

Clinical aspects of allergic disease

Discontinuing venom immunotherapy: Extended observations

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Background: Our studies of discontinuing venom immunotherapy after at least 5 years have led to the conclusion that the residual risk of a systemic reaction to a sting was in the range of 5% to 10% in adults, and no severe or life-threatening reaction occurred with 270 challenge stings in 74 patients after 1 to 5 years without venom immunotherapy.

Objective: The objective of this study was to extend our observation of patients who discontinue venom immunotherapy over 5 to 10 years and to determine which patients are at higher risk for a reaction.

Methods: Patients who discontinued venom immunotherapy were surveyed for 3 consecutive years to determine the frequency of systemic reactions to field stings and the fate of venom sensitivity. The evaluation included the 74 patients previously studied (group 1) and 51 additional patients followed after stopping therapy in our clinical center (group 2). **Results:** Of the original 74 patients, 11 had field stings again after 3 to 7 years without venom immunotherapy, with one systemic reaction (dyspnea). Of the 51 patients in the other group, 15 were stung, of whom four (26%) had systemic reactions, including respiratory symptoms requiring epinephrine. Review of group 1 and group 2 revealed that half of the patients who had systemic reactions to a sting after stopping venom immunotherapy had a history of a systemic reaction occurring during venom immunotherapy (to an injection or a sting). Systemic reactions occurred in three patients who had negative skin test reactions; all three had very low but detectable venom-specific serum IgE antibody levels as determined by RAST and had a history of systemic reactions during venom immunotherapy. Greater severity of the pretreatment reaction was not associated with higher frequency of reaction to stings after stopping therapy but was associated with greater severity if a reaction did occur.

Conclusions: Venom immunotherapy (yellow jacket/mixed vespids) in adults can be discontinued after 5 to 6 years with a 5% to 10% residual risk of a systemic reaction. Risk factors may include history of a systemic reaction during venom immunotherapy, persistent strongly positive skin test sensitivity, and the severity of the pretreatment reaction. (*J Allergy Clin Immunol* 1998;101:298-305.)

Key words: *Venom immunotherapy, Hymenoptera, insect sting allergy*

Venom immunotherapy with standardized extracts has been widely accepted as a model for allergen immunotherapy and provides greater than 95% protection from insect sting anaphylaxis. Since the introduction of the commercial venom extracts in 1979, the product package insert has described the necessity for indefinite therapy. Stopping treatment when venom skin test results become negative has been considered, but only 25% to 30% of patients treated for 5 years become skin test-negative.¹ Several potential criteria have since emerged to help determine when it might be safe to discontinue venom immunotherapy. They include the duration of therapy (e.g., 5 years), loss or decrease of indices of sensitivity (RAST/skin test), and historical factors (age and severity of pretreatment reaction).¹⁻⁶ We have previously reported the success of discontinuing treatment after at least 5 years of maintenance therapy.⁷ In 74 patients subjected to challenge stings every 1 to 2 years for up to 5 years after stopping treatment, no serious reactions occurred and only a few cutaneous systemic reactions were observed. These patients included many with a pretreatment history of life-threatening anaphylaxis and most still had positive skin test results. This almost-universal approach to stopping treatment would benefit a larger number of patients than does the limited approach of stopping only if indices of IgE-mediated sensitivity disappear or only if the history is more benign, two criteria that exclude 50% to 75% of adult patients receiving venom immunotherapy. After the initial success of this approach, and because of persistent concerns about the safety of discontinuing treatment in all patients, we have attempted periodic surveillance of these study patients, as well as other patients who discontinued treatment at the discretion of their attending allergist after we ended our formal challenge study. We now report the outcome of field stings in these groups of patients and the emergence of additional criteria for the discontinuation of venom immunotherapy.

METHODS

Patients

Volunteers enrolled from our clinic population of patients had been receiving maintenance venom immunotherapy for 5 years or longer. Group 1 consisted of the previously described group of 74 patients⁷ who have now been observed for an additional 2 years and are now reporting the outcome of intervening field stings. Group 2 consisted of 51 additional patients who had completed at least 5 years of venom immu-

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TABLE I. Characteristics of venom immunotherapy in patients studied after discontinuation

Study years/group	Patients		Sting type	Years with VIT (mean)	Years without VIT* (mean)	Venom skin test	
	(n)	Stung				Declined 10-fold	Negative
Previous (years 1-5)							
Group 1	74	74	Challenge	5-8 (6)	1-5 (3.7)	60%	25%
Current (years 6-7)							
Group 1	74	11	Field	5-8 (6)	3-7 (4.9)	100%	60%
Group 2	51	15	Field	5-12 (8.6)	1-4 (1.9)	96%	71%

VIT, Venom immunotherapy.

*Years without venom immunotherapy at the time of the challenge or field sting.

notherapy and who agreed with the advice of their attending allergist to discontinue treatment and report any field stings. The study period is indicated in Tables I and II as "Years 6-7." The first 5 years of the study were devoted to challenge stings, at various intervals, of the 74 patients in group 1, as previously reported.⁷ The current study period involved no challenge stings but only observation of the outcome of field stings both in the original 74 patients in group 1 and in additional patients who had discontinued venom immunotherapy after the patients in group 1.

Both groups had a patient distribution comparable to our general population of adults receiving venom immunotherapy: 86% had a history of respiratory or vascular symptoms of anaphylaxis after a sting (14% had hives and angioedema only); the concentration for mean pretreatment skin test positivity was 0.1 µg/ml venom for a 2+ reaction, and mean age was 45 years (after 5 to 8 years of venom immunotherapy). Table I shows the characteristics of the two groups. All patients gave informed consent for all aspects of the investigation in accordance with the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions.

Procedure

Patient evaluations occurred at the outset of venom immunotherapy, again when therapy was discontinued, and then annually for the patients in group 1 and after reported field stings for those in group 2. Venom skin tests were performed at each visit with freshly prepared yellow jacket and honeybee venoms (ALK Laboratories) at concentrations of 0.01 to 1.0 µg/ml. Skin tests were graded 0, ±, or 1+ to 4+, according to the system of Norman.⁸ A systemic reaction to a sting was recorded as any signs or symptoms, however mild, of a generalized allergic reaction. Typically these included urticaria, angioedema, throat tightness, dyspnea, dizziness, or hypotension, but in some cases only focal systemic erythema and pruritus of the ears or face or a single isolated hive at a site distant from the sting occurred. Some reactions involved symptoms so mild as to be questionable because of the lack of objective signs; these are still included as reactions in our results but are clearly identified as questionable or unconfirmed. The symptoms were also compared with the historical pretreatment reactions for similarity in pattern. Our chosen policy in studies of insect sting allergy has been to report all symptoms noted by the patient as potentially indicative of systemic reactions but to identify those that are clinically questionable.

Venom-specific antibody measurements

Blood samples were obtained at each patient visit, and the sera were frozen at -20° C until assayed. Venom-specific IgG antibody levels were measured with a staphylococcal protein A solid-phase radioimmunoassay as previously described.⁹ Venom-specific IgE antibody levels were measured with the same Sepharose 4B sorbent systems as previously described.¹⁰ A positive-result RAST is defined as 1.0 ng/ml or more of venom-specific IgE antibodies. Although no clinical threshold has been established, the assay can detect as little as 0.5 ng/ml.

RESULTS

On entering the 2-year observation period, the 74 patients in group 1 had previously completed 5 to 8 years of therapy (mean, 6 years) and had not received venom therapy for 2 to 5 years (mean, 3.7 years); a mean of 9.5 years had elapsed since initial venom immunotherapy. The 51 patients in group 2 had received 5 to 12 years of treatment; a mean of 8.6 years had elapsed since initial treatment. Skin test result changes were similar in both groups: 60% to 70% had become negative, and 96% to 100% showed at least a 10-fold decline in skin test sensitivity. This frequency of reduced and absent sensitivity was consistent with the trend to diminishing sensitivity over time previously reported for the patients in group 1. At the time of retesting during our extended observation period, 7 to 10 years had elapsed since initial diagnosis and treatment in most cases.

Insect stings occurring in the field were reported by 11 of the 74 patients in group 1 (14 stings) and by 15 of the 51 patients in group 2 (25 stings) (Table II). In group 1, one of the 11 patients stung had a possible systemic reaction to a sting on two separate occasions in the third year without therapy, although she had previously tolerated a challenge sting after 2 years without therapy. At the time of the field sting, the 11 patients in group 1 had been without venom immunotherapy for 3 to 7 years (mean, 4.9 years). The patient who had a systemic reaction was one of three who had been without therapy for 3 years; none of the eight patients who had been without therapy for 4 to 7 years had any reaction to the field sting. We have previously reported on the challenge sting studies of group 1, in which systemic reactions

TABLE II. Sting reactions after discontinuing venom immunotherapy

Study years/group	Patients stung	Systemic symptoms to sting	
		Patients	Stings
Previous (years 1-5)			
Group 1	74/74	7/74 (9.5%)	8/270 (3%)
Current (years 6-7)			
Group 1	11/74	1/11	2/14
Group 2	15/51	4/15	4/25
Total (to date)	89	12/89 (13.5%)	14/309 (4.5%)

occurred in 7 of 74 patients (9.5%). In these studies, the follow-up period for sting reactions was 2 to 5 years after discontinuing venom immunotherapy (mean, 3.7 years). The additional patient with a systemic reaction described in this extended follow-up report now results in an adjusted reaction rate of 8 of 74 patients (11%) for the original group under investigation. As in our previous report, we note that most reactions were mild or even questionable.

In group 2, four patients had systemic reactions, for a reaction rate of 4 of 25 stings (16%) in 4 of 15 patients (27%). At the time of the field sting, most of these 15 patients had been without venom immunotherapy for 1 to 2 years (six patients each), one patient was without therapy for 3 years, and two patients were without therapy for 4 years (mean, 1.9 years off therapy). The follow-up period of 1.9 years is similar to that of our early observations of group 1.^{1,7,11} The limited numbers in group 2 do not permit meaningful analysis or comparison with other groups. Their results are presented to describe the extended and different observations on additional patients and do not significantly alter our total experience to date with the discontinuation of venom immunotherapy after 5 years. Our overall results for the total patients in groups 1 and 2 (i.e., all patients stung to date) now reveal systemic symptoms for 14 of 309 stings (4.5%) in 12 of 89 patients (13.5%).

Not only were there more reactions than expected in group 2, but some reactions in these patients were more severe than the generally benign reactions reported in our previous observations on the 74 patients in group 1.⁷ We examined the severity of reactions before and after venom immunotherapy in the 89 patients stung (74 in group 1 and 15 in group 2), as shown in Table III. Before immunotherapy, we found the usual distribution of reaction types reported in our previous study populations for venom immunotherapy: 13 (14%) cutaneous only, 41 (46%) respiratory, and 35 (39%) hypotension or dizziness. The seven reactors previously reported from group 1 included five with minimal symptoms and two with generalized urticaria on challenge sting (after treatment). The eighth reactor now reported for group 1 had dyspnea. The four reactors in group 2 included two with respiratory symptoms, one with hypotension, and one with minimal symptoms.

Review of the case histories of the reactors showed several instances of previous systemic reactions to venom injections or to stings during immunotherapy. Among our 89 patients stung after discontinuing venom immunotherapy, 13 had a history of such systemic reactions during therapy (Table IV). These 13 reactors subsequently had a 46% reaction rate to stings after stopping venom immunotherapy. The other 76 patients who had had no reaction during therapy showed a significantly lower 8% reaction rate to stings after stopping venom therapy. The patients in group 2 may have been self-selected for higher risk; they may have been reluctant to enroll in our earlier studies of group 1, in some cases potentially because of their history of more severe reactions or of problems during therapy. Of the patients in group 2 who were stung after stopping therapy, 8 of 15 (53%) had a history of systemic reactions during therapy; four of these 15 (27%) had a systemic sting reaction after discontinuing therapy. Review of the cases also reveals four patients (of the 12 reactors) who suspected a wasp as the culprit insect for their systemic reaction after stopping treatment. All four were treated for concomitant mixed vespid venom sensitivity, but only one had received *Polistes* immunotherapy.

Case studies

The following cases are presented not necessarily as typical or average but to demonstrate some of the most severe outcomes or atypical situations that occurred in both research and clinical practice settings. Other cases, as shown in the overall description in Table III, were generally milder and in fact, some were trivial or questionable, as in our previous reports. There is a gray area of mild subjective symptoms that can resemble anxiety in some of these patients but are potentially true systemic reactions. We have consistently chosen over the past 20 years to report the data as accurately as possible and to avoid underestimation of the rate of reaction. Some patients described in these studies had received venom immunotherapy in clinical studies of vespid venom cross-reactivity in which treatment was restricted to specific venoms regardless of the history. In these studies, patients received yellow jacket venom or mixed vespid venoms but not *Polistes* venoms. In other cases *Polistes*, hornet venoms, or both were excluded from treatment in a clinical practice setting because of their reported cross-reactivity and because some investigators have recommended treatment limited to yellow jacket venom only.¹²

Patient 1 had hypotension, dyspnea, and near-syncope when stung in 1976 at age 32 years. Skin test results were positive at 0.1 µg/ml to the four vespid venoms (yellow jacket, yellow hornet, white-faced hornet, and *Polistes* wasp), and he received mixed vespid venom immunotherapy from 1977 to 1986. During the treatment period, several yellow jacket field stings caused no reaction, but a wasp sting caused mild tachycardia and dyspnea without dizziness. When he stopped therapy, his venom skin

test reactions were negative to all venoms up to 1.0 $\mu\text{g/ml}$, and the yellow jacket and *Polistes* wasp venom-specific serum IgE antibody levels were both 1.0 ng/ml. In 1988, a field sting caused tachycardia only, and no treatment was administered; skin test results and venom-specific serum IgE antibodies were unchanged. In 1990, a field sting (wasp suspected) caused dyspnea, dizziness, and unconsciousness requiring emergency resuscitation. Two days later, skin tests and venom-specific serum IgE antibodies were unchanged from 1986. Three weeks later, both yellow jacket-specific and *Polistes*-specific IgE antibody levels were increased to 13 ng/ml, and skin test results were positive at 1.0 $\mu\text{g/ml}$ for both insects. He resumed venom immunotherapy with mixed vespid and *Polistes* wasp venoms.

Patient 2 had urticaria, angioedema, laryngeal edema, and loss of consciousness when stung in 1976 at age 59 years. Venom skin tests were positive at 0.01 $\mu\text{g/ml}$ to all four vespid venoms, and venom immunotherapy was started in 1977 with mixed vespid venoms. She had throat tightness after a venom injection in 1977 but subsequently tolerated therapy. A yellow jacket challenge sting in 1979 caused no reaction. Treatment was interrupted for 6 months in 1981 and was resumed but with yellow jacket venom only. A challenge sting with a yellow jacket caused no reaction in 1981, but in 1982 and 1983 she reported tingling lips and throat tightness after a yellow jacket sting. Her treatment dose was increased to 200 μg of yellow jacket venom, and field stings (suspected yellow jackets) in 1986 caused no reaction. When she discontinued therapy in 1988, her yellow jacket venom skin test results were negative, and the yellow jacket venom-specific serum IgE antibody level was 2 ng/ml. A field sting in 1990 (wasp suspected) caused dyspnea, and epinephrine provided gradual relief. Subsequent skin test results remained negative to yellow jacket and *Polistes* venoms, and the venom-specific serum IgE antibody level was 1.0 ng/ml (for both venoms). She refused to resume venom immunotherapy.

Patient 3 had angioedema, dyspnea, dizziness, and abdominal cramps when stung in 1975 at age 36 years. Skin test results were positive to yellow jacket, hornet, and wasp venoms at 0.1 $\mu\text{g/ml}$ in 1979. She began immunotherapy in 1980 with yellow jacket venom, but a challenge sting after reaching maintenance dose caused facial flush, itchy eyes, and nasal congestion. Her maintenance dose was increased from 100 to 200 μg , and yellow jacket challenge stings caused no reaction in 1981 and 1982. When she stopped treatment in 1986, her skin test sensitivity to yellow jacket venom had decreased to 1.0 $\mu\text{g/ml}$. In 1988, yellow jacket skin test results were negative, and a yellow jacket challenge sting caused no reaction. In 1989, field stings (yellow jackets suspected) on two occasions caused dyspnea. Skin test reactions to yellow jacket venom were positive at 1.0 $\mu\text{g/ml}$, and her yellow jacket venom-specific serum IgE antibody level was 5 ng/ml. She resumed immunotherapy with yellow jacket venom.

Patient 4 had urticaria, laryngeal edema, dyspnea, and

TABLE III. Severity of systemic reactions before and after venom immunotherapy

Sting reaction	Before VIT	After VIT
Minimal	0	6
Gen urt/angio only	13	2
Respiratory*	41	3
Hypotension†	35	1

VIT, Venom immunotherapy; Gen urt, general urticaria; angio, angioedema.

*Dyspnea, throat tightness, asthma, cough.

†Dizziness, unconscious, blood pressure less than 90/60 mm Hg.

wheezing on three occasions when stung before and in 1978 (age 31 years). Skin test results were positive at 0.1 $\mu\text{g/ml}$ to yellow jacket and hornet venoms; mixed vespid venom immunotherapy was uneventful from 1979 to 1988. After stopping therapy, a field sting in 1989 caused a mild local reaction, but in 1990 a sting caused severe dyspnea for which epinephrine was administered twice. He refused immunotherapy, and no follow-up skin test data are available.

Patient 5 had throat tightness and lost consciousness when stung in 1977 at age 32 years. Skin test results were positive at 0.01 $\mu\text{g/ml}$ to yellow jacket and hornet venoms, and he had uneventful therapy with mixed vespid venoms from 1977 to 1983 (5 years of maintenance therapy). When he stopped therapy, skin test sensitivity was unchanged. Challenge stings caused no reactions in 1984 or 1985, but in 1986 he had generalized pruritus and flushing after a yellow jacket challenge sting. Skin test results were unchanged to yellow jacket and hornet venoms, and the yellow jacket venom-specific serum IgE antibody level was 8 ng/ml. He chose to remain without therapy and has shown progressive decline in sensitivity on skin testing to all venoms. A field sting in 1989 (yellow jacket suspected) caused no reaction.

DISCUSSION

The rationale for venom immunotherapy is to reduce the risk of a potentially life-threatening systemic allergic reaction from the mean reported pretreatment level of 50% to less than 5% (less than 1% in many studies).¹³⁻¹⁵ In published reports on discontinuing venom immunotherapy either after venom-specific RAST becomes negative or after 3 to 5 years of treatment, the rate of systemic reactions to stings after therapy was stopped has been described to be in the range of 5% to 14%, with most reactions being markedly less severe than those that occurred before immunotherapy.¹⁻⁷ The accumulating data now suggest that neither criterion is absolute and that secondary considerations are necessary, probably including (but not limited to) the occurrence of systemic reactions during therapy and possibly the severity of the pretreatment sting reaction and our reported concern about patients whose venom skin test results (or venom-specific serum IgE antibody level)

TABLE IV. Systemic reactions after venom immunotherapy

	Patients (n)	After venom immunotherapy	
		No reaction	Systemic reaction
No reaction during VIT	76	70	6 (8%)
Systemic reaction during VIT	13	7	6 (46%)

VIT, Venom immunotherapy.

indicate persistent, strongly positive sensitivity.^{7, 11} The long-term outcome of discontinuing venom immunotherapy has not been well described, but previous results have suggested that the risk of reaction would disappear in time as the result of loss of sensitivity and the relatively benign nature of posttreatment reactions. The current results now suggest the possibility that these expectations too are not absolute and that neither the absence of venom skin test sensitivity nor the passage of time can guarantee that a patient will not react to a subsequent sting.

It is generally agreed that the clearest indication for discontinuation of therapy is negative venom skin test results (or RASTs) because it is assumed that this indicates no residual risk of anaphylaxis. This was certainly true in almost all of the many patients in this study who had become skin test-negative and did not react to stings after discontinuing therapy. We report herein, however, three patients who became convincingly negative on venom skin testing and yet had a subsequent episode of symptoms after a sting with, in one case, life-threatening anaphylaxis. In two of the three cases, the symptoms were mild and therefore open to question. In all three cases, there had been a systemic reaction during maintenance venom therapy. Also, all three patients did show detectable residual venom-specific IgE antibodies in their serum, but with levels so low as to be potentially undetectable in some commercial assays. These three cases are of practical importance from a clinical perspective because these patients would have been counseled to stop therapy by most allergists on the basis of the level of safety presumed to be associated with negative skin test results. The persistent traces of venom-specific serum IgE antibodies in their serum indicate that in some individuals, even 1 ng/ml or less of venom-specific serum IgE antibodies is apparently sufficient for a generalized allergic reaction. It is not clear what differs about these patients compared with others with negative venom skin test results (even with detectable venom-specific serum IgE antibodies) who show no signs of recurrent sensitization or reaction despite intervening stings. These cases may represent a "desuppression" of the venom-specific IgE antibody response because there was a marked rise in venom-specific serum IgE antibodies after the reaction. This contrasts with patients who do not react, who show minimal and transient increases in specific serum IgE antibodies. This

phenomenon was most clear-cut in patient 1 above. We have previously described the immunologic features of attenuated venom reactivity after prolonged therapy.⁷ Despite repeated challenge stings in those patients, venom sensitivity did not return or showed only a transient increase in venom-specific serum IgE antibodies. Indeed, the risk of reaction was no greater on the second of two challenge stings performed 1 month apart. The skin test sensitivity and venom-specific serum IgE antibody levels continued to decline steadily with time, with more and more of the patients becoming negative to one or both tests. The current results conflict with those earlier impressions that the risk of reaction would likely vanish in time (like the skin tests) and that even patients with severe pretreatment reactions did not seem to show the more severe manifestations in posttreatment reactions. Previous studies of discontinuing venom immunotherapy, both after a duration of 5 years and in patients with negative RAST results, have reported a 5% to 14% rate of systemic reaction to a sting after stopping treatment.¹⁻⁷ Most reactions in those studies were mild to moderate in severity, and the risk was judged to be acceptable. In light of the individual cases reported here and the observation that patients generally follow a very individual but repetitive and predictable pattern of systemic reactions, new considerations may be necessary for those patients with a history of very severe and truly life-threatening reactions. Such patients may be reluctant to stop venom immunotherapy despite the favorable overall statistics and perhaps should be given the security of extended maintenance therapy at intervals of 8 weeks up to 12 weeks, according to some recent reports.^{12, 16} Indeed, the severity of the pretreatment sting reaction has been suggested as a risk factor to be considered when deciding whether to discontinue treatment.^{4, 6} Our data, like those of Müller et al.,³ do not show any such differential in frequency of reaction, with reactions occurring in both mild and severe (historical) reactors.

The results described for groups 1 and 2 are not presented for direct comparison because the patients were at very different stages of observation. In this report, group 1 is presented for extended follow-up, and the short-term follow-up of group 2 is presented because of the greater-than-expected number of reactions and the possible factors distinguishing the group. The patients in group 2 had had a higher frequency of systemic reactions during their 5 years or more of immunotherapy and had a longer mean duration of therapy than did the 74 patients in group 1. The reaction rate for group 2 represents the first 1 to 2 years without venom immunotherapy, which was previously reported for group 1.^{7, 11, 17} That the reaction rate in group 2 was higher than in the previous reports does not necessarily indicate that discontinuing therapy is more risky than previously thought because of the small numbers involved and the possibility of specific characteristics of these patients that may have led to more frequent reactions. Indeed, the 15 patients are a very incomplete sample of the

overall group of 51 patients available for follow-up, and realistic conclusions must await the outcome of stings in a larger number of these patients. Similarly, the 11 patients in group 1 are a very limited sample of the 74 patients previously studied. It is interesting to note that the reaction rate seems to hold at about 10% for patients stung during any given time period and that there could be a cumulative prevalence of reaction over time that will become higher and higher. However, it is not clear from these data whether there will be sustained risk more than 5 years after stopping venom immunotherapy: No reactions occurred in the eight patients stung after 4 to 7 years without therapy (group 1). The final estimation of risk of a systemic reaction after stopping venom immunotherapy may be apparent once the 5-year follow-up of all 74 patients (and as many others as possible) has been completed, but thus far, that risk appears to be consistent in the literature in the range of 10% to 15%. The results of the field stings in the 11 group 1 patients reported here could theoretically have been influenced by their prior challenge stings, but there is no comparison group who had no stings for 4 to 7 years before ultimate field or challenge stings. We have reported that allowing 2 years to elapse between challenge stings instead of doing annual stings did not significantly affect either the risk of reaction or the long-term immune response because the venom skin test and IgE antibody levels continued to decline steadily with time regardless of the frequency of stings.⁷ There are not yet sufficient numbers of patients who have been stung after 4 years or more without therapy without any intervening stings to draw definitive conclusions.

Müller et al.³ were the first to note that patients who had had systemic reactions during venom immunotherapy were at higher risk for a reaction after discontinuing therapy. Our data strongly support this observation, with a 46% reaction rate (to stings after stopping therapy) in such patients. The unusually high rate of systemic reactions in group 2 could be explained by the higher proportion of patients in this group who had experienced a reaction during therapy. In general, systemic reactions occur in 10% to 15% of patients receiving venom immunotherapy, but it is not clear if all such patients are at higher risk when they ultimately discontinue treatment. Some of those whose sting reactions were quite mild could perhaps discontinue therapy with impunity. The longer average duration of therapy in group 2 should, if anything, have led us to expect less risk of systemic reaction, but it is simply a reflection (like the more frequent history of reactions during therapy) of the initial reluctance of many of these patients to stop therapy as potential participants in our earlier studies (in years 1 through 5), although they later agreed to stop in view of the success of this approach in group 1. In this respect, group 2 patients may have been self-selected for risk factors including severity of reaction or difficulties during therapy, which made them more hesitant to stop therapy. In any event, group 2 was clearly self-selected in that they chose to respond to the

survey, and the response rate is possibly higher for reactors than those who experience uneventful stings or no stings at all. None of these potential factors mitigate the fact that there were significant treatment failures in some of these patients, which is different from our previous observations and possibly related to their unique characteristics.

An alternative explanation for some apparent failures after stopping venom immunotherapy would be that the reaction occurred because the patient was stung by a different insect than that for which they had received immunotherapy. This possibility is evident in at least two of our reported failures (cases 1 and 2 above) who suspected wasp stings but had been treated with only mixed vespoid or yellow jacket venom. There are many patients who have had *Polistes* wasp venom excluded from therapy because of its known cross-reactivity with the other vespoid venoms. However, we have shown by RAST inhibition analysis that not all patients with *Polistes* wasp venom-specific serum IgE antibodies show cross-reactivity with yellow jacket venom.^{18, 19} Our reported success in eliminating *Polistes* venom from therapy involved only patients selected by RAST inhibition,¹⁸ but in the past, patients and physicians did not always have the benefit of such studies. In our patient 1, RAST inhibition studies had not been done before therapy in 1977, but we note that the *Polistes* and yellow jacket skin tests and venom-specific serum IgE antibody levels showed identical increases after the sting that caused the posttherapy reaction. Our patient 2 did have RAST inhibition in 1981 showing complete cross-reactivity of her *Polistes* and yellow jacket-specific IgE antibodies. In both cases, of course, it is not certain that a wasp was the actual culprit in the field stings. In fact, there is notoriously limited reliability in the patient's ability to correctly identify the stinging insect. Nevertheless, these concerns would support the rationale for excluding *Polistes* venom from the therapeutic regimen only if cross-reactivity with the yellow jacket can be established in that patient.

Our results continue to support the recommendation for at least 5 years of venom immunotherapy as the primary criterion in adults. Those reports suggesting a 3-year minimum for treatment have some differences in patient characteristics, which makes comparison difficult, and have limited data to support their conclusions. Many of the patients in the 3-year studies were children in whom the possibility of shorter therapy is more consistent with the benign natural history and expected responses in the pediatric age group. The patients studied by Müller et al.³ were stung only after 1 year without treatment and were all allergic to honeybees: They may therefore have had a different outcome from our study population.²⁰ Although Haugaard et al.⁵ studied adults allergic to yellow jackets, only 17 patients had 3 years of therapy and only half of the stings occurred more than 24 months after stopping therapy. Their results need to be confirmed in a much larger number of patients treated for only 3 years. Similarly, Reisman⁶

reports on patients of whom more than half were children and one third were allergic to honeybees. Also, only 21 of the patients they describe were treated for 3 years. It is interesting that they did show the reaction rate in adults (15%) to be higher than that in children (5%), although not statistically significant in the small number of patients reported. Although they recommended 3 years of venom immunotherapy, the median duration of therapy was 43 months in the report of Haugaard et al.⁵ and 56 months in the study by Müller et al.³ In our group 1 patients, the mean duration of therapy was 6 years; almost half had 5 years, and another third had 6 years, but only 23% had more than 6 years of venom immunotherapy. The 15 patients in group 2 who were stung did have a longer mean duration of therapy, but because of their small number, they have little effect on our overall experience; the 89 patients who were stung during follow-up observation had a mean duration of therapy of 6.5 years. In combining these results, we are trying to capture the overall experience of a cohort of patients who began venom immunotherapy during the first 5 years of the program at Johns Hopkins (1977 to 1982) and then stopped therapy at various times over the subsequent 5 to 6 years because of our advice and patient preference (hence the variation in duration of therapy in the groups we have studied).

In addition to the duration of therapy, Müller and colleagues,³ Haugaard et al.,⁵ and Keating et al.⁴ also included a negative challenge sting as another criterion for discontinuation. Müller et al. noted that the risk of a posttherapy sting reaction was higher in those patients who had withstood only field stings during therapy than in those who had also had challenge stings to verify their response to therapy. Keating et al.⁴ also studied patients with a range of duration of therapy (2 to 10 years) and concluded, as we do, that 5 years or more of treatment led to significantly better suppression of the venom-specific serum IgE antibody response and a significantly lower rate of reaction to challenge stings than did therapy of less than 5 years' duration. They also found, as we have, that the recurrence of insect sting-induced anaphylaxis did not necessarily occur on the first sting after stopping venom immunotherapy or even in the first 2 years afterward. Our experience now suggests that recurrent and occasionally severe systemic reactions can occur more than 3 years after discontinuation of therapy, even after field or challenge stings without reaction and even when skin test and RAST results indicate little or no residual IgE antibodies to Hymenoptera venoms. This is in agreement with the report of Reisman,⁶ although other reports, including our own, have concluded that the risk of reaction tended to decline with time.^{7,13,14,21,22} Although this report emphasizes some of the pitfalls and failures of discontinuing venom immunotherapy, the overall results remain quite encouraging. The 10% or more of patients who have systemic reactions during therapy,²³ together with the 5% of patients in whom sensitivity remains strong and unchanged even after 5 or more years of therapy,⁷ constitute the 15% or

more of patients who should not discontinue venom immunotherapy even after 5 years. However, in the other 80% to 85% of patients, the risk of a sting reaction after stopping therapy is in the range of 5%, and the few reactions that occur are very mild. There is clearly a need for more long-term observations and challenge stings at various intervals after stopping venom immunotherapy.

We continue to conclude that venom immunotherapy can be discontinued after 5 to 6 years in more than 80% of patients, with relatively low risk for a systemic reaction to a sting. The patients who should not discontinue therapy because they may have a 30% to 50% chance of reaction include those who had a systemic reaction during venom immunotherapy and possibly patients whose venom skin test or RAST results indicate persistent, strongly positive sensitivity. Another possible concern is for the most severely affected patients whose pretreatment sting reaction was life threatening or near fatal. Although we have had excellent outcome in such patients (excluding the above caveats), the likelihood that any recurrent reaction (however small the chance of reaction) would again be of the same severe type makes the risk of stopping therapy significantly greater. There is relatively less concern about stopping therapy in patients with a history of mild reactions because even a recurrent reaction is likely to be relatively mild again. Criteria for discontinuing venom immunotherapy in other possible low-risk groups, such as children and adult cutaneous reactors, are under investigation since a shorter duration of therapy of 3 years has been suggested for such patients.^{4,6} Our results and therefore our conclusions are limited to adults, most of whom had yellow jacket or mixed vespoid venom therapy, and may not necessarily apply to *Polistes* or honeybee venom therapy, the latter having been reported to have potentially different patterns of reactions.^{20,24,25} The long-term outcome of discontinuing venom immunotherapy by any criteria needs further study.

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Correction

There is a typographic error in the June 1997, Part 1 issue of The Journal (J Allergy Clin Immunol 1997;99:853-4). All instances where *ml/min* are indicated should read *ml/sec*.