

Natural history of Hymenoptera venom sensitivity in adults

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Background: Epidemiologic studies of Hymenoptera venom allergy in adults show a prevalence of positive venom skin test results, RASTs of 15% to 25%, or both, but most such individuals have had no systemic reactions to stings. The clinical significance and natural history of this apparently common sensitivity is uncertain.

Objective: We sought to determine the natural history of venom sensitization by observing the rate of decrease or increase in sensitivity in normal adults over 5 to 10 years. The clinical significance of these findings is related to the frequency of systemic reactions to stings during the period of observation.

Methods: Serial observations were planned in 520 volunteers and randomly selected subjects. Two follow-up visits were attempted, once after 2 to 3 years and again after 5 to 9 years, to perform repeat venom skin tests and RASTs and to review any history of interim stings and their outcomes.

Results: Follow-up visits were conducted with 398 subjects (375 early visits and 205 late visits). Overall, in the 398 subjects with one or more visits after a mean of 4 years, skin test responses changed from positive to negative in 44 of 98 (45%) and from negative to positive in 27 of 309 (8.7%) of the subjects. Skin test responses changed from positive to negative in 29 of 87 (33%) subjects after 2.5 years and in 43 of 54 (80%) after 6.8 years. Even when the skin test response became negative, venom-specific IgE remained positive in 11 of 29 (38%) subjects after 2.5 years and in 13 of 43 (30%) after 6.8 years. The rate of loss of sensitivity was 12% per year, similar to retrospective estimates. Skin test sensitivity to venoms disappears more rapidly in these subjects without symptoms (half-life, 4 years) than in patients receiving venom immunotherapy (half-life, 7 years). Skin test responses changed from negative to positive in 23 of 288 (8%) subjects after 2.5 years and in 9 of 151 (6%) after 6.8 years. Insect stings caused no reaction in 120 subjects with a negative skin test response, but 17% (11 of 65) of subjects with a positive skin test response (but with a negative history) had systemic reactions when stung. There was no difference between the early and late visits in the frequency of systemic reactions reported. The risk may be higher than 17% for the specific

individuals (67% after 2.5 years and 20% after 6.8 years) whose positive skin test responses persist for years. This risk is lower than that of patients with a positive history (50%) but higher than that of "normal" adults or venom-treated patients (<2%). It is still not clear whether any subset of adults with a positive skin test response but a negative history can be identified, in whom the risk of systemic sting reaction would justify venom immunotherapy even before any reaction occurs.

Conclusion: Asymptomatic venom sensitization in adults is common but transient, disappearing at the rate of 12% per year. However, the risk of a systemic reaction to a subsequent sting is significant in adults without symptoms but with positive venom skin test responses (17%) and may be higher when skin test sensitivity does persist for years. (J Allergy Clin Immunol 1997;100:760-6.)

Venom immunotherapy, despite its remarkable short-term and long-term efficacy, is only indicated for individuals who have already had an anaphylactic reaction to an insect sting. It has been pointed out, however, that 40% of insect sting fatalities occur in individuals with no history of a previous sting reaction.¹ The fatal reactions could not have been prevented in those patients without some way of identifying the risk before any reaction occurs. Skin tests and laboratory parameters have, unfortunately, been shown to have only limited predictive value, even when there is a positive history of systemic reactions.²⁻⁶ The actual clinical significance of a positive venom skin test response (especially in screening normal subjects) without regard to clinical history is unknown.

We reported previously that in a stratified random sample of 320 adults, 3.3% had a history of a systemic reaction to a sting, but 17% had a positive venom skin test response and 26% had venom-specific IgE antibodies measured by RAST.⁷ That study showed retrospectively that venom-specific IgE was more likely to be detectable by skin test or RAST when the subject had been stung within the previous 3 years. The significance and outcome relating to this frequent asymptomatic allergic sensitization to Hymenoptera venoms is unknown. It is likely that some of these patients will ultimately have an overt allergic reaction to a sting but that others will either not react or will lose sensitivity spontaneously. We have prospectively observed these and other sensitized individuals to determine the natural history of the venom-specific IgE antibodies and the clinical reactivity to insect stings.

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METHODS

Patients

The total target population has been previously described in reports of our genetic-epidemiologic study of human immune responsiveness to allergens in a population of adult workers in a suburban-rural light industry.^{8,9} In the first 5 years of our studies of insect sting allergy, 269 subjects ("random") were evaluated as part of a stratified random sample of this target population. However, 251 other employees ("volunteers") also requested to participate in the study outside of the random selection and were evaluated in the same way as the random subjects. Thus a total of 520 subjects were enrolled in this prospective study of the evolution and outcome of venom sensitization over time. The 251 volunteers were clearly self-selected for personal and family history of insect sting allergy and atopy in general. The frequency of a history of systemic sting reaction was 12% in the volunteers but only 3.3% in the random subjects. Skin test responses were positive in 26% of the volunteers and in 17% of random subjects. However, the fate of venom sensitization and the risk of sting reaction were analyzed only in relation to the historical and immunologic markers at intake without respect to motivation for enrolling.

Three visits were planned for each subject in the study. The first occurred for all 520 subjects over a 5-year period. We have previously reported the results of this first encounter for the 269 subjects in the stratified random sample.⁹ Two follow-up encounters were attempted. Visit 2 was planned for 2 to 3 years after the initial visit, and visit 3 was planned for 5 to 10 years after the initial visit. Fig. 1 shows the distribution of the intervals between visits with two peak time intervals for the two follow-up visits. The early follow-up visits occurred 0.6 to 4.4 years after the initial visit, and the late follow-up visits occurred 4.5 to 9.5 years after the initial visit.

Informed consent was obtained for all procedures at the time of each visit, as approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Skin testing

Intradermal skin tests were performed by injection of 0.02 ml each of honeybee and yellow jacket venoms (concentration, 1.0 μ g/ml) to form a 3 to 4 mm bleb and were graded according to the system described by Norman.¹⁰ Skin test results graded 1+ or higher are considered positive for yellow jacket venom; results 2+ or higher are positive for honeybee venom. Previous studies^{11,12} have established the immunologic basis for these criteria. Venoms were standard, commercial, lyophilized venom protein extracts reconstituted with albumin-saline diluent according to the product package insert.

Questionnaire

The subjects were asked about their histories of previous stings and possible allergic reactions, as well as personal and family history of allergies. Systemic sting reactions were defined as immediate reactions occurring within 30 to 40 minutes of a sting causing generalized cutaneous, respiratory, and/or vascular manifestations of anaphylaxis. Large local reactions were defined as indurations contiguous with the sting site, which were estimated to have been 8 cm or larger and persisted for 2 days or more.

IgE antibody measurements

Blood samples were obtained at each patient visit, and the sera were frozen at -20°C until assayed. Venom-specific IgE antibody levels were measured with Sepharose 4B sorbent

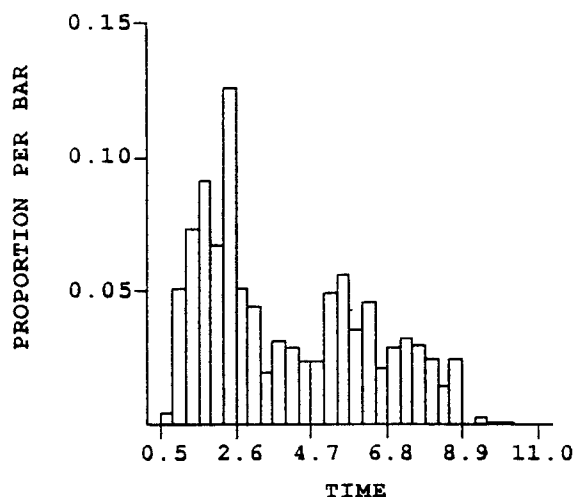


FIG. 1. Distribution of time (years) between intake visit and follow-up visit shown for each time interval as proportion of total visits ($n = 582$ [375 early + 205 late] visits).

systems (Pharmacia) as previously described.¹³ A positive RAST result is defined as 1.0 ng/ml or greater, although no clinical threshold has been established (the assay can detect as little as 0.5 ng/ml).

RESULTS

Of the 520 subjects evaluated at intake, 122 did not return for follow-up visits. There was no apparent selection for positive skin test responses in the 398 subjects who did return for follow-up visits because the frequency of positive skin test responses was the same for those who did and did not return. Fig. 1 shows the distribution of the follow-up visits. There were 375 early follow-up visits, with a mean ($\pm$ SD) time interval of 2.5 ($\pm$ 1.5) years (range, 0.6 to 4.4 years). There were 205 late follow-up visits with a mean ($\pm$ SD) time interval of 6.8 ($\pm$ 1.5) years (range, 4.5 to 10 years). Overall, there were 398 patients who returned for follow-up at least once, with a mean time interval of 4.0 ($\pm$ 2.3) years.

The results of the follow-up venom skin tests are shown in Fig. 2 in relation to the original skin test result at intake and the time elapsed between visits. Of the 375 subjects seen for the first (early) follow-up visit, 87 had had positive venom skin test responses at intake. Fifty-eight of those 87 subjects (67%) continued to respond positively after a mean of 2.5 years, and 29 of 87 (33%) began to respond negatively. By the time of the second (late) follow-up visit (mean, 6.8 years), 11 (20%) of the 54 subjects with positive skin test responses seen still had positive venom skin test responses, and 43 had negative responses. Even when the skin test responses became negative, venom-specific IgE remained positive in 11 of 29 (38%) subjects after 2.5 years and in 13 of 43 (30%) subjects after 6.8 years.

Skin test responses had been negative at intake in 288 of the 375 subjects seen for a first (early) follow-up and in 151 of the 205 subjects seen for a second (late) follow-up visit. At the first follow-up visit, 23 of 288 (8%)

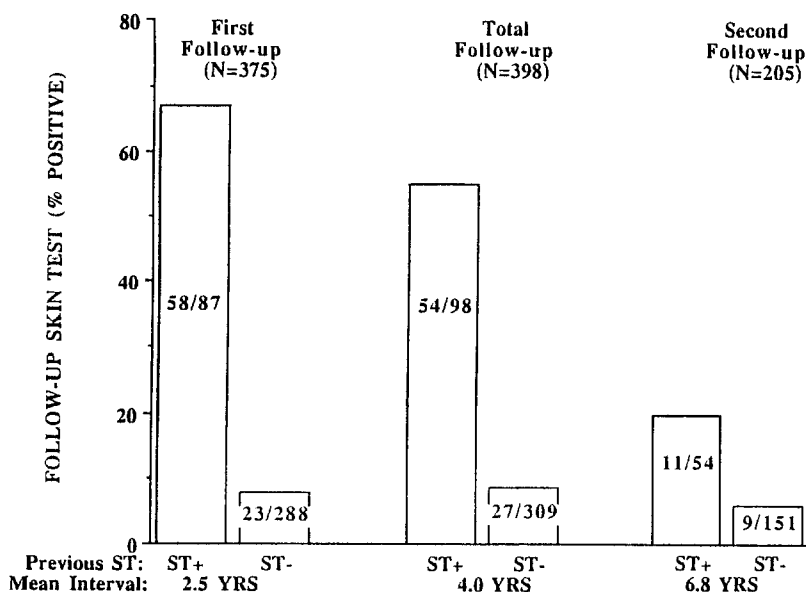


FIG. 2. Skin test results at follow-up visits in relation to time elapsed and original skin test result at intake. Total follow-up was done for 398 patients in 582 visits. ST+, positive skin test result; ST-, negative skin test result.

subjects with negative skin test responses were found to have positive skin test responses. By the second (late) follow-up visit after 6.8 years, 9 of 151 (6%) subjects with negative skin test responses were found to have positive responses. Overall, in 398 subjects with at least one visit after a mean of 4 years, the skin test responses changed from positive to negative in 44 of 98 (45%) subjects and from negative to positive in 27 of 309 (8.7%). For these 27 patients whose skin test responses became positive, possible explanations were sought. Eight had had a positive venom RAST result at intake, and 18 had been stung between visits. There were seven subjects who had neither occurrence and had no other obvious reason for the skin test response becoming positive. Among the patients who had had positive skin test responses at intake, the persistence of venom sensitivity was not attributable to stings between visits because there was an equal frequency of intervening stings among the subjects whose skin test responses became negative.

The risk of a systemic reaction to a sting was evaluated in relation to the skin test results and the time elapsed. Of the subjects with positive skin test responses, 65 were stung, and 11 (17%) reported a systemic reaction. There was no significant difference in the frequency of systemic reactions between patients stung less than 4.5 years after their initial evaluation and those stung more than 4.5 years after intake (Fig. 3). In the group of subjects with negative skin test responses, 120 stings were reported with no reactions (data not shown). Patients who reported systemic reactions to stings at any time in the course of the study were advised to begin venom immunotherapy. But as we reported in our initial epidemio-

logic survey, all these individuals refused therapy for the same reason that they almost never reported the event to their personal physicians—they did not believe that any severe reaction would occur in the future.

The risk of a systemic sting reaction, which has been reported for several subgroups of patients with positive venom skin test responses, can be used for statistical comparison with the 17% risk of reaction shown here for subjects with a negative history but positive skin test response. Fig. 4 shows such a comparison of five clinical subgroups. We find the 17% risk to be significantly less than the 50% risk for those with a history of sting anaphylaxis ($p < 0.005$) but significantly higher than the 2% to 5% risk they would have if they were receiving venom immunotherapy ($p < 0.0001$).

For further perspective on the long-term significance of this asymptomatic venom sensitization, we compared the rate of loss of venom sensitivity in these patients without symptoms with the patients with symptoms who had undergone 5 years of venom immunotherapy and were then observed for another 5 years after discontinuing therapy. Fig. 5 shows decay curves for venom skin test sensitivity, which are estimated from the data available in these two groups of patients. The skin test results described above in our subjects without symptoms showed a half-life of approximately 4 years, with 15% to 20% of these patients still showing a positive response after 8 to 10 years. Patients who had symptoms and were treated with venom immunotherapy for 5 to 8 years showed a significantly longer skin test half-life of almost 7 years because 70% of the patients still had positive responses at 5 years and 20% to 30% remained positive after 10 years.¹⁴

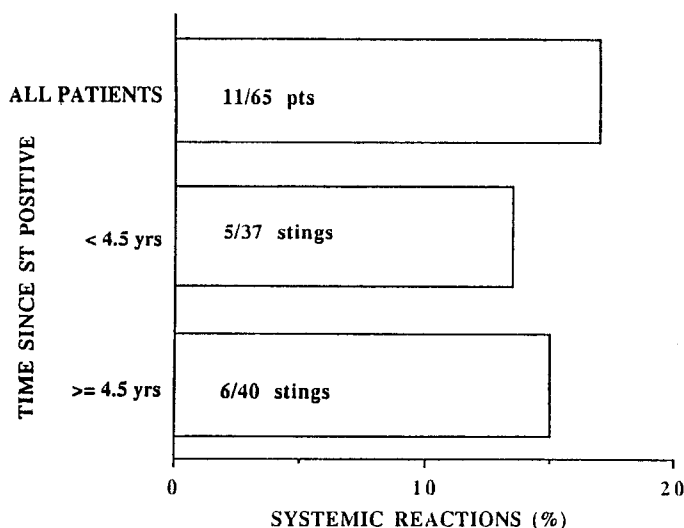


FIG. 3. Systemic reactions to field stings in subjects with positive skin test results reported at the early and late follow-up visits.

DISCUSSION

Advancing knowledge of the natural history of insect sting anaphylaxis has demonstrated how and why whole-body extracts were ineffective for diagnosis or therapy,^{9, 15-17} and has more recently helped to provide rational criteria for discontinuing therapy on the basis of observations in patients receiving venom immunotherapy.^{7, 14, 18-21} However, there remains some uncertainty in the criteria (indications) for beginning immunotherapy because of the limited knowledge of the risk factors for systemic sting reactions and the fact that the best clinical marker, the venom skin test, has only a 50% predictive value at best, and then only in conjunction with a positive history. The risk of reaction in individuals with a positive skin test response but a negative history has been unknown, and there has been no way to identify those at risk for sting anaphylaxis before the first reaction occurs.

Having observed in the initial phase of our epidemiologic studies of insect sting allergy that more than 1 in 5 adults has venom-specific IgE antibodies,⁹ we felt a need to determine both the chance that the sensitivity would persist over time and the chance that a systemic reaction would occur if the person was stung. In that report we found evidence retrospectively that venom sensitivity was much more common when there had been a recent sting (in the previous 1 to 3 years). In fact, allergic sensitization to Hymenoptera venom may occur in over 30% of adults in the months after a sting, with approximately 10% still having a positive skin test response more than 3 years after a sting.^{9, 22} Our previous estimate that skin test sensitivity in adults without symptoms disappears at the rate of 10% per year^{9, 22} is supported by the current data (Figs. 2 and 5). The likelihood that skin test sensitivity will disappear in the first 3 to 5 years is higher in these adults without symptoms than in patients who had a history of a

systemic reaction (Fig. 5). In the patients with symptoms who had venom immunotherapy, it is interesting that treatment did not seem to accelerate the loss of skin test sensitivity, nor does it appear that venom immunotherapy prolongs the sensitivity because patients with systemic reactions who refuse venom immunotherapy lose their sensitivity at the same rate as those being treated.^{7, 16} It is likely that the frequency of positive venom skin test responses in all of these groups converges after 10 years toward the 17% frequency reported for the adult population.

It is of interest that the prevalence of venom skin test sensitivity remained fairly stable for the first 4 years, with 81 of 375 patients having a positive response at follow-up (the same 21% as in the original 520 subjects). As shown in Fig. 2, the development of new sensitivity in 23 subjects made up for the loss of sensitivity in 29 of the subjects with positive skin test responses. However, after 6.8 years, even the continued 6% rate of de novo sensitization could not make up for the increasing loss of venom sensitivity, and the overall prevalence of positive skin test responses at the late follow-up visits was only 20 of 205 (10%). These results are almost identical to the retrospective observations of the initial epidemiologic survey in which skin test responses were positive in 20% of subjects stung within the previous 3 years but only in 10% of subjects stung more than 3 years before testing. The retrospective analysis had suggested that venom sensitivity disappears at a rate of approximately 10% per year, which is very similar to our current observations of skin test responses becoming negative in 33% of subjects after 2.5 years and in 80% after 6.8 years. It should be noted that changes in skin test sensitivity may theoretically be related to differences in the extract itself. Although batch-to-batch variation in these standardized extracts should be negligible, the possibility cannot be ruled out (such as in the few individuals whose skin test

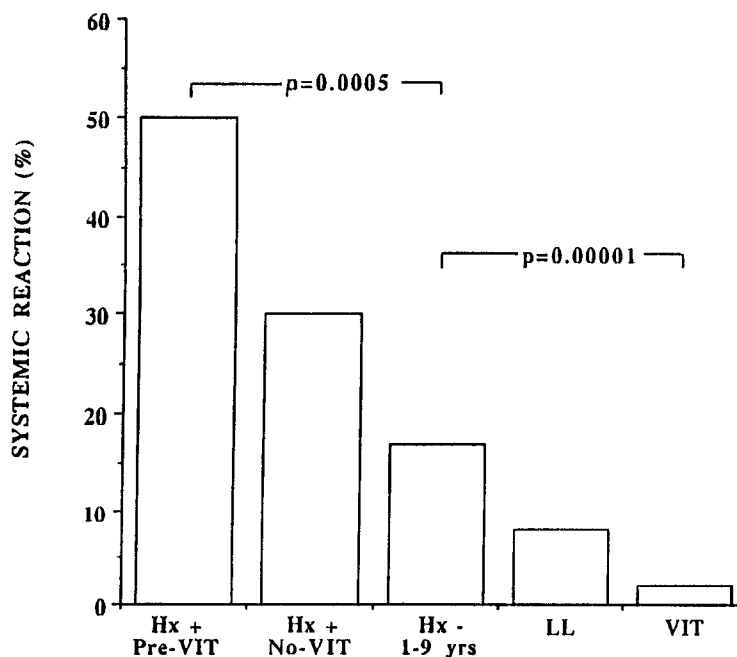


FIG. 4. Risk of a systemic reaction in various groups of patients with positive skin test responses. This study of patients with a negative history, who were followed up for 1 to 9 years, is compared with reports on other clinical subgroups by history and treatment. Hx+, Positive history; Hx-, negative history; VIT, venom immunotherapy; LL, local reactions.

responses converted from negative to positive without any intervening sting). It was also noted, however, that some of these individuals did have detectable venom-specific IgE antibodies at the time of the negative skin test response, and therefore the conversion to a positive skin test is not so surprising.

It is reassuring to know that in adults without symptoms, venom sensitivity is usually transient, with a half-life of about 4 years. However, the risk of a systemic reaction during the time when skin test results remain positive certainly exists (Fig. 2). Although the reaction rate was 17% for subjects who had positive skin test responses at intake, if we assume all reactors were among the subgroup of subjects who continued to have a positive skin test response, then the reaction rate is actually higher for the individuals with persistent sensitization. At the early follow-up visits, the five reactions occurred in 35 patients, but we can estimate from the data presented here that only 67% (23 subjects) still had positive skin test responses after 2.5 years. If we assume that these 23 subjects with positive skin test responses included all five reactors, then the estimated reaction rate is 22% after 2.5 years. The total follow-up of all subjects for a mean of 4 years revealed 11 systemic reactors among 65 patients of whom only 55% would have continued to have a positive response. If these 36 patients with positive skin test responses included all 11 reactors, the reaction rate would be estimated at 30%. These extrapolations would place the risk of systemic sting reaction in adults without symptoms but with positive venom skin test responses that persist for 2.5 to

4.5 years in the moderate range (20% to 30%). This percentage is similar to the risk found in affected patients who have not been stung for 10 years since their last systemic sting reactions and in patients who discontinue venom immunotherapy prematurely (after 1 to 2 years). To provide further contrasts and comparisons, Fig. 4 shows the risk of a systemic sting reaction associated with various subgroups of patients on the basis of their history, skin test responses, and treatment. The difficulty in evaluating the clinical significance of our findings is readily apparent from the fact that the moderate risk in our adults with positive skin test responses but negative histories was significantly greater than the minimal risk in treated patients or in the general adult population but was significantly less than the risk in the patients traditionally considered the best candidates for venom immunotherapy (i.e., those with positive skin test responses and recent history of reaction). Other intermediate risk groups have also been controversial in terms of indications for therapy, such as those also shown in Fig. 4 (large local reactors who have 5% to 10% risk and affected patients who refuse therapy and are stung 10 years later with a 20% to 30% risk of reaction).

It is nevertheless reassuring that even among the 11 patients who had systemic reactions, there were signs that the venom sensitivity continued to decrease (or disappear) with time despite the stings and the reactions. We noted that seven of these patients reported nine subsequent stings with no further systemic reactions. By the time of the subsequent follow-up visit, the skin test

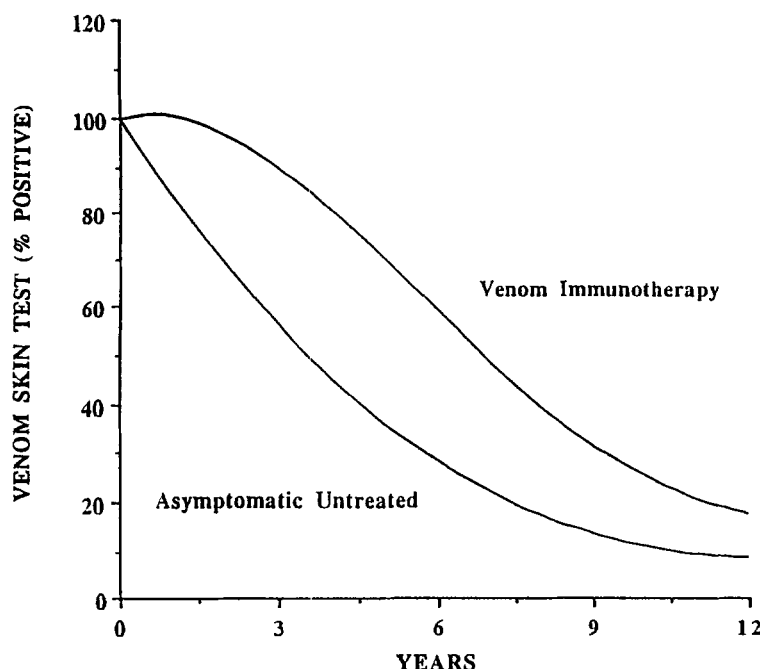


FIG. 5. Estimated decay curves showing reported skin test changes over time in study subjects who had a negative history and a positive skin test response (*Asymptomatic Untreated*) compared with reported results in patients with a positive history treated with venom immunotherapy.

response was still positive in only 5 of 11 patients (45%), although the RAST results still showed detectable venom-specific IgE antibodies in 80% of the subjects (9 of 11 patients). The differential changes in skin test and IgE antibody results suggest that some individuals whose skin test responses become negative still have residual venom-specific IgE antibodies, with the associated risk of systemic sting reaction. Our report on the initial visits of these subjects described the epidemiology of Hymenoptera venom sensitivity and noted some differences between the venom skin test results and venom-specific IgE antibody measurements.⁹ As in all allergen systems, differences between the RAST and the skin test results may be due to numerous factors including possible differences in the allergen specificities presented in the allergosorbent compared with the skin test extract. These differences and disparities between the two test methods have been noted in patients with both a positive and a negative history and in patients who have discontinued venom immunotherapy.^{9, 13, 14} However, there has been no evidence that one test is more specific or more clinically relevant than the other. It may therefore be that the only truly nonallergic individual would be one with both a negative skin test response and a negative RAST result. It is not within the scope of this report to describe the long-term changes in venom-specific antibody levels or to compare them with skin test changes and clinical outcomes. It appears that there are numerous patterns of changes in these variables, which can be related to the passage of time, intervening stings, and the inherent coefficient of variation of the tests

themselves. The complex analysis of these data is proceeding toward a separate report in the future.

The presence of asymptomatic sensitization and its attendant risk of anaphylaxis is of special interest in light of the reports of fatal anaphylaxis occurring in patients with no history of reaction¹ and the demonstration of venom-specific IgE antibodies in a significant proportion of cases of unexplained sudden death.²³ It would seem likely that such cases represent one possible outcome in individuals, such as those reported here, who have asymptomatic sensitization. However, our observations have conflicting implications regarding the clinical significance of positive venom skin test responses in adults without symptoms. On the one hand, the risk of a systemic reaction to a sting is 17% to 30% when the skin test response remains positive for 3 to 5 years, a level of risk significantly greater than the baseline level of 2% seen in the general population and in patients receiving venom immunotherapy (but also significantly less than the risk in patients with a positive history). On the other hand, venom skin test sensitivity disappears more rapidly in adults without symptoms than in those with a positive history and seems to continue to decline even in the subjects who did report a systemic reaction to an intervening sting. As generally observed in the literature, there was no specific marker, immunologic or clinical, that was indicative of which subjects would react to a sting.²⁻⁶ Thus it is difficult to make any conclusion about the utility of venom skin testing as a screening procedure when attempting to discover those at risk before the occurrence of a potentially life-threatening reaction. It

does appear that there is moderate, but not high, risk of a systemic reaction to a sting in adults who have a positive venom skin test response that persists for several years. Our population studies suggest that 14% of adults have asymptomatic sensitivity (positive skin test response and negative history) and that 8% to 10% of normal adults would still have positive skin test responses after 3 to 5 years of observation. This would make venom immunotherapy a consideration in 3 to 4 times as many patients as are already considered eligible. Two percent to three percent of adults have a positive history and skin test response, and few of those ever seek medical advice for prophylaxis. Certainly, this is inconsistent with the current approach to treatment, especially on the basis of recent observations that even those who have a systemic reaction to a sting may still be at low enough risk to defer venom immunotherapy if their sting reaction was not severe or life-threatening.⁶ This is possible on the basis of the clinical observation that patients tend to have more or less the same pattern of reaction to subsequent stings.^{17,18} For the time being then, and until some other marker or index is described, it is still not possible to justify the testing of individuals without symptoms for insect sting allergy because of the limited prognostic value of the result, in the absence of any history, to establish the pattern of reaction in the individual.

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