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Allergy to Hymenoptera Venoms

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I. HUMANS AND HYMENOPTERA VENOMS

Consistent characteristic attitudes of North American residents towards insects are (1) ignorance about them, (2) fear or dislike of them, and (3) a desire to avoid them or to kill them on sight (Olkowski and Olkowski, 1976; Byrne *et al.*, 1984). Such statements might appear to be an unusual introduction to a chapter on human allergy to Hymenoptera venoms. In actuality, however, the problem of venom allergy is twofold: the overt physiological consequences of venom hypersensitivity (allergy) and the more subtle psychological aspects of insect venom hypersensitivity. The latter is undoubtedly the much more difficult problem and the one which ultimately has the greatest impact on the lives of most people. Previous reviews of venom

hypersensitivity were primarily by medical researchers whose entrusted roles are to discover medical solutions and save lives (Lichtenstein *et al.*, 1979; Reisman, 1983). Good progress has recently occurred in understanding the immunological causes of venom hypersensitivity and, especially, in how to prevent sensitive individuals from having future reactions. Unfortunately, the psychological aspect of venom hypersensitivity has received very little attention by the medical profession. In this paper the psychological as well as physical, clinical, and immunological aspects of Hymenoptera venom hypersensitivity will be discussed. The goal is to provide the reader with enough information to understand the phenomenon of hypersensitivity and to allow him/her to make rational decisions based on this knowledge.

II. STINGS AND STATISTICS

Adverse reactions to stings from Hymenoptera (bees, wasps, ants) arouse great interest and attention in both lay and medical people. Unfortunately, discussion and treatment of sting reactions often occur with little regard for, or appraisal of, the actual medical (i.e., physiological) risks, if any, resulting from the envenomation. Thus a discussion of the actual risks of death from Hymenoptera stings and the causes of those deaths is in order.

Death rates in the United States from various selected causes are presented in Table I. The top two causes in this list, smoking and alcohol, constitute 13% of all causes of death and are preventable. Other major causes including motor vehicle accidents, diabetes, handgun deaths, etc., could also be reduced by appropriate action and habits. Deaths resulting from Hymenoptera stings are very minor, being only 40 per year or $\sim\frac{2}{1000}$ of 1%. Familiar causes of death that are more important than Hymenoptera stings include drowning, 125 times more frequent than sting deaths; home fire deaths, 100 times more frequent, and fatal falls, 12 times more frequent. Even lightning and (nonvenomous) animal accidents cause twice as many deaths as Hymenoptera stings. In fact, deaths due to Hymenoptera stings are so infrequent that they are listed under the category of 'deaths by venomous animals and insects (62 per year)' in the *Vital Statistics of the U.S., 1978* (1982).

Because most deaths from Hymenoptera stings are caused by dysfunctions of the body's immune system, asthma and penicillin allergy are also included in Table I. Both of these allergy–immune system-related causes of death kill many more people per year than venomous Hymenoptera. Perhaps surprisingly, penicillin allergy kills seven times more people than Hymenoptera venom allergy. The point of these statistics is that the risk of death from bee, wasp, or ant stings is exceedingly small, and if it were not for the great

Table I

Death Rates from Various Causes in the United States

Cause	Number of deaths/yr	Death rate per 1,000,000/yr	Percentage of total deaths	Reference
All causes	1,927,786	9639	100	[a]
Smoking	150,000	750	7.8	[b]
Alcohol	100,000	500	5.2	[b]
Motor vehicles	50,000	250	2.6	[b]
Diabetes mellitus	34,000	170	1.8	[a]
Suicide	27,000	135	1.4	[a]
Handguns	17,000	85	.88	[a]
Pedestrian-vehicle	8100	40	.42	[b]
Drowning	5800	29	.30	[a]
Fire in home	4500	22	.23	[a]
X-rays	2300	12	.12	[b]
Asthma	1900	8.5	.098	[a]
Bicycles	760	3.8	.036	[a]
Freezing	650	3.2	.034	[a]
Falls (tripping, slips, etc.)	480	2.4	.025	[a]
Penicillin allergy	300	1.5	.016	[c]
Animal accidents	105	.52	.0054	[a]
Lightning	98	.49	.0051	[a]
Hymenoptera stings	40	.20	.0021	[d]
Scholastic football	23	.12	.0012	[b]

[a] *Vital Statistics of U. S., 1978* (1982).
[b] Upton (1982).
[c] Idsoe *et al.* (1968).
[d] Parrish (1963); Barnard, (1973).

psychological effects of these deaths, insect stings would be an almost ignored and unheard of cause of death.

The incidence of hypersensitivity to stings of Hymenoptera is considerably greater than the incidence of death from such stings. Within the general population, true systemic hypersensitivity rates are reported to vary from about 0.15 to 4.0% (Settipane and Boyd, 1970; Chafee, 1970; Abrishami *et al.*, 1971; Settipane *et al.*, 1972; Herbert and Salkie, 1982; Golden *et al.*, 1982b; Zora *et al.*, 1984). If a United States population of 225 million and a known hypersensitivity rate of 2% is assumed (lowest estimate projected by D. B. K. Golden, personal communication), 4.5 million United States inhabitants are actually hypersensitive to stings of bees, wasps, and/or ants. Simple arithmetic yields the figure that for every 112,000 known hypersensitive people, only one actually dies each year as a result of that hypersensitivity. Thus, the realistic threat of dying from a sting is exceedingly small, even for those truly hypersensitive to insect stings. In fact, the chances of dying in an automobile accident while en route to a hospital following a sting may be greater than the chances of dying due to the sting (Rubenstein, 1980).

The economics of medical treatment for bee, wasp, and ant venom hypersensitivity can be rather startling. The current cost per year for venom immunotherapy ranges from 300 to 1000 United States dollars per patient (Lockey, 1980; Rubenstein, 1980) and is likely to be recommended for life. Thus, if a patient begins treatment at age 20 and lives to age 70, he will have spent $15,000–$50,000 on his treatments alone. Assuming an intentionally low estimate that 25% of hypersensitive individuals are life-threateningly hypersensitive (exhibit unconsciousness or respiratory distress) and that only those individuals are given immunotherapy, then 28,000 people receive the treatment for every fatality. Thus, assuming that immunotherapy could prevent all deaths, treatments would cost somewhere between 8.4 and 28.0 million United States dollars per life saved. That is assuming that all deaths could be prevented, a gross exaggeration: the probable actual immunotherapy preventative success rate is no more than 15% (Rubenstein, 1982; and author's impressions based on discussions at allergy meetings) (there are no published estimates of the numbers of deaths prevented by immunotherapy). On top of this cost, during the first weeks of therapy, immunotherapy may actually enhance the risk by increasing the immunoglobulin E (IgE) levels before they are reduced, thereby leaving the individual more vulnerable at that time than before treatment (Lichtenstein *et al.*, 1979).

The actual causes of death in cases of Hymenoptera sting fatalities provide insight into the pathology of the problem and how it can be handled medically should a life-threatening situation arise. The etiology based on autopsy reports of 150 sting-induced deaths is presented in Table II. Seventy percent of these

Table II

Cause of Death following Hymenoptera Stings[a]

Cause of death	Total deaths		Time to death (hr)					Age at death (years)	
	Number	%	<1 %	1–6 %	6–96 %	>96 %	Unknown %	<50 %	>50 %
Respiratory	105	70	46	13	4	1	7	75	63
Anaphylaxis	22	15	9	3	1	0	1	13	17
Vascular	14	9	2	4	1	2	0	4	17
Neurologic	9	6	1	0	1	4	0	8	3
Total	150	100	58	20	7	7	8	100	100

[a]Data from Barnard (1973) and unpublished report of Committee on Insect Hypersensitivity of the American Academy of Allergy (1984).

deaths are caused by respiratory failure, usually in the form of massive, often epiglottal, secretions, and/or edema which results in fatal obstruction of the air passages. Anaphylactic shock, though second in importance, is much lower in incidence than respiratory blockage. Anaphylaxis is characterized by vascular engorgement, hyperemia, edematic congestion of internal organs, excess secretions, and/or alveolar rupture or emphysema of the lungs. Vascular causes of death include coronary occlusion, generalized hemorrhage, extracardial infarction, etc. Atherosclerosis is a major contributing factor in many deaths (Barnard, 1967, 1973; O'Connor *et al.*, 1964). Neurological causes of death are the least frequent of the major categories and are typified by requiring days to weeks for death to occur (Barnard, 1973).

A second striking feature of deaths following stings is the rapidity of death: 58% die in less than 1 hr and over three-fourths die within 6 hr (Table II). This is in marked contrast to the times of death for fatal envenomations from snakes, spiders, scorpions, and even massive Hymenoptera envenomations that cause death via direct poisoning (Parrish, 1963; Ennik, 1980). The right side of Table II lists the percentages of deaths for each of the four categories according to age of victim. The notable difference between the various ages is that those over 50 years of age more frequently die due to vascular causes, a finding supporting the contribution mentioned above of atherosclerosis in causing death.

The correlation between age of victim and death exhibits a distinct skewness toward death in mid- to late life (Table III). Of over 1000 deaths recorded mainly from the United States only 2% occurred in children under 10 years of age, about 7% occurred in the under-20-year age group, about one-quarter occurred in people under age 40, and about half occurred in individuals older than 50 years. The increased risk of sting-induced death with age becomes even more clearly evident when the death rates for age groups are compared with the populations in those age groups (Table III). The conclusion that emerges is that death from stinging Hymenoptera is most prevalent in the over-40-year age group whereas it is very infrequent in children.

Like venom allergy, atopy (asthma, hay fever, chronic rhinitis) is immunologically mediated. A reasonable question particularly relevant to the psychology of allergy to bee, wasp, or ant venoms is the relationship between atopy and venom hypersensitivity. The reason for seeking the answer is logical: is an atopic person more susceptible to venom hypersensitivity than a nonatopic person? The normal incidence of asthma and rhinitis is ~25% (see Settipane *et al.*, 1978). When venom hypersensitivity patients are analyzed for incidence of asthma and/or rhinitis, respective values of 13, 14, 22, 25, 26, 27, 41, and 41% are reported (Settipane *et al.*, 1972, 1978, 1980; Huber *et al.*, 1983; Kailin, 1961; Insect Allergy Committee, 1965; Schwartz and Kahn, 1970; Barr, 1974). Despite the variety of techniques and patient groups

Table III

Ages of Death of Victims of Hymenoptera Stings and the Relative Risk of Death from Stings for Various Age Groups

Age at death	Earlier reports[a] (% deaths, n = 343)	Nall (1985)[b] (% deaths, n = 677)	Percentage United States population in age bracket	Relative risk compared to the >50 year group
3–10		2	13.3 (1–9 yr)	.08
0–20	6.7	50	32.9	.11
20–40	20.1		30.8	.35
40–50	23.3		10.4	1.19
>50	49.9	48 (51–75 yrs)	25.9	1

[a]Combined data of Jensen (1962), Parrish (1963), Somerville *et al.* (1975), and Ennik (1980).
[b]Report includes the data of Barnard (1973).

in these studies, the conclusions are that hay fever (rhinitis) or asthma do not predispose one to venom hypersensitivity. When people with asthma or rhinitis are compared to nonatopic people, the same incidence, 0.8–0.9%, of venom hypersensitivity within the two groups is obtained (Settipane *et al.*, 1972). Thus, the evidence suggests that a history of other allergies in no way predisposes a person to venom hypersensitivity.

Although asthma does not predispose a person to venom hypersensitivity, individuals who have asthma and also develop hypersensitivity to Hymenoptera venoms generally have more severe reactions than those without asthma (Settipane *et al.*, 1978, 1980). Moreover, atopic individuals who become hypersensitive also develop their hypersensitivity at a significantly younger age than those without atopy (Huber *et al.*, 1983), though the fact that atopics might frequent the offices of allergists more than individuals without atopy and therefore have their venom hypersensitivity diagnosed earlier cannot be ruled out. Asthmatic individuals appear to have more severe venom hypersensitive reactions than nonasthmatics mainly because they are less able to withstand challenges to the respiratory system resulting from venom hypersensitivity. Hence their air flow may be more severely restricted. To exacerbate the situation further, asthmatics also suffer a higher rate of intolerance to allergy shots than nonasthmatic individuals (H. S. Rubenstein, personal communication).

One final little-studied feature of hypersensitivity to Hymenoptera venom is the high incidence of penicillin intolerance (allergy) among this group. Individuals hypersensitive to venoms also have a penicillin allergy rate of 10 to 11% (Kailin, 1961; Brown and Bernton, 1970), a figure much higher than that of the general public (Idsoe *et al.*, 1968). The causes of this correlation are unknown.

III. PSYCHOLOGICAL ASPECTS

Hypersensitive reactions after a bee, wasp, or ant sting are terrifying, but, as shown in the previous section, extremely rarely fatal. Nevertheless, an almost uncontrollable fear, often referred to as morbidity, that the next sting likely will cause death is present in much of the public. For example, Chipps *et al.* (1980) reported that 80% of the parents of children with systemic reactions to stings believed their child would be at risk of death after a subsequent sting. This fear is strong and is so unresponsive to change that 35% of the parents continued to believe that a modified life style was necessary to avoid future stings, even when immunotherapy followed by an uneventful actual sting demonstrated the child was no longer reactive (Chipps *et al.*, 1980).

Uncontrollable public fear of insects, especially those perceived as being able to sting, is very common (Crane, 1976; Olkowski and Olkowski, 1976; Stoner and Wilson, 1977). In fact, the problem is so great that the term 'entomophobia' has been coined to describe the phenomenon of irrational fear of insects (Olkowski and Olkowski, 1976; Keh, 1983). Entomophobia of buzzing, flying insects that may resemble bees or wasps is particularly severe. At least one case was reported in which a man died of fright on the mistaken belief that he had been stung (Crane, 1976). Another man yelled, 'I am going to die', after receiving two stings and died within 15 min (McCormick, 1963), quite possibly either of fright or with fright being a major contributing factor. Rubenstein (1982) discusses further the medical potential of fright causing death in such situations.

Fear, albeit generally irrational, of stinging insects is real, will not easily go away, and must be given serious consideration whenever venom hypersensitivity is discussed. In the great majority of instances, venom hypersensitivity is really more of a psychological problem that should be handled by psychiatrists, psychologists, physicians, therapists, friends, and associates than a medical (physiological) problem. To understand why this morbidity of stinging insects is so prevalent, some biological background is necessary.

Hymenoptera stings hurt. They hurt because natural selection has operated on stinging insects to produce venoms that are maximally effective for defending themselves and their nests (Schmidt, 1983). Painfulness, rather than acute toxicity, is more useful in this context because it provides the attacker (potential predator) immediate feedback that it has been injured or will soon be injured. Whether damage actually occurs as a result of the sting is not crucial; the animal receives the message of pain (the body's early warning system that damage has occurred, is occurring, or is about to occur) and often responds by leaving the hymenopteran alone. Thus, it is not surprising that people associate sting pain with real personal danger—natural selection on both humans and Hymenoptera has resulted in that situation.

Another psychological aspect related to venom hypersensitivity is that stings by Hymenoptera are real, visceral experiences that are in no way esoteric. For this reason, people readily perceive and 'understand' their potential threat. Less immediate, less concrete, and more intuitive threats, such as the dangers of smoking, alcohol, or sugar- and fat-rich diets, are not readily learned and internalized to the extent of causing major behavioral changes in the person. Thus, although these latter threats to life are many thousands of times greater than Hymenoptera stings, because of the manner they are experienced by the public, they are esoteric and cause much less emotional concern than stings.

There is one further characteristic of Hymenoptera that causes fear in people. The very survival of the human species has depended on successfully recognizing and avoiding predators and other threatening animals. This fear and avoidance is why a human death by a bear, crocodile, shark, or even a wasp attack commands so much more attention than does a death by allergy to penicillin, by consuming too much alcoholic spirits, or by being hit by an automobile. We are, so to speak, biologically programmed to fear the former, but not the latter causes of death. This in large part explains why individuals are so preoccupied with a fear of stinging Hymenoptera.

IV. HISTORICAL PERSPECTIVES

One way to understand the current status of medical treatment for envenomation-related problems, how they developed, and why they are in their present state, is to study the historical development of medical attention to allergy of Hymenoptera venoms. Until modern times the emphasis on venom hypersensitivity consisted almost entirely of reports of mysterious deaths of individuals by one or a few stings. The first recorded such death is that of King Menes of Egypt 4600 years ago from an apparent wasp sting (Waddell, 1930). The next major event, which subtly affected the development of later theories on venom hypersensitivity, was the discovery that ants in the genus *Formica* contained venom composed mainly of formic acid (Wray, 1670) (see Chapter 1). Unjustified extrapolations from that discovery initiated the misconception that Hymenoptera venoms in general contained formic acid, a material that is not antigenic. This misconception by medical specialists, who are not generally knowledgeable in insect or toxinological literature, slowed progress in understanding the cause of venom hypersensitivity.

The term *anaphylaxis* was coined in 1902 as a description of the phenomenon whereby an animal reacts with enhanced sensitivity to a toxin previously administered, usually ending in death (Portier and Richet, 1902). Waterhouse (1914) correlated the unusual human reactions to the venom of bees with the experimental induction of anaphylaxis in animals. The first therapeutic use of this knowledge was by Braun (1925), who successfully demonstrated that a hypersensitive person could be desensitized by administering over time increasing doses of venom (homogenate of the terminal one-eighth inch of a bee's abdomen). He also illustrated the use of epinephrine as the best means to control anaphylactic reactions. His treatment embodied the essentials currently used in immunotherapy (desensitization).

Clinical treatment of venom hypersensitivity increased dramatically after a landmark paper by Benson and Semenov (1930) in which they desensitized a patient allergic to both bee venom and bee body proteins. This combination of dual sensitivities was unfortunate because it set the precedent for the belief that patients were allergic to body protein contaminents in the venom and that an extract of the *entire* body of the bee was the extract of choice for immunotherapy. This conclusion was not totally inconceivable based on the data at hand (Benson, 1939), although the equally reasonable and subsequently demonstrated conclusion of dual occurrences of separate allergies to venom and to body parts was not pursued further. This work ushered in the era of whole body extracts for desensitization, which lasted until nearly 1980.

Part of the reason whole body extracts remained so popular until the 1980s was their apparent effectiveness, their ease of preparation, human nature and the placebo effect, and the natural etiology of the disease. The report of the Insect Allergy Committee (1965), representing the most esteemed and respected elements of the allergy profession, gave glowing figures to document the successful use of whole body extracts. For example, of 574 patients with systemic reactions to venom and who had been given whole body extract immunotherapy, 89.7% had better, 6.1% the same, and 4.2% worse reactions to a sting than they had previously. Moreover, of 624 untreated patients, only 0.1% had better reactions and 22.8% the same, while 68.1% had worse reactions. This clear-cut success of the whole body extract (see also Coleman *et al.*, 1975) was considered the general rule by the vast majority of allergists (Barr, 1971; Mueller, 1981).

Human factors were also involved in the success of whole body extract immunotherapy. People naturally appreciate a physician's concern for their problems and when receiving medical attention, often adopt an optimistic or hopeful approach to the problem. Thus, even if their actual reactions may not be better, they want them to be better and may inadvertently report them as such. This is the all-too-familiar placebo effect. In the early years of investigations using whole body extracts or venom preparations, this placebo effect was not taken into account. Loveless (1957) recognized this problem in cases of pollen allergies where many patients responded to placebos as well as to the treatment. Nevertheless, 'wishful thinking' as a factor in treatments with whole body extract was not seriously considered until much later.

The last factor contributing to the perception that whole body immunotherapy was successful is the natural etiology of venom hypersensitivity. Studies such as that of Brown and Bernton (1970) indicated that stung patients not treated with immunotherapy were as protected as those

that were treated; both groups had a 93% protection rate against systemic reactions. Or put another way, only 7% of either group reacted with systemic reactions. This study, like almost all other studies, had nonrandom elements entering into the results and these could be used to explain the unexpected findings. Settipane and Chafee (1979) also reported in nontreated patients that only 12.6% of patients had worse reactions to subsequent stings. They cite several other studies indicating the low incidence of worse reactions in nontreated people who are restung and point out the important fact that people who experience worse reactions are likely to seek continued medical attention while those with improvements generally are not seen by the physician. Hence, studies based on clinical lists are likely to be biased in favor of people whose subsequent reactions were as bad as or worse than the first. There is much debate concerning the actual percentage of patients who spontaneously become less sensitive, but there is little debate that the figure is high and probably contributed in large part to the impression of the apparent successful immunotherapy with whole body extracts.

During the height of whole body extract usage for immunotherapy, one physician, Dr. Mary Loveless, dissented and believed venom was better than whole body extracts. She reasoned that since only venom proteins are injected, then venom proteins are the logical allergens. She treated patients successfully from the early 1950s through the mid-1970s using pure venoms (Loveless and Fackler, 1956; Loveless, 1977), yet received very little serious attention. This may have been because she used what appeared to be unorthodox procedures, because she never performed a well-designed double blind test of venom versus whole body extract for immunotherapy, and because there was no affordable technology for production of vespid venoms.

The incidence of fatal failures of whole body extract (Torsney, 1973) initiated further thought in other research teams along the lines pursued by Loveless. First, whole body extracts were confirmed to be no better than controls for detecting hypersensitivity to Hymenoptera venoms and that venoms or venom sac extracts were effective (Schwartz, 1965; Sobotka *et al.*, 1974; Zeleznick *et al.*, 1977). Then, whole body extracts were demonstrated to be no better than a placebo for immunotherapy treatment of hypersensitive patients, whereas venom sac extract was effective (Busse *et al.*, 1974; Hunt *et al.*, 1978). A debate briefly ensued in the literature concerning the merits of whole body extracts versus venom sac extract, but the mass of evidence now supports the greater effectiveness of sac extracts and the small or lack of effectiveness of whole body extracts for treating venom hypersensitivity symptoms. This is the current state of affairs: venoms and venom sac extracts clearly can reduce the clinical reactions to stings in probably 95% + of patients receiving immunotherapy. These treatments also clearly reduce the psychological morbidity (that is, the fear of fatality from

the next sting) associated with venom hypersensitivity (D. B. K. Golden and K. C. Schuberth, personal communication). One question remains to be addressed: does venom immunotherapy *actually* save lives, and if not, why is it being administered? The answer to the question is that immunotherapy should not be administered primarily to 'save lives'; rather, when administration is necessary, it should be mainly for the prevention of the mental and physical suffering that can accompany stings. Perhaps more explanation of this to the patient, more psychological assistance, and greater use of immediate treatment with epinephrine at the time of the sting would be a more economical and efficacious approach to a great many cases of venom hypersensitivity than immunotherapy.

V. MEDICAL CAUSES OF VENOM ALLERGY

Hypersensitivity to Hymenoptera venoms is an immunological process in which venom allergens react principally with cellbound IgE to induce massive release of histamine, leukotrienes (slow-reacting substances of anaphylaxis), prostaglandins, chemotatic factors, and a myriad of other factors (Wasserman, 1983). These factors then promote a variety of dermal, circulatory, respiratory, and anaphylactic reactions, among others. Although tissue damage resulting from allergic reactions is classified into four categories called Type I, or anaphylaxis, Type II, or cytotoxic, Type III, or Arthus and sermum sickness reactions, and Type IV, or delayed hypersensitivity, also called cell-mediated hypersensitivity (Wells, 1980; Frick, 1980), type I reactions are the usual forms in venom allergy. These reactions are often called 'immediate hypersensitivity' and are the most thoroughly investigated.

Type I hypersensitive reactions usually occur in response to stings subsequent to one or a few initial sensitizing stings. Until first exposed, the body has no venom-specific antibodies. After a sting, immunoglobulin G (IgG), the main blood-borne antibody, and sometimes IgE, the reagenic, or allergy-inducing antibody, are synthesized. Other classes of antibodies, IgM, IgA, and IgD, appear to play little overall role in venom hypersensitivity. IgE antibodies attach themselves to mast cells in the tissues and basophils in the blood, where they serve to activate those cells in response to contact with antigens. In the case of venom hypersensitivity, venom-specific IgE activates the cells in response to the venom proteins that were injected during the stinging process. The activiated cells then release the factors responsible for the reaction. Classes of antibodies other than IgE either do not attach to mast cell and basophil membranes or do so with less avidity (Ishizaka, 1982; Aalberse *et al.*, 1983; Perelmutter, 1984). At present, IgE is believed to be the antibody solely responsible for causing allergic reactions, though

the exact role, if any, of subclass four IgG (IgG_4) in allergy is being debated (Nakagawa, *et al.*, 1981; Cheung *et al.*, 1983; Perelmutter, 1984).

Why some people are susceptible to venom-induced allergic reactions and others are not is not well understood. Genetics do appear to play a role in that some families show greater tendencies to develop hypersensitivity than others. A great deal of information concerning the mechanisms of venom allergy has been forthcoming, but we are still far from a complete understanding. Complete understanding would be desirable in that we could then predict those people at risk and treat only them. So far, we are nowhere near that point and probably will not be for some time; for that reason the medical approach has tended toward recommending treatment of all cases exhibiting severe systemic reactions under the unproven assumption that these symptoms portend possibilities of future fatal reactions.

Current research indicates that the primary immunological factors in venom hypersensitivity are IgE, the antibody responsible for triggering the reactions, and IgG, often called the blocking antibody, which probably plays a major role in suppressing the IgE-mediated symptoms. Space here does not permit a detailed presentation of the findings pertaining to these two antibodies and venom hypersensitivity, but numerous reports address that question (Urbanek *et al.*, 1980, 1981, 1983; Nakagawa *et al.*, 1981; Golden *et al.*, 1982a; Aalberse *et al.*, 1983; Cheung *et al.*, 1983).

VI. BIOCHEMISTRY OF VENOM ALLERGENS

The venoms of all stinging social Hymenoptera are probably capable of inducing human allergy. The major offending species include the yellow jacket wasps of the genus *Paravespula* (often called *Vespula* subgenus *Parvespula* in the United States), honeybees (*Apis mellifera*), the white-faced hornet and yellow hornet (*Dolichovespula maculata* and *D. arenaria*) and other members of their genus (which are actually aerial yellow jackets, not true hornets), paper wasps (*Polistes*), and the true hornets (*Vespa crabro, V. orientalis, V. mandarinia*, etc.) (Parrish, 1963; Brown and Bernton, 1970; Barnard, 1973; Barr, 1974; Ori and Hiyama, 1977). Other species less frequently inducing allergy are fire ants (*Solenopsis* spp.) and harvester ants (*Pogonomyrmex* spp.) (Schmidt, Chapter 9), bumblebees (*Bombus* spp.) (Donovan, 1978; Hoffman, 1982) and sweat bees (Halictidae) (Pence *et al.*, 1985). These Hymenoptera all possess antigenic proteins that, when injected during the stinging act, can become allergens. The biochemistry of nonallergenic components in these venoms will not be discussed in detail here and the reader is referred to reviews in this volume as well as those by Schmidt (1982) and Bettini (1978).

The major allergen in honeybee venom appears to be phospholipase A_2 (King *et al.*, 1976; Kemeny *et al.*, 1983; Nordvall *et al.*, 1984; Wahn *et al.*, 1984). Hyaluronidase (Hoffman and Shipman, 1976; King *et al.*, 1976; Kemeny *et al.*, 1983; Wahn *et al.*, 1984) and acid phosphatase are also important allergens (Hoffman, 1977; Kemeny *et al.*, 1983; Wahn *et al.*, 1984). Melittin, though by far the major protein in honeybee venom, is only weakly antigenic (Mackler *et al.*, 1972; King *et al.*, 1976; Paull *et al.*, 1977; Kemeny *et al.*, 1983) and none of the remaining small peptides, including the neurotoxin apamine, have been found to be allergenic (Shkenderov, 1974; King *et al.*, 1976). Among vespid wasp venoms, phospholipase, hyaluronidase, antigen 5, acid phosphatase, Vmac3 and Vmac1 appear to be the major allergens (King *et al.*, 1978, 1983; Hoffman, 1978a; Hoffman and Wood, 1984). Antigen 5 is a nonenzymatic polypeptide of molecular weight 22,000–25,000 (King *et al.*, 1978, 1983; Hoffman and Wood, 1984). Bumblebee venom allergens appear to be similar to those of honeybees (Hoffman, 1982). In fire ant venoms phospholipase is known to be allergenic (Baer *et al.*, 1979) and other antigens were present, but quantities of material were too small for further determinations. At present, no allergens have been identified from harvester ant venoms, although they are known to possess numerous enzymatic activities including high levels of phospholipases A_2 and B, hyaluronidase, acid phosphatase, esterase, and lipase (Schmidt and Blum, 1978).

Many of the venom allergens have several features in common. They are all proteins, most are enzymes, and most of those analyzed have molecular weights in the range 15,000–50,000. For example, the major allergens of both honeybee and yellow jacket venoms are phospholipases with respective molecular weights of 15,000 and 34,000 (Shipolini *et al.*, 1971; Hoffman and Wood, 1984). Smaller peptides such as melittin, though weakly antigenic, do not appear to be major allergens. Moreover, with the exception of phospholipase, none of the strong allergens are known to have any profound toxic or pharmacological activities; that is, apamine, the neurotoxic honeybee peptide, the honeybee mast cell degranulating peptide (MCD-peptide), the mastolytically active vespid polypeptides (see Nakajima, Chapter 6), and even the direct hemolytic peptides of bees and wasps, and the pharmacologically active wasp kinins, appear to be weak or devoid of allergenic properties. The small, active amines in Hymenoptera venoms, including histamine, 5-hydroxytryptamine, acetycholine, dopamine, and norepinephrine, that are so important in causing pain and other reactions are also nonallergenic.

One property of venom allergens that appears to enhance the antigenic activity is the presence of a carbohydrate moiety on the proteins. Phospholipase from bee venom is glycosylated (Shipolini *et al.*, 1971), as

probably are the phospholipase, hyaluronidase, and antigen 5 of *Paravespula* venom (King *et al.*, 1983).

VII. CROSS-REACTIVITY BETWEEN TAXA

Virtually all Hymenoptera venoms contain phospholipase and hyaluronidase and many, including the honeybee, the vespids, and the harvester ants contain acid phosphatase. Since the Hymenoptera venoms appear to have the same enzymatic activities and since these enzymes are potent allergens, a natural a priori conclusion is that patients should be cross-reactive (cross-sensitive) to many Hymenoptera venoms. This phenomenon of species cross-reactivity versus species specificity has received considerable attention and is far from being resolved. As with most statements concerning venom hypersensitivity, only broad generalizations are possible. This is partly because individual patients who exhibit cross-sensitivity to several venoms may do so either because their immune system perceives the antigens of the different venoms as similar (true cross-reactivity) or because the patient was stung by both species and independently developed sensitivity to each (cf. Hoffman *et al.*, 1980). This issue is not easily resolved and not all individuals react the same. Some patients sensitive to one venom may be more likely to develop IgE antibodies to another venom if exposed. Also, in patients with dual reactions, two patterns have been observed: unique antibody sensitivity and sensitivity to a major antigen in one venom (e.g., yellow jacket) that cross-reacts with a minor antigen in another venom (e.g. honeybee, Reisman *et al.*, 1982).

The venoms within the paper wasp genus (*Polistes*) appear to be antigenically very similar when analyzed by RAST (radioallergosorbent test) or RAST inhibition using the sera of hypersensitive patients. There were, however, some allergenic differences among the venoms, but not enough differences to merit concern in terms of diagnostic or therapeutic use of the venoms (Hoffman and McDonald, 1982b). Similar results were obtained by Reisman *et al.* (1982) who found that patients tested RAST positive to one *Polistes* venom generally reacted positively to the venoms of the other species of *Polistes*. They observed some species differences in reactivity toward rabbit antibodies, confirming that the venoms, though allergenically similar, were not identical. Comparisons with venoms of other vespids led to the conclusion that the genus *Polistes* appears to have a genus-specific antigen as well as some antigens that cross-react with venoms of *Paravespula* and *Dolichovespula* (Reisman *et al.*, 1982). In an extensive test of *Polistes* sensitive patients whose sensitivities were analyzed by skin test, RAST and leukocyte histamine release

test, Grant *et al.* (1983) reinforced the previous conclusions. They found the reactions of their patients to the venoms of five species of *Polistes* to be nearly identical by all three tests. These same patients did not exhibit cross-reactivity to the venoms of *Dolichovespula, Paravespula*, or *Apis* to nearly the same degree.

The common yellow jackets in the genus *Paravespula*, like *Polistes*, possess venoms with close intrageneric allergenic similarity; though some differences, especially quantitative, among the venoms were observed (Wicher *et al.*, 1980; Hoffman and McDonald, 1982a; King *et al.*, 1983). *Vespula squamosa* and *V. sulphurea*, two yellow jacket species that are often combined by many North American systematists with *Paravespula* (they call all of them *Vespula*) exhibit antigenic differences from the *Paravespula* (Wicher *et al.*, 1980; Hoffman and McDonald, 1982a). These differences support the author's belief that the two groups are sufficiently morphologically, behaviorally, and toxinologically different that they merit taxonomic separation, a view not entirely opposed by some systematists (R. S. Jacobson, personal communication).

As in the vespids, the venoms of the two most studied species of fire ants (genus *Solenopsis*) appear to be highly similar allergenically and therefore cross-reactive (James *et al.*, 1976; Baer *et al.*, 1979). The same situation applies to the venoms of the harvester ants in the genus *Pogonomyrmex*. When analyzed, nine species within the genus were found to be antigenically very similar, if not identical, by RAST and RAST inhibition techniques (Schmidt *et al.*, 1984).

Based on the analysis of venoms from four different genera of Hymenoptera, the observation that venoms within a natural genus are very similar in their abilities to induce hypersensitivity in patients is emerging. This also appears to describe the situation exhibited by the venoms of a fifth genus, *Dolichovespula*, the aerial yellow jackets. Studies have revealed the rather close antigenic similarity of the venoms of *D. maculata* and *D. arenaria* (Kern *et al.*, 1976; Lowenstein *et al.*, 1980; Mueller *et al.*, 1981). This similarity of reactions to the two venoms by hypersensitive patients indicates that the practice of testing patients both for *D. maculata* (white-faced hornet) and *D. arenaria* (yellow hornet) is without justification. These two venoms are no more distinctive from each other than are the venoms from members within the *Paravespula* and could in practical terms be combined for diagnostic and therapeutic purposes. The two are currently considered separate mainly because of historical precedent. In the years when venom sac extracts for immunotherapy were being developed, *D. arenaria* and *D. maculata* were easily collected and visually separated and, since their allergenic relationships were unknown, they were considered separate. Now that their antigenic

similarities are known the two species could be combined for medical use, thus eliminating one of them from the battery of 'multivenoms' routinely used. This could achieve saving for both the physician and the patient.

The picture concerning the cross-allergenicity of Hymenoptera venoms becomes less well defined when venoms from different genera are considered. When purified antibodies to venoms from laboratory animals are obtained, the sensitizing venom antigens from different genera within the family Vespidae are often found to be different (Nair *et al.*, 1976; Reisman *et al.*, 1982). When vespid venoms are tested against hypersensitive patients, cross-reactivity among the venoms is rather frequent (Settipane and Carlisle, 1980; Hoffman, 1981; Schuberth *et al.*, 1982). This is true not only among the venoms within the subfamily Vespinae but also includes the venom of *Polistes* in the subfamily Polistinae. In the case of *Polistes* some reports cite a degree of genus specificity, whereas others cite extensive cross-reactivity with the *Paravespula* and *Dolichovespula* (Grant *et al.*, 1983; Hoffman *et al.*, 1980; Ramirez *et al.*, 1981; Schuberth *et al.*, 1982).

The least antigenic similarity of venoms is found between members of different families. The antigens from honeybee venoms and from yellow jacket venoms often appear to be different (Charavejasarn *et al.*, 1975; Nair *et al.*, 1976; Hoffman, 1978a; Hoffman and Wood, 1984). In the case of patient cross-sensitivity, the differences are not as distinct; nevertheless, patients sensitive to honeybee venom are frequently not sensitive to any of the vespid venoms or vice versa (Kern *et al.*, 1976; Hoffman *et al.*, 1980; McQueen *et al.*, 1980; Bousquet *et al.*, 1984b). Ant venoms have not been found to cross-react with venoms of either bees or vespids (James *et al.*, 1976; Pinnas *et al.*, 1977). Although a substantial number of patients react to both bee and vespid venoms (Hoffman *et al.*, 1980; Schuberth *et al.*, 1982; Hoffman and Wood, 1984; Reisman *et al.*, 1985), whether this arises as the result of cross-reactivity of venom antigens or by multiple sensitization by each of the species involved is not clear. Apparently, at least some of the multiple reactions are the result of cross-reactivity of venom antigens as demonstrated by Hoffman and Wood (1984) in a detailed study of chemically purified yellow jacket venom antigens. They discovered that sera from patients primarily sensitive to honeybee venom exhibited extensive cross-reactivity with all four of the least allergenic yellow jacket allergens, yet cross-reacted very little or none with yellow jacket venom phospholipase A, the major yellow jacket allergen. This finding might explain the previous results: individuals who are sensitive to both yellow jacket and honeybee venom are probably sensitive to one or more of the allergens of lesser importance (with or without sensitivity to phospholipase); individuals sensitive to only one venom are probably sensitive primarly to venom phospholipase.

In practical terms, medical treatment has taken the approach that if a patient is sensitive by skin test to only one venom, say that of the honeybee, only that venom is used for treatment; if the patient is sensitive to two or more venoms (for whatever reason), each venom is used in treatment.

VIII. REACTIONS TO HYMENOPTERA STINGS AND CLINICAL SYMPTOMS OF VENOM HYPERSENSITIVITY

The lay public, and to a lesser extent the medical profession, has confused normal and hypersensitive reactions to stings by Hymenoptera. The injection by Hymenoptera of venom causes pain and local symptoms around the sting, both normal reactions to the pharmacologically active components in the venom. Because the pain resulting from most stings is far greater than the actual physiological damage induced, the initial belief by many people that they are seriously threatened is not surprising. The difficulty arises in distinguishing between normal, albeit painful reactions, large local reactions, minor systemic reactions, and systemic reactions that are potentially dangerous. These types of reactions as well as those of beekeepers will be discussed.

A. Normal Nonimmune Responses to Hymenoptera Stings

The typical human response to a sting by a honeybee, yellow jacket, hornet, or paper wasp (*Polistes*) is intense, immediate pain with a burning sensation. This usually lasts for a few minutes, after which the pain subsides. A white wheal with a central red spot often forms soon after the sting, then rapidly fades. A red flare and some local swelling form around the sting site, which by this time is usually warm or hot to the touch. These symptoms subside and generally after a day or two all that remains is an itchy spot at the sting site.

Stings by the individual fire ants (*Solenopsis*) initially feel similar to those of the other Hymenoptera just described, but the pain is less intense. Frequently, however, tens to hundreds of fire ant stings occur and the combined sensations can be rather striking. Twenty-four to 48 hr after envenomation by *S. invicta* or *S. richteri*, white pimple-like pustules usually form at each sting site.

The reactions to stings of harvester ants (*Pogonomyrmex*) differs from those to other Hymenoptera. Often no immediate pulse of pain is felt; rather the pain quickly builds within the first few minutes and persists from 4 to 24 hr. Sweating and hair erection (piloerection) around the sting site usually

occur during this time and tenderness in nearby lymph nodes often is felt. The pain and normal responses for these and other stinging Hymenoptera are described in greater detail elsewhere (Schmidt, 1983; Schmidt, Chapter 9).

B. Large Local Reactions

Individuals stung on repeated occasions often experience what are termed 'large local' reactions. These are large, usually 10 to 50 cm in length, edematous swellings that begin forming around the sting site usually within 4–12 hr following envenomation and may persist 3 or more days. To be considered large local reactions, these reactions must be contiguous with the sting site; if swelling occurs away from the sting site, the reaction is systemic rather than large local in nature. Beekeepers and scientists who study honeybees or wasps or ants frequently report small swellings after their initial stings, followed by increasingly larger local reactions to stings on subsequent occasions (see also Chapter 7, Sections IV,A,4 and IV,B,4 for sensitization of researchers to toxins from bee venom). Finally, after continued stinging occasions, small or very little local reactions are experienced. This occurs because the individual's immune system eventually becomes tolerant to the venom and has elevated levels of IgG.

The exact cause and clinical importance of large local reactions has been widely debated in the medical literature. The consensus of opinion is that these reactions are at least in part mediated by IgE (Müller *et al.*, 1977; Hoffman, 1978b; Green *et al.*, 1980; Graft *et al.*, 1982; Mauriello *et al.*, 1984) but the exact mechanism of formation is uncertain. Large local reactions could be a result of individual patient differences in susceptibility to the direct pharmacologic activity of the venom (Mackler *et al.*, 1972; Green *et al.*, 1980). Alternatively, they could be a result of late phase IgE reactions (Type I reaction), possibly with the induration that lasts longer than 24 hr being a cell-mediated response (type IV) (Case *et al.*, 1981). Large local reactions appear to be quite common in cases of bee sting (Abrecht *et al.*, 1980; Graft *et al.*, 1982) and pure melittin, which is known to be a direct irritant and a poor immunogen, can cause delayed large local reactions (Mackler *et al.*, 1972).

The immunological peculiarities of large local reactions not withstanding, large local reaction to stings are not considered serious. The reactions, though causing discomfort, cannot threaten an individual's life (unless massive swelling around a sting to the neck or in the mouth occurs), and the frequency of large locals progressing to systemic reactions with subsequent stings is very low (Abrecht *et al.*, 1980; Graft *et al.*, 1982; Georgitis *et al.*, 1980; Golden *et al.*, 1984; Mauriello *et al.*, 1984). The general medical practice is not to treat these reactions with the possible exception of administering antihistamines and/or other anti-inflammatory agents simply to improve the

person's comfort and possibly ease his or her anxiety. Neither skin testing nor immunotherapy is recommended for people experiencing large local reactions (Mauriello *et al.*, 1984).

C. Systemic Reactions

Normal local reactions as well as large local reactions are not generally considered sting reactions severe enough to merit medical concern. The reactions of medical concern are the systemic reactions. In systemic reactions the body responds to the envenomation not just at the sting location but at areas distant and discontinuous from the sting site. Systemic reactions, often called generalized reactions, are IgE-mediated (with a few possible exceptions) and are the consequence of mediator release by basophils and mast cells located in various areas within the body. For convenience, systemic reactions can be categorized as cutaneous reactions, vascular reactions, or respiratory reactions. Cutaneous reactions affect only the skin and consist of urticaria, angioedema, and various rashes, itches, swellings, hives, general reddenings, etc. These reactions often occur on the face, neck and palms of hands, but can form at any distant part of the body. Vascular reactions involve the circulatory system, often with massive vascular permeability and/or drop in blood pressure. Vascular reactions can lead to dizziness, fainting, and unconsciousness. Respiratory reactions consist of swellings and/or massive increases in fluids in the respiratory system. Respiratory reactions are characterized by difficulty in breathing, sneezing, constrictions in the throat or lungs, or production of fluid or froth. These reactions are quite terrifying to the individual because he often perceives that he is about to suffocate. Other reactions that hypersensitive patients occasionally experience are gastrointestinal disorders such as cramps, diarrhea, nausea, vomiting, incontinence, anxiety, feeling of doom, headache, chills or fever, malaise, etc. Table IV is a listing of systemic reactions frequently reported by hypersensitive people. The table is not intended to be a total listing but to represent the types of typical systemic reactions experienced by various populations as reported by several authors.

The systemic reactions of major medical concern are those that affect the life support systems: the respiratory and circulatory systems. Obviously, an inability to obtain air or a very low or absent blood pressure portends serious oxygen deprivation to the brain and possible death. Reactions which cause congestion of the heart, brain, or other organs and are anaphylactic in nature are also extremely serious. Cutaneous reactions, on the other hand, are not imminently serious as they cannot cause death. Cutaneous reactions are also the most common systemic reactions and are of concern simply because they indicate a state of hypersensitivity. They in themselves indicate no immediate threat because future reactions often duplicate previous reactions, that is,

Table IV

Symptoms of Systemic Reactions

Symptoms	Percentage of patients with symptoms (number of patients; category of patients)[a]			
	Brown and Bernton (1970) (n = 400; from general practice)	Barnard (1979) (n = 100; near-fatal cases)	Chipps *et al.* (1980) (n = 44; children)	Grant *et al.* (1983) (n = 48; *Polistes*-sensitive patients)
Uticaria	49	74	100	52
Generalized swelling (angioedema)	59	—	93	38
Puritus (rash, itching)	—	—	82	67
Dysphea	43	38	48	73
Wheeze	—		11	35
Unconsciousness	29	91	7	31
Hypotension (dizziness, faintness, etc.)	44		7	75
Erythema (redness)	—	—	75	42
Nausea or vomiting	34	16	—	48
Upper airway swelling	—	—	—	60
Throat swelling (dysphagia)	8	—	34	—
Anxiety	13	—	—	—
Headache	12	—	—	—
Asthma	8	—	—	—
Chills or fever	7	—	—	—
Incontinence	6	—	—	—

[a]Author interpreted some of the reported symptoms for purposes of comparison; —, no mention of symptom per se in report.

the progression from cutaneous to vascular and respiratory reactions on subsequent stings is rare (Chipps *et al.*, 1980; Yunginger *et al.*, 1979; Lichtenstein *et al.*, 1979; Mauriello *et al.*, 1984). Moreover, the majority of patients spontaneously improve with time even if not treated (Settipane and Chafee, 1979; Lichtenstein *et al.*, 1979; Reisman *et al.*, 1979).

There is currently no consistent means to diagnose venom hypersensitivity except the personal case history. Various diagnostic means including the skin test, the RAST test, the leukocyte histamine-releasing test, and diagnostic sting challenge are available, but none, either alone or in combination with the others, is completely predictive. These methods generally range in accuracy of prediction from 80 to 95 + % (Hoffman, 1979a,b, 1980; Patrizzi *et al.*, 1979; Kemeny *et al.*, 1980; Santrach *et al.*, 1980; Bar-Sela *et al.*, 1983). Moreover, these tests are only useful in conjunction with a case history for diagnosing who is hypersensitive. They are not good predictors of who will have a systemic reaction in the future, though they may be useful in helping to determine the cause of death in cases of sudden death of suspected hypersensitivity (Hoffman *et al.*, 1983; Schwartz *et al.*, 1984). These tests can give rough statistical predictions of chances of reaction, but an individual who is apprehensive (as well as his or her physician) wants certainty and that cannot be delivered at present. The substantial incidence of positive responses to these tests in the general public that have never experienced systemic reactions (Stuckey *et al.*, 1982; Zora *et al.*, 1984) also precludes the use of such tests to screen the general population for susceptibility to stings. Thus, at this time there is not only no effective means to predict future anaphylaxis (Gottlieb, 1979) but there is even less, if any, ability to predict which of the hypersensitive patients is truly at risk of a fatal reaction to the next sting (Rubenstein, 1980).

The assumption that the risk of a future fatal reaction is correlated with the severity of past reactions has not been supported by data. Although the assumption might seem reasonable, it is hardly a strong foundation upon which to base medical (and economic) decisions. Part of the problem is the fact that with such minute numbers of deaths per year due to stings there is little opportunity to test hypotheses relating to hypersensitivity and fatal consequences. To make matters worse, the etiology of hypersensitivity in many fatal cases is not conducive to prophylactic measures. That is, ~50% or more of all fatalities for which information is available occurred in individuals who had no previous warning of adverse sting reactions (Jensen, 1962; Barnard, 1967; Hunt and McLean, 1970). Medicine can do nothing for this half of the fatal population. On the other hand, several patients consistently became unconscious following each of the eight to 15 times that they were stung and survived all stings without increase in severity (Kailin, 1961; Brown and Bernton, 1970). The discouraging conclusion emerges that

modern medicine has a chance of helping to prevent mortality in only half or fewer (under 20/year in the United States) of people who die from Hymenoptera stings, and that the chances of helping even these individuals is low.

Unusual reactions involving the neurological and vascular systems are observed in a small percentage of the population that reacts to stings of Hymenoptera. These reactions usually are delayed hours to several days after the sting and last several to many days (Bernard, 1966, 1973; Levine, 1976; Lim *et al.*, 1976). The exact causes of these reactions are not known, but hypersensitivity does not appear to be involved. Renal failure is a common symptom following 50 or more simultaneous stings by vespid wasps (rarely for honeybees), but these reactions are related to the toxicity of the venom, rather than to hypersensitivity (Bousquet *et al.*, 1984b; Chugh *et al.*, 1976; Hoh *et al.*, 1966; Scragg and Szent-Ivany, 1965; Shilkin *et al.*, 1972).

D. Beekeepers

Beekeepers and others who receive stings repeatedly over time represent a special group unique among the general populace. The frequency and repetitive nature of the stings received by these people presents a situation in which the ongoing processes governing hypersensitivity and tolerance to venom can be observed. In some respects beekeepers represent ultimate examples of naturally occurring venom immunotherapy.

Not all beekeepers become hyperimmune to bee stings. Of 369 beekeepers and family members in one study, 8.9% experienced systemic reactions, most of which were severe reactions (Bell and Hahlbohm, 1983). In another study, 42% of 250 surveyed beekeepers were hypersensitive (Bousquet *et al.*, 1982). The number of stings per year received by beekeepers was inversely related to the incidence of hypersensitivity: those with >200 stings per year had no reactions, whereas those with <25 stings per year had a 45% incidence of systemic reaction (Bousquet *et al.*, 1984b).

Beekeepers may represent a subpopulation that, unlike the general population, might exhibit a correlation between atopy to inhalent allergens and venom hypersensitivity. The levels of atopy were significantly higher in hypersensitive beekeepers than in nonsensitive beekeepers or controls (Miyachi *et al.*, 1979; Bousquet *et al.*, 1982). The exact meaning of these findings is unclear because the immune response to bee venom PLA_2 is clearly distinct from that to rye I from rye grass or P_1 from the dust mite (Kemeny *et al.*, 1982).

Several different patterns of immunoglobulin levels are observed in beekeepers. Individuals who are not sensitive typically have elevated levels of IgG and may or may not have high levels of IgE (Yunginger *et al.*, 1978;

Kemeny *et al.*, 1980, 1982; Bousquet *et al.*, 1982, 1984b). Those beekeepers who are hypersensitive tend to have lower levels of IgG than their tolerant colleagues, but there is overlap in the values of the two groups (Yunginger *et al.*, 1978; Kemeny *et al.*, 1980; Bousquet *et al.*, 1984b), as there is in the values of IgE levels in the two groups.

Immunoglobulin G has four subgroups that each behave differently. For this reason, simple measurements of IgG and IgE levels in the serum of beekeepers may in itself not be enough to explain the findings. The subclass IgG_4 may be of special interest as either a potential blocking antibody or as a mediator of hypersensitive reactions (Urbanek *et al.*, 1983; Cheung *et al.*, 1983). When hypersensitive patients were placed on venom immunotherapy, their IgG_4 levels rose 7.3-fold while their levels of total honeybee venom IgG rose only 1.6-fold (Cheung *et al.*, 1983). Whether or not IgG_4 is the only, or principal, blocking antibody in the serum of tolerant or desensitized individuals remains to be determined. In the meantime, it does appear to be a promising laboratory marker indicating projection from a hypersensitive reaction (Cheung *et al.*, 1983).

IX. TREATMENT OF HYPERSENSITIVITY PROBLEMS

A. Avoidance

If an individual is hypersensitive to the venom of a bee, wasp, or ant, one means to reduce the problem is avoidance. Because avoidance of a culprit species requires knowledge of the species and would drastically alter a person's lifestyle, only individuals who reacted severely (e.g., circulatory or respiratory problems) to a previous sting should seriously consider pursuing this behavioral modification approach. To do so involves avoiding outdoor activities, changes in clothes and lifestyles, and a constant mental preoccupation with avoidance. In short, it can make life a nightmare. People who are not hypersensitive or who have only mild cutaneous reactions might do well just to avoid being around known colonies of offending species, not to swat at them, and if sensitive to honeybees, not to walk barefoot in grassy areas where bees might be visiting flowers. These minimal avoidance behaviors do not require major alterations in lifestyle and are good ideas for most of use who do not appreciate being stung.

If a person is severely hypersensitive, then any reasonable action that reduces the probability of a sting by the offending species would be helpful. If at all possible, the person should determine the species that induced the hypersensitivity. By doing so, he or she reduces the number of behavioral modifications necessary. For example, if a person is sensitive to fire ants,

no cautions about hairstyles or clothing colors are necessary, while cognizance of where he or she is walking or sitting is very important. Likewise, if sensitivity is caused by yellow jacket wasps only, no special concern about a neighbor's beehives is necessary. If the honeybee is the sensitizing species, no concern about eating out of doors is necessary (as opposed to someone who has sensitivity to yellow jackets, which tend to scavenge available food). For further approaches to avoiding stinging insects and their habitats, see Schmidt (1983).

B. Local Treatments

The first local treatment is the removal of stingers left in the skin by bees or some species of harvester ants. This can best be accomplished by scraping them out with a fingernail or knife blade. Other local treatments consist mostly of home remedies designed mainly to reduce the severity of the pain. Such remedies include the application of vinegar, ammonia, ice, baking soda packs, meat tenderizers, boric acid, tobacco juice, etc. Although the logic of applying many of these is not easily comprehended, such application serves two purposes: it cools the sting site, thereby reducing pain, and keeps the people involved preoccupied with the procedure and less occupied with thinking about the pain (the pain naturally decreases anyway in a few minutes). Some remedies might actually help, as demonstrated recently in the case of using wet salt for a bee sting (Weathersby, 1984). Another treatment is the application for 10 to 15 min of cold (ice) followed by topical antihistamine (T. Piek, personal communication). Commercial products containing benzalkonium chloride, ammonium sulfate, or other ingredients might also be helpful (Henderson and Easton, 1980; Carlile, 1981). If the individual experiences large local reactions, antiinflammatory agents such as aspirin or antihistamines can be taken. Steroids can also be used for treating large locals, but because of the negative side effects of steroids they should be taken only after consulting a physician.

C. Sting Kits

Sting kits contain epinephrine (adrenaline) and sometimes antihistamine tablets and are the primary treatment available for stopping severe systemic reactions. Epinephrine has been widely used to arrest immediate hypersensitive reactions and is the only known effective control of such reactions (Braun, 1925; Barr, 1971; Barnard, 1979; Gottlieb, 1979; Rubenstein, 1980). To be effective, epinephrine should be administered as soon as possible because delay can allow the reaction to progress to a point at which it is difficult, if not impossible, to stop (Gottlieb, 1979; Fudenberg

et al., 1980). Sting kits are inexpensive ($12-30 United States) and are considered an absolute must to be 'on person' at all times for severely hypersensitive people (i.e., vascular and respiratory reactions); they are not a bad idea for individuals who have severe cutaneous or other reactions. Kits are available today with convenient self-injecting devices for those people who either cannot, or are afraid to inject themselves, but such kits are expensive (Ganderton, 1979; Schmidt, 1983). Severely hypersensitive people may also wish to wear a medical identification necklace or bracelet that indicates that they are hypersensitive and are carrying a sting kit. Individuals with coronary disease present a special problem as epinephrine could conceivably precipitate a heart attack.

D. Immunotherapy

Unlike sting kits, which are designed to stop the occurrence of a hypersensitive reaction after a sting, immunotherapy is designed to prevent the hypersensitive reaction by making the body nonreactive or tolerant to the venom. Originally, whole body extracts of the envenomating insects were used, but their effectiveness is questionable and they are not recommended for treatment of venom hypersensitivity (see Section IV). Today the expertise of providing immunotherapy is so highly developed that success rates are greater than 95% (Lichtenstein *et al.*, 1979; Yunginger, 1979). In this regard, immunotherapy has been a great success and research is ongoing to further improve it.

Immunotherapy is a complicated procedure that requires the patient to receive numerous injections starting at 0.1 μg or less and increasing over time to 100 μg of venom preparation. The procedure must take place either in a doctor's office or a hospital. The traditional approach required 18 visits over 20 weeks. Modified 'rush' procedures required only eight visits in 19 weeks followed by monthly injections thereafter (Golden *et al.*, 1980). Today there are vastly more convenient schedules, which may be as short as 3 days or even 6 hr (van der Zwan *et al.*, 1983; Thurnheer *et al.*, 1983; Bousquet *et al.*, 1984a; Nataf *et al.*, 1984) and are as effective as the longer procedures [though in at least the case of Yunginger *et al.* (1979) more adverse reactions were experienced with rapid than slow protocols]. From a patient's point of view, these more rapid procedures are certainly less inconvenient than the slower methods and are worth considering. Rapid methods also obviate Lichtenstein's caveat that during the initial period of immunotherapy, the person may be at greater risk of experiencing a systemic reaction than he was before immunotherapy commenced (Lichenstein *et al.*, 1979).

Several important technical details relating to venom immunotherapy have not been resolved. First, must the injections be given for life as widely

suspected (Lichtenstein *et al.*, 1979) or can they be stopped at some future date? Second, must injections be given every month or can the interval be expanded? Third, what is the optimal maximum dose for maintenance therapy? The first question is of prime importance: an individual certainly does not desire to be on immunotherapy forever if that is not necessary. Unfortunately, criteria for discontinuing treatment (i.e., confirmation of successful desensitization) are by no means agreed upon. Some investigators are proposing that levels of venom specific IgE, or IgE and IgG, or negative skin tests should be criteria for discontinuing the treatment (Georgitis *et al.*, 1980; Thurnheer *et al.*, 1983; Barde *et al.*, 1983; Urbanek *et al.*, 1984; Schuberth *et al.*, 1984, 1985; Randolf and Reisman, 1985; Golden *et al.*, 1985). These results are at least encouraging, but probably will only apply to a minority of people; the rest must continue treatments. The prospects of a lifetime, or even several years, of treatments are not only psychologically discouraging to the individuals involved but pose a medical problem. Failure of individuals to maintain therapy is common, with estimates of a 50% dropout rate being common (unpublished statements by practitioners at the 1984 American Academy of Allergy Meeting). A 50% dropout rate of children being treated for asthma is also reported (Fireman *et al.*, 1984), indicating complicance in general is a serious problem in lengthy treatment regimens. How this dropout rate affects, if at all, the safety of the individuals involved is uncertain.

The interval between maintenance injections and the optimal dose are somewhat less crucial problems. The period appears to be expandable to at least 6 weeks and possibly more (Golden *et al.*, 1981b). The upper dose required appears to be between 50 and 200 μg with 50 μg not offering enough protection for all individuals (Golden *et al.*, 1981a) and occasionally 100 μg not being enough (Hoffman *et al.*, 1981; Ménardo *et al.*, 1984). So far, 200 μg has always been adequate. The problem is expense; 200 μg costs much more than 50 or 100 μg.

The final problem, who to treat, is by far the most serious. Some guidelines have been published (Lichtenstein *et al.*, 1979), but little attention is given to the real statistical prospects of death occurring with or without treatment, or to the patient's psychological requirements. If any individuals should seriously consider immunotherapy, they are those who experience respiratory blockage or vascular collapse after a sting. Even these individuals should bear in mind that the epinephrine sting kits are the primary defense against systemic reactions and appear to have saved lives (Barnard, 1979), whereas immunotherapy, though possibly saving a few lives, is still unproven. A careful scrutiny of the statistics presented earlier is worthwhile in helping an individual to come to a conclusion concerning immunotherapy.

E. Education and Psychological Support

The main overlooked feature of hypersensitivity to venom is the human psychological aspect. Given the facts presented in a proper fashion, the average person is eminently capable of making good decisions for himself. There are, of course, individuals who are particularly emotionally labile, especially in their reactions toward insects, who are not capable of making (or willing to make) rational decisions for themselves in this matter (for discussion, see Lichtenstein *et al.*, 1980). These people should probably have decisions regarding hypersensitivity made by their physician. The population should be given the facts about the realistic threats of death, the options available, and the costs and benefits of each *vis*-à-vis the threat of mortality. Family, friends, social workers, religious leaders, and psychiatric personnel can all provide personal input and support in making the decision the patient feels is best.

The real problem concerning venom hypersensitivity is morbidity, not mortality. How can a person's irrational fear of stinging insects and fright that he or she could die on the next sting be treated best? The medical profession, to a large extent, has complicated the problem through statements that grossly overemphasize the true dangers (for discussion, see Rubenstein, 1980, 1982 and for opposing view points, see Lichtenstein *et al.*, 1980) and has not provided the psychological support to dispel unnecessary patient anxiety. The main medical approaches have focused on advice concerning how to avoid stinging insects and on providing sting kits and immunotherapy. Rarely has the medical profession attempted to reduce fears except via assuring patients receiving immunotherapy that they are protected.

Because morbidity is the real problem to be treated in the vast majority of hypersensitive individuals, solutions of this problem should be addressed. Education is one means. Terrified individuals can be shown pictures or specimens of insects including Hymenoptera and given a chance to experience, albeit even in a distant way, their beauty. Many insects, especially stinging Hymenoptera, also have fascinating life histories which can be illustrated in story or pictorial form. Honeybees are especially suitable in this regard. Most hobbyist beekeepers are delighted to talk about bees and will often show an interested person their bees and explain their fascinating habits. These approaches are all designed to reduce a person's dislike of, revulsion of, or fear of insects. If the insects themselves can be at least tolerated and admired, even if not really liked, a large portion of the morbidity problem will have been solved.

Along with information directed toward understanding the insects, education should relate to the actual risks of death. Showing people information such as that in Table I should be particularly helpful in this

regard. The fact that morbidity is a normal and natural response (see Section III on psychological aspects, this chapter) and is, for the most part, the real problem should be explained. At least some people, once they have seen the figures and understood why they have a natural fear, can overcome their own fear and learn to live with insects with a minimum of risk and lifestyle alteration.

Finally, education can help in one last way even if it fails in all others. The person can be taught the habits of the hypersensitizing species, where they are found, when they are found, and what mainly *not* to do when they are seen. Such knowledge will help reduce the threat of the insects to the hypersensitive person.

If education and psychological support do not reduce a person's fears to a point at which he or she can make good personal judgements relating to hypersensitivity problems, then that individual should probably seek medical help. Perhaps medical help in these cases is the only solution to morbidity problems, and if immunotherapy for mild systemic reactions eliminates the morbidity, the perhaps the cost and incovenience of the person are worthwhile even if otherwise unjustified. Physicians should discourage unnecessary treatment and give treatment only if no other solution for the morbidity problem is apparent.

In addition to education about insects, hypersensitivity, and the chances of mortality, a hypersensitive person should be provided information of a consumer protection nature relating to the various potential courses of action. The initial costs as well as the continuing yearly costs for treatments should be provided. Also, the potential hazards, benefits and inconveniences should be presented. The success rates of treatments and the predictive accuracy of tests should also be given. In this way the individual can weigh the costs and benefits resulting from decisions ranging from doing nothing except avoidance behavior, to carrying a sting kit, to receiving immunotherapy plus carrying a sting kit. In the final analysis, the choice of what to do about insect hypersensitivity is up to the individual and he or she should have access to accurate, realistic information upon which to base a decision.

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