

Clinical and immunological surveys in bee keepers

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Summary

Two hundred and fifty bee keepers in the South of France, working seasonally, were clinically investigated by means of a questionnaire. Forty-three per cent had presented anaphylactic symptoms and 7.0% toxic reactions when stung by bees. The personal atopic history was found to be significantly ($P < 0.01$) elevated in bee keepers who experienced anaphylaxis. Total serum IgE and bee venom-specific IgE were titrated in 100 subjects. Total serum IgE was significantly elevated in allergic bee keepers ($P = 0.02$). Although bee venom-specific IgE were significantly ($P < 0.01$) higher in allergic bee keepers this parameter cannot discriminate between allergic and non-allergic bee keepers owing to a considerable overlap. Bee venom-specific IgG was assayed in seventy subjects. Their level was significantly ($P < 0.001$) higher in allergic and non-allergic bee keepers as compared with non-allergic blood donors and non-bee-keeping allergic patients. In both bee keeper groups there was no difference in bee venom-specific IgG titres.

Introduction

Bee keepers represent a 'high-allergic risk' population since they may have at least three categories of allergic disorders. They are repeatedly stung by honey bees during their work and they may experience the occurrence of anaphylactic symptoms which can be classified as 'allergic' but not as 'atopic', although IgE-mediated. When bee keepers are stung by numerous bees at the same time they may present toxic reactions which mimic anaphylaxis, but whose pathogenesis is completely different. Bee keepers may also suffer from rhinitis and/or asthma when they inhale bee bodies and dusts from hives. Finally, they are exposed to contact dermatitis after sensitization to propolis, a bee product. However, these two latter allergic conditions are less frequent and severe than anaphylaxis.

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European and American bee keepers work differently. In Europe, professional and amateur bee keepers work seasonally, starting bee keeping in April and ending in the autumn. In contrast, in the U.S.A. professional bee keepers work all-the-year-round, whereas amateurs only work seasonally as in Europe. These two different work-schedules are undoubtedly very important for the onset of anaphylaxis since the gap between the working seasons may induce immunological changes.

Honey-bee venom (BV) induces the synthesis of specific IgE- and IgG-antibodies in bee keepers who are often stung, and it has been shown that these two classes of specific antibodies are often elevated in such subjects (Jarisch & Moran, 1980; Light *et al.*, 1975; Miyachi, Lessof & Kemeny, 1979a; Muller, Speiss & Roth, 1977; Van der Zwan *et al.*, 1980; Yunginger *et al.*, 1978). However, many discrepancies are seen because in some studies both bee keepers and their families are studied (Yunginger *et al.*, 1978; Miyachi *et al.*, 1979a) and because American and European studies show immunological differences. More controversial studies have been published for BV-specific IgG antibodies. Light *et al.* (1975) and Miyachi *et al.* (1979a) have found that allergic and non-allergic bee keepers could be differentiated by the titre of these antibodies whereas others (Jarisch & Moran, 1980) did not find such results.

A personal atopic history was not found to be more common in non-bee keeping allergic patients reacting to a bee sting (Insect Allergy Committee of the American Academy of Allergy, 1965; Schwartz & Kahn, 1970; Settupane, Newstead & Boyd, 1972) but the data for bee keepers are still unclear, since the only study has been reported in bee keepers and their families (Miyachi *et al.*, 1979). They found that these two groups had a higher incidence of atopic history when they were stung and presented allergic symptoms.

Most published studies involve a relatively low number of bee keepers and the largest (Yunginger *et al.*, 1978) included both bee keepers and their families. In the present study 250 bee keepers (excluding their families) in southern France were clinically assessed by means of a questionnaire. Allergic, toxic and atopic symptoms were differentiated. In 100 subjects serum total and BV-specific IgE were titrated, and BV-specific IgG were examined in seventy subjects.

Material and Methods

Subjects

Two hundred and fifty subjects ranging in age from 19 to 75 years (mean, 43.5 ± 13.3 years) were studied. All of them were active bee keepers but some of them were only amateurs. No member of their families were included in the study. All bee keepers were living in the South of France. In this area, bee keepers start work in April and finish in the late autumn. The subjects had been bee keepers for between 3 and 44 years (mean, 18.2 ± 12.4 years). They possessed from 12 to 700 hives each. Bee keepers who had fewer than ten hives were not included in the study.

Design of the study

All bee keepers filled a questionnaire including the following items: (1) the overall importance of bee stings was examined by asking the number of years of bee keeping, the number of hives, the estimated number of stings received every year and the type of bee keeping, i.e. amateur or professional, (2) the personal atopic history was requested, and (3) the anaphylactic reactions were sought. The form was very precise for the latter

item, since the bee keepers were asked the number of bee stings likely to induce anaphylactic symptoms, the description of symptoms and the delay between the bee sting and the onset of the symptoms. It was therefore possible to differentiate toxic and anaphylactic reactions, the former appearing after at least fifty stings received at the same time.

Blood samples were collected from 100 bee keepers, seventeen non-allergic blood donors and eighteen BV-allergic patients who were not bee keepers. Blood was collected in bee keepers after the working season in October and November.

Methods of evaluation

Total serum IgE was measured using the Phadebas PRIST® technique (Pharmacia AB Diagnostics, Sweden). Bee venom-specific IgE antibodies were measured by means of the RAST® (Pharmacia AB Diagnostics). Bee venom-specific IgG antibodies were sought in seventy bee keepers by the technique of Light *et al.* (1976) which, briefly, is a modification of the Phadebas RAST®. Pharmacia Phadebas-RAST discs were used as a solid phase support, anti-IgG antibodies were raised in goats and fractionated by absorption chromatography. Serum IgE were inactivated by heating the serum for 4 hr at 56°C.

For both serum BV-specific IgE and IgE antibodies the results were expressed in classes 0–4 according to the antibody titres or in percentage of binding according to the following formula:

$$\text{Percentage of binding (\%)} = \frac{\text{Serum tested (ct/min)} - \text{Control (ct/min)}}{\text{Control (ct/min)}}$$

The RAST-interference was tested to define whether high titres of BV-specific IgG may interfere with the RAST. A pool of sera of six bee keepers who had very high BV-specific IgG-antibody titres was heated at 56°C for four hours to destroy the IgE antibody. Serial amounts of this serum pool were subsequently added to the sera of four BV-allergic patients, who did not present any BV-specific IgG antibodies in their serum. After an incubation of 30 min, the RAST was performed.

Results

Clinical studies

All the bee keepers studied had kept bees for between 3 and 44 years. Thirty of them were professional bee keepers, but most subjects studied were farmers and bee keeping was part of their work. Bee keeping was a hobby in only twenty-five subjects.

Fifty per cent of the subjects did not present any symptoms when stung by bees. In contrast 7.0% had toxic reactions, 40% anaphylactic reactions and 3.0% had both toxic and anaphylactic reactions. Three bee keepers had anaphylactic reactions severe enough to start a BV immunotherapy. Usually most patients describe their anaphylactic symptoms when they receive their first stings in the spring and they disappear after subsequent stings. Some other subjects only suffered from anaphylactic symptoms during the first years of their work. In patients having asthma or rhinitis induced by bee strings, symptoms may last a few days to a few weeks after the working season, a time when the patient does not receive any more stings.

Anaphylactic symptoms usually occurred in the minutes following the sting, rarely

later and although some very rare (five) late reactions appeared from 24 to 48 hr after a sting, they could not be classified as anaphylactic. In all cases they were in the form of an inflammatory reaction in the joints which lasted a few hours. Symptoms varied from one subject to another, 60% of them having a single reaction, the others multiple reactions at the same time. Large local reactions that persisted longer than 48 hr were present in 40% of allergic bee keepers. Generalized urticaria occurred in 17%, other systemic reactions in 65% of allergic bee keepers, but, in most cases the reactions were minor to moderate. Only three subjects had severe and long-lasting reactions which ought to be treated by means of BV immunotherapy. Anaphylactic shock was not usually severe and was present in 15% of the patients, wheezing and asthma in 12%, nasal obstruction and/or nasal discharge in 11%, vomiting and/or abdominal cramps and/or diarrhoea in 7.0%, non-life threatening laryngeal oedema in 14% and transient neurologic symptoms such as paraesthesia and/or ataxia and/or tremor in 7.0%.

All these symptoms could be separated from either toxic reactions, which mimic them, but appeared after at least fifty bee stings at the same time or from allergic reactions induced by the inhalation of bee bodies and dusts of the hives. The latter symptoms were present in four subjects who had both asthma and rhinitis.

Three bee keepers described a severe transient outbreak of anaphylaxis. A 59-year-old man, who had not presented any anaphylactic symptoms before being given a yellow fever vaccination, experienced several anaphylactic shocks after the vaccination when stung by bees. This condition lasted 3 months. Two other bee keepers were also symptom-free when stung by bees, but after a surgical procedure they had anaphylactic reactions lasting a few weeks. One of these two subjects had two procedures and presented two outbreaks of anaphylaxis.

A personal atopic history, only assessed by a questionnaire, was found to be significantly ($P < 0.02$) elevated in bee keepers who had anaphylactic symptoms, since 41% of them had asthma, and/or hay fever and/or atopic dermatitis as opposed to 16% of bee keepers who had anaphylaxis.

Immunological studies

Total serum IgE ranged from 5 to 100 ku/l (Fig. 1). Bee keepers who had anaphylaxis had a significantly ($P = 0.02$) higher mean-level (170 ± 241 ku/l) than those who were symptom-free (75 ± 256 ku/l), although there is an important overlap between both groups.

Bee venom-specific IgE was found to be present in six out of seventeen non-allergic blood donors, seventeen out of eighteen allergic non-bee keeper patients, forty-three out of fifty-nine non-allergic bee keepers and thirty-six out of forty-one allergic bee keepers (Fig. 2). Non-allergic blood donors had low titers of BV-specific IgE when they existed. Very high titres of BV-specific IgE were found only in allergic patients (non-bee keepers and the three bee keepers who had immunotherapy). The mean difference between both groups of bee keepers is significant ($P < 0.01$) although there is an important overlap between them.

The correlation between total and BV-specific IgE in bee keepers (Fig. 3) shows that the higher the BV-specific IgE titre the higher the total serum IgE titre ($P < 0.01$). Bee keepers without serum BV-specific IgE had a median total serum IgE-level (44 ± 74 ku/l) very similar to normal subjects (38 ± 45 ku/l) (Bousquet *et al.*, 1982). Non-atopic bee keepers had BV-specific IgE median-levels significantly ($P < 0.01$) lower than atopic bee keepers (Fig. 4).

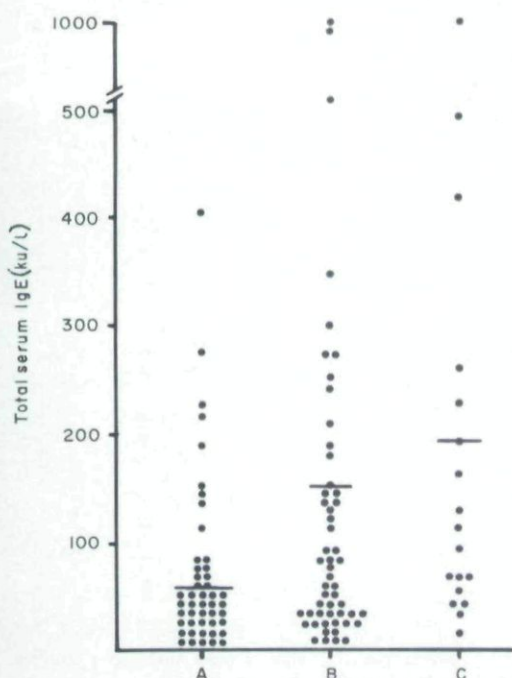


Fig. 1. Total serum-IgE concentrations in (A) non-allergic bee keepers, (B) allergic bee keepers and (C) non-bee keeping allergic patients; $P_{A/B}=0.02$, $P_{B/C}$ =Not significant.

Bee venom-specific IgG was found to be elevated in both bee keeper groups (Fig. 5). There is no difference between allergic and non-allergic bee keepers. On the other hand, normal blood-donors and non-bee keeping allergic patients had very low BV-specific IgG. There is no overlap between both bee keeper groups and both non-bee keeper groups. The correlation between BV-specific IgE and IgG antibodies is shown in Fig. 6. Although there is a tendency for low BV-specific IgE to be associated with high BV-specific IgG, the difference is not statistically significant.

Some bee keepers had no BV-specific IgE in their serum whereas BV-specific IgG titres were very high. In order to find out whether this high BV-specific IgG titre could interfere with the RAST, a RAST-interference was made. The results are presented in Table 1 and it can be seen that there is no interference for two sera (S3 and S4) whereas a certain percentage of interference (24 and 42%) was observed for the other two (S1 and S2).

Discussion

Bee keepers represent a 'high risk' population for anaphylaxis since it was experienced by 42% of the 250 subjects included in the present study. Moreover 8.0% had a toxic reaction. In most cases anaphylactic symptoms were transient and rarely severe. The results presented are in accordance with previous studies (Muller *et al.*, 1978; Miyachi *et al.*, 1979b) made in Europe whereas Light *et al.* (1975) in the U.S.A. and Weill *et al.* (1978) in a much smaller study in Europe found a lower rate of anaphylaxis. The discrepancies may be related to the type of work, since anaphylaxis occurred more frequently in Europe where bee keeping is seasonal than in the U.S.A. where they work

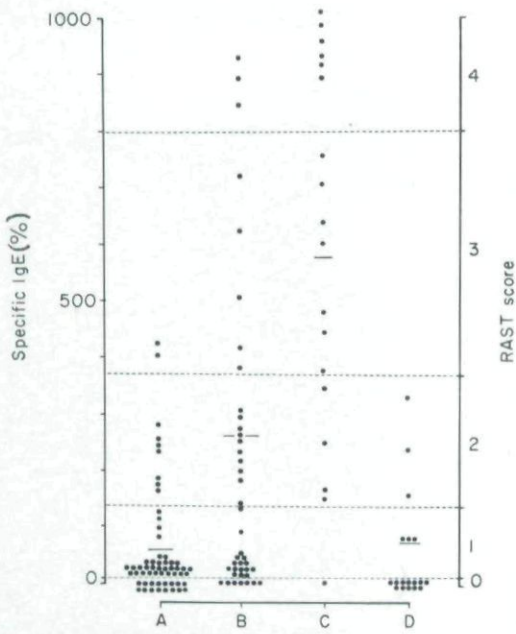


Fig. 2. Bee venom-specific serum IgE in (A) non-allergic bee keepers, (B) allergic bee keepers, (C) non-bee keeping allergic patients and (D) non-allergic blood donors; $P_{A/B} < 0.01$, $P_{B/C} < 0.02$.

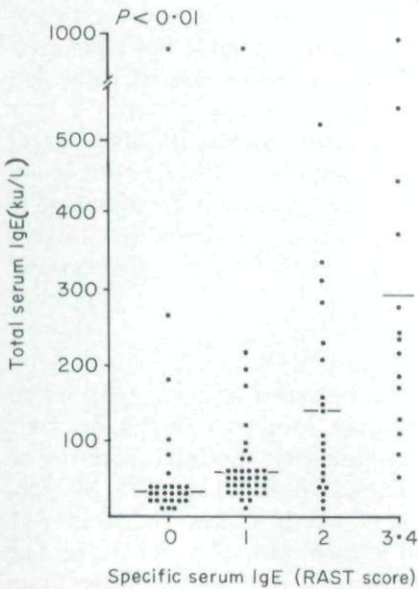


Fig. 3. Variation of total serum-IgE according to the concentration of BV-specific serum IgE.

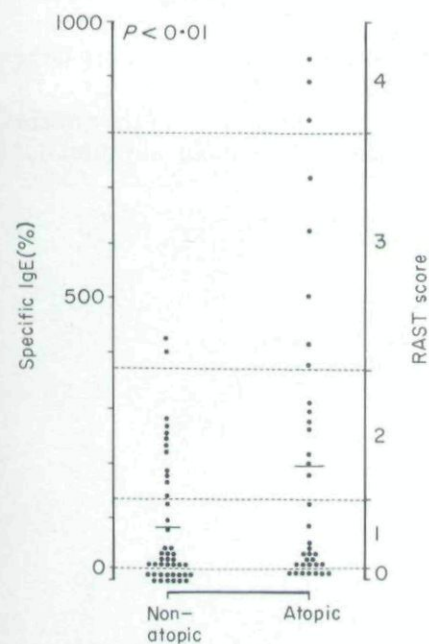


Fig. 4. Bee venom-specific IgE in atopic and non-atopic bee keepers.

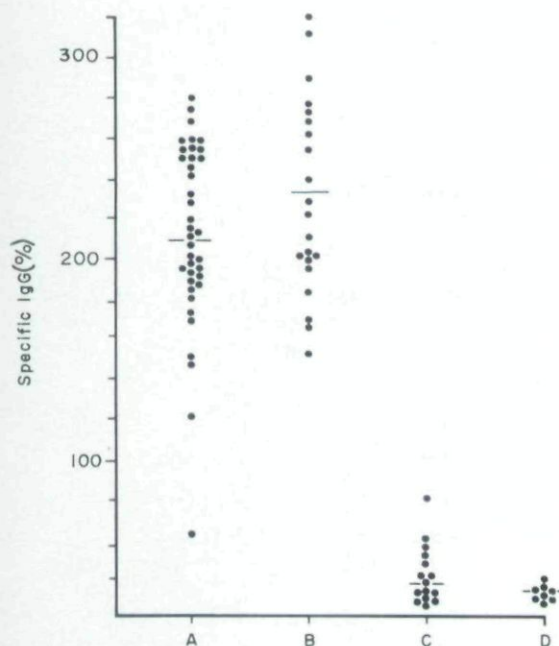


Fig. 5. Bee venom-specific IgG in (A) non-allergic bee keepers, (B) allergic bee keepers, (C) non-bee keeping allergic patients and (D) non-allergic blood donors; $P_{A/B}$ = Not significant, $P_{A/D} < 0.001$, $P_{B/C} < 0.001$.

throughout the year. The gap between the working seasons in Europe may induce some immunological changes resulting in a higher rate of anaphylaxis. Finally, in the large study of Yunginger *et al.* (1978) both bee keepers and their families were studied and it appears that there is a considerable difference between both groups. In the present study the great majority of anaphylactic symptoms were not severe and only three out

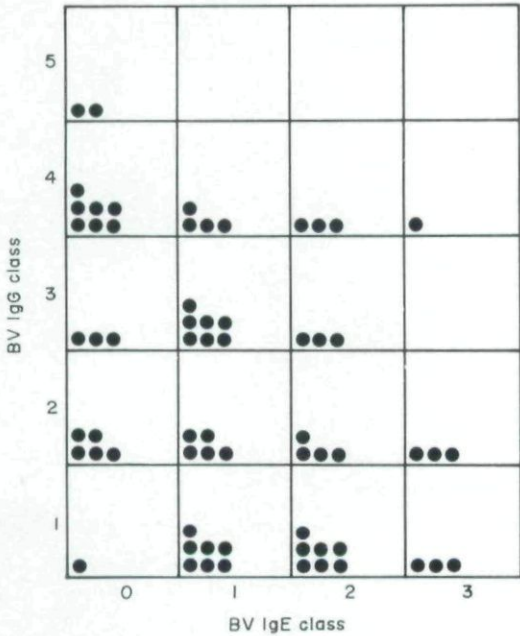


Fig. 6. Correlation between BV-specific IgE and IgG.

Table 1. Interference in honey-bee venom RAST.

Pool of heated serum of bee keepers		0.0 ml	0.1 ml	0.2 ml	0.3 ml
Serum of allergic patient		0.4 ml	0.4 ml	0.4 ml	0.4 ml
S1	ct/min	1323	1252	1004	954
	Interference (%)		4.0	24	28
S2	ct/min	4360	3205	2522	3189
	Interference (%)		25	42	26
S3	ct/min	7095	6717	6884	7257
	Interference (%)		5.0	3.0	-2.0
S4	ct/min	4570	4818	3780	5241
	Interference (%)		-5.0	7.0	-15.0
Pool of heated serum of bee keepers					
	(ct/min)		97	195	292
	(ml)		0.1	0.2	0.3

S1, S2, S3, S4: serum of allergic patients

of 250 bee keepers had life-threatening attacks of anaphylaxis. Moreover three patients had a transient outbreak of anaphylaxis. These three patients had never before presented any anaphylactic symptom. Symptoms appeared immediately after a yellow fever vaccination or surgical procedures, they were transient, lasting less than 3 months, and did not reappear. These three attacks can be related to events which induced a breakdown of the tolerance. These observations lead to the conclusion that bee keepers should be aware of emergency kits and should be told of possible outbreaks of anaphylaxis. These features could also explain some unexplained side-reactions in patients undergoing BV-specific immunotherapy when they have reached the maintenance doses.

A personal atopic history was found to be present in more than two-fifths of allergic bee keepers. This high rate of atopic patients is very close to that found by Miyachi *et al.* (1979), who detected an atopic history in 47% of allergic bee keepers. In contrast, Yunginger *et al.* (1978) only disclosed 29% of atopic subjects in bee keepers and their families who had anaphylaxis. Members of the bee keepers' families usually represent an intermediate group between bee keepers who are repeatedly stung and non-bee keepers who are occasionally stung. Thus, although BV allergy occurs with a similar incidence in atopic and non-atopic subjects who are non-bee keepers (Insect Allergy Committee, 1967; Schwartz & Kahn, 1970; Settiple *et al.*, 1972) an atopic history seems to pre-dispose bee keepers to anaphylactic reactions to bee stings.

Immunological studies made in bee keepers show that a large proportion of subjects have elevated titres of BV-specific IgG antibodies and some also have BV-specific IgE antibodies in their serum (Kagey-Sobokta & Lichtenstein, 1981). The incidence of whole BV- or phospholipase A2-specific IgE antibodies in the sera of bee keepers ranges from 20% (Jarisch & Moran, 1980) to 81% (Yunginger *et al.*, 1978) as presented in Table 2. However, the presence of BV-specific IgE antibodies cannot discriminate allergic from non-allergic bee keepers whatever the study (Muller *et al.*, 1977; Light *et al.* 1975; Yunginger *et al.*, 1978; Jarisch & Moran, 1980). The present study is in agreement with previous data and showed that:

- (1) atopic bee keepers had significantly ($P < 0.01$) elevated levels of BV-specific IgE,
- (2) bee keepers who had anaphylaxis had a significantly ($P < 0.01$) higher median-level of serum BV-specific IgE than non-allergic bee keepers,
- (3) the titre of total serum IgE is more or less related to that of BV-specific IgE and
- (4) some bee keepers did not present any BV-specific IgE in their serum.

As the latter data could arise from a RAST-interference (Vervloet *et al.*, 1975; Aalberse, Reerink-Brongers & Verneulen, 1973; Zimmermann, Yunginger & Gleich, 1980) the blocking activity of BV-specific IgG was sought. Although such a phenomenon does exist, at least for some sera (Table 1), it does not explain the reasons why some bee keepers had no serum BV-specific IgE at the end of the working season. Another hypothesis may be postulated. A natural, specific immunotherapy may exist in some patients leading to a decreased synthesis of BV-specific IgE; however, there is no direct inverse relationship between BV-specific IgE and IgG antibodies. Or some bee keepers could only respond to BV by an IgG response; however, this hypothesis is not very attractive since some rare, allergic bee keepers who presented anaphylaxis several years ago had no serum BV-specific IgE antibodies detectable. Georgitis *et al.* (1981) clinically and immunologically studied patients who had anaphylactic symptoms in the

Table 2. Serum bee venom-specific IgE antibodies in bee keepers

Studies	n	All bee keepers (%)	Bee keepers (%)	
			Allergic	Non-allergic
Jarisch and Moran (1980)	115	21		
Light <i>et al.</i> (1975)	34	33		
Muller <i>et al.</i> (1977)	57	40		
Yunginger <i>et al.</i> (1978)	132	81	95	74
Present study	100	79	88	73

past, but who did not present any venom-specific IgE when they were assessed. Twenty-one re-stings occurred in these non-treated patients and they experienced nine systemic reactions. These results are in accordance with the present study and suggest that factors other than venom-specific IgE antibodies clinically affect anaphylaxis. STS-IgG specific antibodies should be studied in bee keepers.

Bee keepers who experienced anaphylaxis could not be discriminated by BV-specific IgE although they had a significantly higher mean-level of BV-specific IgE than those who had no anaphylaxis. Very high BV-specific IgE titres were only disclosed in allergic patients (bee keepers and non-bee keepers). Atopy was shown to pre-dispose to anaphylaxis in bee keepers, but not because there is an increased synthesis of IgE. It is therefore possible that atopic patients have an imbalance between IgE and IgG synthesis and the gap between the working seasons may pre-dispose to anaphylaxis. Or atopic patients may have an increased mediator-release, leading to symptoms when they are stung in very particular occasions such as the beginning of the working season.

Bee venom- (BV) or BV phospholipase A2-specific IgG were titrated in some studies (Light *et al.*, 1975; Yunginger *et al.*, 1978; Jarisch & Moran, 1980; Van der Zwan *et al.*, 1980) whereas Muller *et al.* (1977) studied haemagglutinating antibodies directed against BV. In all studies non-bee keepers had low titres of BV-specific IgG antibodies, whereas bee keepers had elevated titres except in the study of Yunginger *et al.* (1978) which included bee keepers and non-bee keepers. Light *et al.* (1975) and Miyachi *et al.* (1979a) could discriminate between allergic and non-allergic bee keepers by their titre of BV-specific IgG allergic bee keepers having lower titres. They suggested that BV-specific and IgG could protect bee keepers, acting as blocking antibodies. Lessof, Sobotka and Lichtenstein (1976) demonstrated a successful protection of bee stings in allergic patients by passive immunization with sera of bee keepers suggesting also a direct protective effect of IgG-blocking antibodies. Other studies (Jarisch & Moran, 1980; Muller *et al.*, 1977) did not find a direct relationship between BV-specific IgG antibodies and a significant protection of bee keepers against bee stings. Other mechanisms may therefore play a role in the protection of non-allergic bee keepers who usually have both BV-specific IgE and IgG antibodies. Bee venom-specific IgG₁ and IgG₄ were examined by Van der Zwan *et al.* (1980) who disclosed that an initial elevated IgG₄ titre and a decreasing IgG₁:IgG₄ ratio was found in bee keepers who tolerated bee stings perfectly. The kinetics of the immune response, following bee stings shows that the increase in IgG-antibody response appears to be slightly delayed as compared with the IgE-antibody response. Moreover, the IgE response persists

longer than the IgG response (Kagey-Sobokta & Lichtenstein, 1981). Thus French bee keepers who are not normally stung during the winter may have at the beginning of the working season an IgE:IgG ratio which favours, at least in some selected cases, the occurrence of anaphylaxis. Atopic bee keepers who have significantly higher mean-values of BV-specific IgE are probably more sensitive than non atopics.

Atopy seems to pre-dispose to anaphylaxis in bee keepers (Miyachi *et al.*, 1979; present study) although the tendency is lower than for inhalant allergens. Most bee keepers are capable of synthesizing a high IgE-antibody level and very high amounts of BV-specific IgG antibodies. Both allergic and non-allergic bee keepers synthesize BV-specific IgE and this parameter cannot differentiate between the two groups.

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