

The clinical spectrum of anaphylaxis in north-west England

R. S. H. PUMPHREY and S. J. STANWORTH

Department of Immunology, Central Manchester Trust Hospitals, Manchester, UK

Summary

Objective To assess the clinical spectrum of anaphylaxis with a view to developing management guidelines and as a foundation for an epidemiological study.

Methods Study of the reaction histories and investigations of 172 patients, including children and adults, referred because of anaphylactic reactions

Results Over 700 reactions occurred in 172 patients from age 5 months to 69 years. There were equal numbers of males and females; when ranked by age at worst reaction, the youngest quartile (0–4 years) was 75% male and the oldest quartile (40+ years) was 74% female. The severity of reactions graded continuously from fatal to mild. One hundred and twenty of 172 had two or more reactions; the worst reaction was the first in 33, midsequence in 35 and the most recent in 52. Suspected causes of each patient's worst reaction associated with positive allergy tests include peanuts (42), tree nuts (23), other foods (25, in five associated with exercise), venoms (six bee, 22 wasp), muscle relaxants (seven) and latex (six). Twenty were classified as idiopathic and, in a further 13, investigation of the suspected cause proved negative. There was doubt about the nature of some of the 'reactions' reported even though these had been treated as for anaphylactic reactions.

Conclusion The clinical spectrum of anaphylaxis has been defined for the area served by our unit. Management guidelines and future epidemiological studies will have to address the continuous distribution of severity of reactions, the wide age range and the multiplicity of causes.

Keywords: anaphylaxis-diagnosis, anaphylaxis-aetiology, severity-of-disease-index, infant, child, adolescent, adult

Clinical and Experimental Allergy, Vol. 26, pp. 1364–1370. Submitted 4 December 1995; revised 13 May 1996; accepted 24 June 1996.

Introduction

Anaphylaxis is characterized by the occurrence of acute, severe reactions, often with bronchospasm, angioedema and hypotension, and often occurring within minutes of exposure to specific allergens. There have been many case reports and some studies of anaphylaxis due to selected causes but the clinical spectrum of anaphylaxis in the UK has not been defined. Recently a 3-year study of anaphylactic reactions seen in a single centre provided valuable information about the scope of anaphylaxis seen in an emergency referral centre in the USA [1]; this is the first report of a study of the clinical spectrum of anaphylaxis in the UK and reflects the experience of an

Immunology Department providing a specialist service in the investigation and long-term management of these patients. The information was collected prospectively following an audit workshop sponsored by the Royal College of Physicians and British Society for Allergy and Clinical Immunology in December 1993 which highlighted lack of knowledge about the clinical spectrum of anaphylaxis.

Materials and methods

Selection of patients

Patients attending the clinics since January 1994 with acute allergic or angioedematous reactions were considered and those whose reactions had at least two of the main indicators of anaphylactic reactions (hypotension, bronchospasm and angioedema/urticaria) were included. As

Correspondence: R. S. H. Pumphrey, Department of Immunology, Central Manchester Trust Hospitals, Manchester M13 0JH, UK.

Table 1. Severity scores used for recording symptoms during acute reactions reported by patients.

	Score			
	1	2	3	4
Hypotension	Faint/dizzy	Unconscious	Prolonged unconsciousness	Cardiac arrest
Bronchospasm	Wheezy	Severe	Poor response to therapy	
Angioedema	Lips/face	Generalized	Severe	
Pharyngeal oedema	Hoarse	Difficulty in swallowing	Severe difficulty in breathing	
Urticaria	Mild	Generalized	Generalized and severe	
Pruritus	Mild	Severe		
Conjunctivitis	Mild	Severe	Ulcerated	
Vomiting	Once	Severe	Prolonged over hours	
Diarrhoea	Once	Severe	Prolonged over hours	
Uterine	Period pains	Severe cramps	Bleeding	
CNS	Describe all			

CNS, Central nervous system.

this study was undertaken to provide information for management guidelines, and because an adrenaline kit for self-treatment poses specific management problems, all patients who had been prescribed adrenaline for self-treatment of their reactions were included in the study even if they did not meet the main criteria for inclusion. Although all patients were seen in the Central Manchester clinics, most of the patients were referred from seven adjacent districts through our liaison with physicians, paediatricians and accident and emergency departments in other hospitals. Two patients who were referred for investigation of anaphylactic reactions *post mortem* during this time have also been included. Patients whose reactions were due entirely to angiotensin converting enzyme (ACE) inhibitors were not included, nor were the details of a patient who had been treated in casualty on four occasions for anaphylactic reactions whose symptoms were subsequently found to be due to acquired C1 esterase inhibitor deficiency.

History of reactions

A proforma was developed for use in the clinic to ensure consistent recording of the date, time and progression of all reactions together with any treatment given and by whom, and the effects of this treatment. The following symptoms were scored on a point scale (Table 1): faintness, dizziness, loss of consciousness (as measures of hypotension), difficulty in breathing (where possible distinguishing between wheezing and obstruction due to swelling in the throat), other swellings, rashes, itching, sneezing, vomiting, diarrhoea, pain (abdominal, chest, period-pain) and any other symptoms starting suddenly during the course of the reaction.

Grades of reaction

Reactions were classified as fatal, major or minor. Major reactions were taken as those where the sum of the scores for the principal symptoms (hypotension, bronchospasm and angioedema) was ≥ 3 , or was 2 with ≥ 3 additional points from the other symptoms. The worst reaction for each patient was either identified by the patient or by analysis of the accumulated score of symptoms in the case of multiple reactions. An empirical formula was used to combine the symptom scores to allow ranking of the severity of the worst reaction for each patient: severity index = $4 \times$ (score for hypotension + bronchospasm + pharyngeal oedema) + $2 \times$ (score for angioedema + urticaria) + (sum of all other scores).

Investigation of potential allergens

Skin prick tests (SPT) were performed in duplicate using allergen extracts (supplied by ALK, Denmark or Bencard, UK, where available, otherwise fresh extracts) applied using Morrow-Brown needles; 1000-, 100- and 10-fold dilutions were used in turn for allergens suspected of provoking severe reactions. Negative and positive (histamine 1 mg/ml) controls were always used. Pharmalgen venoms were used for bee and wasp; negative SPT were followed by intradermal tests.

Allergen-specific IgE was measured using the Pharmacia, Sweden, Cap system; total IgE was measured by an ELISA-based chemiluminescence assay. Mast cell tryptase was measured using the Pharmacia radioimmunoassay.

In some cases negative investigations for suspected food-related anaphylaxis were followed by open food challenge.

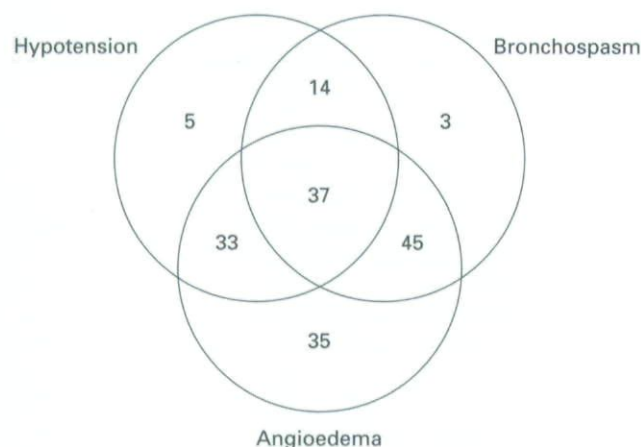


Fig. 1. Venn diagram showing overlap between principal features (our interpretation of patients' symptoms, see text) during the worst reaction in 172 patients. Records of blood pressure during their worst reaction were available for very few patients and it was often difficult to distinguish whether difficulty in breathing was due to pharyngeal oedema or bronchospasm.

Results

Between them the 86 females and 86 males included in this study experienced a total of two fatal reactions, 280 major reactions (as defined in the materials and methods) and over 430 minor reactions (the equal numbers of male and female was a chance finding, not selected). As well as the three major symptoms shown in Fig. 1, 80 patients reported pruritus (often the first symptom of a reaction), 54 vomiting, 32 conjunctivitis, 10 diarrhoea, six sneezing, four excessive salivation, three rhinorrhoea and in one case clear fluid was said to have discharged from both ears. Others experienced abdominal or back pain and transient CNS disturbances (three deafness, four loss of vision, one paralysis of limbs, one possible epileptic fit). Two patients reported severe pain similar to that experienced at menstruation; in one this was accompanied by bleeding.

One hundred and twenty-nine patients had been prescribed adrenaline for emergency self-treatment. Of these, 16 had only one of the main features of an anaphylactic reaction in their worst reaction; their ages ranged from 9 months to 18 years; 13 were male and three female; 15 had reacted to nuts and/or peanuts and one was an apparently idiopathic reaction; 12 had angioedema/pharyngeal oedema, two asthma and two urticaria.

A severity index was calculated for each patient's worst reaction; reactions in females ranked significantly higher than those in males ($P = 0.002$, Wilcoxon Mann-Witney) and, when patients were ranked by age at worst reaction, the lowest quartile had the least severe

reactions and the third quartile (19–39 years) the most severe reactions ($P < 0.0001$, Kruskal-Wallis one-way Anova) (Table 2, Fig. 2). There was no significant relationship between multiplicity of reactions and severity, or atopy and severity.

A history of asthma, atopic eczema or allergic rhinitis unrelated to the reactions was taken as an indication of atopy. One hundred and two patients (59%) fell into this category; the association between atopy and anaphylaxis was most noticeable in young patients, and for reactions to foods (Table 2). Six patients were on β -blockers at the time of their reaction and one also on an ACE inhibitor; these medications may have contributed to the severity of their reactions [2,3].

Multiple reactions were seen in 120 patients (78 of 102 atopics and 42 of 70 non-atopics) and were not confined to any particular age or sex group, nor was there an apparent relationship between the severity of the worst reaction and a history of multiple reactions. The worst reaction was the first in 33, and the most recent in 52; further analysis of these sub-groups did not suggest that patients with anaphylaxis due to particular allergens showed a different pattern with respect to earlier and later reactions except for latex where the last reaction was the worst in six of six patients. There was a strong tendency for multiple reactions to follow the same pattern in each patient but with severity varying apparently randomly from one attack to the next.

Skin prick tests and allergen-specific IgE testing were used to investigate the cause of reactions suggested by the history; the results are summarized in Fig. 2 and Table 2. In 90 of 103 cases related to food there was a good correlation between history, SPT and specific IgE. However, in 13 of 103 cases, despite a history suggesting anaphylaxis related to foods, no allergen could be identified or the suspected allergen was disproved by negative tests followed by open challenge. In a further 20 cases the reactions were classified as 'idiopathic' [4]. Interpretation of negative challenge tests (including double-blind placebo-controlled food challenges (DBPCFC)) in patients with a history of anaphylactic reactions is complicated by the common requirement for cofactors, such as exercise, for the allergen to cause a reaction. We feel that negative open challenge combined with negative specific IgE and SPT constitutes strong negative evidence for implication of an allergen with a reaction.

One fatal reaction was to walnuts in an 18-year-old male previously known to be sensitive to peanuts; the other, in a 33-year-old male, is thought to have been due to atracurium. In both, the serum mast cell tryptase measured immediately *post mortem* was raised (15 and 60 ng/ml, respectively).

Table 2. The cause of the worst reaction in each of the 172 patients

	Age (years)								Subtotal		Total
	0-4		5-18		19-39		40 +				
	M	F	M	F	M	F	M	F	M	F	
Muscle relaxants	0	0	0	0	1	3	0	3	1	6	7
Other drugs*	0	0	0	0	2	1	1	4	3	5	8
Wasp venom	0	0	1	1	5	3	4	8	10	12	22
Bee venom	0	0	0	1	1	0	1	3	2	4	6
Latex	0	0	1	0	0	3	1	1	2	4	6
Peanut	19	4	10	7	1	0	1	0	31	11	42
Other nuts†	7	3	4	5	2	2	0	0	13	10	23
Other food‡	6	2	5	4	2	4	0	2	13	12	25
?Food§	1	0	0	1	3	4	2	2	6	7	13
Idiopathic	1	0	1	2	1	5	2	8	5	15	20
Total	34	9	22	21	18	25	12	31	86	86	172

									Subtotal		Total
	A		N		A		N		A	N	
	A	N	A	N	A	N	A	N	A	N	
Muscle relaxants	0	0	0	0	2	2	2	1	4	3	7
Other drugs*	0	0	0	0	1	2	1	4	2	6	8
Wasp venom	0	0	0	2	0	8	3	9	3	19	22
Bee venom	0	0	0	1	0	1	1	3	1	5	6
Latex	0	0	0	1	3	0	1	1	4	2	6
Peanut	20	3	14	3	1	0	0	1	35	7	42
Other nuts†	8	2	8	1	4	0	0	0	20	3	23
Other food‡	7	1	6	3	3	3	0	2	16	9	25
?Food§	0	1	1	0	4	3	2	2	7	6	13
Idiopathic	1	0	3	0	4	2	2	8	10	10	20
Total	36	7	32	11	22	21	12	31	102	70	172
Number in quartile	43		43		43		43				

*Includes gelofusine, haemaccel, lignocaine, penicillin and naproxin.

†Includes walnut (three), almond (three), brazil nut (nine), hazel nut, pistachio (four) and cashew (three).

‡Includes eggs (four), milk (three), gelatine, sesame (two), soya (two), lentils, potato, apple, strawberry (two), banana (two), peach, cherry, fish (two) and shellfish (two).

§Comprises those patients where the history suggested that a food was the cause of their reactions but the specific food could not be identified by positive allergy tests.

The first quartile includes three males and one female in the first year of life (7, 8, 9 and 10 months of age, two reacting to egg, two to peanut) and six males and one female in the second year of life (one reacting to milk, one to eggs and five to peanuts). The age of the patient is the age at worst reaction.

M, male; F, female; A, atopic; N, non-atopic.

Discussion

We have collated the details of over 700 reactions in 172 patients providing information on the clinical spectrum of anaphylaxis, an area which has not been well reported.

Anaphylaxis occurs at all ages in both sexes, and frequently in the setting of a history of atopy. A majority of patients in this study reported multiple reactions but there was no clear evidence to support a commonly held belief that reactions become progressively more severe

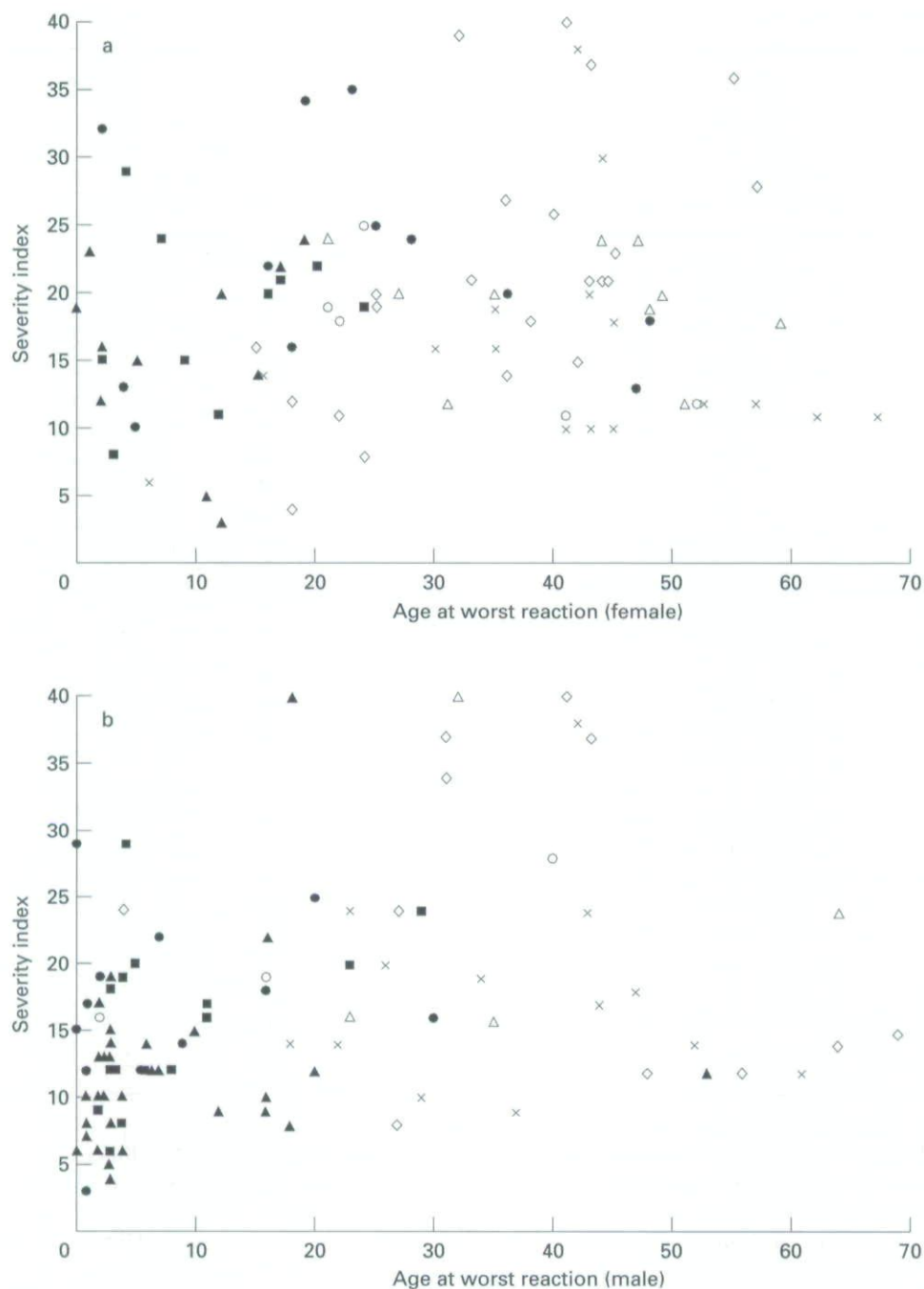


Fig. 2. Scatter plots for (a) females and (b) males of severity against age at worst reaction indicating the cause of the reactions. ●, food; ■, nut; ▲, peanut; ○, latex; x, venom; △, drug; ◇, idiopathic.

[5,6]; we found that comparable numbers of patients reported that their worst reaction was either the first, last or mid-sequence.

There was a significant ($\chi^2 = 24$ with 3 degrees of freedom; $P < 0.0001$) trend for males to experience their worst reaction younger than females, partly as the result of an excess of young atopic males reacting to foods and

of older non-atopic females with idiopathic, drug or insect venom reactions. It will be of interest to see whether further studies support these apparent biases in sex distribution. The association of food reactions with atopy and the lack of such an association for drug and venom reactions is in line with previous studies [7,8]. Reactions to nuts in very young children (we found seven

in children under 1 year old with reactions to peanuts) generate great anxiety but must rarely be fatal.

Fifty of the 72 patients with multiple reactions to food had histories of reactions and allergy tests that suggested that they reacted to more than one allergen. In some cases this may have been due to cross-reacting allergens (e.g. banana and latex) [9], in others cross-reaction seems unlikely (e.g. egg and peanut). It seems more likely that this is a reflection of an underlying tendency to severe allergic reactions rather than an unrecognized similarity between the allergens involved. As DBPCFC were not performed it is always possible that this test would have been negative in up to 60% of these patients.

In some cases it was difficult to interpret the symptoms described by the patients; for example, it was not always possible to ascertain whether difficulty in breathing was due to pharyngeal oedema or bronchospasm, or whether their faintness, dizziness, deafness or loss of vision were due to hypotension. There were records of low blood pressure at the time of the reaction for only a minority of patients and objective measurement of airways resistance for none. The differential diagnosis of anaphylaxis as a medical emergency is clearly wide, and we accept that it is possible that we and others over-diagnosed anaphylactic reactions in these patients. Mast cell tryptase measurements have been proposed as a useful indicator of anaphylactic reactions [10]. In the few patients where we had results for this analyte it proved helpful in understanding the nature of their reactions; we now strongly recommend that blood samples for tryptase measurements are taken during all acute reactions for which anaphylaxis is considered. In those patients with negative allergy tests, and particularly where there was no rise in mast cell tryptase, the anaphylactic nature of their reaction must be in doubt. In some of our cases this doubt was enhanced by other features such as dermatitis artefacta, raising the possibility of Münchhausen's syndrome, a previously reported cause of anaphylactic symptoms [11]; admitted exaggeration of symptoms in order to manipulate a domestic situation; the possibility of extreme anxiety resulting in symptoms mistaken for an anaphylactic reaction [12], and so on. Even in cases where allergy tests were positive, the severity of subsequent 'reactions' in some cases seems to have been augmented by anxiety, reflecting an expectation of increased severity of their next reaction. Further study is needed to investigate the part played by their advisors in generating anxiety in these patients.

Precipitating allergens were identified in 76% of cases based on the history and results of SPT and specific IgE testing; 4.6% were thought to have reacted to drugs or infusions where no satisfactory tests could be performed to confirm the association. Some 11.6% of patients had

reactions classified as idiopathic because of their apparent lack of cause; in several of these there was a slower evolution of symptoms and often recurrence on a regular basis for a few cycles [4]. In a further 7.6% the putative causal factor could not be confirmed and so these might be regarded as idiopathic, giving a total similar to the 19% reported from the Mayo Clinic [1]. We have not performed DBPCFC but 8 of 13 with negative allergy tests subsequently underwent open food challenge without reaction.

We recognize that there may be biases in the referral of patients to our clinics. We are aware of cases of anaphylactoid reactions in our district in the last 18 months which have not been seen by us, such as two severe reactions to contrast media. We might have expected one to three anaphylactic reactions from immunizations based on unpublished information from the vaccine manufacturers. The units in our district involved in haemodialysis, plasmapheresis, leukapheresis or transfusion of blood products have reported to us that none of their patients have experienced anaphylactic or anaphylactoid reactions resulting from these procedures in the last 18 months.

The proportion of reactions to wasp venom is lower than might have been expected from previous reports, this is due in part to a recent increase in the rate of referral for nut/peanut allergy, and we think it may also reflect a lower wasp population in the north-west compared with the south of England; certainly deaths from wasp venom anaphylaxis are less common in the north than the south of England (Lawrence Youlten, personal communication).

It is of some concern that potentially aggravating medications were still being taken by 4% of patients with anaphylaxis when seen by us up to several months following their reaction. It has been suggested that patients on β -blocker therapy may have an increased risk for more severe reactions [5], possibly mediated by a direct blockade of adrenoceptors on mast cells which suppress the tendency to degranulate [13]. Similarly, by blocking the protective release of angiotensin II, ACE inhibitors may also increase the risk of more severe reactions where bradykinin is involved [14,15]. Clearly, alternative medication should be considered for patients on such drugs who develop reactions.

The finding of a continuous distribution of severity of reactions will make determination of the prevalence of anaphylaxis and incidence of anaphylactic reactions dependent on the arbitrary selection of a threshold for inclusion; this might yield widely different conclusions depending on the level selected. Such studies will also need to address the wide age range, and the possibility of different causes affecting different age and sex groups.

Guidelines aiming to share the management of patients with acute allergic reactions rationally between primary and secondary care will need to clarify how the risk of a future life-threatening reaction might be assessed. This stratification of risk is complicated by the unpredictability of anaphylactic reactions; our data suggest there is no relationship between atopy and severity of reactions, nor is there any consistent pattern of severity in a sequence of reactions.

Acknowledgements

We would like to thank all the other clinicians (paediatricians and anaesthetists) with whom we have seen these patients and the Faculty of Medicine Computational Group for help with statistical analysis. Some of the mast cell tryptase measurements were performed by the Sheffield Protein Reference Unit.

References

- 1 Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994; 69:16–23.
- 2 Herriot R. Hymenoptera stings and beta-blockers. *Lancet* 1989; 2:1159.
- 3 Verresen L, Fink E, Lemke H-D, Vanrenterghem Y. Bradykinin is a mediator of anaphylactoid reactions during haemodialysis with AN69 membranes. *Kidney Int* 1994; 45:1497–503.
- 4 Khan DA, Yocum MW. Clinical course of idiopathic anaphylaxis. *Ann Allergy* 1994; 73:370–4.
- 5 Wilkinson JRW, Lee TH. General anaphylaxis. Lachmann PJ, Peters KD, Rosen FS, Walport MJ, eds. *Oxford: Blackwell Scientific*, 1993; 999–1014.
- 6 Chapel HM. Abnormalities of the immune system. In: eds. Weatherall DJ, Ledingham JGG, Warrell DA, *Oxford textbook of medicine*. 2nd edn. Oxford: Oxford University Press, 1987; 4.65.
- 7 Müller UR. Clinical presentation and pathogenesis. In: *Insect sting allergy*. New York: Gustav Fischer, 1990; 33–65.
- 8 Loza C, Brostoff J. Peanut allergy. *Clin Exp Allergy* 1995; 25:493–502.
- 9 Lavaud F, Prevost A, Cossart C, Guerin L, Bernard J, Kochman S. Allergy to latex, avocado pear and banana: evidence for a 30 kDa antigen in immunoblotting. *J Allergy Clin Immunol* 1995; 95:557–64.
- 10 Schwartz LB, Metcalf DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indication of mast cell activation in systemic anaphylaxis and mastocytosis. *NEJM* 1987; 316:1622–6.
- 11 Longley AJ, Fiset L, Getz T, van Arsdel PP. Apparent latex allergy provoked by fear. *J Allergy Clin Immunol* 1994; 94:561.
- 12 Hendrix S, Sale S, Zeiss CR, Utley J, Patterson R. Factitious Hymenoptera allergic emergency: a report of a new variant of Munchausen's syndrome. *J Allergy Clin Immunol* 1981; 67:8–13.
- 13 Butchers PR, Skidmore IF, Vardney CJ, Wheeldon A. Characterisation of the receptor mediating the anti-anaphylactic effects of beta-adrenoreceptor agonists in human lung tissue in vitro. *Br J Pharmacol* 1980; 71: 663–7.
- 14 Wachtfogel YT, DeLa Cardena RA, Colman RW. Structural biology, cellular interactions and pathophysiology of the contact system. *Thrombosis Res* 1993; 72:1–21.
- 15 Inagami T. The renin-angiotensin system. *Essays Biochem* 1994; 28:147–64.

Copyright of Clinical & Experimental Allergy is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.