

Epidemiology of Insect Venom Sensitivity

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The prevalence of insect sting reaction and of venom sensitization in adults is unknown. We report the results of intake evaluation of a stratified random sample of a large adult population previously studied for the determinants of atopic disease. In 269 subjects, the prevalence of systemic allergic sting reactions was 3.3% and 26.5% had IgE antibodies to venom demonstrated by skin test or radioallergosorbent test. Asymptomatic sensitization (positive venom skin test) was observed in 15% of subjects with no history of an allergic sting reaction. Positive venom skin tests were more frequent in men, in those with positive skin tests to inhalant allergens, and in subjects aged 20 through 29 years. A positive venom skin test or radioallergosorbent test was more frequent in subjects who had been stung within the previous 3 years (35%) than in those stung more than 3 years before (20%). We conclude that both systemic allergic reactions to insect stings and asymptomatic sensitivity to venom are common and that most affected persons never seek medical advice. The significance of asymptomatic venom sensitization is unknown.

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IMMEDIATE hypersensitivity reactions to insect stings can be effectively prevented by Hymenoptera venom immunotherapy.¹⁻³ In the first decade of its development, this treatment has been most appropriately aimed at patients who are judged to be at greatest risk for anaphylactic sting reactions; namely, those with both a history of previous systemic allergic sting reactions as well as objective evidence of venom allergy by skin test or radioallergosorbent test (RAST).^{2,3} The risk of anaphylactic sting reactions is uncertain in any but the highest-risk group. However, many severe or even fatal sting reactions occur as the first sign of the disease and are therefore not currently preventable.⁴ The ability to diagnose the disease accurately and to prevent anaphylactic reactions specifically requires a thorough understanding of the risk factors that determine the outcome of the sting. To this end, we have designed investigations to describe the epidemiology and

natural history of allergic sensitivity to Hymenoptera venoms and stings.

The first phase of these studies was designed to establish the prevalence of insect sting reactions. There have been no previous reports of the epidemiology of sting reactions in adults and no data on the prevalence of venom sensitivity in any age group, to our knowledge (since purified venoms were not readily available until the mid-1970s). The only published data^{5,6} suggested that 0.4% to 0.8% of young boys had a history of systemic sting reactions. We thought it likely from our clinical experience that the prevalence of sting reactions was much greater and that venom sensitivity must exist in many individuals who had never experienced allergic sting reactions. We report the surveys of a well-defined and well-characterized stratified random sample of a large population of employees at a light industrial plant. Our aim was to describe the scope of insect sting allergy and to characterize groups of subjects to be observed prospectively to clarify the natural history of Hymenoptera venom sensitivity.

METHODS Study Design

The target population has been previously described in reports of our genetic epidemiologic study of human immune

responsiveness to allergens in an industrial population.⁷⁻⁹ The current studies have been done in two phases. In 1977 through 1978, seventy-six percent of 2097 employees at Westinghouse Electric Corporation in northern Baltimore County, Maryland, responded to a brief questionnaire about their allergic symptoms and treatment. A 10% random sample of the total population (210 individuals) was selected for further study (interview, skin tests, blood samples for measurement of total and specific IgE antibodies, and HLA typing). Of 174 respondents in this random sample, 131 completed the study, but only 115 whites were included in the reported analysis of data, since the nonwhites were too few to yield meaningful data. For the current study of insect sting allergy, we aimed to survey and test these 115 subjects in 1980 through 1981.

The aim of the second phase of these studies, performed in 1981 through 1982, was to examine an enlarged sample of the original target population that was more balanced for age and gender. This would also provide a larger database for long-term observations. Because the original (phase I) random sample was preponderantly male and middle-aged (like the total work force at this plant), the sample was expanded by the addition of 205 subjects from the initial population of 2097 employees. They were selected randomly but within guidelines for age and sex, so as to form a stratified random sample of 320 whites equally distributed with respect to age and sex (40 persons of each sex for each of the age ranges 20 through 30, 31 through 40, 41 through 50, and 51 through 60 years).

Informed consent was obtained at the beginning of the program as approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Skin Testing

Intradermal skin tests were performed by injection of 0.02 mL of honeybee and yellow jacket venoms (1.0 µg/mL concentration) to form a 3- to 4-mm bleb and were graded after 20 minutes according to the system of Nor-

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Table 1.—Characteristics of Subjects in Stratified Random Sample

	n	Age, y (± SEM)	% Male	IgE Level, μg/L (± SEM)	Inhalant Skin Test Sensitivity, %
Phase I	91	42.1 (± 1.3)	80	74.6 (± 12.7)	27
Phase II	178	39.8 (± 1.2)	36	78.5 (± 17.7)	23
Not seen	51	38.6 (± 1.7)	45	72.6 (± 17.8)	15.5
Total	320	40.2 (± 0.6)	50	76.6 (± 6.9)	25

Table 2.—Insect Sting Allergy by Clinical History and by Venom Skin Test in the Stratified Random Sample

	n	History			Skin Test	
		Systemic Reaction, %	Large Local Reaction, %	No Reaction, %	Positive, %	Negative, %
Phase I	91	4.4	13.2	82.4	20	80
Phase II	178	2.8	21.3	75.9	16	84
Total	269	3.3	18.6	78.1	17	83

man.¹⁰ Skin tests graded 1+ or stronger are considered positive for yellow jacket venom (YJV); 2+ or stronger are positive for honeybee venom (HBV). 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 package insert.

Skin tests using inhalant allergens had been performed as part of the original evaluation in 1977 through 1978 using a well-validated puncture technique with a panel of common inhalant allergens, as described in detail elsewhere.⁷⁻⁹

Questionnaire

Subjects were asked about their histories of previous stings and possible allergic reactions, as well as personal allergic history (hay fever, asthma, hives, drug allergy, or food allergy) and immediate family history of sting reactions (parents, siblings, or grandparents). Systemic sting reactions were defined as immediate reactions within 30 minutes of a sting causing generalized cutaneous, respiratory, or vascular manifestations of anaphylaxis. Large local reactions were defined as indurations contiguous with the sting site that were estimated to be 8 cm or larger and persisted for 2 days or more.

IgE Antibody Measurements

Total serum IgE levels were obtained using an anti-IgE Sepharose 4B sorbent system and radiolabeled anti-IgE as the detection protein as described.⁸ Venom-specific IgE antibodies were measured using Sepharose 4B sorbent systems as previously described.¹³ This RAST assay is sufficiently sensitive to detect venom-specific IgE antibody concentrations as low as 0.5 μg/L. A positive RAST is defined as 1.0 μg/L or greater, although no clinical threshold has been established. The same venom prepara-

tions were used as described above for skin test materials.

Statistical Analysis

Comparison of groups was performed by Fisher's Exact Test (two tailed).

RESULTS

We first examined the characteristics of the study populations to determine whether the groups in phase I and phase II were comparable and to detect any selection bias. Table 1 summarizes the demographic variables, results of skin tests for inhalant allergens, and total serum IgE antibody levels for the 91 subjects seen in phase I of the survey on insect allergy, the 178 seen in phase II, and the 51 who were part of the stratified random sample but did not return for insect allergy evaluation. There were no significant differences between the three groups, demonstrating the comparability of the two study phases. The 51 subjects who were "not seen" had a lower frequency of inhalant skin test sensitivity, although the difference was not statistically significant. This demonstrates some selection bias for subjects who suspect allergies, but has little or no impact on the significance of our observations (see "Comment" section).

Comparing the results of venom skin tests and history of sting reactions (Table 2) again reveals the consistency of our observations in the two separate groups evaluated in phase I and phase II of the study. The prevalence of systemic sting reactions was 3.3% (9/269) in the stratified random sample, 4.3% in the phase I group and 2.8% in the phase II group. Large local reactions were reported by 18.6% (50/269) of the total group, 13% of phase I and 21% of phase II subjects. Venom skin tests were positive in 17% (47/269), 20%, and 16% of the total, phase I, and phase II groups, respectively. None of these differences

Table 3.—Correlation of Venom Skin Tests and Clinical History of Sting Reactions

History	n	Venom Skin Tests	
		Positive, No. (%)	Negative, No. (%)
Systemic reaction	9	5 (56)	4 (44)
Large local reaction	50	11 (22)	39 (78)
No reaction	210	31 (15)	179 (85)

Table 4.—Correlation of Yellow Jacket Venom RAST* and Skin Tests

RAST, μg/L	Skin Test	
	Positive	Negative
<1	9 (24%)	190 (89%)
≥1	29 (76%)	23 (11%)
1.0-1.9	8	9
2.0-2.9	5	4
3.0-4.9	4	5
≥5.0	12	5
Total†	38	213

*RAST indicates radioallergosorbent test.

†Skin test and RAST available in 251 subjects; RAST not available in 18 subjects (1 skin test-positive).

were statistically significant. The data thus far have established the similarity of the two subgroups in phase I and phase II. Henceforth, we will describe the results for the combined stratified random sample as a whole.

Table 3 shows the relationship between the history and skin tests. Asymptomatic sensitization (positive skin test but no history of a reaction) occurred in 15%. Positive skin tests to HBV and/or YJV occurred with a significantly higher frequency in subjects who had systemic reactions (56%) than in subjects who had large local reactions (22%) or no reaction (15%) ($P < .01$). Among the nine subjects who reported systemic reactions, three had a history of multiple systemic reactions, three others had been stung after the systemic reaction without any further systemic reaction, and the other three have not been stung since their only reaction.

Figure 1 shows the prevalence of positive venom skin tests and RASTs. Skin tests were positive to HBV in 5% of subjects and to YJV in 14%; 17% of subjects had at least one positive venom skin test. Serum samples were obtained from 251 subjects, but only 221 samples were sufficient to complete the measurements of IgE antibodies to HBV. The RAST was positive for HBV in 6% and for YJV in 21% and 24% of subjects had a positive RAST to at least one venom. Evidence of venom-specific IgE antibodies to at least one venom (HBV and/or YJV) was present in at least one test (skin test and/or RAST) in 26.5% of the population.

Table 4 shows the correlation of the YJV RAST and skin tests in the 251 subjects with complete data. A discor-

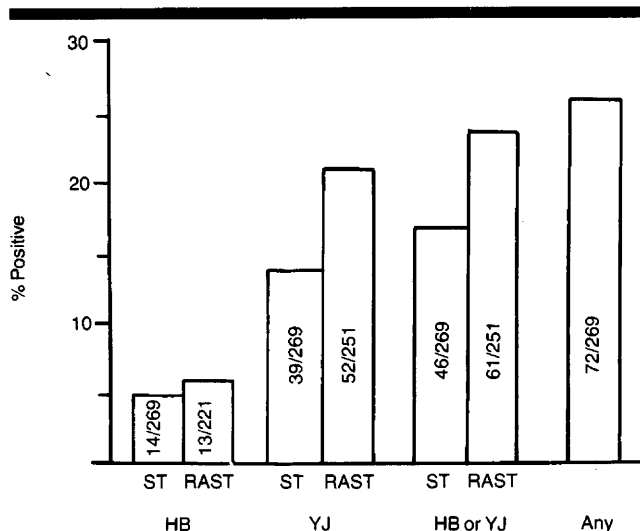


Fig 1.—Prevalence of positive skin test (ST) and/or radioallergosorbent test (RAST) to honeybee (HB) and/or yellow jacket (YJ) venoms.

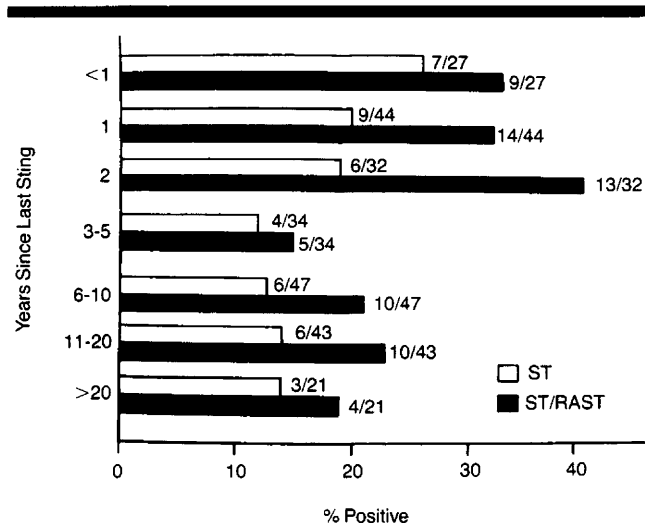


Fig 2.—Frequency of positive venom skin test (ST) or any positive venom test (ST/radioallergosorbent test [RAST]) in relation to the time elapsed since the previous sting.

Table 5.—Correlation of Insect Sting Allergy (Skin Test, RAST,* or History) With Gender, Inhalant Skin Test Sensitivity, and Total Serum IgE Level

	n	% Male	Inhalant Skin Test Sensitivity, No. (%)	IgE Level, $\mu\text{g/L}$ ($\pm$ SEM)
Venom skin test				
Positive	46	67	17 (37)	184 ($\pm$ 47)
Negative	222	47	48 (21)	64 ($\pm$ 7)
		$P < .01$	$P < .025$	$P < .002$
Venom RAST				
Positive	62	74	25 (40)	141 ($\pm$ 26)
Negative	190	45	36 (19)	63 ($\pm$ 7)
		$P < .0001$	$P < .001$	$P < .01$
Sting reaction				
Systemic	9	67	5 (56) [†]	170 ($\pm$ 55) [†]
Large local	50	34	7 (14) [‡]	44 ($\pm$ 9)
None	210	57	54 (25)	86 ($\pm$ 10)
		$P < .3$ [†] $P < .01$ [‡]	$P < .05$ [†] $P < .06$ [‡]	$P < .06$ [†]

*RAST indicates radioallergosorbent test.

[†]Statistical significance of systemic reactors vs nonsystemic reactions (large local and none).

[‡]Statistical significance of large local reactions vs no reaction.

dance of these tests in 15% to 20% of cases was observed in previous studies.¹³ In our survey, 24% of subjects with positive YJV skin tests had a negative RAST. A positive RAST occurred in 11% of subjects with negative YJV skin tests; however, the RAST was reproducible and inhibitable with the homologous venom, indicating the presence of bona fide venom-specific IgE antibodies. Thus, these cases actually represent false-negative skin tests. In subjects with a positive RAST, the mean and distribution of YJV-specific IgE antibody levels was not significantly different in comparison of subjects with negative and positive skin tests. As shown in Table 4, the false-negative skin tests were associated with high YJV-IgE levels as often as with low IgE levels. The sensitivity (76%) and specificity (89%) of the RAST are similar to previous observations of 81% and 84%, respectively.¹³ Data for the HBV RAST

are available for 221 subjects and show a 5% (10/208) frequency of positive RAST in skin test-negative patients. Only 3 of 13 subjects with a positive HBV skin test had a positive RAST.

The indicators of venom hypersensitivity (skin test, RAST, and sting reaction) were examined for correlation with other variables, including age, sex, family history of sting allergy, personal history of allergic symptoms, skin test sensitivity to inhalant allergens, and total serum IgE antibody levels. As shown in Table 5, venom skin tests were more frequently positive in men ($P < .01$) and in subjects with positive skin tests to inhalant allergens ($P < .025$). The total serum IgE level was significantly greater in subjects with positive venom skin tests. Similar correlations existed for the venom RAST and for systemic sting reactions. The 27 subjects who had a positive RAST but negative skin test had a mean

total serum IgE level of 68 $\mu\text{g/L}$, which is not different from nonallergic subjects. None of these venom allergy indicators were correlated with family history of sting allergy or personal history of allergic symptoms.

In this stratified random sample, it was also possible to relate the venom skin test and IgE level to age, by decade. The frequency of positive skin test or RAST was significantly greater in subjects in their 20s (positive skin test, 27%; positive RAST, 39%) than in older subjects in any subsequent decade (positive skin test, 14%; positive RAST, 20%) ($P < .01$ by Fisher's Exact Test; $P < .04$ by χ^2).

The venom skin test and RAST results were analyzed as a function of the time elapsed since the last insect sting. Figure 2 shows that the frequencies of positive venom skin tests and RASTs were significantly greater when the most recent sting occurred within 3 years of testing than when the subjects had been stung more than 3 years previously ($P < .01$).

COMMENT

Gaps in our understanding of the epidemiology and natural history of insect sting allergy led to the belief that whole-body extract injections were effective in preventing anaphylactic sting reactions.¹⁴⁻¹⁶ This report describes the epidemiology of immediate hypersensitivity to Hymenoptera stings and venoms in adults and defines the subgroups of individuals to be studied prospectively to establish the natural history of this allergy. These results will provide a more complete understanding of the risk factors involved in venom hypersensitivity, which form the basis for the selection of patients who require treat-

ment and the long-term management of the disease. The population studied had previously been well defined and well characterized with respect to inhalant allergen sensitivity and symptoms. Comparison of the phase I and phase II subgroups shows no significant difference in age, total serum IgE antibody levels, frequency of positive skin tests to inhalant allergens, frequency of allergic reactions to insect stings, or prevalence of positive venom skin tests.

The prevalence of systemic allergic reactions to insect stings was 3.3% and was similar in the two phases of the study, suggesting that this is a consistent and valid observation. However, given the relatively high proportion of nonrespondents, as well as the fact that there were some important (albeit non-statistically significant) differences between respondents and nonrespondents, the prevalence figures obtained in this study should be generalized with caution. Rather, the study's strength lies in the examination of correlations between a number of important variables, which should be valid estimates of the kinds of correlations encountered in similar groups of volunteers. The fact that the nonrespondents ("not seen" in Table 1) had a lower frequency of inhalant skin test sensitivities than either study group suggests some selection bias for people who think they have allergies, but this must be interpreted in light of our other observations and conclusions. The fact that venom sensitivity was demonstrated primarily in subjects who did not think they had allergies indicates that any selection for subjects who thought they were allergic could have little or no impact on the observed frequency of venom sensitivity.

The 3.3% prevalence of systemic reactions observed in this survey is fivefold to tenfold greater than previous estimates.^{5,6} The previous surveys were of children attending a Boy Scout summer camp and probably underestimated the prevalence of the disease owing to selection factors in camp attendance and retrospective medical reporting. More recently, a number of investigators have reported observations confirming the higher frequency of venom sensitivity and reactivity, although demographic data are lacking in these reports. The prevalence of systemic sting reactions was 2.7% in a survey of 3439 subjects by Stuckey et al,¹⁷ 5% in a community of 178 men (Z. A. Dyer, APA, written communication, April 24, 1986), and 20% in one study of 132 beekeepers.¹⁸ Our data are remarkably similar to the results of the only other large survey of the general population, by Stuckey et al, suggesting a true prevalence of systemic sting reac-

tions in the range of 3%. Although this differs from the previous surveys of children and the experience of most clinicians, there is an explanation. None of our subjects with systemic reactions had sought medical attention or advice from their physicians. In fact, they all refused our advice to enter venom immunotherapy. Obviously, those individuals who present for medical evaluation of insect sting allergy represent only the tip of the iceberg. This situation might be improved by a public education effort to increase awareness of the frequency, prognosis, and preventability of this disease. Our study did not evaluate any possible difference in the prevalence of systemic sting reactions between adults and children.

Large local sting reactions were reported by 19% of the population, a figure distinctly higher than prevalence rates reported by others of 3.9% (Z. A. Dyer, APA, written communication, April 24, 1986) and 3.1%.¹⁷ This may be due to an overstatement of the size or severity of the reaction by some of our subjects. The correlations in Table 5 provide alternative insights. Subjects who had large local reactions were predominantly female, in contrast to subjects who had systemic reactions and subjects with a positive venom skin test or RAST, who were mostly male (2:1). This would explain the lower frequency of inhalant and venom skin tests in subjects who had large local reactions, since it has been previously established that females have a significantly lower frequency than males of skin test sensitivity to inhalant allergens, despite an equal frequency of symptoms.⁸

Venom skin tests were less frequently positive in both subjects who had systemic and subjects who had large local reactions than the 50% to 90% prevalence described in clinical reviews.¹⁹⁻²² This may be due in part to the long interval from sting to testing in most subjects: 60% were not stung in the previous 3 years and 45% had had no sting in 5 years (Fig 2).

The venom skin test and RAST results are startling at first but are, in fact, consistent with the observations of other investigators and with our own data on the frequency of systemic reactions. The prevalence of positive venom skin tests has been reported to be 21% in 53 nonallergic subjects²³ and 22.5% in 62 subjects (29 stung in previous year, 33 not stung in previous 3 years).²⁴ Positive venom RASTs were reported in 16% of the 2429 subjects evaluated by Stuckey et al,¹⁷ in 12% of 86 men,²⁵ and in at least 10.4% of 250 subjects.²⁶ Our data, shown in Fig 2, are in agreement with the hypothesis of Stuckey et al¹⁷ that a larger proportion of persons who are stung will

become sensitized, but that this sensitivity is transient in many cases. Zora et al²⁴ noted that venom skin tests were more frequently positive in subjects stung within the previous 12 months (41%) than in those stung more than 3 years previously (6%). Jarish et al²⁶ found, moreover, that specific sensitization (increased IgE level without IgG) occurred in 14% of nonallergic subjects after one injection of HBV and in 31% after two injections. Another recent report²⁷ describes allergic sensitization of 37% of patients receiving chymopapain injections, confirming the frequency of sensitization to injection of protein allergens. It is now clear that allergic sensitization after a sting is quite common. The data presented have suggested that sensitization may disappear within 3 years in 40% of cases. This conclusion is useful in understanding our 3.3% prevalence of systemic sting reactions with the help of two previous observations. Many venom-sensitive patients develop only large local sting reactions, and even among persons with a history of systemic reactions, only 40% to 60% will have a systemic reaction on deliberate sting challenge.^{2,28,29} In this context, a prevalence of 3.3% for systemic reactions is consistent with the data showing that 25% to 40% may be sensitized by a sting, but only 15% to 20% can be shown to have persistent venom sensitization more than 3 years after a sting. If stung again, many of these would have large local reactions and only half of those with the potential to have systemic reactions would actually have a systemic reaction. The actual risk of a systemic sting reaction in persons with asymptomatic venom sensitivity is unknown but of great importance, because we have found that 14% of subjects with no history of systemic or large local sting reactions have a positive venom skin test. Prospective observation of the outcome of subsequent stings will determine whether patients who develop systemic sting reactions can be identified before they ever have such a reaction. This is of special interest, since most fatal sting reactions occur in individuals who had never experienced an allergic sting reaction.⁴

The correlation of skin test and RAST results supports several conclusions. That 24% of subjects with positive skin tests had a negative RAST is consistent with previous observations.¹³ The RAST was positive in 79% (27/34) of subjects with a 2+ or greater skin test and 67% (8/12) of those with a 1+ YJV skin test, but none of 10 subjects with a 1+ HBV skin test. These results agree with previous reports on the frequency of false-positive venom skin tests,¹² confirming the validity of criteria accepting

a 1+ test grade as positive for YJV but negative for HBV. The fact that 11% of subjects with negative venom skin tests had a positive RAST is of uncertain significance and draws attention to a "gray zone" in interpretation of the RAST. The true clinical sensitivity of patients with negative skin tests and positive RASTs is unknown. The RASTs in these cases were shown to be specific because they were all inhibitable by the homologous venom. One possibility is that these cases represent recent poststing sensitization (possibly transient) or the late phases of disappearing sensitization. Settupane and Carlisle³⁰ also reported a positive RAST in 7% of normal controls. In allergic subjects, they found a lower frequency of positive RASTs in those not stung within 5 years, but noted no correlation between RAST titer and severity of sting reactions. The clinical significance of an isolated positive RAST is unknown, as there has been no report of the systemic sting reaction rate in such individuals. It is also not known whether the clinical correlation of the RAST is quantitative. The 27 subjects who had a positive YJV RAST but negative skin test had a mean total serum IgE level of only 68 µg/L, similar to nonallergic subjects. This is in contrast to the significantly higher total IgE level in all subjects with positive venom skin tests or RASTs or a history of systemic sting reactions (Table 5). This suggests the possibility that a positive RAST associated with a negative skin test may be indicative of a less atopic individual or perhaps a lower risk of clinical reactivity. Prospective observation of this population will clarify the relative risk associated with a positive venom RAST, skin test, or both. The poor correlation of the HBV RAST and skin test is difficult to interpret because of the small sample size.

Venom skin test sensitivity was more common in men. Males were previously found to have a greater frequency of positive inhalant skin tests,^{7,8} and to outnumber females two to one in most studies of insect sting anaphylaxis in adults and children.^{4,29,31,32} Venom skin tests were also more frequently positive in subjects with positive inhalant allergen skin tests. Most studies have reported no association between clinical insect sting allergy and inhalant allergies.^{6,33-35} Our data confirm these observations, but show for the first time an association of venom-specific IgE antibodies with inhalant allergen-specific IgE regardless of clinical history. With respect to age, this population has previously been reported to show a significantly greater (virtually double) total serum IgE level and frequency of positive inhalant skin tests in subjects in their third decade of

life (aged 20 to 29 years) than in older subjects.^{7,9} We have found almost identical results with respect to venom-specific IgE antibodies and skin tests.

We conclude that systemic allergic sensitivity to insect stings is much more common than previously thought and that most affected individuals never seek medical attention or advice. Allergic sensitization to Hymenoptera venom allergens occurs in more than 30% of individuals who are stung, but is much less frequent more than 3 years after a sting, suggesting that the sensitivity is transient in about half of those who are initially sensitized. The clinical significance of asymptomatic sensitization in those who have never had an allergic sting reaction is unknown. Extensive long-term prospective evaluation of such individuals is in progress to determine the prognosis for regression of the sensitivity and the risk of anaphylaxis in such sensitized subjects.

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