

USE OF POLISTES VENOM IN PETROLATUM:ARLACEL REPOSITORIES TO IMMUNIZE AGAINST YELLOW JACKET WASP-STING ALLERGY¹

MARY HEWITT LOVELESS² AND THOMAS M. NALL³

*From The New York Hospital and the Department of Medicine, Cornell University Medical College,
New York, New York*

Received for publication July 9, 1964

Evidence for the safety and effectiveness of an annual repository injection of venom-in-petrolatum having been reported for polistes allergy (1), the principle is now extended to patients with histories of yellow jacket (y.j.) anaphylaxis. An initial obstacle was the unavailability of live wasps of this type in winter and spring. Venom sacs which had been aseptically removed from lightly anesthetized y.j. worker wasps the preceding autumn were not suitable for use in repositories because they had been preserved in glycerin, an agent which acts adversely on the rate of antigen release from mineral oil emulsions of pollen extract (2). The problem was solved, however, by the accessibility of *polistes* (pol.) queen wasps in such hibernating haunts as country attics. Fortunately for the purpose intended, earlier cross-neutralization studies of the Prausnitz-Küstner type had shown pol. venom to possess all of the allergenic specificities of y.j. venom (3). It could be assumed, therefore, that pol. venom would engender cross-immunity (blocking antibodies) in y.j. susceptible persons. With this prospect in view, 33 individuals with histories of alarming reaction to y.j. stings were assigned to immunization with pol. venom, 24 to receive the standard annual dose of 6 sacsful of venom in a single, subcutaneous repository while nine took the same amount in saline-diluted form by means of a series of six or more endermal injections completed during a single yearly visit. A control group, comprised of 18 others with marked clinical responses to y.j. stings, took an analogous course of fluid venom of y.j. origin.

¹ This investigation was supported by the Office of Naval Research Contract NONR 401(42) and by a grant from CIBA Pharmaceutical Products, Inc.

² Present address: Cavalry Road, Westport, Connecticut 06882.

³ Present address: Roosevelt Hospital, New York, New York.

Additional control data were derived from past courses of homologous y.j. venom that had been taken by 22 members of the current repository group and by one member of the group now on fluid pol. venom. In all, 139 annual immunizations were available for final comparisons. As stated in preliminary reports (4, 5) and as judged by the outcome of live sting challenges made after nearly half the courses, a high order of clinical immunity usually resulted, regardless of whether the 6 sacsful of venom had been injected in emulsified or in simple diluted form, and regardless of whether homologous or heterologous pol. venom had been chosen for treatment. It would thus appear that pol. venom can be substituted for y.j. venom when necessary, making repository immunization feasible in y.j. allergy.

MATERIALS AND METHODS

Patients. With two exceptions, these gave a history of alarming developments within 20 min of a y.j. sting, notably the loss or near loss of consciousness and, occasionally, laryngeal edema. Usually there were associated allergic manifestations such as generalized pruritic eruptions; nausea, vomiting, abdominal colic; edema of lips and lids; uterine colic and, in one instance, miscarriage. Weakness, apprehension and mental confusion were common, severe headache occasional. Of the two members who had failed to exhibit focal manifestations promptly, one reported an unduly large localized reaction that attained a diameter of 6 in. and disappeared only after a week. The other had noted normal localized redness and discomfort transitorily after being attacked by 34 y.j. wasps that emerged from an underground nest. Eight days later, however, marked urticaria developed at the sting sites as well as over most of his body, and there were joint pains, fever and malaise. Within the ensuing 3 days, rectal edema reached such

proportions that obstruction threatened and steroids were required for 5 days. Prior to their venom therapy the following spring, these previously untreated men gave responses, during endermal and conjunctival instillation tests, to strengths of venom that typified allergic subjects (3).

Of 24 participants in the emulsion experiment (group A), two were receiving their primary therapy with wasp allergen, the rest having taken our standard course of fluid y.j. venom in earlier years. By way of contrast, most of the members of group B, assigned to therapy with fluid pol. venom, were undergoing primary courses, only one of the nine having been immunized before. This female subject had abandoned her long series of weekly injections with commercial, whole body extract 10 months earlier because of disagreeable localized reactions. Two previous members of group A joined group B about 6 months after a repository injection, as added insurance against the still abundant y.j. wasps in their vicinities. A month earlier, one of them had exhibited the only significant adverse response we had evoked by deliberate stinging of treated patients with y.j. wasps, and the other had not been available for test until after this experience, when it seemed discreet to precede the challenge with a course of fluid venom. Among the 100 courses of fluid y.j. venom available for study in the third group, C, there were 31 that were primary. Twelve of these were given during 1961 to 1963, the period covered by the pol. treatments of groups A and B. The remainder had been given earlier, chiefly to 22 members of group A. This situation permitted comparisons of the two types of venom, not only between different persons treated concurrently but also between different years for the same individual.

Procedures. To minimize the number of variables, technical procedures were standardized wherever possible. The annual dose, as stated, was a uniform 6 sacsful of venom; and it was given during a single visit, in one injection if emulsified and in the smallest number of half-hourly injections (usually six) if fluid. To increase the safety of impending therapy, an objective clue to the *degree* of allergy was sought by instilling 0.02 ml of diluted venom in doubling strengths into the eye at 5-min intervals and by injecting i.c. 0.01 ml of graded concentrations until the thresholds of response were located,

correction being made for any reaction to the diluent, isotonic saline solution. Usually these pretreatment tests were repeated weeks or months later, especially on occasions when a challenge was to be made with live wasps, in the hope that an acquisition of blocking antibody would have elevated the minimal reactive requirements (MRR) to reflect acquired immunity. Detailed descriptions of materials and of testing methods have been published (1, 3-5).

The sting test was initiated by placing a non-stinging male wasp (serving as a type of placebo) on the patient's forearm to observe the effect on pulse, blood pressure and psyche during several minutes. Thereafter, at intervals of 20 min, from one to four stinging, worker female wasps were applied successively. The wings were lightly held with two thumb forceps to control the wasp's position so as to prevent insertion of the stinger directly over a vein. The total insertion period was arbitrarily held to 2 min, and involved 1 to 13 punctures, depending on the relative dexterities of wasp and operator. As with adverse reactions to therapy, focal developments (commonly known as "constitutional" or "systemic" reactions) were scored from zero to + + +, trivial sequelae such as flushing or a few hives remote from the sting site being graded as $\pm$ focal signs whereas such alarming situations as unobtainable pulse and blood pressure with momentary loss of consciousness were designated as + + +. (More profound or persistent crises were not encountered but would have been scored + + + +.)

Corrective steps for adverse reactions. Although trivial focal developments require no intervention, significant ones merit an i.m. injection of epinephrine 1:1000 0.2 to 0.3 ml, and assumption of the supine position by the patient. If, as has been our routine for initial challenge experiments with live wasps, an intravascular drip of 5% dextrose is in operation, the adrenergic amine may be injected directly into the tubing at a rate of 0.05 ml/min for 5 to 10 min. This will increase blood flow by raising systolic pressure and by reducing peripheral resistance through arteriolar dilation of most capillary beds, tending also to lower diastolic pressure. To counter anoxia, as revealed by cyanosis or cerebral excitation, intermittent oxygen inhalation is indicated. If the results of capillary leakage and consequent hypovolemia are not quickly reversed, plasma or dextran should be given by vein. Near at hand

TABLE I

Adverse reactions among 48 patients with yellow jacket wasp-sting allergy during 139 annual immunization treatments^a with homologous yellow jacket venom or with heterologous polistes venom and to 64 subsequent challenges with live yellow jacket wasps

Group	No. of Members	Type of Venom Therapy	No. of Annual Courses	Adverse Reactions			Sting Challenges after Treatment					Adverse Reactions to Stings ^b	
				±	+	++	Interval	No. of Insects		Patients stung	Occasions	±	+++
								In office	Field				
A	24	Polistes emulsion	28	VA			<i>weeks</i> 15-27	1-2	1	16	16	VA, SHU	KI ^c
B	11	Fluid polistes	11	LA		BRI	9 days-19 weeks	1-3	1	11	11	LA, BRI, WE	
C	11	Fluid yellow jacket	11	EI, SI, ME			2-21	2-3	0	10	10	EI	SI
	4		23				11 days-14 weeks	1-4	1-4	4	8	WEI, WEI	
	22 ^d		65	KA, VA, TO	SCH		8-17	1-2	1	18	18	KI, SCH, SAU	
	1		1	BRI			8½	2	0	1	1	BRI	

^a Six sacful of venom given during a single annual visit, a single s.c. injection being employed if the dose had been emulsified in Arlacel A:petrolatum whereas about six endermal injections were used when simple, diluted venom was the antigen. Arlacel: petrolatum: venom formula 1:6:5.

^b No + or ++ reactions.

^c Twenty-seven days later KI joined group B and acquired complete tolerance toward stings of two yellow jacket wasps.

^d Current members of group A.

should be a crew of experts who are equipped to cope with cardiac or respiratory arrest and with edematous occlusion of the airways, should these emergencies ever arise.

RESULTS

Table I summarizes the adverse reactions of the 48 members of groups A, B and C to 139 annual immunizations and to 64 subsequent challenges. In essence these two sets of data reveal the safety of single visit treatment and the effectiveness of immunization with heterologous as compared to homologous venom.

Adverse reactions to injection therapy and to later sting challenges. Repository injections, conveying the standard 6 sacful of fresh venom in a total volume of 1.2 ml of emulsion, engendered only one adverse response in the 24 members of

group A who received 28 such single repositories during 1961 to 1962. This trivial development in patient VA consisted of slight dizziness and mild tingling of the neck, which began in 35 min and abated in 5. A similar limitation in tolerance had been manifest after an initial dose of 0.25 sacful of y.j. venom in fluid form when her primary therapy was undertaken the year before. Identical sequelae arose when she was deliberately stung by a lively y.j. wasp 15 weeks after her 1961 repository injection of pol. venom. These ± responses are listed in the appropriate columns for groups A and C. They appear to be characteristic of this individual, as she has seldom failed to exhibit them during sessions of therapy, comprised of intermittent stinging, in the past several years. These responses always abate spontaneously, albeit they persist at times for a few hours.

Her presenting history had indicated marked hypersensitivity which increased with successive field-stings. The first two episodes had been characterized by immediate generalized tingling, impending throat closure associated with widespread urticaria and a sense of being very ill. Twenty minutes after a later sting in 1957 and another in 1958, she had collapsed and been kept in the hospital overnight. By comparison, her reactions to therapy and to sting test seemed trivial. Indeed, her latest sting-treatment has caused no focal response despite the involvement of three pol. queens and an interval of 41 weeks.

Although the other 23 members of group A exhibited full tolerance toward their repository injections, later sting tests given 15 did evoke reactions in two. One of these, SHU, developed four small, pruritic hives in the opposite axilla, when sting tested with a y.j. wasp at 15 weeks. This $\pm$ response abated in 28 min. The reaction of the second member, KI, to the same test 19 weeks after repository treatment proved alarming. As with the other volunteers, he had shown a moderate increase in pulse rate and blood pressure during the routine, preliminary application of a male, nonstinging wasp. Five minutes after the 8-sec sting of a lively y.j. worker wasp, however, he reported slight dizziness, an urge to breathe deeply, faulty vision and hearing, and nausea with sweating and weakness. Extreme pallor, associated with imperceptible pulse and blood pressure, led to an immediate injection of adrenergic amine into the tubing of his intravascular drip set. This, combined with placing him in the supine position, promptly restored normal vision and a palpable pulse. Indeed within 3 min the blood pressure was 86/30. By 12 min the systolic level had risen to 132, only 10 points below the pre-sting resting figure. Recovery was complete 40 min later.

To decide whether this failure of resistance in KI rested on differences in specificity of pol. and y.j. venoms or, rather, on an inefficiency of immunization with emulsified antigen, the patient was persuaded to return in 4 weeks for a course of fluid pol. venom. Nine days after he had completed the standard six-sac course in six divided doses without incident, he submitted, as a new member of group B, to sting test with two y.j. workers. There were no untoward developments. The blood pressure fluctuated between 156/80 and 182/90 during the 2-min stinging periods,

as compared to a preliminary reading of 162/94. (Consonant with his clinical immunity, localized responses to the punctures were only half as large as that observed just before his earlier collapse reaction.) Apparently the shock episode had not rested on a difference in venom specificity but on some other factor. This conclusion was substantiated by the patient's responses to intermittent sting therapy during the next 2 years. Restricted to applications of pol. wasps except for challenge tests with two to three y.j. workers in summer, he manifested uniform tolerance despite treatment-free intervals of 15 and 24 weeks before tests. This demonstration of excellent cross-protection and of sustained immunity precluded heterologous venom as the likely explanation of his earlier failure after repository treatment. His ability to respond to six sacs of *homologous* venom had been observed as early as 1958, when he exhibited full tolerance for the 2-min stings of three y.j. wasps 8 weeks after a primary course of fluid venom. Furthermore, on being stung on the neck by a wild y.j. 14 weeks after an identical single-visit course the following year, he developed only borderline focal symptoms of transitory dizziness and disturbed vision (see Table I, group C).

The rest of the sting challenges given the 16 members of group A evoked no sign of intolerance to the 2-min insertions of two y.j. worker wasps. As the table shows, 15 to 27 weeks had elapsed since repository therapy. For the group as a whole, the incidence of significant adverse response amounted, therefore, to 1 in 16 trials.

During their endermal injections of fluid pol. venom, the 9 original members of group B manifested one borderline (flushing) reaction and one alarming sequel. Both reactors gave a history of critical illness after earlier accidental stings, and both were embarking on primary immunizations with wasp allergen. LA, for example, had been stung on the foot in August 1961. Within 2 min she developed innumerable hives and edemas, as well as throat constriction. Soon she lost consciousness and, despite tourniquet and parenteral epinephrine, had to be hospitalized for recovery. Four weeks later, endermal tests with highly diluted y.j. venom led, in 30 min, to facial flushing and to enlargement with tenderness of the cervical nodes, albeit less than 0.1 sacful of y.j. and pol. venoms combined had been involved. When, later, she took her primary course of wasp

allergen, the total dose of six sacsful of pol. venom in seven injections again evoked these focal signs. They failed to reappear, however, when she was sting tested 22 days later. Whereas the placebo application heightened her resting blood pressure of 122/80 by 10 systolic points, the ensuing 2-min insertion of a y.j. stinger caused no focal responses except fatigue that began in 48 min and persisted for a day—a trivial adverse result placed in the $\pm$ column for group B in the table. The MRR of her eye had risen from 0.24 sac/0.1 ml to 0.94 for pol. venom but remained apparently unchanged at 0.24 for y.j. venom.

The other member of group B to manifest adverse responses to therapy with fluid pol. venom was BRI. His primary series of 6 sacsful took 5 hr to complete, 16 injections being required. His story had forewarned us. As with LA and most highly sensitized persons, BRI had reported early, uneventful encounters with pol. and y.j. wasps. By 1954, however, sting areas exhibited increasing and more persistent inflammation. In August that year a polistes stung him on the back. Within 3 min his lips and tongue became dry and small hives appeared on neck, thorax and arms. Dyspnea with crowing, inspiratory stridor were quickly followed by unconsciousness. When a local physician arrived 20 min after the sting, the blood pressure was 60/0. Epinephrine under the skin promptly revived BRI, whose only residual complaint was drowsiness for the next 10 hr. The following summer he was stung four times by a polistes on his abdomen. Although the typical dryness of lips and tongue was soon followed by slight dizziness and small clusters of hives on the thorax, these as well as drowsiness yielded gradually to a 2-hr nap. One might speculate that he had retained a degree of immunity from his preceding episode.

BRI had lost any such advantage by October of 1958 when he was stung on the finger by a y.j. wasp. In 5 min, the familiar pattern developed—dry mouth, and itchy small hives over limbs and torso. Three minutes later, there was visual blurring and great muscle weakness, followed quickly by profound unconsciousness, absent pulse, and Cheyne-Stokes respiration. Thirty minutes elapsed before a physician could be located. He was revived shortly by means of parenteral epinephrine, after which his lips grew markedly edematous and his face became bright red. Gradually his dyspnea subsided. Deeply

exhausted for the next 12 hr, he remained in hospital for 2 days. Although he was stung again 2 summers later by a polistes wasp on the thigh, customary prodromata and dyspnea abated spontaneously. One summer later, however, dire consequences followed the sting of a single y.j. wasp near his eye. Oral dryness was soon complicated by loss of consciousness, noisy respiration and convulsions. Despite his arrival at a hospital within 10 min of the encounter, he remained comatose for $1\frac{1}{4}$ hr in the face of parenteral administrations of epinephrine, antihistamines and steroids as well as oxygen inhalation. After receiving last rites, he made a surprising recovery, complaining thereafter only of fatigue. For the next few months, however, muscles and joints were painful. As to related allergies, honeybees and mosquitoes evoke no reactions, but on two occasions the sting of a small black ant has induced nausea, vomiting and diarrhea after $1\frac{1}{2}$ hr. There are no atopic allergies.

BRI took his primary course of pol. fluid venom in early May 1962, 8 months after his severe shock reaction. Very low thresholds of response were revealed during preliminary tests with y.j. venom—0.00007 sac/0.1 ml in the skin and 0.156 in the eye. The corresponding figure for the instillation test with pol. venom was 0.312 sac/0.1 ml. Despite the use of substandard doses of immunizing antigen, it was necessary to give 0.3 ml of epinephrine 1:1000 i.m. after about $\frac{3}{4}$ of the assigned 6 sacsful had been injected, to counter his complaints of oral dryness, unpleasant taste, flushed face, mild laryngeal dyspnea and a dry cough as well as a drop in blood pressure to 70/40 that was coupled with tachycardia and conjunctival erythema. Except for ensuing arthralgia and epigastric discomfort, focal responses subsided, permitting resumption of therapy and completion of the course in a total of 16 injections. By $4\frac{1}{2}$ weeks, his ophthalmic tolerance had risen to 0.9 for y.j. venom (nearly 6-fold) and sting test was recommended. A male wasp on his forearm heightened the blood pressure to 170/100 from its resting level of 158/98, evoked the "funny taste" and slight tingling in the fingers. The syndrome abated, along with his apprehension, in 7 min; whereupon a lively y.j. queen was induced to sting his forearm for 3 sec. Eight minutes later, the prodromal symptoms recurred, to be followed shortly by slight dyspnea, hoarseness and dry cough as well as moistness of

the palms and erythema of face and sclerae. However, the blood pressure dropped no lower than 124/70 and, without medical aid, recovery was complete by 18 min. This rather trivial response engendered by the y.j. queen wasp is listed for group B under $\pm$ adverse sequelae to sting test.

Although the outcome encouraged a year's trial with intermittent sting treatment as a means of maintaining immunity, reactions of BRI to wasps, especially y.j., were capricious, sharp hypotension and impaired consciousness resulting on two occasions whereas full tolerance for 2-min stings by three pols. was exhibited on others. In mid-1963 he was transferred to group C for injections of fluid y.j. venom. The 6-sac assignment was met by nine divided doses and elicited only a trivial focal response, as indicated in the table. One month later, an accidental encounter with a y.j. wasp gave rise to another borderline reaction, one of the seven reported for group C. Thirteen, and again 29, weeks after this episode, BRI completed a six-sac course of y.j. venom in the standard six endermal injections without incident. On both occasions his ophthalmic requirement had been found to be 0.9 sac/0.1 ml. With this evidence of acquired immunity, attempts will once more be made to transfer him to the simpler procedure of periodic stingings.

The third instance of a $\pm$ adverse development to sting test among members of group B arose in a woman, WE, who had interrupted a 3-year course of injections of whole body extract at her skilled allergist's suggestion because of undue local responses. Her history revealed that an innocuous sting by a y.j. had been followed by an alarming episode 10 days later when she had a second encounter. Massive urticarial eruption, scattered edemas, a sense of precordial constriction with palpitation and painful breathing promptly ensued. Ten months after her latest injection of whole body extract, her ophthalmic MRR was found to be 0.312 for pol. venom and 0.234 for y.j. venom. She then accepted our standard 6-sac course of fluid pol. venom in six injections without incident. After 13½ weeks she was challenged. Application of a male wasp caused apprehension with a consequent rise in blood pressure to 140/90 from the resting level of 110/80. This was again noted when the first y.j. worker wasp was permitted to sting her fore-

arm for 2 min 10 sec. Pressure had fallen to 130/90 before the second y.j. wasp was applied 20 min later. This insertion continued for 2 min and 25 sec. Four minutes after its completion, face and palms grew flushed and the sclerae became injected (see $\pm$ column for adverse responses to sting tests given group B). During the 18 min it took for the trivial reaction to abate spontaneously, frequent readings showed the blood pressure to be fluctuating between 118/82 and 132/80. The patient has since been maintained on intermittent sting therapy, the last interval being 8½ months, the number of wasps three. She tolerated 2 y.j. field-stings.

The remaining six original members of group B took the standard six-sac, six-injection series of injections of fluid pol. venom without incident, and tolerated fully their subsequent challenges with one to three lively, stinging y.j. workers. All were undergoing injection therapy for the first time. In addition to KI, whose transfer to group B from group A has been discussed, there was also a woman, GR, who likewise was transferred prior to sting test. This interlocutory course was given because 24 weeks had elapsed since her repository injection and the recent adverse response of KI to sting test had somewhat dampened our enthusiasm for emulsion therapy. GR exhibited full tolerance not only toward the standard endermal series of injections given her as a new member of group B, but also toward the challenging y.j. wasp employed 6 weeks later. She has been under intermittent sting therapy ever since, having shown no adverse sequelae despite the use of three pol. queen wasps or y.j. workers at intervals that have reached 6½ months. Indeed, the only persons among the 11 participants of group B who are not on this type of maintenance therapy are two boys, aged 6 and 12 years.

One might summarize the results of group B by stating that the fluid pol. venom provided a highly satisfactory degree of resistance toward subsequent challenges with y.j. wasps within as short a period as 9 days and after as great an interval as 19 weeks. Taken together with the findings of group A, these data indicate that pol. venom served as a satisfactory substitute for homologous venom in y.j. allergy.

As to the control group C, there were a number of sources of data for the 6-sac, once-a-year course of homologous venom. Sixty-five such

treatments had been given 22 members of group A before they joined the repository experiment of 1960-1961, and some of their primary courses dated back to 1956. The table reveals that only three trivial focal reactions and one mild adverse response were engendered by their injections, all in persons whose earlier field episodes had been associated with undetectable pulse and blood pressure, as well as complete or borderline unconsciousness. In addition to the common cutaneous and circulatory developments, one gave a presenting history of concurrent asthma, acute vomiting and abdominal colic, as well as subsequent pain and stiffness of the joints. His focal response to the 6-sac, six-injection primary course consisted of facial erythema, slight edema of the uvula, mild dyspnea and headache, all of which yielded to an oral antihistamine. Ten days after this + reaction, his response to a male wasp application was negligible, whereas the 2½-min sting of a y.j. worker led in 4 min to suggestive flushing, slight headache and malaise, all but the latter abating within 33 min—a ± reaction in the table. After tolerating fully the routine endermal course of y.j. venom in 1960, he exhibited similar acceptance of a single repository injection in 1961, as a member of group A. The sting test reaction of this man, SCH, 6 months later was also negative. He has since been maintained on intermittent stings, having tolerated most recently three y.j. stings after interruption of this type of therapy for 14 months.

The trivial response of KI to one of his sting tests as a member of group C has been mentioned above. The third instance of a minor reaction was encountered in SAU, a young man with a history of prolonged unconsciousness after a field sting, who exhibited full tolerance toward both therapy and challenge as a member of group A, but who had manifested, on one occasion after his many yearly y.j. courses, transitory flushing and headache during a sting test. Of the remaining 35 courses available for analysis in group C, one given BRI has already been discussed, while 23 others received by four men in the usual six injections engendered no adverse signs. The recipients, as Table I shows, proved to be clinically immune, with two trivial exceptions, to planned and accidental stings they experienced on eight occasions. The final 11 courses involved in group C were primary treatments given in 1961-1963. Three trivial focal reactions followed.

When, 2 to 21 weeks later, challenges were made in 10 persons with two or three lively stinging y.j. wasps, eight showed full tolerance, one manifested slight flushing, and one caused considerable concern. The latter's case will be briefly presented.

SI had been stung on three occasions in the summer of 1962 by single pol. wasps, the first two proving innocuous. The third sting, inflicted over the jugular vein, caused weakness and sweating within a few minutes but yielded promptly to parenteral epinephrine. The following August, two y.j. wasps attacked his wrist as he was brushing dozens of them from the person of a youthful gardener who had dug into their nest. Although the wrist remained inflamed for 1½ days, there were no other developments for 10 days. At this time, a syndrome resembling acute serum disease appeared: marked urticaria not only at the sting sites but over most of the body, including the genitalia and anus, along with dysuria and with marked obstipation due to rectal edema. Within a few hours there ensued numbness of the fingers, sciatic pain, pectoral tenderness, dyspnea, anorexia, tender adenopathy of the cervical chains, and fever. Despite overwhelming exhaustion, he walked to a local emergency hospital where injections of Benadryl and epinephrine failed to abolish the urticaria and edemas. Seeking further help, he received adrenocorticotrophic hormone (ACTH) and intensive prednisone therapy by mouth, and improvement began in 24 hr. At 56 hr, he underwent a profuse diaphoresis which left him much improved. Indeed, 3 days later he stopped all medication and returned to work. Two days thereafter he was tested with diluted y.j. venom to reveal minimal responses to 0.312 sac/0.1 ml in the eye and to 0.001 in the skin. (Were these delicate tests responsible for a brief bout of focal hives that occurred 12 days later?)

Twenty-seven days after the 1963 stinging, SI took our standard six-injection, six-sac course of y.j. venom endermally, with only transitory flushing of the face and pruritus of the scalp. He submitted to sting test 6½ weeks later. There was the usual slight elevation in pulse rate and blood pressure during the application of a male wasp. Similarly, the first y.j. worker wasp elevated the pressure to 150/96 from a preliminary level of 140/84 during her 2-min insertion. After 20 min, another 2-min sting which involved two

punctures was inflicted higher on the forearm. Thirty seconds later he reported he felt dizzy, faint and flushed. No pulse or blood pressure could be obtained. Injection i.m. of 0.3 ml 1:1000 epinephrine HCl and 2.5 mg of phenylephrine HCl shortly provided a palpable pulse and subjective improvement. Within 9 min the blood pressure was 98/58, returning to the starting level of 140/70 by another 10 min. An additional hour was devoted to the restoration of the erect posture, the patient then being dismissed. Although he failed to lose consciousness at any stage of the shock reaction, the adverse response has been listed under the +++ column of Table I. On the 5th day there was mild recurrence of his "serum disease," scattered hives arising at sites of earlier skin tests for 2 days while the second sting area itched, reddened and vesiculated recurrently for 11 days.

Three weeks later, encouraged by the fact his ophthalmic MRR had risen nearly 3-fold from its original and also its pre-sting level of 0.312, SI was advised to undergo another challenge with y.j. wasps. Although he was apprehensive, his only adverse developments were facial flushing and heightened blood pressure to 158/96 after the second 2-min sting. Furthermore, he exhibited full tolerance to challenges by three pol. queen wasps 10 and then 13 weeks thereafter, also having no difficulties when attacked by a wild y.j. wasp 3 months later. Nevertheless, when sting tested 7 weeks after the field encounter, he promptly went into shock. His future management therefore poses a problem.

To summarize findings for this large control group C, there were seven trivial adverse reactions and one + focal response during 100 courses of fluid y.j. venom. When live wasps were encountered 1½ to 24 weeks later, usually in the hospital but occasionally in the field, 29 stings received by 33 persons on 37 occasions were fully tolerated, seven evoked trivial focal signs, and one brought a near loss of consciousness. As with the single significant adverse response to sting test in groups A and B, this exceptional shock reaction in group C was followed by full acceptance of stings on several occasions (only to recur very recently). In any case, the failure of KI after polistes-emulsion therapy seems amply counterbalanced by the failure of SI after homologous venom treatment, thus permitting the deduction that some factor other than speci-

ficity difference between pol. and y.j. venom was probably operative.

Tests of eye and skin. Although space forbids detailed presentation of test end points, the urgent need of allergists for some objective clue to patient-tolerance before treatments and sting testing justifies a brief synopsis of results. Prior to their yearly courses, 28 members of groups A, B or C who were tested by instillation on 99 occasions gave minimal responses to strengths that ranged from 0.078 to 2½ sacs/0.1 ml, a span of six tubes in our series of doubling dilutions, the median value being 0.97 sac. The corresponding figures for the endermal procedure ranged from 0.00003 to 0.156 sac (12 tubes) with a median value of 0.006. The relationship of these reactivities to subsequent tolerance for parenteral antigen was hard to judge because of the paucity of adverse reactions—only two significant ones to therapy and two more to sting test. It was noted, however, that the current requirements during skin and eye tests fell below those of the group as a whole. The MRR of BRI, for example, was 0.00007 for the skin and 0.156 for the eye just prior to his ++ reaction to injections of fluid pol. venom, while SCH showed end points of 0.00014 and 0.625 on the day of his + adverse response to fluid y.j. venom therapy. Similarly, the shock response of SI to sting rest was associated with a preliminary conjunctival MRR of 0.312, unchanged from the original pretreatment value and in contrast to a determination of 0.9 at a time when full tolerance was later exhibited toward two y.j. stings.

In summary, endermal and ophthalmic tests done *before* therapy reveal the intensity of allergy and thus the likely tolerance of the patient for parenteral antigen. *After* therapy, the requirement for the threshold response is usually heightened. Presumably this increase rests on the acquisition of blocking antibody, known to result from specific immunization in pollen hay fever (2) and in venom allergy (3), and distinguished from reagin by its failure to be inactivated by mercaptoethanol as well as by its sedimentation rate (6). (Whereas blocking antibody for venom was associated with 7 S components during gradient ultracentrifugation, skin-sensitizing activity moved at a rate intermediate between 7 S and 19 S.)

Comment. Having established that pol. venom serves to cross-protect y.j. allergic patients, it

will be of interest to reverse the experiment, and such studies are under way.

Acknowledgments. The authors are indebted to Mrs. Gertrude Zisowitz and Mrs. Jean Stein for technical and secretarial assistance and to Dr. Milton Zisowitz for editorial help.

SUMMARY AND CONCLUSIONS

1. Twenty-four persons with extreme allergy toward yellow jacket wasp stings were immunized safely with single, yearly, subcutaneous repositories of emulsified heterologous venom from the polistes wasp, there being no significant adverse developments on treatment day and no longterm sequelae such as abscess, cyst or neoplasm in the next 3 to 4 years. By contrast, control groups with identical allergy exhibited two adverse responses among 111 single-visit courses of fluid venom prepared from the homologous wasp or from polistes wasps.

2. Effectiveness of therapy was judged by the clinical response to later stings, of which 60 took place by plan in the hospital and four in the field by accident. Aside from trivial focal developments in 12 instances, only two significant adverse episodes were engendered, one in a repository-treated man and one after an immunization with homologous fluid venom. Subsequent repetition of the challenge found both men fully tolerant, one having taken a booster of fluid polistes venom in the meantime while the second merely rested. It was deduced that factors other than specificity differences in the two immunizing venoms probably had been responsible for the clinical failure after repository.

The 64 challenges involved one to four insects and post-treatment periods that ranged from 9 days to 21 weeks for courses of fluid venom, and from 15 to 27 weeks for depot therapy.

3. All but a few of the sting tested subjects have been transferred to intermittent sting-therapy to maintain their demonstrated immunity and are now receiving 2-min stings from 3 to 4 wasps—polistes in cold months, yellow jacket wasps in summer—at intervals approaching a year.

4. Threshold tests of skin and eye may afford a clue, before immunization, to the patient's tolerance for injected venom. After therapy, there is a small but statistically significant elevation in requirement, due to induced blocking antibody.

5. As to the indication for specific prophylaxis in sting allergy, probably only those victims whose next encounter threatens disaster merit immunization, in view of the implied long-term risk of using foreign proteins parenterally. Obviously, only the simplest preparations and the smallest effective amounts are justified in any case, *viz.*, venom as opposed to whole body extracts, and a single annual treatment as opposed to weekly and monthly injections over protracted periods.

REFERENCES

1. Loveless, M. H., *J. Immun.*, 89: 204, 1962.
2. Loveless, M. H., *J. Immun.*, 79: 68, 1957.
3. Loveless, M. H. and Fackler, W. R., *Ann. Allerg.*, 14: 347, 1956.
4. Loveless, M. H., *Fed. Proc.*, 21: 271, 1962.
5. Loveless, M. H., *New York J. Med.*, 62: 3563, 1962.
6. Rockey, J. and Loveless, M. H., Unpublished studies.