

Diagnosis and treatment of anaphylactic reactions to Hymenoptera stings in children

Forty-four children (mean age 9.6 years) with a history of an allergic reaction(s) to an insect sting and with positive insect venom skin tests were studied. IgE antibodies (RAST) to honeybee phospholipase A and to yellow jacket venom were found in the sera of 78% and 77%, respectively, of these patients. The patients were immunized with the appropriate venoms over a 15-week course and most were then subjected to an in-hospital sting; there was a 3% reaction rate (1/37). Clinical protection was associated with a fivefold increase in anti-venom IgG. Five patients did not develop a significant increase in IgG antibody and they were treated more vigorously; four were stung subsequently without reaction. Two patients did not react when stung in the field; positive identification of the culprit insect was obtained. Twenty patients were re-stung after one year of maintenance therapy; there was a single mild, delayed reaction. Immunotherapy also increased the IgE antibody against venom 3.7-fold at three months; after one year of therapy the IgE antibody level had decreased but was still 40% greater than at the outset. Immunotherapy was associated with a 25% incidence of local pain and swelling and a 6% incidence of systemic reactions. We conclude that venom therapy in children is safe and effective. The indications for initiating immunotherapy require further definition.

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ALTHOUGH anaphylaxis after Hymenoptera stings has been recognized for many years, the incidence of such reactions is not known. Retrospective studies suggest that 0.4 to 0.8% of the population have a history of a systemic reaction,^{1, 2} but a prospective epidemiologic study has not been done. Actuarial statistics indicate that at least 40 deaths occur each year in the United States as a result of Hymenoptera sensitivity^{3, 4}; this is likely to be an underestimate.

IgE antibodies against insect venom antigens appear to mediate these reactions.⁵ Until recently, skin testing with

extracts of whole insect bodies was the only method to confirm a history of an anaphylactic reaction to a Hymenoptera sting.^{4, 5} Treatment of patients with these extracts has been regarded as an effective mode of therapy,⁶⁻⁸ but more recently published studies indicate that, in adults,

Abbreviations used

RAST: radioallergosorbent test
WBE: whole body extract
IgE: immunoglobulin E
HSA: human serum albumin
PL-A: phospholipase A
cpm: counts per minute
RIA: radioimmunoassay

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skin tests with WBE antigens do not discriminate between patients allergic to insect stings and normal individuals.^{9, 10} In a controlled study, treatment with WBE was no better than placebo in protecting patients from reactions to an in-hospital sting, and immunotherapy with insect venoms specific to the patient's sensitivity was significantly better

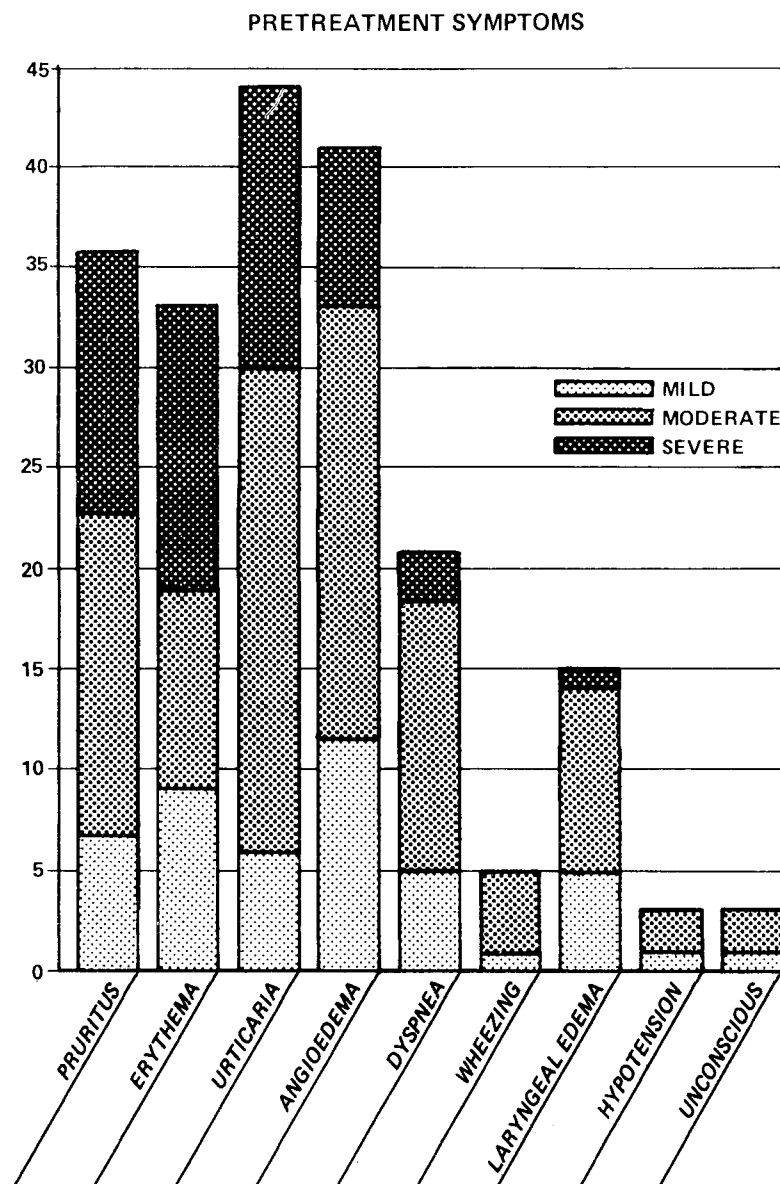


Fig. 1. A summary of reaction histories for 44 insect allergic children. The type of response is indicated on the abscissa, the number reacting on the ordinate. Mild reactions resolved without therapy and moderate reactions subsided rapidly following therapy (epinephrine or anti-histamines). Severe reactions resolved slowly even with appropriate therapy.

than WBE or placebo in protecting patients from an anaphylactic reaction after a sting.¹⁰

We studied 44 children with a history of an anaphylactic reaction(s) to a Hymenoptera sting and a positive venom skin test(s). Venom therapy was then administered based on skin test sensitivity; venom-specific IgE and IgG antibody levels were followed. The efficacy of the therapeutic program was tested by in-hospital challenge stings with the offending insect.

MATERIALS AND METHODS

Patients. Forty-four children with a history of an anaphylactic reaction(s) to a Hymenoptera sting and with a positive venom skin test(s) were referred to The Johns Hopkins University School of Medicine during 1976-1978. The mean age was 9.6 years (range 4 to 14 years). Twenty-three patients began treatment in the spring of 1977 and 21 patients in the spring of 1978. Twelve of these patients had previously been treated with WBE; of these,

three were stung and had reactions while receiving WBE therapy. Reactions were categorized and graded as to the severity (Fig. 1). Symptoms categorized as "mild" resolved without treatment, "moderate" symptoms resolved after appropriate treatment, and "severe" symptoms persisted even with appropriate therapy.

Venoms. For the 1977 group, honeybee venom was collected by electrical stimulation and vespid venoms were extracted from the venom sac by the method described by Benton et al.^{11, 12} Venom was freeze-dried after collection, and the protein concentration was determined by the method of Lowry et al.¹³ The venom was then diluted to 100 $\mu\text{g}/\text{ml}$ in saline buffer, pH 6.8, containing 0.03% human serum albumin and stored at -70°C until used. Phospholipase A, an allergen from honeybee venom, was purchased from Sigma Chemical Company, St. Louis. In 1978, venoms used for skin testing and immunotherapy were furnished by Pharmacia (Piscataway, N.J.). The venoms were reconstituted with a diluent containing 0.03% HSA, 0.4% phenol, and 0.9% sodium chloride, and were used within one week.

Three techniques were initially employed to demonstrate IgE antibodies to venom proteins: (1) venom skin tests; (2) venom specific IgE (RAST) titers, and (3) basophil histamine release. Basophil histamine release was subsequently discontinued, since an unusually high proportion of this group of patients failed to release histamine either to venom or to anti-IgE.

Antibody measurements and skin tests. IgE antibodies to yellow jacket venom and honeybee PL-A were measured by a RAST technique.¹⁴ Results for the yellow jacket RAST are reported as cpm per tube. Background binding (c 600 CPM) has been subtracted from all values. A positive RAST is defined as 2 SD above the cpm bound by sera from individuals without a history of insect allergy.¹⁴

During the course of therapy and before the in-hospital sting, venom-specific IgG antibody levels were determined. IgG antibody was measured by a double-antibody radioimmunoassay which has been described in detail.¹⁵ Results of IgG antibody measurements are reported as the reciprocal of the dilution required to bind 50% of the immunoreactive-labeled yellow jacket venom.

Venom skin tests were performed by the intradermal technique as previously described.¹⁶ Venom concentrations of 0.01, 0.1, and 1 $\mu\text{g}/\text{ml}$ were used. Skin testing was with honeybee venom, honeybee phospholipase A, the vespid venoms (yellow hornet, white-faced hornet, yellow jacket), and polistes (wasp). Skin tests were read 15 minutes after the injection of 0.02 ml; a 2+ reaction (wheal size 5×5 mm or greater) was considered positive.

Occasionally, when the clinical history was severe, a 1+ reaction was used as a basis for therapy. Skin testing with a standard panel of inhalant allergens was by the prick technique.¹⁷

Therapeutic regimen and in-hospital sting. Immunotherapy was carried out with venoms specific for the patient's sensitivity, as determined by skin test results. Honeybee and yellow jacket venoms were used as separate allergens. Patients sensitive to more than one vespid were treated with a mixture containing equal amounts of white-faced hornet, yellow jacket, and yellow hornet venoms. Immunotherapy was begun at 0.01 μg of each of the venoms. Multiple injections were given on day 1 so that a total dose of 1.1 μg was administered. The quantity of venom was increased weekly until a dose of 100 μg (300 μg of the mixed vespid) was achieved, usually at six weeks. This dose was chosen on the basis of recent experience with adults.¹⁰ After the maintenance dose of 100 μg was tolerated for two successive weeks, the interval between injections was sequentially increased from one to four weeks. If at any time a systemic reaction resulted, the injections were stopped for that day. The next week a dose equal to $\frac{1}{2}$ the dose causing the systemic reaction was administered. Large local reactions that caused excessive pain or swelling were treated with oral antihistamines and/or aspirin. If large local reactions were particularly troublesome, the same dose of venom was repeated the next week before resuming the usual schedule.

In-hospital challenge stings were performed after informed consent was obtained from the parents and, when appropriate, from the patients. An intravenous infusion was begun, and the sting accomplished by inverting an insect-containing vial on the arm. Completion of a sting could be assessed by clear-cut subjective and objective criteria. The patient was then monitored for three hours for evidence of a systemic reaction. Of the 23 patients treated in 1977, 20 were stung in August, 1977. Two patients had been stung in the field and provided positive identification of the insect; one patient refused a sting. In August of 1978, both groups were offered a challenge sting; 20 patients from the 1977 group and 19 patients from the 1978 group were stung.

Toxicity studies, done at 3-month intervals, included complete blood count, sedimentation rate, automated chemistry screen, and urinalysis. No significant abnormalities were noted.

RESULTS

Presenting symptoms for the 44 patients are shown in Fig. 1. Reactions may be classified into three general types: cutaneous (erythema, pruritus, urticaria, or

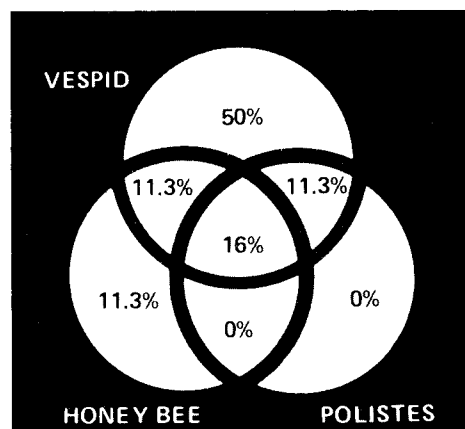


Fig. 2. A summary of the skin test reactivity of 44 children to honey bee, vespid (yellow jacket, yellow hornet, white hornet), and polistes venoms. The percentages in the outer portions of the large circles indicate the skin sensitivity to a single type of insect (i.e., 50% to vespid). The areas of overlap indicate the incidence of multiple sensitivity.

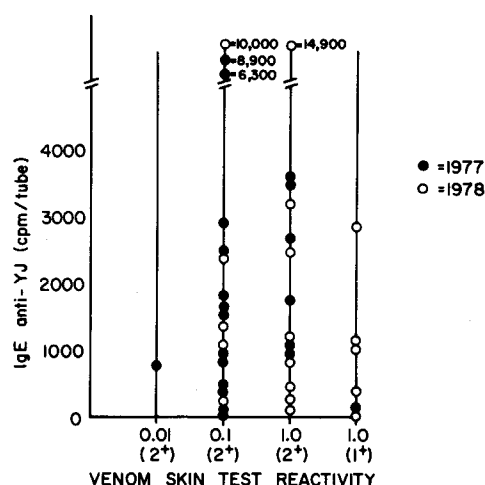


Fig. 3. Scattergram comparing the skin test sensitivity and RAST titers of 39 children to unfractionated yellow jacket venom. Background cpm have been subtracted from the RAST values. The numbers immediately under the abscissa indicate the venom dose ($\mu\text{g}/\text{ml}$) which elicited the skin test response shown below.

angioedema), airway (dyspnea, wheezing, or laryngeal edema), and shock. Most of the patients, 43/44 (98%), experienced at least one cutaneous manifestation, and 21/44 (48%) had at least some degree of respiratory embarrassment. Only 4/44 (9%) of the patients had documented evidence of hypotension. Of the total number of reactions, 12/44 (27%) were considered by the physicians treating them to be imminently life-threatening. Eighty percent of the parents believed that their child

Table. Reactions to venom immunotherapy

	Children		Adults	
	Patients (%)	Reactions per 100 injections	Patients (%)	Reactions per 100 injections
Systemic	6.8	0.3	18	1.7
Large local	27	2.5	50	9.8

would be at risk of death after a subsequent sting. Patients who had had more than one reaction before therapy tended to experience the same type of reaction with each sting.

A past medical history of allergic disease was present in 11 of the patients: five had allergic rhinitis, four allergic rhinitis and asthma, one urticaria, and one eczema. The history of other allergic diseases in our patients was not supported by results of skin tests or total IgE levels. In the 24 patients skin tested for inhalant allergens (grasses, trees, ragweed, and molds) only three tests were positive. The mean total serum IgE concentration for these 24 patients was 258 ± 37 ng/ml (SEM); although higher than the normal total serum IgE for this age group (52 ± 21 ng/ml; $P < 0.01$),¹⁸ this value is markedly less than that from an age-matched group of 44 atopic children randomly selected from our Pediatric Allergy Clinic ($1,192 \pm 207$ ng/ml; $P < 0.01$). The family history was positive for an anaphylactic reaction to a Hymenoptera sting in four patients, for seasonal allergic rhinitis in 12 patients, for asthma in six patients, and for urticaria in two patients. These figures are not different from a control population. Our finding, then, was that insect allergy was not associated with other allergic diseases.

To be included in this study, each patient was required to have a positive skin test to at least one venom. Fifty percent of the patients were sensitive only to vespid venoms (yellow jacket, white-faced hornet and/or yellow hornet) (Fig. 2). The majority of these patients had more than one positive vespid skin test, a pattern also found in an adult study.¹⁶ The honeybee venom skin test was positive in 38% of the patients, with 11% having honeybee as the only positive skin test. There were no patients with polistes as the only positive skin test (11 patients were not tested for polistes); this finding is in keeping with adult studies and with the apparently low incidence of polistes stings in the mid-Atlantic states.

There was no correlation between the degree of skin test reactivity and specific IgE antibody titers for the honeybee (PL-A) antigen (data not shown) or the yellow jacket venom (Fig. 3). Twenty-two percent of patients with positive yellow jacket skin tests had a negative yellow jacket RAST; 23% of the patients with positive honeybee

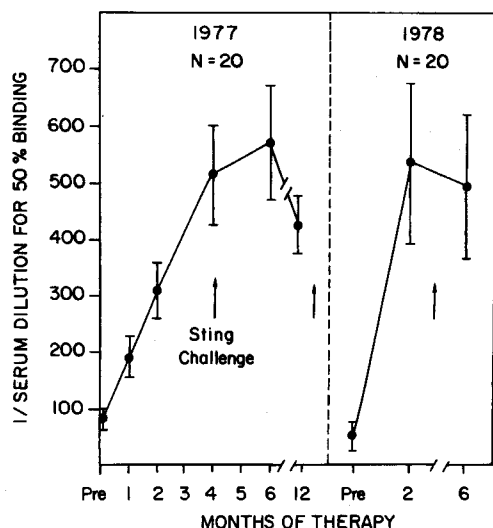


Fig. 4. The IgG antibody response to yellow jacket venom immunotherapy (mean $\pm$ SEM). Both the 1977 and 1978 groups were sting challenged at 16 weeks when the average titer was $\approx$ 500 arbitrary units. Following a year on monthly 100 μ g maintenance doses, the specific antibody titers of the 1977 group fell only slightly (400 units) and all patients were re-stung without reactions.

skin tests had a negative honeybee (PL-A) RAST.

During the course of immunotherapy, three mild systemic reactions occurred (Table I). The manifestations were tachycardia, nausea, and chest tightness without wheezing. One reaction required treatment with epinephrine and the other two resolved without therapy. These reactions occurred at doses of 30, 60, and at the first dose of 100 μ g of venom, respectively. In each patient, one-half the dose causing the reaction was given the next week without incident and the immunotherapy schedule was resumed. Twelve of the 44 patients (27%) experienced at least one large local reaction during therapy (Table I). These reactions usually began within 15 minutes after the injection, plateaued at four to six hours, and resolved within 36 hours. Although lengthening the interval between maintenance injections resulted in a transient increase in large local reactions, all the patients were able to tolerate these injections and to continue daily activities. Rarely, the previous week's dose of venom was repeated when there had been an exaggerated large local reaction.

In-hospital stings in 20 of the 23 children were performed in August, 1977, after 15 weeks of venom therapy; there were no reactions. In August, 1978, 20/21 patients in the newly started group were stung in the hospital; there was one systemic reaction (see below). Also in August, 1978, 20 patients from the 1977 group were re-stung after

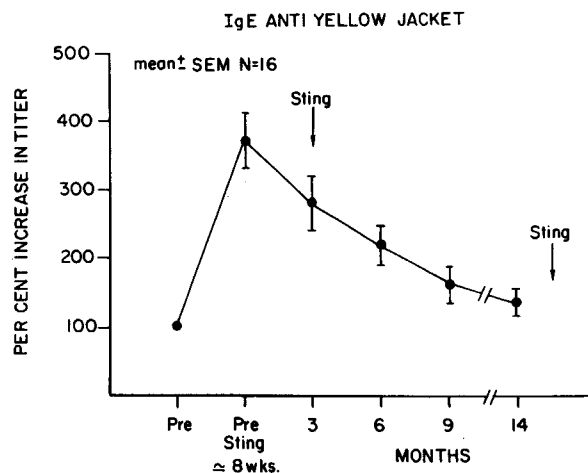


Fig. 5. The specific IgE antibody response to yellow jacket venom immunotherapy in the 1977 patients over time. A rapid rise in titer occurred during the first two months which declined during a year of monthly maintenance injections to $\approx$ twice the pretreatment titers. For these data, the pretreatment titer for each patient was considered 100%, individual ratios were obtained, and the mean increase was calculated. Note that the first challenge sting occurred when the IgE antibody titers were quite elevated; no reactions occurred.

16 months of therapy; there were no immediate reactions. One patient had urticaria six hours after the sting, localized to the site of the sting. The lesions lasted less than 24 hours and required only oral administration of antihistamines for symptomatic control. Overall, 42 children were stung after the initial or extended course of venom immunotherapy, with a 2% reaction rate.

IgG blocking antibodies to yellow jacket venom and to honeybee PL-A were followed during the course of immunotherapy. The patterns were similar. Mean anti-yellow jacket IgG antibody levels for the 1977 and 1978 groups are shown in Fig. 4. Pretreatment values in 1977 averaged 90. There was an increase in the IgG antibody level of greater than 500% in the four months prior to challenge sting. The mean pretreatment titer of anti-yellow jacket IgG antibody for the 1978 group was 40 (Fig. 4). There was a substantial increase during the first 15 weeks of immunotherapy; on the week prior to the challenge sting the level averaged 500 (Fig. 4). Four patients did not respond with production of the expected amounts of anti-yellow jacket IgG after the standard 15 initial weeks of therapy. One additional patient did not make IgG antibody to honeybee venom PL-A. When one patient from the group having low IgG antibody titers was challenged with an in-hospital sting, a reaction consisting of wheezing, urticaria, and hypotension occurred. Subsequently the maintenance venom dose for these five

patients was increased to 200 μ g of each venom and the interval between injections was decreased to two weeks. This regimen resulted in a twofold rise in yellow jacket IgG antibody after 12 weeks in the four patients sensitive to this insect. Subsequent challenge sting of the patient who had previously reacted resulted only in transient bronchospasm and one urticarial lesion that did not require therapy. Three of the other patients, with a documented twofold rise in IgG antibody, were challenged after 12 weeks on the modified regimen, with no reactions. A review of the case of the one patient who persistently failed to mount an IgG antibody response to yellow jacket venom revealed that his predominant sensitivities were to yellow hornet and polistes venoms. He has not been stung by these insects. The dose interval in these patients was subsequently increased to every four weeks. Twenty patients of the 1977 group were re-stung after 16 months of therapy; the mean anti-yellow jacket IgG antibody titer just prior to the sting averaged 420 (Fig. 4).

The changes in the specific IgE antibody against yellow jacket venom during immunotherapy are shown for the 16 patients treated in 1977 with this venom (Fig. 5). The IgE peaked at eight weeks with a 370% increase over baseline and then fell as maintenance therapy was continued. After 14 months of therapy the IgE antibody level remained 40% above the pretreatment value.

Skin testing with the venoms was repeated in the 1977 group after 16 months of therapy. There were no consistent changes, but no patient had lost his sensitivity.

DISCUSSION

In recent years, the reliability of WBE for the diagnosis and therapy of anaphylactic reactions to Hymenoptera stings has been questioned.^{9, 10, 19-23} The use of WBE skin tests to confirm anaphylactic sensitivity to Hymenoptera can be traced to a single case report in which an allergic beekeeper was found to be sensitive to both venom extract and WBE.²⁴ The use of WBE skin tests for the general population was rarely questioned until 35 years later, when two reports were published documenting the occurrence of positive WBE skin tests in 40 to 95% of individuals without insect allergy,^{9, 23} presumably related to the nonspecific irritant effects of materials in WBE.

Immunotherapy with WBE was felt to be responsible for lessening the reaction after subsequent stings in 80 to 90% of allergic patients,^{6, 7, 26} but this impression was based on uncontrolled, retrospective studies which suffered from lack of complete reporting. The failure of WBE to protect a beekeeper's son whose sister had died from an insect sting led us to try, successfully, the use of venom treatment in honeybee sensitivity.²⁰ In a subse-

quent controlled trial, venom immunotherapy was compared to WBE and placebo. The venom-treated patients had a 5% reaction rate after challenge sting, whereas the reaction rate for WBE-treated patients was 64%, and for placebo patients 58%.¹⁰ This study demonstrated the efficacy and safety of venom therapy and suggested that there was little difference between placebo and WBE in providing protection against a subsequent sting; it also demonstrated the association between clinical immunity and elevated serum IgG antibody levels against venom proteins. Studies by Lessof et al²⁷ also showed that passive infusion of hyperimmune globulin from beekeepers decreased the clinical sensitivity to injections of honeybee venom.

In this open trial of venom immunotherapy in children, all of the patients were selected for treatment on the basis of a clinical history of an anaphylactic reaction to an insect sting and at least one positive venom skin test. Specific pretreatment IgG and IgE antibody levels were analyzed but did not influence decisions concerning treatment.

The immunotherapeutic regimen for the present study was identical to that used for adults. The frequency of systemic reactions to venom was lower than expected from our experience with pollen immunotherapy, and children experienced fewer reactions from venom therapy than occurred in adults.^{28, 29} Most systemic reactions occur during the initial six to eight weeks of therapy, but rarely these happen during maintenance injections. We suggest, therefore, that maintenance injections administered by primary care physicians should be given in an outpatient facility equipped to handle anaphylaxis, as might occur with any allergenic extract.

IgE antibody against yellow jacket venom (Fig. 5) increased during the initial phase of immunotherapy. This increase occurred earlier than that observed with respect to the IgG antibody (Fig. 4) but peaked and fell to a level only slightly higher than baseline after one year of therapy. There is no clinical experience to support the concept that heightened sensitivity to stings occurs during the early weeks of immunotherapy, but the possibility exists. Of the patients who had negative RAST titers before therapy, three of 11 developed measurable IgE antibody during immunotherapy with venom.

In our study, the only patient who experienced a systemic reaction on challenge sting had a low IgG antibody titer after the initial course of therapy. The severity of his systemic reactions decreased as his IgG antibody titer increased.

After the immunotherapy was completed and successful challenge was accomplished, most of the parents stated that they no longer believed that their child was at risk of

future reactions, but 35% continued to believe that a modified life-style was necessary to avoid stings, and 40% required their child to carry an insect reaction kit when leaving the home, although that was not specifically recommended by the physician. When dealing with a potentially fatal situation, such as anaphylactic reactions to insect stings, a sizeable percentage of parents apparently will continue to believe that special attention for the child is necessary, even if protection has been demonstrated by a supervised challenge sting.

In view of the excellent results which can be obtained with venom immunotherapy, it would be understandable if physicians were reluctant to withhold treatment. However, even when a physician is presented with a patient having an unequivocal history of an anaphylactic reaction to a sting and a clear-cut positive skin test, no definite statement can be made concerning the "degree" of risk that the patient has for a subsequent reaction if he is stung again. In the process of identifying patients for their controlled trial of venom immunotherapy, Hunt et al¹⁰ examined the question of the reliability of historical information in the diagnosis of Hymenoptera sensitivity. Of 180 patients with a history of anaphylaxis, 120 had negative skin tests.¹⁰ There was a definite trend of decreasing skin test positivity with time since sting. If Hymenoptera allergy is analogous to penicillin allergy, one could expect that patients who are skin test negative are at a considerably lower risk for allergic reactions than are skin test positive patients.³⁰ Many of the patients with negative skin tests had not been stung recently, suggesting that the IgE antibody titer spontaneously declines over time and that the patient with a negative skin test is no longer at risk. The possibility that a subsequent sting might induce another IgE response, with resultant increased sensitivity, is implicit.

Further studies are needed to define the percentage of children with positive skin tests who are truly at risk for reaction to future stings. The indications for the initiation of immunotherapy and the length of time that therapy should be continued have not been clearly defined. Until that time, all patients with positive skin tests and a clinical history of sensitivity must be counseled before starting immunotherapy. To choose not to begin immunotherapy carries the risk of a serious reaction to a future sting. No serious adverse effects of long-term venom administration, either by immunotherapy or stings, have been documented.^{31, 32} On the other hand, it seems likely that most children will naturally lose their sensitivity. Venom immunotherapy, by maintaining the IgE antibody level, will prevent this "natural" cure.

We conclude that venom immunotherapy in children is effective and safe. However, it is also expensive, time

consuming, and must be carried out for an indefinite period of time. Because reactions in children are often not life-threatening, we are attempting to refine our criteria for the use of venom immunotherapy. If many children spontaneously lose sensitivity over time, it may be necessary to treat only those children with severe reactions, i.e., those in whom respiratory symptoms or hypotension have occurred. If these criteria were applied to the current group, approximately 50% would not have been treated. An epidemiologic study to examine the natural history of mild, non-life-threatening systemic reactions is now in progress. Until the results are available, the decision to treat children with milder systemic reactions should be made only after a thorough discussion of the risks and benefits between the physician and parents of each child.

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