Bronchial hyperresponsiveness, measured by methacholine provocation testing (as we reported in our article), clearly supports the clinical data. As described in the text, it is possible that the careful registration of symptoms with a focus on asthma is the reason that we found more children with asthma than earlier reported.

In addition to our accepted diagnostic criteria for asthma, one of the centers included other, more sensitive tests that increased the possibility of finding asthma in comparison with what was done at the other centers, as described in the article. Despite the contradictory results from this center, the pooled data showed development of significantly fewer cases of new asthma in the specific immunotherapy group. It is often the case that only pooled data from multicenter studies are shown. We also showed the results from each individual center, allowing the reader to make his own evaluation.

Peak-flow values are similar in both groups, which is to be expected, given that all of the children with asthma were treated adequately; this included treatment with inhaled glucocorticosteroids when needed.

As described in our article, the visual analog scale asthma scores are very limited, inasmuch as the asthma found in our study represents mostly mild asthma. Furthermore, asthma symptoms were treated adequately. Our aim in the article was not to describe the severity of asthma but to note whether the children developed asthma or not.

It is obvious that the findings in our study add to the already well-established indications for specific immunotherapy. It is our intention to present our data and draw conclusions from them, but we leave it to international as well as national expert groups to develop future guidelines for optimal treatment of the allergic patient. This has recently been done by the World Health Organization: In the ARIA document, specific immunotherapy is integrated into the optimal treatment concept because of the long-term and preventive outcome of the treatment.

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Can immunotherapy prevent progression to asthma in allergic individuals?

To the Editor:

In their interesting and provocative article, Möller et al1 demonstrate that allergen-specific immunotherapy (SIT) is effective in preventing progression to asthma in allergic individuals, thus supporting the view that SIT should be considered earlier in the treatment of rhinitis to prevent progression to more advanced and irreversible type of allergic diseases, such as asthma. Their findings are in agreement with our recent observations in a randomized, double-blind, placebo-controlled, parallel-group study of nonasthmatic subjects with seasonal allergic rhinitis.2 By the end of this study, 47% of the subjects in the placebo group had asthma symptoms as opposed to only 14% of those in the SIT group. Moreover, in a large retrospective survey of nonasthmatic subjects with allergic rhinitis, we have reported that patients receiving immunotherapy have a 40% less chance of having asthma compared with untreated patients.3

Although the findings by Möller et al1 clearly support the evidence that use of immunotherapy in nonasthmatic children with rhinitis can reduce their risk of asthma development in the future, the ample variability in the results between study centers is of importance, deserves attention, and should have been discussed more in detail. Because bronchial hyperresponsiveness (BHR) might identify patients with rhinitis who are at risk for asthma progression,4 it would be important to verify whether the absence of prevention in asthma progression by SIT is associated with a lack of protective effect on methacholine BHR in the same centers.

The discrepant protective effects of SIT on the development of asthma between centers might be related also to the specific characteristics of the inhalant allergen type in that particular region or area. Recurrent exposure to allergens with strong allergenic properties might eventually dictate progression of the allergic march toward asthma, and a situation like this is less likely to be influenced by the protective effect of SIT. Therefore more information regarding the most representative inhalant allergen type associated with each center would have been important in providing an explanation for the observed variation between centers.

In addition, because it is possible that some sex-dependent reduction in asthma prevalence around the time of puberty occurs as a result of hormonal modifications,5 any important difference in terms of age or sex distribution in both treatment groups at each center might influence results and justify the variability between study centers.

It is not known why SIT should prevent progression to asthma in some allergic individuals, but one explanation rests in the potential of SIT to attenuate BHR and lower airway inflammation. In the study by Möller et al,1 changes in BHR to methacholine appear to be negligible (well within the challenge repeatability of 1 doubling dilution), and I fear that nonparametric analysis is producing a statistically significant result that has trivial clinical importance: the end of the study, PC20 methacholine increased from 12.2 to 14.9 mg/mL for the control and SIT groups, respectively. We also failed to detect an important effect of SIT against BHR to inhaled methacholine (and sputum eosinophils) in nonasthmatic subjects with allergic rhinitis.2 However, our data indicate that SIT can prevent seasonal deterioration of airway responsiveness to inhaled AMP. All participants in the placebo group became hyperresponsive to AMP (with 3 new patients having hyperresponsiveness to AMP), whereas no new cases of AMP hyperresponsiveness were observed in the SIT-treated group (one patient became hyporesponsive to AMP). Further analyses of this study revealed that low values of AMP PC15 (but not methacholine PC15) are good predictors of subsequent asthma progression in nonasthmatic subjects with allergic rhinitis. In addition, logistic regressions showed that AMP PC15 is likely to
forecast the prophylactic effects of SIT in preventing the natural course of the disease. Although larger studies are needed to define the characteristics of the patients who would benefit most from such a therapeutic approach, this observation indicates that BHR to inhaled AMP might be useful to identify those in whom SIT might be effective at preventing progression to asthma.

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REFERENCES

Reply
To the Editor:
In his comments about our article,1 Dr Polosa2 points out that the article should have discussed the relationship between bronchial hyperresponsiveness (BHR) and the risk for asthma more thoroughly, especially considering the divergent findings by different groups (or centers). We basically agree, and after we have now published our primary end point of the study, we have planned a forthcoming publication in which we will present detailed information about the correlation between BHR, allergen-specific immunotherapy, and the development of asthma.

Also, it would be interesting to investigate whether differences in allergen exposure might influence our primary outcome measures. This could add to the explanation of the difference between centers, and we plan to do this analysis later. However, there were no important differences between the centers regarding age or sex.

The statistical differences in BHR to methacholine between the active and control groups are limited and might seem to be without clinical significance. All our patients with asthma at base season had only very mild asthma. Most of the nonasthmatic children never had asthma, and in case they did, the patients, with few exceptions, only had very mild asthma. Therefore we believe that it is very interesting to find a difference between the groups. We suspect that the differences would have been far more clinically significant if we had studied children with moderate or severe asthma at randomization. The variations in BHR in our patient material were extremely large and could explain the lack of statistically significant differences at some points.

The findings by Dr Polosa that the responsiveness to AMP is a much better predictor than methacholine of later asthma in patients with rhinitis is an interesting observation that should indeed be investigated further. However, this information was not available at the time of designing the study in 1990 to 1991.

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