

Correspondence

Sublingual immunotherapy for cat allergy

To the Editor:

We read with interest the article by Nelson et al. (Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J ALLERGY CLIN IMMUNOL* 1993;92:229-37) published in the August 1993 issue of the *JOURNAL*. This article is of importance because it attempts to measure the effects of alternative-route immunotherapy (i.e., sublingual) with a rigorous approach. The study, which used a standardized extract, was double-blind and placebo-controlled, and the efficacy of immunotherapy was based on the cat room challenge.^{1,2} Both subjective and objective methods have been used for the assessment of efficacy. The dose of allergen received by the patients is high enough, but it appears that the duration of immunotherapy may not be long enough to make a definite conclusion.

We are, however, concerned about some methodological problems and the conclusions of the study that are not entirely supported by the data. The authors state that "sublingual immunotherapy . . . was no more effective than placebo," whereas the only objective measure of nasal symptoms shows that there is an almost seven-fold reduction in mean nasal blockage index in the active treatment group ($p < 0.001$) and a 1.26-fold reduction for the same parameter in the placebo group (not significant). We think this a very good result obtained with immunotherapy. There may not be significant differences between the two groups after 105 days, but the standard error of the mean is extremely high, explaining the lack of significant difference between the two groups. On the other hand, the results of the symptom score are more difficult to interpret. In the active treatment group there was a 2.38-fold reduction in this score ($p < 0.001$), and in the placebo group there was a 1.9-fold reduction ($p < 0.01$). This result raises the question of the reproducibility of symptom scores in the cat room and the reproducibility of allergen exposure. First, the levels of allergens were above the level of detection in one of eight samples during the baseline weeks and in seven of eight samples in the second postimmunotherapy week. It therefore appears that the levels of *Fel d* I are less reproducible than those in a previous study.³ Second, it is very surprising that patients receiving placebo have significantly fewer symptoms when they are exposed to a higher amount of allergen. These differences in allergen content in the cat room may explain the very large standard error of the mean obtained. The authors should therefore attempt to make their provocation method reproducible before drawing firm conclusions.

In conclusion, although methodologic problems are of importance in this study, it seems that if any conclusion may be drawn, it is that sublingual immunotherapy may

be effective in treating cat allergy and that further studies are required to fully assess its efficacy.

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3. Van Metre TE, Marsh DG, Adkinson NF Jr, et al. Dose of cat (*Felis domesticus*) allergen 1 (*Fel d* 1) that induces asthma. *J ALLERGY CLIN IMMUNOL* 1986;78:62-75.

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Reply

To the Editor:

We thank Dr. Bousquet and Dr. Michel for their interest in our article on sublingual immunotherapy. We believe that our conclusion that "in our study high dose sublingual therapy with cat extract was no more effective than placebo in reducing the symptoms of allergic rhinitis or nasal obstruction when subjects were exposed to an apartment containing cat dander" is valid. We appreciate the methodological problems pointed out by Dr. Bousquet and Dr. Michel, particularly regarding the variations in cat dander levels in the apartment. The amount of cat dander in the air at any one time is small compared with the reservoir on surfaces and is markedly affected by the level of human activity within in the room, as well as by the amount of ventilation. We effectively limited the latter, as indicated by the rising levels of cat dander over the course of the study. The proportion of airborne dander is more difficult to control. However, patients tend to report consistent recurrence of symptoms on visiting homes with cats where the same variation would be expected.

Perhaps of more serious concern is the degree of improvement reported by the patients who received placebo. This may have prevented detection of a true effect from the sublingual therapy. This improvement in the placebo group is unfortunately characteristic of immunotherapy studies.

The final problem mentioned is the duration of the study. Although it is recognized that continuing im-

provement probably occurs over several years with conventional immunotherapy, it is also clear that changes in end organ sensitivity are detectable by the time maintenance therapy is achieved.¹ Furthermore, the study by Ohman et al.,² which demonstrated the efficacy of injection immunotherapy with cat extract, used only 16 weekly injections, with many patients not reaching the projected maintenance dose even by the end of the study. Thus it seems unlikely that the failure to demonstrate a significant difference between active treatment and placebo groups in our study, by any parameter, can be attributed solely to the duration of the study.

We agree that further studies of sublingual immunotherapy should and probably will be conducted. We hope that an attempt will be made in these studies to differentiate between the effect of sublingual and oral immunotherapy by having, as in our study, the patients expectorate the extract rather than swallowing it after a period of residence in the mouth.

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Breath-actuated metered-dose inhaler

To the Editor:

In their article, Schecker et al. (*J ALLERGY CLIN IMMUNOL* 1993;92:783-9) pointed the advantage of delivering aerosols through a metered-dose inhaler (MDI) for persons who have discoordination problems. However, the evaluated Autohaler device (3M Pharmaceuticals, St. Paul, Minn.) has some practical limitations, especially for use in small children which should be mentioned. First, we observed that some children stopped inspiration because of the sudden, noisy and automatically actuated puff. This may lead to insufficient deposition of the aerosol. Second, the flow needed for actuation (about 30 L/min) seems to be too high, especially in the presence of acute airway obstruction, as demonstrated by Ruggins et al.,¹ for some children under the age of 6 years. Third, the Autohaler is not

compatible with the use of large volume spacers, which would be desirable, particularly when it is used as a conventional MDI. Fourth, the device is marketed only for a β -agonist (pirbuterol) and not for the combination of a β -agonist with sodium cromoglycate or for topical steroids. Finally, the device is difficult to clean and maintain and less robust than conventional MDIs. In conclusion, the Autohaler is indeed useful for a subgroup of patients with poor coordination, but it does not "overcome" all problems inherent in the use of MDIs.

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REFERENCE

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Reply

To the Editor:

Dr. Niggemann points out that the Autohaler device (3M Pharmaceuticals, St. Paul, Minn.) will not solve all problems that patients, particularly small children, may have in association with the use of MDIs. We certainly agree (and noted in the article) that a minimum flow rate is required. We do not disagree with the other points raised by Dr. Niggemann but want to comment further to avoid possible misinterpretation of his remarks.

There is probably little reason to use Autohaler in conjunction with large volume spacers such as Nebuhaler (Astra Pharmaceuticals, Sweden) (which is available in Germany but not in the United States) because this spacer tends to overcome discoordination problems. In our experience and that of others, pirbuterol is essentially equivalent to albuterol in effectiveness, side effects, and duration of action. Autohaler is marketed in the United States as a device to be used with one MDI only, and hence should be used for a maximum of 400 inhalations and then discarded. The manufacturer has found that Autohaler can be used for at least 4000 inhalations—a reliability factor of 10-fold.

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