Allergy to insect stings: a review[1]

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Allergy to bee and wasp stings presents a fascinating problem both clinically and immunologically. Although no figures are available, this disorder is certainly not uncommon. At St Mary's Hospital, one or two patients allergic to bee and wasp stings are referred to me each week, and we are frequently consulted by telephone by general practitioners who see many more patients.

The following case history illustrates some of the problems this disorder raises and the reasons it is of great interest. A 47-year-old man had been a beekeeper for 2 years when he presented to the clinic in 1981. In the years before he became a beekeeper he had been stung by a bee on 6 occasions, always without allergic reaction. During his first year as a beekeeper he was stung on 6 occasions (each time a single sting), again without unusual reaction. He was then stung by 20 bees simultaneously and developed a severe generalized allergic reaction consisting of hypotension, fainting and angio-oedema, and another less common feature, transient blindness. Subsequently, without any specific therapy, he was stung on 2 occasions, each time developing only slight oedema at the site of sting, but no symptoms of a generalized allergic reaction.

One of the clinical features highlighted by this case is that patients can undergo spontaneous cure. This of course raises a further question: can we identify patients at risk of repeated anaphylactic reaction and distinguish them from those who will not react seriously to a subsequent sting? Clearly such information would modify the approach to therapy. This is of particular relevance since a new and effective form of desensitization, using pure venom extracts, was introduced in the late 1970s. Since this treatment has disadvantages and side effects, it would be of value to define a 'high-risk' group where treatment is indicated.

Patients with this disorder are of great interest to the immunologist as they provide a clearly defined model of allergic disease. During a sting, venom (the allergen) is injected systemically, yet in one patient a variety of different reactions may occur following the same challenge. This is likely to be a result of immunological events.

Entomology

In any consideration of bee or wasp allergy some knowledge of the classification of stinging insects is necessary. A summary of the order Hymenoptera is shown in Figure 1. Two distinct families exist, the Apidae and the Vespidae. The genus Apis contains only the honeybee, while the genus Polistes and the genus Vespula contain wasp, yellow jacket and hornet. The various subspecies occur with different frequencies in different parts of the world.

Bees are entomologically and allergenically distinct from the vespids. There appears to be variable cross-reactivity between the vespid venoms. This is important, as insect venoms are used for diagnosis and treatment.

Pathogenesis

Insect sting allergy is a local or systemic type I immediate hypersensitivity reaction, mediated by IgE antibodies. This has been demonstrated in a number of ways: patients have positive skin-prick tests to venoms (Hunt *et al.* 1978), their leukocytes release histamine on exposure to

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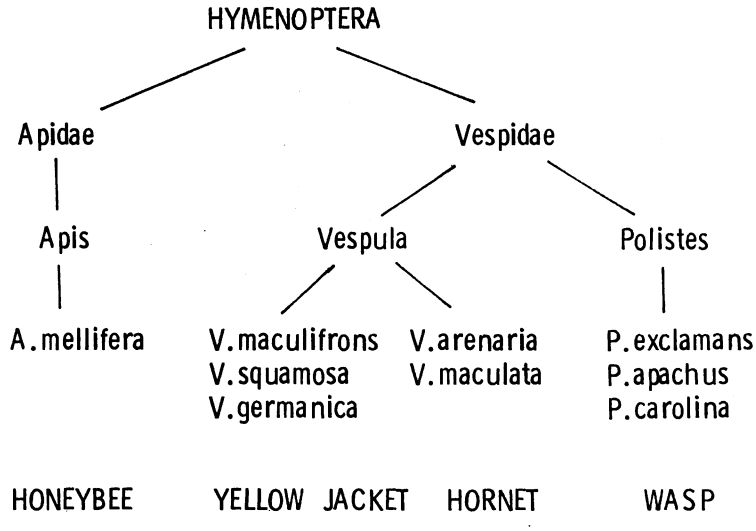

Figure 1. Classification of the order Hymenoptera

venom, and passive sensitization of leukocytes with insect venom can be abrogated by removal of IgE antivenom antibodies from the sera of sensitive patients (Sobotka *et al.* 1974). The clinical features of the disease are those of an immediate hypersensitivity reaction.

Venom allergens

Bees sting only in defence, and during a sting approximately 50 μg of venom is injected into the skin. This represents the entire contents of the venom sac. The barbed sting is normally left *in situ,* resulting in evisceration and death of the bee. Wasps can sting several times in succession and it is not clear how much venom is injected per sting.

Bees venom contains three main allergens: phospholipase A (to which most patients are sensitive), hyaluronidase (to which a smaller number are allergic) and mellitin (which is an important allergen in only a few patients). Less is known about the allergens in vespid venoms; phospholipase A is present but does not cross-react with the enzyme in bee venom.

A few patients, usually beekeepers, become sensitized by the inhalant route to allergens derived from the insect bodies. These are distinct from the allergens in venom. These patients have inhaled 'bee-dust' while working amongst bees.

Clinical features

Reactions to bee and wasp stings may consist of local or systemic allergic reactions. These frequently occur together. The severity varies from a small localized oedematous reaction to death from systemic anaphylaxis.

Localized reactions: These vary in size from swellings a few centimetres in diameter to marked oedema of the entire hand, the forearm or even most of the leg. The most alarming localized reactions are those involving the eyelid or the subcutaneous tissues of the neck, although these are smaller than many of the swellings affecting the limbs. Whilst such reactions are frightening and may cause considerable discomfort, they are not dangerous. Large swellings take several days to subside.

Systemic or generalized reactions: Most of the symptoms are similar to those found in other immediate type hypersensitivity reactions, however there are some clinical features particular to insect sting allergy.

The development of allergy to bee stings appears to require much greater exposure to allergen than allergy to wasp stings. In a study into the natural history of the disease carried

out at St Mary's, patients allergic to bee venom had been stung on average 81 times (and on 23 occasions before an allergic reaction occurred), while the mean number of stings sustained by wasp-allergic patients was 4, and they required only 2 or 3 stings before developing allergic symptoms (Ewan 1984). Most of the patients who became allergic to bees are beekeepers or their relatives, where clearly there is a high risk of being stung repeatedly. In contrast, the development of wasp allergy seems to be a random process (Ewan, unpublished). This difference has not been appreciated previously, it having been assumed that observations on bee sting allergy apply equally to wasp venom allergy.

The commonest clinical features of the anaphylactic reaction to bee and wasp venom are cutaneous (pruritus, urticaria and angio-oedema) and respiratory (asthma and laryngeal oedema). Features particular to insect sting allergy are gastrointestinal symptoms (diarrhoea, abdominal pain and incontinence) and visual problems, including transient amblyopia. Patients may also suffer from tachycardia, sweating, hypotension, fainting and loss of consciousness.

In some patients a severe generalized reaction can occur very rapidly, sometimes within a few minutes of the sting. Many patients suffer from a sensation of impending doom.

Pattern of reaction

An important question is whether the response to the next sting may be predicted from the history of responses to previous stings. However there is no consistent pattern of reaction (Ewan, in preparation), and patients having severe generalized reactions often have no generalized reaction to the next sting. Patients' reactions may either get worse, improve or both increase and decrease in the course of a series of stings. In controlled studies on hyposensitization using pure venom extracts in bee allergic patients, Hunt *et al.* (1978) showed that there was a 40% spontaneous cure rate, which was observed in the placebo-treated group.

Deaths from insect stings

Insect stings can be fatal. Reported figures vary but suggest there are about 4 deaths a year in England and Wales (OPCS 1977, personal communication) and from 40 to 50 deaths per year in the USA (Barnard 1973, Parish 1963) from bee and wasp stings. The figures are difficult to interpret now since (1) we do not know the prevalence of stings in the population; (2) diagnosis may not have been accurate; and (3) anaphylaxis may not have been optimally treated.

Diagnostic tests

The diagnosis should be largely based on the history. Investigations are of value to confirm the clinical impression, and can be helpful to determine whether the allergy is to bee or wasp venom, if the insect has not been identified. Two tests are available: skin-prick tests to the venoms and measurement of specific IgE antibodies in the serum.

Skin-prick tests: These tests have the advantage of being simple and cheap, and give an immediate answer while the patient is in the clinic. This is done using the standard technique, as for the common allergens. The only difference is the amount of allergen used. Skin testing with venoms presents a special problem in that they can only be used over a very limited range of concentrations (0.01–1 μg/ml) and above this there is a significant incidence of toxic reactions in normal subjects, which makes the interpretation of responses difficult.

Patients seen soon after a sting should have positive skin tests to venom. However, the level of venom-specific IgE is likely to decline with time (as occurs in allergy to penicillin), so that if, as frequently occurs, a patient is tested some years after the last sting, the skin test may be negative.

Serum-specific IgE antibodies: Venom-specific IgE in the serum can be measured by radioimmunoassay, using the RAST test. This does not normally add to the information provided by the skin test.

Treatment

The management of allergy to bee and wasp stings is highly controversial. There are two opinions: either the allergic reaction is treated symptomatically when it occurs, or patients are hyposensitized with the aim of preventing reactions to future stings. Before these alternatives can be considered, some knowledge of the history of hyposensitisation to bees and wasps is necessary.

Immunotherapy

Whole-body extracts were used for many years. This practice, remarkably, was based on a single case report (Benson & Semenov 1930) from which it was concluded that bee-allergic patients were equally sensitive to allergens from the bee body and to venom allergens. The patient was a beekeeper with a history of a generalized allergic reaction to a bee sting (Benson & Semenov 1930). Skin tests showed equal reactions to pure venom and to an extract of bee bodies, from which the venom sacs had been removed. It is likely that this particular patient was allergic to both body allergens and venom allergens, having been sensitized by the inhalent route as well as systemically. Unfortunately, the conclusion was incorrectly drawn that all insect-allergic patients were equally sensitive to both venom and whole-body extracts. Hyposensitization using whole-body extracts of bees or wasps was therefore begun, simply because these were more easily obtainable than extracts of pure venom.

A report by the Insect Allergy Committee of the American Academy of Allergy (1965) concluded that these whole-body extracts were effective. This was based on a retrospective, multi-centre report in which the criteria for 'improvement' were inadequately defined, but it was claimed that 85% or more patients treated in this way had a 'better' reaction following a subsequent sting. The widespread use of these extracts continued until about 1980, and we continue to have patients referred to us who are still having these injections.

It was not until 1978 that a controlled trial of hyposensitization using pure venom extracts, whole-body extracts and placebo injections in bee-allergic patients was reported (Hunt *et al.* 1978). These patients received a challenge sting at the end of 6–10 weeks of treatment. Only one of 18 patients hyposensitized with venom reacted to the challenge sting, suggesting a success rate of almost 95%. Of 12 patients hyposensitized with whole-body extracts, 7 reacted to challenge; of crucial importance, however, was that similar results were obtained in the placebo group (7 of 11 reacted). It was therefore concluded that a high spontaneous cure rate occurred, and that whole-body extracts were inneffective. That considerable numbers of patients naturally lose their sensitivity had not been previously appreciated and probably explains why whole-body extracts were thought to be of some value and were used for such a long time.

Other studies using pure venom in more prolonged regimens have confirmed that this is a highly effective form of therapy (Golden *et al.* 1980, 1981*b*, Clayton *et al.* 1983).

Who should be treated?

Since immunotherapy with pure venom extracts is effective, this would appear to be the treatment of choice. However, the situation is not as simple as this, and a number of other factors must be considered.

The treatment is not without risk of severe allergic reaction, and is therefore only suitable for hospital use, where facilities for resuscitation exist. It is expensive.

The natural history of the disease remains incompletely understood, and our studies show that a variety of patterns of response can occur to a series of stings (Ewan, in preparation). Some patients with generalized reactions improve spontaneously, others get more serious reactions, and some who have lost their systemic reaction go on to develop a serious generalized reaction again. Thus in trials such as that of Hunt *et al.* (1978), failure to respond to a challenge does not necessarily imply longstanding protection.

The optimum duration of therapy is not known, and studies to determine this and the ideal interval between maintenance injections (e.g. one month or two) are being carried out (Golden *et al.* 1981*a*). The current view is that a minimum of 3 years' therapy is necessary. On

immunological grounds, it would seem undesirable to subject a patient to persistent antigenic challenge over a number of years as this might result in the development of immune complex disease.

At present there is no information on the duration of the protection conferred by pure venom immunotherapy. With the exception of beekeepers, most bee- and wasp-allergic patients are stung infrequently, sometimes at intervals of 10–20 years. In these cases, 3 years of immunotherapy can hardly be justified, if the patient is not to be stung for a further 7 or more years.

In addition to these cautions about immunotherapy, it must be remembered that immediate symptomatic treatment of a systemic allergic reaction is highly effective. In the vast majority of patients severe anaphylactic reactions respond to subcutaneous adrenaline. This has occasionally to be supplemented by nebulized salbutamol, intravenous fluids and hydrocortisone. This approach has the advantage that one only treats a reaction if it occurs, and the patient is not subjected to years of a potentially hazardous therapy to prevent a reaction which might never occur. The disadvantage of this approach is that the correct treatment may not be available or administered.

The answer to who should be treated by immunotherapy therefore remains unclear. Lichenstein's group advise 'rigid conservatism' in using venom immunotherapy (Kagey-Sobotka & Lichtenstein 1982) and suggest that the only unequivocal criterion for treatment is a history of a life-threatening reaction and a positive skin test to an insect venom. With the advent of more information on the natural history of the disease and further immunological studies, one suspects that only exceptional patients will warrant treatment with immunotherapy. A quite different approach is taken by physicians in continental Europe who treat quite mild generalized reactions and even children with immunotherapy.

Treatment of the allergic reaction

Localized reactions may respond to oral or, in more severe cases, parenteral antihistamines. Massive oedema may justify the use of hydrocortisone. Oedema, once established, can take days to subside.

The treatment of a generalized allergic reaction depends on the site and the severity. Urticaria and pruritus respond to antihistamines, and isolated asthma should be treated appropriately. The more serious generalized reactions, with either laryngeal oedema, severe asthma, shock or loss of consciousness, should be treated promptly with adrenaline. Additional supportive therapy is occasionally required, as indicated earlier. Patients can be supplied with syringes pre-loaded with adrenaline for self-administration, but these should be reserved for emergency use only with clear instructions for the indications for use. These are particularly useful for patients likely to be in remote areas far from medical assistance or for those travelling abroad.

Mechanism of hyposensitization

Treatment of bee and wasp venom allergy provides an important model for the study of hyposensitization, discussed in a previous review in this journal (Frankland & Lessof 1980). But unlike commoner forms of allergy (e.g. pollens and house-dust mite) in which the allergen is usually inhaled or ingested, in this case the allergen is injected systemically.

Hyposensitization results in a rapid rise in venom-specific IgG antibodies – the so-called 'blocking' antibodies which are thought to be protective (Kagey-Sobotka & Lichtenstein 1982, Golden *et al.* 1982, Urbanek *et al.* 1983). However, any repeated systemic immunization stimulates production of specific IgG antibody, so that one cannot assume its presence signifies protection. In the case of immunotherapy to inhalant allergens, specific IgG antibody is produced but correlates poorly with clinical improvement.

Evidence supporting the concept that IgG antibody may indeed be protective in insect sting allergy was reported by Lessof *et al.* (1978). Hyperimmune gamma-globulin isolated from the plasma of beekeepers was infused into 5 bee venom-allergic patients and resulted in decreased clinical sensitivity to bee venom. In 4 of these, IgG antibody to phospholipase A was measured

pre- and post-infusion. In 3 patients a rise of approximately 2 μg/ml in anti-phospholipase A IgG antibody was demonstrated. However, in the fourth patient the pre-treatment antibody concentration was very high (159 μg/ml) and did not increase following passive immunization, so that this does not account for the clinical improvement observed. There are no studies of passive infusion of highly purified specific IgG.

The specific IgE antibody level also rises and later begins to fall, in one study not reaching pre-treatment level after 2 years (Kagey-Sobotka & Lichtenstein 1982). The suggestion has been made that the balance between the specific IgG and IgE antibodies may be important. Urbanek *et al.* (1983) found a specific IgG antibody concentration of >400 u/ml to be protective in patients with moderate or low specific IgE antibody levels, but the same IgG concentration was less protective when the specific IgE level was high.

However, there are patients in whom protection does not appear to be related to a rise in specific IgG antibodies. In addition, while most treatment failures have low levels of IgG antibody, some have high levels (Lichtenstein *et al.* 1979). This raises the possibility that other immunological mechanisms may be involved. The antibody response may be to only one of the venom allergens, e.g. mellitin, and this has been studied by Kemeny *et al.* (1983). The antibody avidity may alter as a result of immunotherapy, or the production of a subclass of antibody: for example, IgG_4 may be important for protection (van der Gaag *et al.* 1979, Aalberse *et al.* 1983) and this may not be reflected in assays for total specific IgG which underestimate the contribution of IgG_4 antibodies. There have been two studies of cell-mediated immunity in insect sting allergy (Case *et al.* 1981, Ewan 1984) but there are no reported studies of T-cell activity, particularly the induction of antigen-specific suppressor T-cells, during immunotherapy.

Conclusion

Allergy to insect stings provides a model of a systemic type I allergic reaction, of interest to the clinician and the immunologist. Immunotherapy with pure venom extracts is highly effective. However, at present it is difficult to define criteria for its use, and further information on the natural history of the disease and the immunological changes underlying spontaneous cure and remission induced by immunotherapy is needed.

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