

An epidemiologic study of insect allergy in children. I. Characteristics of the disease

Of 235 children with a history of allergic reactions to insect stings studied, 59 had severe life-threatening systemic reactions, 123 had mild, non-life-threatening systemic reactions, and 53 had large local reactions. The overall male-female ratio was 2:1. Venom skin tests were positive in approximately 89% of each group. Prior whole body extract therapy increased the likelihood of venom skin test reactivity to multiple insect venoms from 51 to 78%. Venom skin test results did not correlate with the severity of previous allergic reactions. One hundred and nine children with NLTR and positive venom skin tests were entered into one of two groups—venom immunotherapy or observation only. During the first six months the treatment group had the expected fourfold rise in venom-specific IgE antibody titers, whereas the observation group had a decline of the mean IgE titer. Patients in the observation group who were accidentally stung had a transient rise in IgE antibody titers. The small number of accidental stings which occurred in both groups resulted in reactions milder than the original reactions. Although based on preliminary data, venom immunotherapy may not be necessary for some children with previously mild systemic symptoms.

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SYSTEMIC ALLERGIC REACTIONS following Hymenoptera stings are a common and potentially serious problem. Published studies suggest that 0.4 to 0.8% of the adolescent and young adult¹⁻³ populations have a history of systemic reactions, but our recent, unpublished experience suggests a much higher incidence. Although deaths following stings are uncommon, the morbidity caused by the fear and uncertainty which follow an anaphylactic reaction is significant.

Allergic reactions are mediated by IgE antibodies directed against specific venom proteins.⁴ Immunotherapy

using insect venoms has been shown to be a safe and effective means of preventing future systemic allergic reactions in sensitive patients,⁵⁻⁷ and has supplanted treatment with extracts of crushed insect bodies. However, venom immunotherapy involves patient inconvenience, high cost, and uncertainty regarding potential short—or long-term toxicity. Moreover, the possible need for pro-

Abbreviations used

LTR:	life-threatening reactions
NLTR:	non-life-threatening reactions
LLR:	large local reactions
WBE:	whole body extract

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longed therapy is undetermined. Such treatment should, therefore, be reserved only for those individuals who might otherwise have serious, systemic reactions in the future. A significant percentage of patients with positive venom skin tests will not react when stung,⁶ and others will lose sensitivity spontaneously. Although we are able to detect venom sensitivity with skin and serum tests for specific IgE

Table I. Categorization of the patient population

	N	Age (yr $\pm$ SE)	M:F ratio	Skin tests	
				% Positive	Score*
1. Group I (LTR)	59	9.26 $\pm$ 0.4	2.60:1	90	3.26 $\pm$ 0.1
2. Group II (NLTR)	123	9.31 $\pm$ 0.3	2.00:1	89	3.03 $\pm$ 0.05
3. Group III (LLR)	53	9.04 $\pm$ 0.4	1.30:1	87	2.63 $\pm$ 0.1
Total	235	9.23 $\pm$ 0.3	1.94:1	89	3.00 $\pm$ 0.05

*See Methods section for details. Mean $\pm$ SEM.

antibody, we are unable to predict the risk of future reactions for individual patients.^{6,8,9}

To identify patients who need therapy, we have begun a long-term, prospective study in children who have had mild systemic reactions, i.e., those involving only cutaneous symptoms. Our aims are (1) to delineate the natural history of the disease; (2) to determine whether the benefit of venom immunotherapy outweighs its disadvantages; and (3) to improve our ability to predict the true "risk" of future reactions for individual patients. Children were chosen because the likelihood of death or serious disability after a sting is relatively small, and because the medical and financial costs of potential life-long venom therapy seem highest for young children. We hypothesized that certain children would lose their venom sensitivity spontaneously and might be identifiable by a rapid drop in serum levels of venom-specific IgE antibodies, and that for these children, venom immunotherapy would be of little benefit.

This report deals primarily with the clinical and immunologic characterization of all types of insect-allergic children and includes some of our first year's experience in the prospective, longitudinal study.

METHODS

Patients. Children with "insect allergy" aged 3 to 16 years were recruited to the Allergy Clinic at The Good Samaritan Hospital through a local public relations campaign consisting of educational lectures to physicians and the general public, notices to the media, and letters to pediatricians and allergists in the area. From November, 1978, to November, 1979, 246 children were evaluated. We tried to include youngsters with milder reactions which might not otherwise have brought them to the attention of an allergist.

The initial evaluation consisted of a thorough medical and allergic history, with emphasis on all prior insect sting reactions, a physical examination, venom skin testing, venom-specific IgE and IgG antibody measurements, and baseline toxicity studies.

Venom skin testing. Honeybee, yellow jacket, yellow hornet, white-faced hornet, and *Polistes* (wasp) venoms

were supplied by Pharmacia Diagnostics, Piscataway, NJ. The wheal and erythema which appeared 15 minutes after the intracutaneous administration of 0.02 ml of allergen solution and of control materials were measured after transfer of their traced outline to record paper with adhesive tape. Venoms were tested on the flexor surface of the forearm at concentrations of 0.01, 0.1, and 1.0 μ g/ml; negative (diluent) and positive (histamine 275 μ g/ml) controls were also applied. A 2+ reaction (wheal size 5 $\times$ 5 mm or greater) was considered positive, and the minimum concentration of venom required to elicit a positive test was scored according to the following schema: 4 points for 2+ at 0.01 μ g/ml, 3 points for 2+ at 0.1 μ g/ml, 2 points for 2+ at 1.0 μ g/ml, and 1 point for 1+ at 1.0 μ g/ml.

Antibody measurements. IgE antibodies to whole yellow jacket venom and phospholipase A from honey bee venom were measured by the RAST technique and are expressed as arbitrary units based on a standard curve.⁸ A positive RAST is defined as 2 SD above the counts per minute bound by sera from individuals without a history of insect allergy. Only data on anti-yellow jacket IgE antibody are presented here.

Baseline toxicity studies. Complete blood count, sedimentation rate, automated chemistry screen and urinalysis were obtained initially, and yearly on all treatment patients.

Patient selection. Depending on the clinical history, patients with one or more positive venom skin tests were placed into one of the following categories: (1) Life-threatening reaction—a systemic reaction which includes laryngeal, respiratory, or cardiovascular symptoms. Cutaneous symptoms may or may not be present. (2) Non-life threatening reaction—a systemic reaction which has only cutaneous symptoms, i.e., erythema, pruritus, urticaria or angioedema. (3) Large local reaction—a local reaction, with redness and swelling greater than 2 inches in diameter and lasting longer than 24 hours.

Treatment. Patients with life-threatening reactions (Group I) and positive venom skin tests were treated with the venoms specific for their skin test sensitivity, by a regimen described previously.^{6,7} Patients with large local reactions (Group III) were not treated with venom, but

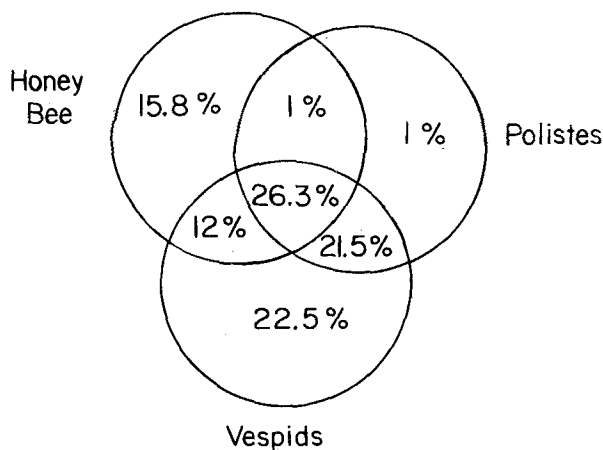
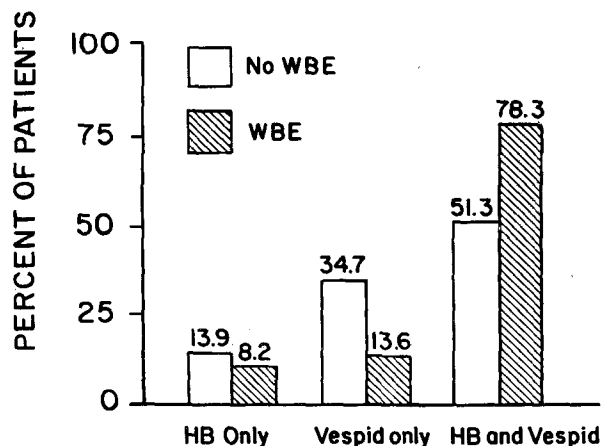


Fig. 1. The distribution of venom skin tests in the children evaluated for insect allergy. Sixteen percent of the patients were sensitive only to honey bee venom, 23% to the vespids, and 1% to polistes alone. Twenty-six percent of these patients reacted to all venoms tested.

EFFECT OF PREVIOUS WBE



VENOM SKIN TEST SENSITIVITY

Fig. 2. Comparison of the effect of prior WBE therapy on specific venom skin test sensitivity. WBE patients were less likely to have single venom sensitivity and more likely to show cross species reactivity.

Table II. Categorization of the 109 patients with NLTR

Group II	N	Age (yr) (mean)	M:F	Previous WBE	Skin test score* (mean)
Random treatment	26	9.15	1.89:1	26.9%	2.73
Random observe	31	9.51	3.43:1	25.8%	3.22
Non-random treatment	10	10.30	1:1	50.0%	3.40
Non-random observe	420	9.03	1.47:1	35.7%	3.00
Total	109	9.31	1.87:1	32.1%	3.02

*See Methods section for details.

were followed. Patients with non-life-threatening reactions (Group II) were entered into the longitudinal study described below.

The longitudinal study. Patients with non-life-threatening reactions (Group II) and positive venom skin tests were offered a program in which one group, by random assignment, received venom immunotherapy and the other did not. The ratio of randomization was 1 to 1.5, treatment to nontreatment. The patients who chose not to be randomized were allowed to select their group. Venom therapy was administered according to an established regimen.^{6,7} Both groups were carefully instructed in the emergency use of adrenalin. Emergency self-treatment kits (Epi-Pen, kindly provided by Center Laboratories, Port Washington, N.Y.) were given to each patient.

Follow-up in both groups consisted of quarterly antibody titers, yearly skin tests and toxicity studies, and skin tests and antibody titers following accidental stings.

RESULTS

The 235 patients who met the clinical criteria for inclusion in one of the study groups during year 1 of the study are characterized in Table I. Sixty-eight percent (123/182) of patients with histories of systemic reactions reported only cutaneous symptoms. An additional 11 patients failed to meet study qualifications because of questionable insect-related reactions (2), toxic reactions (1), small local reactions judged as within the usual range (6), or a serum sicknesslike syndrome after sting (2). The age range was similar in all groups, and the M:F ratio was about 2:1.

Eighty-nine percent (208/235) of patients had positive skin tests. The type of reaction had no bearing on the likelihood of having positive skin tests, since the proportion was essentially the same for all groups (Table I). Although positive skin tests in the LTR group were elicited with lower concentrations of venom than in the other groups

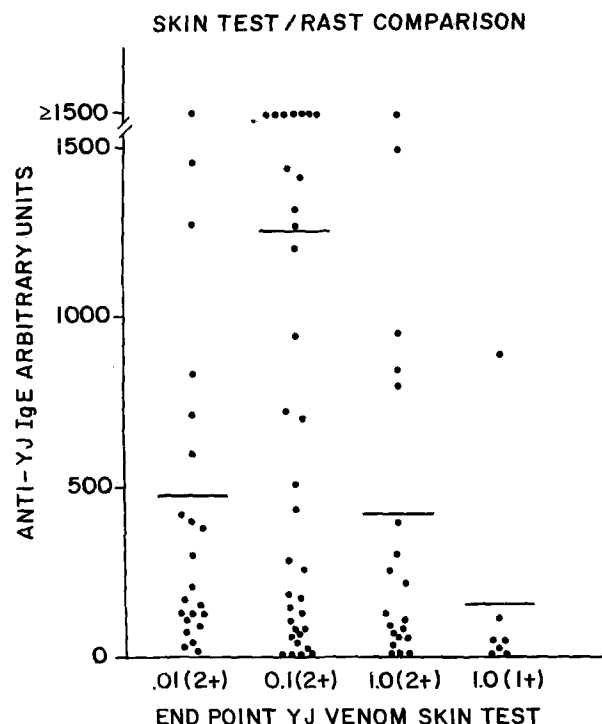


Fig. 3. A scattergram comparing RAST titers vs skin test positivity in yellow jacket-sensitive children. The bar indicates the mean titer for each group. No correlation was found between the two measurements.

($P < 0.05$), the difference was too small to be clinically useful. Sixty-one percent of the patients had skin reactivity to more than one venom (Fig. 1).

Although 28% (66/235) of the patients had been treated with whole body extract, this finding did not affect the likelihood of having a positive venom skin test. However, a history of prior WBE treatment was significantly related ($P < 0.01$) to the appearance of multiple skin test reactivity, e.g., positive skin tests to venoms of the antigenically similar vespids¹⁰ plus the immunologically unique honey bee¹¹ (Fig. 2).

All patients with NLTR and positive skin tests were entered into the prospective longitudinal study. At the end of the first year, 109 patients had entered (Table II), approximately 50% randomly. These groups were relatively small, and there was some intergroup variability in M:F ratios, previous WBE therapy, and initial skin test scores.

Initial yellow jacket RAST titers were elevated in 89% (74/83) of the NLTR patients who were skin test positive to yellow jacket venom, yielding a "false-negative" RAST rate of approximately 11%, which is consistent with previous studies.^{7,8} Also as found in previous studies, there was no correlation between the minimum concentration of

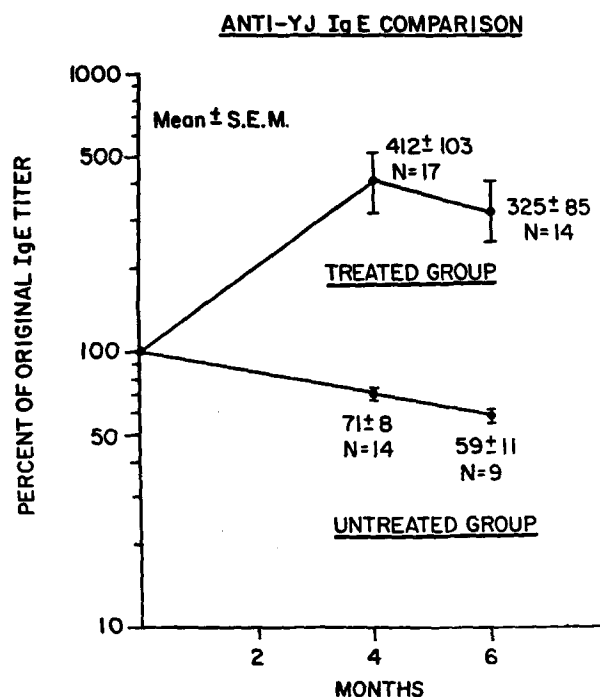


Fig. 4. The mean yellow jacket-specific IgE antibody titers in venom-treated and untreated patients during a six-month period. Therapy induced an early increase in titers (approximately fourfold) which declined despite continued treatment. The untreated group had an overall decline during six months to about 60% of their initial titers.

venom required to elicit a positive skin test and the titer of anti-yellow jacket venom IgE antibody⁷ (Fig. 3).

The titer of yellow jacket venom-specific IgE antibody changed over time as a result of venom treatment and accidental stings. The NLTR patients who were treated had about a fourfold rise in anti-yellow jacket IgE antibody three to four months after beginning therapy; the antibody level then began to decline slowly (Fig. 4). Therapy was also accompanied by a rise in IgG-blocking antibodies (not shown), as previously reported.^{6,7} In untreated patients who were not accidentally stung, there was a decline in the mean anti-yellow jacket IgE antibody titer, with a fall to 71% of original titer by four months, and to 59% at 6 months (Fig. 4). In untreated patients who were stung accidentally, most had a rise in yellow-jacket specific IgE antibody, followed by a prompt decline (data not shown).

Over the first summer of the NLTR study, 27 accidental stings occurred in 19 patients. In the venom-treated groups, seven stings produced one mild systemic reaction and five large local reactions. In the group which was not treated, 20 stings produced two mild systemic reactions and four large local reactions. In no instance was the subsequent systemic reaction as serious as the original, and

all resolved without the use of epinephrine. The treated patient who experienced a mild systemic reaction was subsequently challenge-stung with the insect to which she was most sensitive by skin testing, and no systemic symptoms occurred. The three patients from both groups who had systemic reactions after accidental stings could not be distinguished from the patients who were stung without reaction, by any of their initial evaluation results.

DISCUSSION

Further definition of the indications for venom immunotherapy for insect allergy is necessary for socioeconomic as well as medical reasons. Between one and two million people in the United States have a history of a systemic reaction to an insect sting and a positive skin test. At the current cost of venom immunotherapy, treatment of all such patients would require at least \$500,000,000/year. Furthermore, the necessary duration of therapy is unknown and may be indefinite. In our five years of experience with the treatment of adults, we have seen no patient whose skin tests became negative, nor any whose IgE antibody levels became immeasurable. Finally, although occasional local reactions and rare mild systemic reactions may follow venom injections, there are no current indications of serious short-term toxicity caused by venom treatment. It is not known whether decades of such antigenic stimulation will be innocuous. Thus, although therapy is effective, rational criteria for its use must be defined.

In order to minimize the possible risk of repeated systemic reactions in untreated patients, we have limited our longitudinal, randomized study to patients with histories of systemic reactions restricted to the skin (NLTR). Surprisingly, only 12% of adults in our previous studies presented with such a history; in the present study, almost 70% of children with systemic reactions fell into this category. Although this disparity might be explained by the reluctance of adults to seek medical advice for apparently trivial reactions and the relative willingness of parents (and referring pediatricians) to have a child with even the mildest type of systemic reaction evaluated thoroughly, this finding suggests the possibility of age-related biologic differences in allergic responses to stings.

The skin test results in children also differed from those seen in adults.^{6,7} Although vespid sensitivity was almost as common in children as in adults, sensitivity to honeybee, alone or concomitantly, was more frequently seen in our study group.

We have previously stated that treatment with WBE offers no significant advantage over placebo,^{5,12} and have

reported evidence of sensitization to irrelevant body proteins in some patients who have received such treatment.¹³ Twenty-eight percent of the children in this study had a history of such treatment, which was found to be associated to a significant extent with combined skin test reactivity to both vespid and the immunologically distinct honey bee venoms. If WBE caused such multiple skin test reactivity, sensitization could have resulted from the presence in WBE of quantities of venom insufficient to stimulate appreciable IgG antibody formation, yet sufficient to perpetuate an IgE antibody response detectable by skin testing. Alternatively, prior sensitization to body proteins in WBE might have been detected by skin testing with commercially available venoms, which may contain trace amounts of body proteins. Regardless of which explanation may be tenable, in evaluating the patient in whom positive skin tests are thought to be the result of prior WBE treatment, repeated skin testing 6 to 12 months after cessation of WBE may reveal a significant decline in skin test reactivity in those patients whose positive skin tests were iatrogenic.

Skin tests were not, on an individual patient basis, indicative of the severity of the previous reactions. Although those with severe reactions have statistically greater sensitivity, as might be expected on an immunologic basis, this difference was too small to have clinical utility. Further, IgE anti-venom antibody levels were not helpful because, as previously demonstrated,⁸ there were 10 to 20% false negatives, and the positive titers were almost randomly distributed among patients highly and marginally sensitive by skin test and among patients with variable severity of reaction.⁷ The skin test, then, indicates sensitivity, but is in no sense quantitative or of prognostic value.

Another finding of our study was the difference in the reaction rates and severity of reaction between boys and girls; there were twice as many males as females in our study group. This finding may, of course, have its basis in a referral bias, but we can find no grounds for that conclusion. The difference is not based on immunologic factors, since neither skin test sensitivity nor IgE antibody levels distinguished males and females. Neither is it likely to be caused by hormonal differences, since the average age of the children was 9 years. This suggestion of a male/female difference in the severity of allergic reactions may relate to nonimmunologic factors which influence the biologic response to mediator release, or to the "releasability"¹⁴ of mediators from sensitized mast cells or basophils following antigenic challenge.

The results of the remainder of the study were otherwise either anticipated (though not previously shown) or too preliminary to allow conclusions. Venom immunotherapy

caused an initial increase in IgE antibody whereas the lack of treatment led to a fall. After four and six months the treated and control groups were clearly different in terms of the change in IgE anti-venom antibodies. Too few data are available to discriminate different patterns in the fall in IgE in individual patients or to attempt to utilize the rate of decline to judge prognosis. Although untreated patients were expected to show an increase in IgE antibody after an accidental sting, the magnitude of the rise was more than anticipated. The sting represents only a small fraction of the venom in a therapeutic injection (5 to 50%), and yet clearly causes a marked increase in IgE antibody. The reasons for this difference are not clear.

The field sting data are also too preliminary to allow conclusions, but point out some interesting facets of insect allergy in this selected group of children. The incidence of systemic reactions following re-sting is relatively low. A precise reaction rate cannot be calculated, but it appears lower than that in the only previous study.⁶ In adults, the reaction rate of patients with a history of either cutaneous or more severe reactions was close to 60%. Although this figure is also based on a small number of patients (14 reactions among 22 patients stung), and our current data are based on accidental field stings in which identification is difficult, the reaction rate in children would appear to be lower. More important is the fact that none of the children had a reaction as severe as the previous one. This fact, together with the low reaction rate, allows optimism that we will, in the succeeding years of this study, be able to compile data which allow judgments to be made on the indications for venom treatment in children.

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