

Immunotherapy with Hymenoptera venoms

Position paper of the Working Group on Immunotherapy of the European Academy of Allergy and Clinical Immunology

J. BOUSQUET,¹ U. R. MÜLLER,² S. DREBORG,³ R. JARISCH,⁴ H.-J. MALLING⁵ H. MOSBECH,⁵ R. URBANEK⁶ & L. YOULTEN⁷

¹Clinique des Maladies Respiratoires. Hôpital Aiguelongue Centre Hospitalier Universitaire, Montpellier, France; ²Medical Division, Zieglerspital, Bern, Switzerland; ³Dept. of Pediatrics, University Hospital, Linköping, Sweden; ⁴University Hautklinik 1, Dept. of Dermatology I, Wien, Austria; ⁵Allergy Unit TTA 7511, Rigshospitalet, Copenhagen, Denmark; ⁶Paediatric University Clinic, Freiburg, W. Germany; ⁷Dept. of Medicine, Guy's Hospital Medical School, London, England

Immunotherapy with Hymenoptera venoms is widely used throughout the world and is accepted as an effective treatment for most patients with Hymenoptera venom allergy. There are, however, still some unresolved problems with this form of treatment. At present there is no definite test which makes it possible to identify patients at risk – and thus candidates for immunotherapy – unequivocally. On the basis of prospective studies on the natural history of Hymenoptera allergy, venom immunotherapy is indicated in adults with severe systemic anaphylaxis. It is usually not necessary in patients with large local reactions only. Children with mild systemic reactions, e.g. urticaria, will need immunotherapy only in case of repeated reactions and/or a high risk of re-exposure. The selection of venoms for immunotherapy may lead to some confusion owing to common antigenic determinants shared by venoms of various Hymenoptera species. Many different regimens for immunotherapy have been proposed. At present, the three main are: rush, stepwise or clustered and classical. The maintenance dose of 100 µg usually protects from life-threatening reactions. However, in some patients 200 µg are necessary for complete protection. The usual interval between maintenance injections is 4 to 6 weeks. In many patients a strong increase of venom specific serum IgG-antibodies usually parallels clinical protection induced by venom immunotherapy, although many exceptions have been reported. Allergic side effects of venom immunotherapy are not rare, especially with honey bee venom and during the initial phase of dose increase. The question of the duration of venom immunotherapy is handled differently: although some authors recommend treatment for life, most suggest treating patients until skin tests and RAST become negative.

Key words: Hymenoptera; IgG; IgE; immunotherapy; skin test; venoms.

Accepted for publication 25 February 1987

Systemic reactions to Hymenoptera stings were first described about 5000 years ago when King Menes, the first Pharaoh, appeared to have died after a Hymenoptera sting. However, a

medical description of anaphylaxis to honey bees (HB) and vespids was first reported two centuries ago. The first attempts at specific treatment involved extracts of whole bodies and venom sacs (3), but soon after only whole body extracts were used for almost 50 years. In the late seventies two controlled prospective studies (37, 57) clearly showed that venom

*For some relevant questions, data are lacking to support a consensus and authors have expressed their personal views.

preparations are largely superior to whole body extracts for immunotherapy and that whole body extracts give patients no better protection than placebo. Guidelines for treatment were indicated in the late seventies, and it appeared that a monthly maintenance dose of 100 µg of venom should protect most patients. A recent multi-center study in the USA including more than 1,500 patients treated with venoms according to these guidelines showed that more than 85 % of them are totally protected when stung by bees, wasps or yellow jackets. However, a small proportion is not completely protected (65) and some treatment failures have been reported (31, 46).

Other significant problems have been encountered in patients with venom immunotherapy. Venom allergy appears to be much more common than previously reported (28, 36, 78), the selection of patients for immunotherapy is often difficult, common antigenic determinants among different Hymenoptera species venoms may lead to some confusion, and adverse reactions may occur during the

treatment of patients, thus delaying their protection.

Selection of patients requiring venom immunotherapy

Serum venom specific IgE can be detected in 7 to 20 % of the non-allergic population (28, 36, 40, 78), and a similar proportion of the population has positive intracutaneous skin tests with Hymenoptera venoms at a concentration of 10–3 g/l (1 µg/ml) (5, 19, 28, 64). Positive diagnostic tests, however, do not mean that these patients will develop a systemic reaction when stung by the corresponding insect (93). The majority of such individuals may only be subclinically sensitized. They do appear, however, to be at a higher risk of developing anaphylaxis than subjects with negative skin test and RAST (21). According to prospective studies (Table 1) 20–84 % of patients who have experienced systemic anaphylactic symptoms and demonstrate venom specific IgE do not have another systemic reaction when resting by the same insect species. It appears that the rate

Table 1
Prospective studies on the natural history of Hymenoptera sting allergy

Author	Type of reaction	No. patients	Reexposure by* % with systemic reaction	
Hunt et al. (37)	systemic	12	CH	57
Parker et al. (63)	systemic	16	CH	44
Müller et al. (58)	systemic, mild	29	FS	24
Schubert et al. (75)	systemic, mild in children	85	FS	16
Reisman et al. (69)	systemic	28	FS	50
	mild	18		33
	severe	10		80
Blaauw et al. (6)	systemic	88	CH	35
	mild	30		20
	severe	58		48
Graft et al. (29)	large local, children	64	FS	4
Mauriello et al. (48)	large local (> 5 cm diameter)	28	FS	4
Müller et al. (58)	large local (> 10 cm diameter)	22	FS	14
Golden et al. (21)	no reaction, positive diagnostic tests	16	FS	19

* CH = sting challenge
FS = field sting

of spontaneous hyposensitization is higher in mild than in severe systemic reactions (6, 29, 37, 47, 58, 63, 69, 70, 75, 76) in children than in adults (see Table 1), and in vespid than in honey bee sting allergy (6). Some authors claim that the IgG/IgE ratio may help to define high risk patients (81, 85).

The diagnosis of allergy to venoms is based on a suggestive history of anaphylaxis, positive skin tests to venoms, or the presence of serum venom specific IgE. Wüthrich et al. (49, 89) proposed adding basophil degranulation tests to this panel, since this was shown to enhance the diagnosis in difficult cases. The diagnostic criteria differ according to investigators. In the USA, intradermal tests positive for a venom concentration of 1 µg/ml were considered to effectively discriminate allergic patients from normal individuals (91). However, there is some concern about this threshold dose, since as many as 30 % of non-allergic individuals have positive intracutaneous tests with 1 µg/ml (14,

19). However, it appeared from a study of Georgitis et al. (19) that 80.5 % of venom-allergic patients had a positive intradermal test to a venom concentration ranging from 0.001 to 0.1 µg/ml and 8.5 % of venom allergic patients had a positive intradermal test with only 1 µg/ml of venom. On the other hand, almost 50 % of non-allergic subjects had a positive intradermal test with the latter concentration. These authors suggest therefore that patients who have had a systemic reaction when stung and who present a positive intradermal test with a venom concentration of 1 µg/ml should be further investigated by *in vitro* testing. Prick tests can be used to test patients allergic to venoms, and the threshold concentration discriminating allergic patients appeared to be 100 µg/ml in some studies (5, 32) and 1,000 µg/ml in others (51).

It is relatively easy to differentiate a toxic reaction elicited by a large number of stings received at one time (9) from IgE-mediated

Table 2
Indications for venom immunotherapy

Type of reaction	Age group	Diagnostic test		Venom immunotherapy
		Skin test	RAST	
Severe systemic respiratory cardiovascular	all ages	+	+	yes
		+	-	most authors propose VIT
		-	+	many authors propose VIT
		-	-	no
Mild systemic urticaria non-life threatening angioedema	adults	+	+	most authors propose VIT
				some authors only propose VIT in highly exposed subjects or when recurrent reactions occur
		+	-	usually no
		-	+	usually no
		-	-	no
	children	+	+	usually no except in highly exposed subjects or when recurrent reactions increasing in severity occur
		+/-	+/-	no
Large local	all ages	+/-	+/-	no exceptionally, in professionally exposed patients with recurrent reactions increasing in severity VIT may be started

allergic symptoms. However, toxic reactions may be combined with allergic reactions, and it has also been shown that multiple stings are often followed by an increase in the corresponding serum venom specific IgE (9), regarded as a normal response to allergen exposure in susceptible individuals. Anaphylaxis should also be differentiated from non-allergic anaphylactoid reactions presenting with similar manifestations. Thus, patients suffering from systemic mastocytosis or urticaria pigmentosa may experience anaphylactoid symptoms without any IgE immune response, since cutaneous mast cells can be easily activated by potent degranulating substances present in Hymenoptera venoms (54). After single stings, anaphylactic-like reactions have also been observed in a small proportion of patients who showed no sign of IgE production to venom proteins (51). When re-stung, 30 % of these patients presented a systemic reaction (72). Furthermore, some drugs, such as beta-blockers (2, 38) and maybe also anti-inflammatory drugs (4), can aggravate the sting reaction. These examples illustrate some of the problems encountered in the diagnosis of venom-induced anaphylaxis.

Venom immunotherapy (VIT) should be performed in patients with a history of a life-threatening reaction with severe respiratory and/or cardiovascular symptoms and positive diagnostic tests (Table 2).

Children with mild systemic reactions (see Table 2) (47, 75, 76) do not appear to be candidates for VIT, even in the presence of positive diagnostic tests, unless they are at a high risk of re-exposure and have presented several systemic reactions of increasing severity following Hymenoptera stings. However, if VIT is withheld, patients should be informed that severe anaphylactic reactions at a re-exposure, although unlikely, are still possible, and an emergency treatment set including adrenaline must be prescribed and self-administered if these patients are accidentally stung and develop symptoms.

There is at present some disagreement concerning adults with mild systemic reactions. Müller, Malling and Mosbech (45) estimate that, like children, they may not be candidates

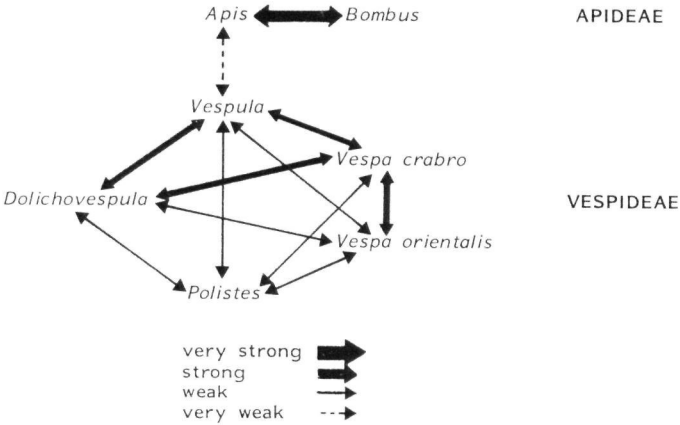


Fig. 1. Cross reactivities among Hymenoptera venoms

for VIT, whereas Bousquet & Valentine (11) prefer to desensitize the patients, and Dreborg suggests desensitizing patients over 50 years of age as they are at higher risk, probably in relation to cardiovascular complications.

Patients with large local reactions do not usually require VIT (48) (Tables 1, 2), even in the presence of positive diagnostic tests. However, family members of beekeepers or other highly exposed patients, such as farmers or gardeners, may be exceptions, especially when the local reactions increase in severity. Changes in skin tests and venom serum antibodies may help to indicate VIT (81, 83).

Selection of venom

In areas with many different species, a large proportion of patients, except beekeepers and their family members, are often unable to identify the offending insect. It may be helpful to know that after a bee sting the sting usually remains in the skin, whereas it does not after most vespid stings. Most patients cannot give information about the Hymenoptera nest which would otherwise be useful. Identification of the offending insect must therefore often rely on skin tests and RAST, which are frequently positive with more than one venom. Some antigenic determinants are common for different vespids (Fig. 1) (33, 42, 43, 73), but not between honey bee and vespid venoms (35, 71). In cases where the offending insect cannot be identified by history or positive tests, VIT should be per-

formed with both honey bee and vespid venoms. In the case of multiple positive tests with vespid venoms, treatment with *Vespula* alone may generally be sufficient although a vespid mix may be more effective. *Vespa crabro* venom possesses some common antigens with *Vespula* venom, but one third of *Vespa crabro*-allergic individuals have positive skin tests and RAST restricted to *Vespa crabro* venom (Bousquet, unpublished data).

Schedules for venom immunotherapy

Many schedules have been devised. All endeavour to obtain satisfactory protection in the majority, minimize side effects, and optimize convenience for the patients. Rush protocols (11, 57, 59, 82, 86, 88, 90) usually achieve rapid protection but give a higher frequency of untoward systemic reactions. Slow schedules

are better tolerated but protective doses are only reached after several months (66). Classical, step or cluster protocols (27) are a valid alternative and side reactions are about the same (44). Many investigators use different protocols. Some examples are indicated in Table 3. Protocols with aluminium hydroxide adsorbed venoms have also been proposed (52).

The maintenance dose is still under consideration. In most American papers, especially those published by the Baltimore group who use mostly mixed vespid venoms, the documentation is based on 100 µg of each vespid venom. They found that 50 µg of each venom (24) did not protect more than 80 % of the patients from general reactions, whereas 100 µg of each venom protected 95 % of all patients. The amount of material injected with 100 µg of each venom (mixed vespid venom) corresponds to 200 µg of yellow jacket as estimated by RAST-inhibition

Table 3
Protocols for venom immunotherapy with unmodified extracts

Regimen	Rush	Semi-rush	Classical	Cluster	Slow
Day 1	0.001	0.001	0.001	0.001	0.0001
	0.01	0.01	0.01	0.01	0.001
	0.1	0.1	0.1	0.1	0.01
Day 2	1	1			
	5	5			
	10	10			
Day 3	20	20			
	30	30			
Day 4	50		1		
	50		2		
			5		
Day 5	100				
Day 8		50	10	1	0.1
		50	20	5	0.5
				10	1
Day 9		100			
Day 15	100	100	30	20	5
			50	30	10
Day 21			50	50	20
			50	50	30
Day 28	100	100	100	100	50
					50
Day 35			100	100	100

Doses in µg
Maintenance dose every 4 to 6 weeks
After 6 to 8 maintenance doses, venom specific IgG should be titrated and, if the titer is not increased from baseline, it is advised to increase the maintenance dose to 200 µg.

procedure. In the case of honey bee venom sensitivity, treatment failures or only incomplete treatment success have been reported for up to 20 % of the patients (31, 46, 79) when a maintenance dose of 100 µg is used, and therefore in some cases a monthly dose of 200 µg may be needed.

Although there are some doubts about the protective role of IgG, estimation of the IgG-response to single venoms has been proposed for adjusting the maintenance dose. As a practical approach we suggest giving six monthly doses of 100 µg of venom and titrating venom IgG thereafter. If the level is under 150 IU/ml (Pharmacia IgG-RAST) or under 5 µg/ml (18, 26) the maintenance dose could be increased to 200 µg or even higher. It should also be increased in patients with incomplete protection following a re-exposure.

The interval between maintenance injections normally ranges between 4 to 6 weeks (25). To avoid side effects, some highly sensitive

patients have been given injections every second week.

Side effects during venom immunotherapy

Immediate allergic reactions. In VIT adverse reactions most often occur during the first phase of dose increase, particularly between 10 and 50 µg. Large local reactions have been described in up to 100 %, systemic reactions in 5–35 % of patients. For unknown reasons it appears that honey bee venom elicits more systemic reactions than vespid venoms. Rush protocols were also shown to induce more reactions than slower regimens except for vespid venoms (8, 86, 88, 90) (Table 4).

To reduce the relatively high incidence of systemic reactions during VIT, several procedures are under clinical evaluation. A combination of active and passive immunotherapy with honey bee venom and beekeeper's gammaglobulin was studied by two groups (8, 56).

Table 4
Side effects of venom immunotherapy according to the protocol used

	No. patients	Dose increase phase	Side effects %	
			local	systemic
<i>Classical immunotherapy</i>				
Hunt et al. (37)	20	?	?	5
Golden et al. (27)	22	14 weeks	41	16
Gillman et al. (20)	23	11 weeks	67	13
Ramirez et al. (66)	22	24 weeks	50	0
Thurnheer et al. (63)	21	9 weeks	25	40
<i>Rush immunotherapy</i>				
Urbanek et al. (82)	?	7 days	36	64
Yunginger (90)	20	3 days	100	55
Müller et al. (55)	16	?	39	39
Golden et al. (27)	22	6 weeks ¹	50	19
Thurnheer et al. (63)	21	10 days	15	38
Van der Zwan et al. (86)	11	6 h ²	100	0
Nataf et al. (59)	52	3 days	?	0
Bousquet	36	5 days	100	33
<i>Clustered immunotherapy</i>				
Golden et al. (27)	20	11 weeks	60	10
Malling et al. (44)	21	4 weeks	80	16
Bousquet	120	5 weeks	60	11

¹This protocol was indicated as a rush regimen but cannot be considered to be rush *per se*.
²Only vespid venom was used.

This allowed the investigators to reach maintenance dose after a few hours to a few days in all patients and was accompanied by a highly significant reduction of allergic side effects. In one of the studies dealing with highly sensitive patients with previous treatment failure, systemic reactions to bee venom injections re-occurred after disappearance of the transfused beekeeper gammaglobulin from the patient's blood (56). This method may be of some value in highly sensitive and heavily exposed patients in order to reach a protective maintenance dose as fast as possible with a minimum of side effects.

Chemical modification of honey bee venom by coupling to monomethoxy polyethylene glycol results in reduction of allergenicity with maintained immunogenicity. It induced significantly fewer side effects than crude honey bee venom but seemed clinically somewhat less effective than crude venom, maybe because of insufficient dosage (55, 61, 62).

Adsorption to aluminium hydroxide makes it possible to increase the interval to 6 weeks but does not reduce side effects (52).

Reactions to venom injections should be treated in the same way as field-sting induced reactions. Life-threatening reactions may require adrenaline, oxygen therapy, treatment of bronchospasm, plasma expanders and resuscitation procedures. In all systemic reactions the treatment should be started as early as possible. Anti histamines may be valuable in the treatment of urticaria and/or angioedema. Oral or parenteral corticosteroids are the most effective drugs for treating large local reactions and for preventing symptom recurrence. However, both preparations, alone or combined, are insufficient for the emergency treatment of respiratory or cardiovascular symptoms, where adrenaline is the only possible drug.

Precautions. To avoid a general reaction injections should be given deep subcutaneously and slowly for at least 1 min, with repeated aspirations before and during the injection to reduce the possibility of inadvertent intravascular administration.

In animal experiments Hymenoptera venoms

have been shown to cause degeneration of the peripheral nerves (74). This observation has also been reported in patients, thus venom injections should not be given close to peripheral nerves. The risk of damaging the radial nerve should be especially considered.

Long-term side effects. The safety of long-term treatment with venom has been questioned (53). For honey bee venom it may be postulated that the treatment is safe since no particular disease has been associated with continuous exposure as seen in beekeeping. With vespid venoms, which have a different pharmacological activity, a possible risk, though low, cannot be totally excluded. Moreover, immune-complex formation was not detected in the sera of allergenic patients treated with venoms (13).

No change in electrolytes, kidney, liver or hematological function has been found in several hundred patients investigated during Hymenoptera venom immunotherapy (Pharmacia Diagnostics, Internal Report).

Efficacy of venom immunotherapy

Results. Complete protection following VIT has been described in 75 to over 90% of patients (37, 57, 65). However, treatment failures have been reported in most studies (25, 341, 46, 57, 65, 69). In the "Insect Venom Group of the Arbeitsgemeinschaft Dermatologische Forschung", 41 treatment failures were observed, 36 patients were allergic to bee venom and five to vespid venoms (Rzany, personal communication). However, it must be stressed that in this evaluation many more patients were treated with honey bee venom than with yellow jacket venom. These failures decreased with increasing maintenance dose. Some patients, however, may also be unable to mount an immune response to a given venom antigen (24, 41, 56). In a small percentage of patients, especially allergic to honey bee venom, a protective maintenance dose cannot be reached because of recurrent severe allergic side effects. Finally, after some years of treatment a few patients may present a sudden unexplained failure (46).

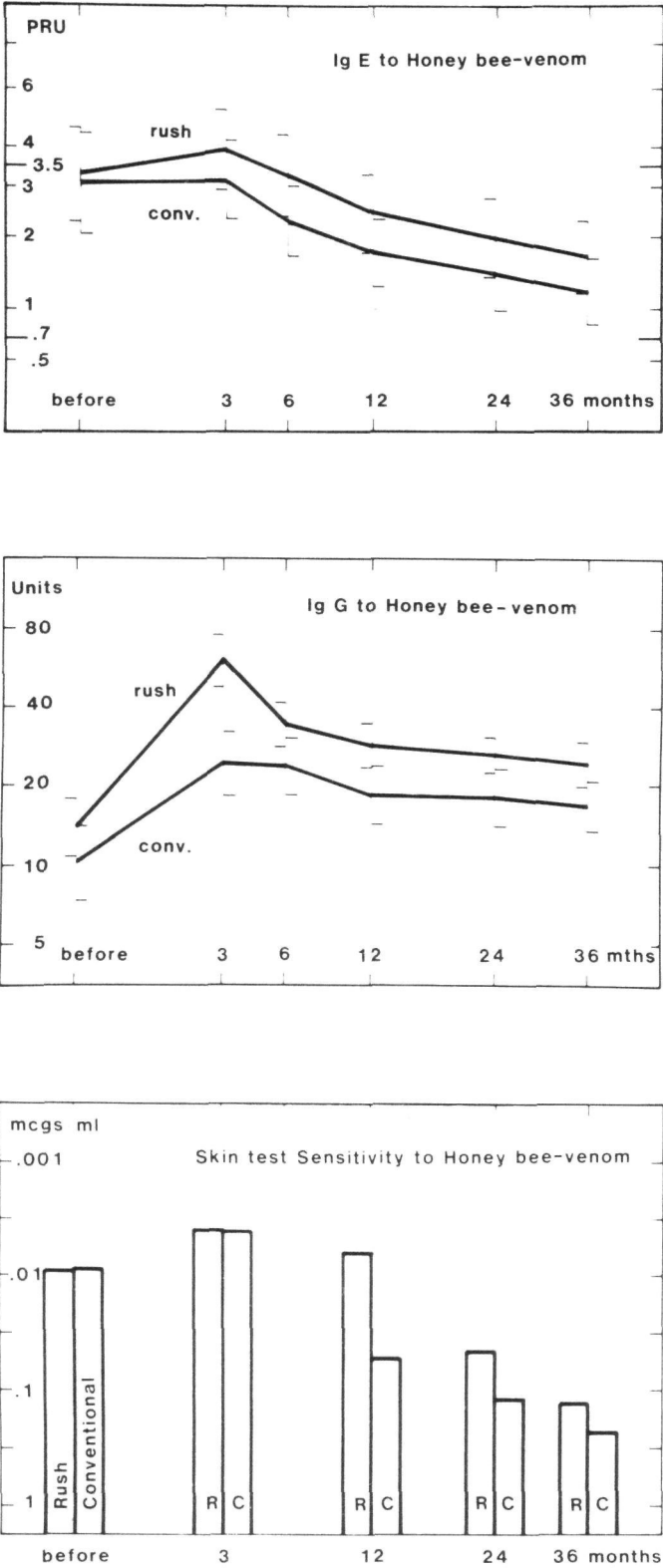


Fig. 2. Evolution of specific IgE, specific IgG and skin test reactivity to honey bee venom in 37 patients during 3 years of bee venom immunotherapy. From Thurnheer et al. (79).

Prediction of the efficacy of immunotherapy

The immune response during VIT varies widely from patient to patient. However, when mean values of venom specific serum antibodies

and skin test sensitivity are followed, there appears to be a decline in venom specific IgE and skin test reactivity and a rise in venom specific IgG within a few months. IgG then declines, and after some years of treatment the level may not be very different from naturally occurring levels in untreated patients (17) (Fig. 2). A protective IgG-antibody level has been postulated by several authors (10, 26, 85) and estimated at greater than 5 µg venom specific IgG/ml or over 150 U/ml by Pharmacia IgG-RAST or 1 ng/ml of phospholipase-IgG (39). Most individuals with venom specific IgG levels above these limits are in fact protected. In all large series, however, there are some patients whose serum IgG largely exceeds these limits and who still react to re-exposure. Most of these patients are usually highly sensitive with very high IgE titers and/or had previously experienced a severe anaphylactic reaction. The lack of protection may be related to a heterogeneous IgG response towards some specific venom components (41) or to a very high IgE immune response. On the other hand, many patients with low or even undetectable venom IgG were protected. Thus the absolute level of venom IgG may not be the “gold standard” for the prediction of efficacy of VIT nor for the selection of at risk patients (6). The increase of venom specific IgG expressed as the ratio of levels before and after 3 or 6 months of VIT may actually be a better predictive test. The interpretation of venom specific IgG titers must consider some further factors. Titration of vespid specific IgG seems to be less reliable than that of honey bee venom specific IgG. IgG subclasses may play different biological roles (15) and it has been observed in several studies (56) that the most intense response is noted in the IgG₄ subclass (1). The determination of specific IgG to purified venom proteins by specific assays, IgG-CRIE (56, 60) or immunoblotting (16), may serve as a better guide in the future. However, it has been shown that patients responding with specific IgG production to all allergenic components to which they produce specific IgE are not protected, whereas some patients without specific IgG production to major allergens do not react to stings (61,

80), thus further complicating the picture. Finally, the IgG response is clearly dependent on the age of the patient and on the treatment protocol (Fig. 2).

The most reliable test to judge the efficacy of VIT is the provocative sting challenge with a live insect (6, 63); this must be done in an intensive care unit. The amount of venom delivered by one sting seems fairly constant in the honey bee, where the sting is left in the skin (6, 34). It varies considerably, however, in vespids and may explain the more frequent negative sting challenges in vespid allergic patients (6, 34). When a patient has presented no reaction after a sting challenge, this does not necessarily mean that he is definitely protected since resensitizations during VIT have been described (46), although others (6, 63) observed no systemic reactions in a limited number of patients during repeated sting challenge. However, in an allergic patient Molkou (personal communication) recently performed two subsequent sting challenges within 2 months with a honey bee. The first challenge did not elicit any reaction whereas during the second the patient experienced a severe anaphylactic shock. A similar severe systemic reaction was also noted by Blaauw and Smithuis (personal communication) in a beekeeper's daughter who was stung by a honey bee on two occasions at a 1 year interval.

Duration of venom immunotherapy

The question as to whether VIT can be discontinued after a certain time is not yet settled. It has been suggested that it can be stopped once the skin test and RAST become negative (67, 79). In a recent study, Randolph & Reisman (68) observed that patients who had a negative RAST could stop immunotherapy whatever the result of the skin test as they did not experience systemic reactions when stung by a living Hymenoptera. Mokry et al. (49) suggested using basophil degranulation tests with washed cells as a complement to skin tests and RAST. In one study, after 3 years of treatment (79) only 15 out of 42 adult patients were negative. Disappearance of positive diagnostic tests seems

to occur more frequently in children (30, 76). It must, however, be realized that RAST interference due to the presence of high titers of venom specific IgG might cause false negative IgE-RAST results in patients under VIT (92). Duration of VIT, at least in bee venom allergy in childhood, could be predicted by considering IgE and IgG antibody levels and clinical reactivity in challenged patients. IgG < 1 PRU/ml in association with high IgG titers might indicate that discontinuation is possible (84).

In a recent study (23), VIT was stopped in 29 patients after 5 years, irrespective of diagnostic tests, and the patients were restung after an interval of 1 year without treatment. No systemic reactions were observed. On the other hand, formerly heavily exposed and totally protected bee keepers may develop severe systemic reactions after they have stopped working with bees for some time. This suggests that protective mechanisms disappear earlier than the allergy. A retrospective survey of the clinical and immunological patterns of 82 patients who had stopped immunotherapy without the consent of their physicians showed a 22% risk of systemic reactions. Some of them were extremely severe (22). This study shows that there is a substantial risk of anaphylactic reactions if immunotherapy is stopped while venom sensitivity persists and favours lifelong treatment when sensitivity remains. Further prospective studies will have to deal with the problem of the necessary duration of VIT.

Immunotherapy in particular situations

Beekeepers are at high risk for bee venom allergy. In several studies the prevalence has been estimated to be from 15 up to 43% as compared with 0.8 to 7% in the total population (7). Within the beekeeper population the degree of sensitization is inversely related to the number of stings per year (10). Most individuals who are stung by less than 50 honey bees per year have both a positive skin test and venom specific IgE-antibodies, although only a minority of them experience anaphylaxis (7). Bee venom immunotherapy should only be proposed to beekeepers with recent anaphylaxis who wish to

continue beekeeping. A minimal maintenance dose of 200 µg per month is advised and patients should be re-exposed with a sting challenge on the intensive care unit before they return to work with bees. Once the sting challenge has been tolerated, VIT can be continued possibly by the beekeeper himself with at least weekly exposures to bee stings from his own hive. Care should be taken that no more than one to two stings are given at a time and that this treatment is continued during the winter. Any beekeeper with a history of systemic anaphylactic reactions should have adrenaline for injection and inhalation available at his work place.

Should pregnant women be desensitized? Continuation of an established and well-tolerated immunotherapy is not contra-indicated during pregnancy, but VIT is not generally started during pregnancy. However, a severe anaphylactic reaction can cause an abortion and such an event is not uncommon among beekeepers' wives. In this special situation, the benefits and risks of VIT must be carefully analysed. In the exceptional case of a pregnant patient at high risk of re-exposure, VIT may be started but the protocol should be slow so as to avoid systemic reactions. No serious side effects were reported in a recent study (77).

In infancy severe allergic reactions are extremely rare (75) and mostly occur in beekeepers' families. In some cases of exceptional severity immunotherapy may be indicated. It should be remembered that symptoms of anaphylactic shock in infancy differ from those in later life.

In elderly patients allergic reactions to Hymenoptera stings may be more severe and the fatality rate is higher than in children and younger adults, probably due to the more frequent association with chronic cardiovascular and/or respiratory diseases, and in this age group more reactions may be caused by toxic mechanisms (50). On the other hand, some investigators, but not all (12), found the risk of re-exposure to be lower in the elderly. VIT is indicated in highly exposed patients or in those with severe

systemic reactions after careful examination of cardiovascular and respiratory organs. A slow protocol is recommended. Care should also be taken to avoid beta-blocking agents during VIT; these may aggravate systemic anaphylactic reactions and neutralize the effect of emergency treatment with adrenaline.

ACKNOWLEDGEMENTS

We thank Doctors P. J. Blaauw, B. Chandler-Lorenz, L. O. M. J. Smithuis & B. Wüthrich for their valuable comments, and Mrs. M. C. Anton for her typing assistance.

REFERENCES

1. Aalberse, R. C., Van Der Gaag, R. & Van Leuwen, J.: Serologic aspects of IgG₄ antibodies. I. Prolonged immunization results in an IgG₄ restricted response J. Immunol. 130, 132-138, 1983.
2. Awai, L. E. & Mekri, Y. A.: Insect sting anaphylaxis and beta adrenergic blockade: A relative contra-indication. Ann. Allergy 53, 48-49, 1984.
3. Benson, R. L. & Semenov, H.: Allergy in its relation to bee stings. J. Allergy 1, 105-112, 1930.
4. Bernard, A. A. & Kersley, J. B.: Sensitivity to insect stings in patient taking anti-inflammatory drugs. Br. Med. J. 292, 378-379, 1986.
5. Björkander, J. & Belin, L.: Diagnostic testing in hymenoptera sensitivity. In Oehling, A., et al. (eds.): Advances in allergology and applied immunology, p. 733. Oxford, Pergamon Press, 1980.
6. Blaauw, P. J. & Smithuis, L. O. M. N.: The evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital insect sting. J. Allergy Clin. Immunol. 75, 556-562, 1985.
7. Bousquet, J., Coulomb, Y., Robinet-Lévy, M. & Michel, F. B.: Clinical and immunological surveys in beekeepers. Clin. Allergy 12, 331-342, 1982.
8. Bousquet, J., Fontes, A., Robinet-Lévy, M., Aznar, R. & Michel, F. B.: Combination of passive and active immunotherapy in the treatment of honey bee venom allergy. J. Allergy Clin. Immunol. 1987, 79(In press).
9. Bousquet, J., Huchard, G. & Michel, F. B.: Toxic reactions induced by hymenoptera venoms. Ann. Allergy 52, 371-374, 1984.
10. Bousquet, J., Ménardo, J. L., Aznar, R., Robinet-Lévy, M. & Michel, F. B.: Clinical and immunological parameters in beekeepers in relation to their sensitization. J. Allergy Clin. Immunol. 73, 332-340, 1984.
11. Bousquet, J. & Valentine, M. D.: Immunotherapy with Hymenoptera venoms. In Reed, C. E. (ed.): Proceedings of the XII International Congress of Allergology and Clinical Immunology, pp. 326-334. C. V. Mosby,

- St. Louis, 1986.
12. Chandler-Lorenz, B. & Youlten, L.: How common is allergy to Hymenoptera stings in Great-Britain? Charles Blackley Symposium, Nottingham, 1984.
13. Clausen R. W.: Immune complex mediated complications of venom immunotherapy. *J. Allergy Clin. Immunol.* 72, 199-203, 1983.
14. Day, J.: A comparison of venom concentrations of 0.1 µg/ml and 1 µg/ml as indicator of sensitivity to honey bee stings. *J. Allergy Clin. Immunol.* 77, 179, 1986.
15. Djurup, R., Mallng, H.-J., Søndergaard, I. & Weeke, B.: The IgE and IgG subclass antibody response in patients allergic to yellow jacket venom undergoing different regimens of venom immunotherapy. *J. Allergy Clin. Immunol.* 76, 46-55, 1985.
16. Einarsson, R. & Persson, B.: Antibody detection in patients on immunotherapy (IT) with the immunoprint procedure. *J. Allergy Clin. Immunol.* 77, 219, 1986.
17. Engler, R. J. M., Evans, R., Smith, L., et al.: Venom-specific (VS) IgG levels after long term immunotherapy (IT): Absolute levels may not be significantly different from naturally occurring levels in untreated patients (PTS) with a history of anaphylaxis (ANA). *J. Allergy Clin. Immunol.* 77, 142, 1986.
18. Gentlesk, M. J., Hamilton, R. G., Adkinson, N. F. Jr. & Mansmann, H. C. Jr.: Assessment of venom specific IgG antibody in patients treated for hymenoptera allergy. *Int. Arch. Allergy Appl. Immunol.* 71, 233-240, 1983.
19. Georgitis, J. W. & Reisman, R. E.: Venom skin tests in insect- allergic and insect non-allergic populations. *J. Allergy Clin. Immunol.* 76, 803-807, 1985.
20. Gillman, S. A., Cummins, L. H., Kozak, P. R. & Hoffman, D. R.: Venom immunotherapy: comparison of "rush" vs. "conventional" schedules. *Ann. Allergy* 45, 351-357, 1980.
21. Golden, D. B. K., Addison, B. T., Freidoff, L. R., et al.: Epidemiology of Hymenoptera venom allergy (HVA): Prospective observations. *J. Allergy Clin. Immunol.* 77, 142, 1986.
22. Golden, D. B. K., Johanson, K., Addison, B. I., Valentine, M. D., Kagey-Sobotka, A. & Lichtenstein, L. M.: Clinical and immunological observations in patients who stopped venom-immunotherapy. *J. Allergy Clin. Immunol.* 77, 435-442, 1986.
23. Golden, D. B. K., Kagey-Sobotka, A., Gadde, J., Valentine, M. & Lichtenstein, L.: Is venom immunotherapy for ever? *J. Allergy Clin. Immunol.* 75, 208, 1985.
24. Golden, D. B. K., Kagey-Sobotka, A., Valentine, M. D. & Lichtenstein, L. M.: Dose-dependence of Hymenoptera venom immunotherapy. *J. Allergy Clin. Immunol.* 67, 370-374, 1981.
25. Golden, D. B. K., Kagey-Sobotka, A., Valentine, M. D. & Lichtenstein, L. M.: Prolonged maintenance interval in Hymenoptera venom immunotherapy. *J. Allergy Clin. Immunol.* 67, 482-484, 1981.
26. Golden, D. B. K., Meyers, D. A., Kagey-Sobotka, A. K., Valentine, M. D. & Lichtenstein, L. M.: Clinical relevance of the venom specific IgG antibody during immunotherapy. *J. Allergy Clin. Immunol.* 69, 489-493, 1982.
27. Golden, D. B. K., Valentine, M. D., Kagey-Sobotka, A. & Lichtenstein, L. M.: Regimens of Hymenoptera venom immunotherapy. *Ann. Intern. Med.* 92, 620-624, 1980.
28. Golden, D. B. K., Valentine, M. D., Kagey-Sobotka, A. K. & Lichtenstein, L. M.: Prevalence of hymenoptera venom allergy. *J. Allergy Clin. Immunol.* 69, 124, 1982.
29. Graft, D., Schuberth, K. C., Kagey-Sobotka, A., Kviterovich, K., Lichtenstein, L. & Valentine, M.: Large local reactions following hymenoptera stings in children. *J. Allergy Clin. Immunol.* 69, 124, 1982.
30. Graft, D. F., Schuberth, K. C., Kagey-Sobotka, A., et al.: The development of negative skin tests in children treated with venom immunotherapy. *J. Allergy Clin. Immunol.* 73, 61-70, 1984.
31. Grant, A. J.: Traitement de l'allergie aux piqûres de guêpes. *Rev. Franç. Allergol.* 23, 69-74, 1983.
32. Harries, M. G., Kemeny, D. M., Youlten, L. J. F., Marie, K., McMills, M. & Lessof, M. H.: Skin and radioallergosorbent tests in patients with sensitivity to bee and wasp venom. *Clin. Allergy* 14, 407-412, 1984.
33. Hoffman, D. R. & McDonald, C. A.: Allergens in hymenoptera venoms. IX. Species specificity to *Polistes* (paper wasps) venoms. *Ann. Allergy* 48, 82-86, 1982.
34. Hoffman, D. & Jacobson, R.: Allergens in Hymenoptera venom XII: How much protein is in a sting? *Ann. Allergy* 52, 276-278, 1984.
35. Hoffman, D. & Wood, C.: Allergens in Hymenoptera venom XII: Isolation of protein allergens from *Vespula maculifrons* venom. *J. Allergy Clin. Immunol.* 74, 93-103, 1984.
36. Hoveler, H., Pullman, H. & Gottmann-Lückerat, I.: Latent sensibilisierung auf Bienen- und Wespengift. *Z. Hautkr.* 58, 161-170, 1983.
38. Ingall, M., Goldman, G. & Page, L. E.: Betablockade in stinging insect anaphylaxis. *J.A.M.A.* 251, 1432, 1984.
39. Jarish, R.: Die Bienengattallergie (Model einer IgE-medierten Soforttypallergie). *Wien Klin. Wochenschr.* 92, Suppl. 122, 1-27, 1980.
40. Jarish, R., Zajc, J. & Buzath, A.: The risk of sensitization of non-allergic persons to bee venom. *Arch. Dermatol. Res.* 273, 173-174, 1982.
41. Kemeny, D. M., Mackenzie-Mills, M., Harries, M. G., Youlten, L. F. & Lessof, M. H.: Antibodies to purified bee venom proteins and peptides. II. A detailed study of changes in IgE and IgG antibodies to individual bee venom antigens. *J. Allergy Clin. Immunol.* 72, 376-385, 1983.
42. King, T. P., Joslyn, A. & Kochoumian, L.: Antigenic cross reactivity of venom proteins from hornets, wasps and yellow jackets. *J. Allergy Clin. Immunol.* 75, 621-628, 1985.
43. King, T. P., Sobotka, A. K., Alagon, A., Kochoumian, L. & Lichtenstein, L. M.: Protein allergens of white faced hornets, yellow hornet and yellow jacket venoms. *Biochemistry* 17, 5165-5171, 1978.
44. Mallng, H.-J., Djurup, R., Søndergaard, I. & Weeke,

- B.: Clustered immunotherapy with yellow jacket-venom. *Allergy* 40, 373-383, 1985.
45. Malling, H.-J. & Mosbech, H.: The indications for and the clinical effects of immunotherapy in allergy to insect stings. *Ugeskr. Laeger* 148, 1953-1957, 1986.
 46. Ménardo, J. L., Bousquet, J., Delair, L. & Michel, F. B.: Treatment failures in bee venom maintenance immunotherapy. *J. Allergy Clin. Immunol.* 73, 188, 1984.
 47. Ménardo, J. L., Bousquet, J., Ville, G. & Michel, F. B.: Allergie aux venins d'hyménoptères chez l'enfant. *Arch. Franç. Pédiatr.* 40, 543-547, 1983.
 48. Mauriello, P., Barde, S., Georgitis, J. & Reisman, R.: Natural history of large local reactions from stinging insects. *J. Allergy Clin. Immunol.* 74, 494-498, 1984.
 49. Morkry, L., Wüthrich, B. & Dietschi, R.: Zur kausalen Behandlung der Hymenopterenstichallergie. *Praxis* 38, 1005-1016, 1985.
 50. Mosbech, H.: Death caused by wasp and bee stings in Denmark 1960-1980. *Allergy* 38, 195-200, 1983.
 51. Mosbech, H.: Insect allergy. A comparative study including case histories and immunological parameters. *Allergy* 39, 543-549, 1984.
 52. Mosbech, H., Malling, H.-J., Biering, I. et al.: Immunotherapy with yellow jacket venom. A comparative study including three different extracts, one adsorbed to aluminium hydroxide and two unmodified. *Allergy* 41, 95-103, 1986.
 53. Mueller, H. L.: Stinging insect hypersensitivity: speaking out. *Ann. Allergy* 46, 83-86, 1981.
 54. Müller, U., Horat, W., Wuthrich, B., Conroy, M. & Reisman, R. E.: Anaphylaxis after hymenoptera stings in three patients with urticaria pigmentosa. *J. Allergy Clin. Immunol.* 72, 685-691, 1983.
 55. Müller, U., Lanner, A., Schmid, P., Bischof, M., Dreborg, S. & Hoigné, R.: A double blind study on immunotherapy with chemically modified honey bee venom in PEG-coupled versus crude honey bee venom. *Int. Arch. Allergy Appl. Immunol.* 77, 201-203, 1985.
 56. Müller, U., Morris, T., Bischof, M., Friedli, H. & Skvaril, F.: Combined active and passive immunotherapy in honey bee sting allergy. *J. Allergy Clin. Immunol.* 78, 115-122, 1986.
 57. Müller, U., Thurnheer, U., Patrizzi, R., Spies, J. & Hoigne, R.: Immunotherapy in bee-sting hypersensitivity. *Allergy* 34, 369-378, 1979.
 58. Müller, U. & Woermann, U.: The retrospective and prospective value of diagnostic tests in Hymenoptera sting allergy. Annual Meeting, European Academy of Allergy, Brussels 1984.
 59. Nataf, P., Guinepain, M. R. & Herman, D.: Rush venom immunotherapy: a 3 day programme. *Clin. Allergy* 14, 269-276, 1984.
 60. Nordvall, S. L., Uhlin, T., Einarsson, R., Johansson, S. G. O. & Ohman, S.: Beekeepers' IgG and IgE antibody responses to bee venom studied by means of crossed radioimmunoelectrophoresis. *Clin. Allergy* 14, 341-350, 1984.
 61. Nordvall, S. L., Uhlin, T., Ohman, S. et al.: IgG and IgE antibody patterns after immunotherapy with monomethoxy polyethylene glycol modified honey bee venom. *Allergy* 41, 89-94, 1986.
 62. Ohman, S., Björkander, J., Dreborg, S., Lanner, A., Malling, H.-J. & Weeke, B.: A preliminary study of immunotherapy with a monomethoxy polyethylene glycol modified bee venom preparation. *Allergy* 41, 81-88, 1986.
 63. Parker, J. L., Santrach, P. J., Dahlbez, M. J. E. & Yunginger, J. W.: Evaluation of Hymenoptera-sting sensitivity with deliberate sting challenges. Inadequacy of present diagnostic methods. *J. Allergy Clin. Immunol.* 96, 200-207, 1982.
 64. Patrizzi, R., Müller, U., Yman, L. & Hoigné, R.: Comparison of skin tests and RAST for the diagnosis of bee sting allergy. *Allergy* 34, 249-256, 1979.
 65. Peppe, B. C., Lockey, R. F., Madden, E. E., Baird, I. & Turkeltaub, P.: Hymenoptera venom study (HVS), treatment results, 9/30.82. *J. Allergy Clin. Immunol.* 71, 120, 1983.
 66. Ramirez, D. A., Londono, S. A. & Evans, R. III: Adverse reactions to venom immunotherapy. *Ann. Allergy* 47, 435-439, 1981.
 67. Randolph, C. S., Georgitis, J. W. & Reisman, R. E.: Clinical and immunologic response to longterm venom immunotherapy. *J. Allergy Clin. Immunol.* 73, 140, 1984.
 68. Randolph, C. C. & Reisman, R. E.: Evaluation of decline in serum venom-specific IgE as a criterion of stopping venom immunotherapy. *J. Allergy Clin. Immunol.* 77, 823-827, 1986.
 69. Reisman, R. E.: Insect allergy. In Middleton, E. Jr., et al. (eds.): *Allergy principles and practice*, pp. 1361-1377. C. V. Mosby, Saint Louis, 1983.
 70. Reisman, R. E., Dvorin, D., Randolph, C. & Georgitis, J.: Stinging insect allergy: Natural history and modification with venom immunotherapy. *J. Allergy Clin. Immunol.* 75, 735-740, 1985.
 71. Reisman, R., Müller, U., Wypych, J. & Lazell, M.: Studies on coexisting honey bee and vespidae venom sensitivity. *J. Allergy Clin. Immunol.* 73, 246-252, 1984.
 72. Reisman, R. E. & Osur, S. L.: Allergic reactions following first sting exposure: A non-IgE mediated pathogenesis? *J. Allergy Clin. Immunol.* 77, 140, 1986.
 73. Reisman, R. E., Wicher, K., Wypych, J. I., Müller, U., Lazell, M. & Arbesman, C. E.: Comparison of the allergenicity and antigenicity of yellow jacket and hornet venoms. *J. Allergy Clin. Immunol.* 65, 200-209, 1980.
 74. Saida, K., Mendell, J. R. & Sahenk, Z.: Peripheral nerve changes induced by local application of bee venom. *J. Neuropathol. Exp. Neurol.* 36, 783-796, 1977.
 75. Schuberth, K. C., Graft, D. F., Kagey-Sobotka, A. K., et al.: Do all children with insect allergy need venom immunotherapy? *J. Allergy Clin. Immunol.* 71, 140, 1983.
 76. Schuberth, K. C., Kagey-Sobotka, A. K., Kwiterovich, K. et al.: A comparison of venom treatment and a treatment in insect allergic children. *J. Allergy Clin. Immunol.* 69, 124, 1982.
 77. Schwartz, H. J., Golden, D. B. K. & Lockey, R. F.: Venom immunotherapy and the pregnant woman with

- hymenoptera allergy. *J. Allergy Clin. Immunol.* 77, 141, 1986.
78. Stuckley, M., Cabain, T., Sears, M., Cheney, J. & Dawkins, R. L.: Bee venom hypersensitivity in Busseton. *Lancet* *ii*, 41-42, 1982.
 79. Thurnheer, U., Müller, U., Stoller, R., Lanner, A. & Hoigné, R.: Venom immunotherapy in Hymenoptera sting allergy. Observations during longterm treatment. *Allergy* 38, 465-475, 1983.
 80. Uhlin, T., Nordvall, S. L. Ohman, S. & Einarsson, R.: Detailed IgG and IgE antibody patterns during immunotherapy with honey bee venom. *Allergy* (In press).
 81. Urbanek, R.: Criteria for starting and stopping venom immunotherapy. In Boström, H. & Ljungsted, N. (eds.): Theoretical and clinical aspects of allergic diseases, pp. 289-296. Stockholm, Skandia International Symposia, 1982.
 82. Urbanek, R.: Rush hyposensitization of children allergic to Hymenoptera venom. In Johansson, S. G. O. (ed.): Diagnosis and treatment of IgE-mediated diseases, pp. 146-152. Excerpta Medica, Amsterdam, 1980.
 83. Urbanek, R., Forster, J. & Kuhn, W.: Insektenstichallergie - gelöste und ungelöste Probleme. *Dtsch. Med. Wochenschr.* 107, 506-509, 1982.
 84. Urbanek, R., Forster, J., Huhn, W. Ziupa, J.: Discontinuation of bee venom immunotherapy in children and adolescents. *J. Pediatr.* 107, 367-371, 1985.
 85. Urbanek, R., Krauss, U., Ziupa, J. & Smedegard, G.: Venom specific IgE and IgG antibodies as a measurement of the degree of protection in insect sting sensitive patients. *Clin. Allergy* 13, 229-234, 1983.
 86. Van Der Zwan, J. C., Flinterman, J., Jankowski, I. G. & Kerchaert, J. A. M.: Hyposensitization to wasp venom in six hours. *Br. Med. J.* 287, 1329-1331, 1983.
 87. Wüthrich, B.: Specific immunotherapy in Hymenoptera sting allergy: Immunological aspects. *Folia Allergol. Immunol. Clin.* 33, 59-72, 1986.
 88. Wüthrich, B., Arrendal, H. & Lanner, A.: Monitoring of venom-specific IgE and IgG antibodies during immunotherapy. In Johansson, S. G. O. (ed.): Diagnosis and treatment of IgE-mediated diseases, pp. 94-106. Excerpta Medica, Amsterdam, 1980.
 89. Wüthrich, B., Dietschi, R., Marti-Wyss, S. & Cuhat, J.: Stelenwert der Basophilen-Degranulationstestes (BDT) als Verlaufskontroll einer Immunotherapie mit Hymenopterengiften. *Z. Hautkr.* (In press).
 90. Yunginger, J. W., Paull, B. R., Jones, R. P. & Santrach, P. J.: Rush immunotherapy programme for honey bee sting sensitivity. *J. Allergy Clin. Immunol.* 63, 340-347, 1979.
 91. Zelesnick, L. D., Hunt, K. J., Sobotka, A. K., Valentine, M. D., Tippet, L. O. & Lichtenstein, L. M.: Diagnosis of hymenoptera hypersensitivity by skin testing with hymenoptera venoms. *J. Allergy Clin. Immunol.* 59, 2-9, 1977.
 92. Zimmerman, E. M., Yunginger, J. W. & Gleich, G. J.: Interference in ragweed pollen and honey bee venom radioallergosorbent tests. *J. Allergy Clin. Immunol.* 66, 386-389, 1980.
 93. Zora, J., Swanson, B. & Yunginger, J. W.: How common is unrecognized Hymenoptera venom allergy in the general population. *J. Allergy Clin. Immunol.* 73, 139, 1984.

Address:

Dr. J. Bousquet

Clinique des Maladies Respiratoires

Hôpital Aiguelongue

Centre Hospitalier Universitaire

34059 Montpellier Cedex

France

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.