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Editorial

**A reappraisal of sting challenges: To whom
should we offer venom immunotherapy?**

It is difficult, as one ages, to change one's mind: it is not, however, impossible. I have long believed that the stinging of unprotected patients with insect allergy in order to decide to whom we should offer immunotherapy is far too dangerous and would in fact lead to serious anaphylactic reactions and without question, to deaths. The work reported in this issue of the JOURNAL by van der Linden and colleagues has forced the issue for me: their data suggest that I was wrong and that we must reconsider this approach.

Being a part of the group that began trials of venom immunotherapy has no doubt given me a somewhat distorted view of this syndrome. The first patient that we treated with insect venom was the sibling of a child who had died as a result of an insect sting.¹ Although 2 decades of subsequent studies illustrate precisely how rare such an event is, its emotional impact remains. Moreover, because we were among the first to offer venom immunotherapy, our early patients, who were studied in an open, uncontrolled fashion, were from all over the world and were very highly motivated because they had experienced, while

receiving whole body extract therapy, multiple, life-threatening reactions to stings.² There was no question, in these individuals, of withholding therapy. Finally, in the initial controlled trial of venom immunotherapy, we were forced to discontinue the study when after a sting, an unprotected control patient became hypotensive and remained in shock for 5 hours, despite our rather heroic therapeutic endeavors.^{3, 4} With this as an introduction to insect hypersensitivity, it is perhaps not unanticipated that I and the Hopkins group would take a somewhat more cautious approach to this disease than do others.

Dr. van der Linden and his colleagues have sting-challenged a very large number of individuals—324—with a history of yellow jacket or honeybee sting anaphylaxis. Only 25% of the former and 50% of the latter had any reaction at all. Their study was mounted in an attempt to find immunologic or other criteria that would allow the physician to predict which patients with a positive history would have a repeat reaction on insect sting. In this they failed, as have we and all others who made this effort.^{5, 6} It is clear that with our current inadequate understanding of this disease, further analyses of the known parameters of insect hypersensitivity will not be productive. In fact, our finding that patients, after 4 years of immunotherapy (even though skin test and RAST results remain positive), virtually never have a reaction to a field sting fits in well with van der Linden's observations.⁷ He suggests in fact that most individuals who have an anaphylactic reaction are "tolerized" by the sting that caused it and

From Johns Hopkins Asthma and Allergy Center, Clinical Immunology Division, Baltimore.

Reprint requests: Lawrence M. Lichtenstein, MD, PhD, Johns Hopkins Asthma and Allergy Center, Clinical Immunology Division, 5501 Hopkins Bayview Circle, Baltimore, MD 21224.

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do not require the 4 plus years of immunotherapy currently recommended.

These results suggest that we should reconsider whether a diagnostic sting to evaluate the need for immunotherapy, as is carried out in many parts of Europe, is not also appropriate in the United States. The study by van der Linden et al. indicates that 10% or 15% of patients with a positive history but without positive skin test results or measurable IgE antibodies to venom can indeed have a reaction on being stung. These individuals would certainly benefit from such a change in practice because according to present criteria, they are denied immunotherapy. However, the most important findings in this study are that of all of the patients stung, most had no reaction, whereas in those who did, the response was invariably milder than the initial reaction: *none* of the 324 patients who were sting-challenged had a more severe reaction. This was precisely our finding in the several hundred untreated children that we have studied: there was only a 9% incidence of a second reaction on a field sting, and in *no* instance was the reaction more serious than the first field sting.⁸ As a result, we have suggested that 60% to 70% of venom-sensitive children, those who have a history of only cutaneous symptoms on sting, do not require immunotherapy; that is, we recommend that children with so-called Mueller reactions of grades 1 and 2 not be treated.⁹ The work by van der Linden et al. suggests that this practice should be extended to adults; that is, they would sting all individuals with a history of an anaphylactic reaction to a sting but would not provide immunotherapy for the vast majority! They would not treat those who failed to have a repeat reaction on in-hospital sting, nor would they treat individuals who have reactions that are very mild or limited to the skin. Adoption of this recommendation would mean that almost three quarters of the patients currently treated would not receive therapy. The authors do make the point, however, that when a patient is not satisfied unless he or she receives immunotherapy, it is allowed. I would certainly subscribe to this practice.

I believe that van der Linden and his colleagues have put forward extremely important data and that their hypothesis must be tested in the United States. As they point out, there are many differences between the natural history of stings in a

small country, such as Holland, and in the United States; and in addition, we are probably a genetically more complex population. Moreover, whatever the situation, we cannot change what is a well-defined set of treatment criteria, based on many years of investigation, on the strength of a single study. Finally, these authors have not proven that patients who have a negative response to in-hospital sting will not have a reaction during a subsequent field sting. Although in their discussion of the data they suggest that this is the case, we certainly have patients who have a history of a reaction in the field after they had a negative sting challenge response in the hospital. If, however, their findings are confirmed in a well-controlled study done in this country, the savings in health care dollars from the change in practice parameters would be tremendous, as would be the benefits to our patients.

Lawrence M. Lichtenstein, MD, PhD
Director, Johns Hopkins Asthma and Allergy Center
Clinical Immunology Division
5501 Hopkins Bayview Circle
Baltimore, MD 21224

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