

Bronchial hyperresponsiveness in two populations of Australian schoolchildren.

III. Effect of exposure to environmental allergens

J. K. PEAT, W. J. BRITTON*, C. M. SALOME and
A. J. WOOLCOCK†

*Departments of Medicine and *Clinical Immunology, University of Sydney, Sydney, Australia*

(Received in original form 28 July 1986 and in revised form 14 December 1986; accepted for publication 6 January 1987)

Summary

Two populations of schoolchildren, one living in an area where the predominant allergens are house dust mites and the other in an area where the predominant allergens are pollens, were studied to investigate in more detail the associations between atopy, bronchial hyperresponsiveness (BHR) and symptoms of asthma. The prevalence of atopy (39%) was the same in both towns but the prevalence of BHR was higher in the inland 'pollen' area (19% *vs* 15%). Atopic children had an increased risk of having BHR and, to a lesser extent, respiratory symptoms, diagnosed asthma and hay fever. The risk of BHR was further increased in children atopic to both pollens and house dust mites, and in children with a high index of atopy (derived from the number and size of the skin reactions to four allergen groups). In addition, the relationship between atopy and BHR was quantitative in that the severity of BHR increased with the severity of atopy. We conclude that there is not a direct causal relationship between atopy and BHR but there may be a common mechanism involved in their development. It appears that, within the atopic population, the type of allergen to which the individual is sensitized, the quantity of aeroallergen present in the environment and the degree of atopy, as measured by the number and size of the skin reactions, are all factors that may interact to increase the risk of BHR.

Introduction

A relationship between atopy, as shown by skin-test reactions, and asthma was first suggested in 1923 in [1] and studies since then have supported the association [2,3]. A similar relation between positive skin tests and bronchial hyperresponsiveness (BHR) has been established [4–7]. However, a direct causal relationship between atopy and BHR has not been shown. It is possible that, over a period of time, repeated inhalation of particles of allergen, with subsequent release of mediators and with late reactions, may cumulatively contribute to the development of BHR [6]. Bryant and Burns [7] have suggested that allergens probably act as 'trigger factors' for acute episodes of

† To whom correspondence should be addressed.

airway narrowing in subjects with BHR. Certainly, levels of BHR can be increased by exposure to [8] or decreased by removal from [6] environmental allergens.

Our data have shown that, in children, atopy has an important association with BHR and that, although the prevalence rates of BHR and respiratory symptoms vary in children living in different climatic areas, the nature of the aeroallergens to which children are exposed does not affect the overall prevalence of atopy [9]. However, it may be that the total aeroallergen load, in the presence of atopy, is of importance in increasing the likelihood of children having BHR and associated respiratory symptoms. This paper examines in more detail the association between atopy, BHR and both respiratory and 'allergic' symptoms. The possible effects of pollen allergens in one town and house dust mite allergens in the other town are explored, and the importance of positive skin reactions to more than one allergen is investigated.

Patients and methods

The children studied were the subjects of the population study conducted in Wagga Wagga and Belmont between 1982 and 1984. The sample studied, the methods of data collection and the methods of measuring BHR, lung function and atopic status are described in detail in the previous two papers [10,11].

Populations

The towns were chosen because of their different climates and different aeroallergen loads. The predominant allergens in the Wagga Wagga region (in common with much of inland New South Wales) are the pollens of grasses and weeds [12] and the predominant allergens in Belmont are house dust mites [9,13]. Initial visits were made to both Wagga Wagga and Belmont in autumn 1982. The second visits were made to Wagga Wagga in spring 1983, at the time of the seasonal increase in the prevalence of pollens, and to Belmont in autumn 1984. A different sample of the population was studied at each visit.

Data collection

Details of the questions concerning respiratory symptoms, hay fever and eczema and of the allergens used for skin testing are outlined in the first two of these three papers [10,11]. In this paper, hay fever and eczema are regarded as 'allergic' symptoms. Allergens used to determine atopic status were divided into four major groups on the basis of similarity: house dust mites, grass and weed pollens, animal danders and moulds. Children were classified as having a reaction to an allergen group if one or more tests within that group were positive.

Data analysis

Data was analysed on a Cyber 825. The statistical package program SPSS version 9.0 was used to calculate median skin weal sizes and chi-square values to assess the statistical significance of contingency tables. The Mantel-Haenzel procedure [14] was used to calculate odds ratios (OR) and their 95% confidence intervals (c.i.). Binomial regression using the package GLIM [15] was used to test for linear trends and to assess the significance of differences between odds ratios. Spearman's rank correlation coefficient was used to determine the association between severity of BHR and severity of atopy.

Table 1. Number of children studied and the prevalence (%) of atopy, bronchial hyperresponsiveness, respiratory symptoms, diagnosed asthma, hay fever and eczema at each study

	Populations studied				
	Wagga Wagga		Belmont		Total (n = 2363)
	Autumn (n = 769)	Spring (n = 602)	Autumn (n = 718)	Autumn (n = 274)	
Atopy	37.6	41.2	38.2	43.6	39.4
Atopy to HDM†	18.8	22.4	27.4	31.3	23.8
Atopy to pollens	29.1	29.1	17.8	20.7	24.7
BHR	18.9	20.6	14.9	16.7	17.9
BHR plus symptoms‡	12.7	13.3	8.5	11.3	11.4
Wheeze ever	23.9	29.8*	19.7	26.4*	24.4
Wheeze in last month	6.0	7.0	3.6	8.4**	5.8
Respiratory symptoms‡	33.7	42.9***	27.4	32.0	33.9
Diagnosed asthma	13.0	16.3	9.1	15.4*	12.9
Hay fever	30.7	33.9	21.1	22.4	27.6
Eczema	23.6	25.9	21.2	22.1	23.3

* $P < 0.05$, ** $P < 0.01$ for the difference between visits and, in parentheses, the difference between towns.

† House dust mites.

‡ Wheeze, exercise wheeze or night cough.

Results

Complete data for 2363 schoolchildren were collected in two visits to Wagga Wagga and two visits to Belmont. The prevalence rates of atopy, BHR, respiratory symptoms, hay fever and eczema at each visit are given in Table 1. There were significantly more children with BHR, respiratory symptoms, diagnosed asthma and hay fever in the inland town of Wagga Wagga [9]. In the total sample, 39% of children were atopic to one or more allergens and more boys were atopic (42% *vs* 35%, $P < 0.01$). In both towns, children were more likely to be atopic if their parents reported diagnosed asthma (OR = 1.7, c.i. = 1.4, 2.1) or 'allergic' illness (OR = 1.5, c.i. = 1.3, 1.8).

The predominant allergens were pollens in inland Wagga Wagga and house dust mites in coastal Belmont [12,13]. There was a trend for the prevalence rates of atopy, including atopy to the predominant allergens, and for the prevalence rates of BHR and all reported symptoms to be higher at the second visit to each town (Table 1). In Wagga Wagga, the prevalence of wheeze was significantly higher at the spring visit (30% *vs* 24%) with, consequently, a higher prevalence of any respiratory symptom reported. However, the prevalence of children reported to have had wheeze in the month prior to study was not significantly different (6% *vs* 8%). In Belmont, where both visits were undertaken in autumn, there was a higher prevalence of wheeze, recent wheeze and asthma diagnosed by a doctor at the second visit. However, the prevalence of exercise wheeze and night cough decreased so that the prevalence of children reported to have had any respiratory symptom was similar. The prevalence and severity of BHR did not change significantly between visits to each town.

Figure 1 shows that the prevalence of atopy was similar in the two areas but in

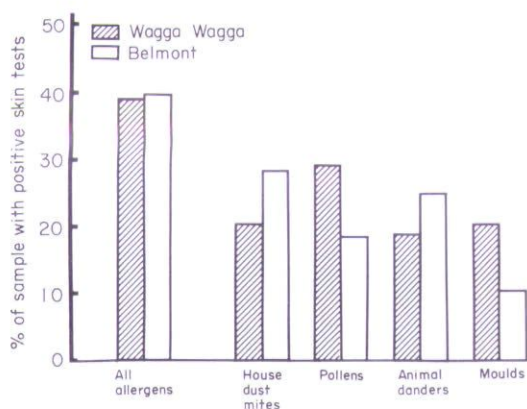


Fig. 1. Percentage of children in Wagga Wagga and Belmont who were atopic to all allergens, and to each of the major allergen groups.

Wagga Wagga more children were reactive to pollens or moulds ($P < 0.001$) and in Belmont more children were reactive to mites or animals ($P < 0.001$). Most children who reacted to moulds also reacted to pollens (84%) and most children who reacted to animal danders also reacted to mites (74%). Only 1.7% of children reacted solely to animal danders and 1.3% solely to moulds. In both areas 13% of children had a positive reaction to both the pollen and mite groups. In Wagga Wagga an additional 9% of children were reactive to pollens but not to mites, and in Belmont an additional 9% of children were reactive to mites but not to pollens.

The towns had different mobility of population. In Wagga Wagga, 41% of children had lived away from the area for more than 6 months, increasing the likelihood of exposure to different allergens, compared with 28% in Belmont. In Wagga Wagga, 17% of the continually resident children were reactive to mites and 29% to pollens, compared with 25% of the mobile children reactive to mites and 18% to pollens ($P < 0.001$). In Belmont, there was no association between mobility and reactivity to an allergen group. In both towns, the prevalence of BHR in mobile children was 3% higher than in continually resident children; this difference was not significant.

The increased risk of BHR and of respiratory symptoms in atopic children is shown in Table 2. The risk was greatest in children who were atopic to both pollens and mites. In the group atopic to mites but not pollens, the odds ratios for respiratory symptoms, with or without BHR, were higher in Belmont where mites are the predominant allergen. In the groups atopic to pollen, regardless of additional mite allergen, the risk of having respiratory symptoms was significantly higher in Wagga Wagga. In the three atopy groups, there was a small difference between towns in the median mite weal size and a larger difference in the median pollen weal size, with the larger pollen weal sizes found in Wagga Wagga (Table 2).

In order to rank children according to both the number and the size of their skin-test reactions, each child was assigned an atopy index. This integer index was the summation of the number of allergen groups to which each child was reactive (0–4) plus the size of the largest reaction, which was given a value of 1 for small (< 4 mm) and 2 for large. The odds ratios for all respiratory symptom groups are shown in Table 3 and increased with the atopy index. For some symptoms the odds ratio was more than ten-fold greater in the high atopy index group. There was a significant linear increase in

Table 2. Risk (odds ratio) of bronchial hyperresponsiveness (BHR), respiratory and 'allergic' symptoms, and median skin weal size, in children atopic to house dust mite and/or pollen allergens

	Allergen group					
	Mites, not pollens		Pollens, not mites		Mites and pollens	
	Wagga Wagga (n = 91)	Belmont (n = 159)	Wagga Wagga (n = 210)	Belmont (n = 61)	Wagga Wagga (n = 189)	Belmont (n = 124)
Odds ratios for BHR and/or symptoms						
BHR	2.5 (1.4,4.1)	5.3 (3.4,8.2)	3.3 (2.5,4.3)	3.0 (3.0,6.0)	7.5 (5.2,10.6)	3.4*** (3.3,8.5)
BHR plus symptoms†	2.4 (1.1,4.9)	13.6* (7.4,24.1)	4.9 (3.0,7.5)	3.4* (1.5,9.6)	15.2 (9.6,23.5)	12.0*** (6.3,22.0)
Wheeze	1.8 (1.1,2.9)	4.1 (2.7,5.9)	2.2 (1.5,2.9)	1.6* (0.8,2.9)	5.8 (4.1,8.0)	3.3*** (2.1,5.0)
Respiratory symptoms†	1.2 (0.7,1.8)	3.8*** (2.6,5.3)	1.9 (1.4,2.5)	1.1*** (0.6,2.1)	3.7 (2.6,5.0)	3.0*** (2.0,4.0)
Diagnosed asthma	2.2 (1.1,4.0)	5.8 (3.6,8.9)	3.2 (2.1,4.8)	2.3* (1.0,5.3)	8.7 (5.8,12.6)	4.9*** (2.8,8.1)
Hay fever	2.6 (1.6,4.0)	4.5* (3.0,6.5)	3.3 (2.2,4.2)	1.1*** (0.5,2.3)	7.6 (5.4,10.7)	5.4*** (3.4,8.0)
Eczema	1.7 (1.1,2.8)	1.3 (0.9,2.1)	1.5 (1.0,2.1)	1.9 (1.1,3.5)	2.5 (1.7,3.4)	2.1 (1.4,3.4)
Median skin weal size (mm)						
Mites						
Median weal size	2.5	3.3	—	—	3.2	3.2
Range	2-8	2-12			2-13	2-10
Pollens						
Median weal size	—	—	4.1	2.6	5.2	3.2
Range			2-16	2-8	2-15	2-13

* $P < 0.05$, *** $P < 0.001$ for the significance of the difference in odds ratios between the two towns.

† Wheeze, exercise wheeze or night cough.

odds ratio with increase in the atopy index for all symptom groups except eczema. The average increase in the odds ratio between consecutive atopy indices was 70% for BHR and asthma, 50% for wheeze and 40% for any respiratory symptom.

The quantitative relationship between the index of atopy and severity of BHR is shown in Fig. 2. In the high atopy index categories, most children had severe or moderately severe levels of BHR; in the low atopy index categories, the BHR was mild or slight. Also, in children with BHR, there was a significant correlation between the number of positive skin tests and the severity of BHR as measured by the PD₂₀ FEV₁ ($r = 0.32$, $P < 0.001$). Conversely, despite this close relationship between BHR and atopy, approximately 50% of children in high atopy index categories had no BHR and 10% of non-atopic children (with an atopy index of zero) had BHR.

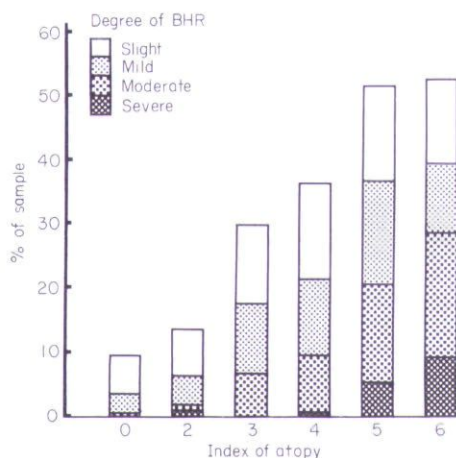
Discussion

Atopic children had an increased risk of having BHR, wheeze, diagnosed asthma, hay fever and eczema. The risk of BHR or of respiratory symptoms was further increased in

Table 3. Risk (odds ratio) of bronchial hyperresponsiveness (BHR), respiratory symptoms and 'allergic' symptoms in atopic children divided into groups according to the degree of atopy

	Index of atopy							
	2		3		4		5 and 6	
	Wagga (n = 135)	Belmont (n = 111)	Wagga (n = 161)	Belmont (n = 146)	Wagga (n = 116)	Belmont (n = 77)	Wagga (n = 126)	Belmont (n = 60)
BHR	1.4	1.7	3.6	5.0	5.2	6.0	12.8	6.5
BHR plus symptoms*	1.0	2.7	4.8	8.0	7.7	10.9	18.2	11.3
Wheeze	1.6	1.4	2.2	3.4	3.3	4.4	7.9	3.7
Respiratory symptoms*	1.5	1.8	1.7	2.7	2.3	3.5	5.8	3.6
Diagnosed asthma	2.1	3.4	2.3	4.9	5.4	3.9	12.7	9.1
Hay fever	1.8	1.3	3.6	3.8	6.3	5.8	11.1	6.6
Eczema	1.5	0.8	1.6	1.4	1.6	2.9	1.8	1.7

* Wheeze, exercise wheeze or night cough.

**Fig. 2.** Relationship between degree of BHR and degree of atopy expressed as an indexed derived from the number of allergen groups to which children were reactive and the size of the reaction.

children living in the inland region and in children who were atopic to both pollens and mites. The relationship between atopy and BHR was quantitative in that the risk of BHR showed a linear increase with an increase in index of atopy. In addition, the severity of BHR was related to the index of atopy, that is the number and the size of the skin-test reactions.

Our study sample was unlikely to be biased and was of adequate size [10] and it seems likely that the data reflect the prevalence of BHR and respiratory symptoms in the community at the time of the study. The degree of accuracy with which the skin-prick tests reflect atopic status is less certain. Although these tests are probably as reliable a guide to atopic status as measurements of circulating specific IgE [16], we recognize that they are not an absolute measure of degree of atopy and, therefore, we have used only two grades of reaction (small or large) in calculating the index of atopy.

In the study populations the prevalence of BHR and of atopy varied only slightly in each community, whereas the prevalence of diagnosed asthma and wheeze, as reported by questionnaires, changed significantly between visits to each town. In Wagga Wagga, where the second visit was made in spring, there was an increase in prevalence of respiratory symptoms, which was not associated with an increase in the prevalence of recent wheeze, BHR or atopy to pollens. The increase in the prevalence of diagnosed asthma was not significant and there was no change in the severity of BHR. This is in contrast to studies of adults in other countries, which have shown that hay fever and asthma sufferers develop increased BHR in the grass pollen season in France [17] and that seasonal pollen exposure increases asthma symptoms and levels of bronchial responsiveness in allergic patients in Canada [18]. In Belmont, the prevalence of diagnosed asthma was higher at the second visit. There was an associated increase in the prevalence of wheeze and recent wheeze, but not of BHR or other respiratory symptoms, which is unexplained. The questions used to collect details of respiratory symptoms were shown to be reliable and were not changed during the course of the study. In Belmont, the use of the term 'asthma' by the media increased prior to the second study because of local concern about environmental pollutants and, thus, the questionnaire information may have been influenced by a changing attitude to the use of the word 'asthma' by medical practitioners and/or parents.

We considered the effects of four different allergen groups on the prevalence of BHR. The independent effects of the animal and mould groups were less important than those of pollens or mites. Also, few children were atopic to moulds and not to pollens, or to animal danders and not to mites. It is not known whether animal or mould allergens were more prevalent in either town. It was established that mites were more prevalent in Belmont [13] and the high prevalence of pollens in inland rural areas has been reported [12]. In this paper, therefore, we have considered the effects of skin reactivity to pollens and mites in more detail.

The prevalence of atopy was almost identical in the two areas but the higher prevalence of BHR found in Wagga Wagga suggests that the environment in the inland town provides one or more additional risk factors for BHR. In a previous paper [9], we have suggested that the total aeroallergen burden in Wagga Wagga may be a major causative factor for the higher prevalence of BHR. Although we found more parental asthma in Wagga Wagga, suggesting that the children in each town may have had a different genetic base, we concluded that the effect was more likely to have been a result of common environmental exposure. In this further analysis, the higher risk of BHR, respiratory symptoms and diagnosed asthma in children reactive to the predominant allergens in each town suggests that the quantity of aeroallergen present is an important risk factor. In addition, the finding of larger pollen skin weals and higher odds ratios for BHR in Wagga Wagga may result from larger quantities of aeroallergens in this town.

Over and above the effect of living in an inland area, children reactive to both pollen and mite allergens have an increased risk of BHR. We found that mobile children, who in Wagga Wagga had a different pattern of atopy, have a slightly higher prevalence of BHR, which could be related to their having been exposed to and, therefore, developed atopy to, a wider range of allergens.

Furthermore, the risk of BHR increases with the total number of allergen groups to which children are reactive. Skin reactions to each additional allergen group, or a large reaction within a group, acted to increase the risk of a child having BHR by an average

of 70%. Thus, it appears that increasing severity of atopy, especially to the predominant allergen groups, further increases the risk of BHR.

It is not known whether an atopic status predisposes children to develop BHR or whether both conditions develop simultaneously in response to environmental stimuli. However, the finding that increasing severity of atopy was associated with increasing severity of BHR provides evidence that there is a common mechanism in their development. The correlation coefficient between atopy and $PD_{20} FEV_1$ was similar to that reported by Cockcroft [4] who concluded that atopic status is one causative factor for BHR and the low correlation between the two characteristics supports the concept that other factors are involved. A quantitative relationship between atopy and asthma has been reported by McNicol and Williams [19] who showed that children with more severe asthma reacted more strongly, and to a wider range of allergens, than children with mild episodic asthma. However, it is clear that there is not a direct causal relationship between atopy and BHR. In our study, atopy did not account for all BHR and most atopy was not associated with respiratory symptoms. We found that approximately 10% of non-atopic children had demonstrable BHR and, conversely, nearly two-thirds of atopic children had neither symptoms nor BHR and 50% of highly atopic children were asymptomatic. Godfrey and Griffiths [20] have also reported that many atopic children are asymptomatic. Welty *et al.* [21] have suggested that airway responsiveness and atopy in adults are independent traits, which are associated with environmental exposure.

It is not known whether children inherit the ability to become atopic and to develop BHR or acquire it after birth. We found that both paternal and maternal asthma were risk factors for atopy in childhood, however, as with the finding of an excess of parental asthma in the inland area, this could result either from a genetic factor or from common environmental exposure. There is evidence that skin-test reactivity occurs more frequently in subjects with a family history of allergy [22,23] and Van Asperen *et al.* [24] reported that in a group of infants with a family history of atopy one-half of the group had rhinitis and one-quarter had wheeze by the age of 20 months. Sibbald and Turner-Warwick [25] suggest that asthma and atopy are inherited independently and that, although atopy itself does not predispose to asthma, it may enhance genetic susceptibility to asthma, thus, increasing the likelihood that the latter will be expressed.

We conclude that, from birth, many environmental factors affect the likelihood of atopic children having BHR and, to a lesser extent, respiratory symptoms and diagnosed asthma. Although it is clear that atopy is not directly causal to BHR, the finding of a quantitative relationship between the two characteristics indicates that a common mechanism may be involved in their development. We found a higher risk of BHR in children living in the inland 'pollen' region, who had larger pollen skin wheal sizes; in children atopic to both pollens and mites; and in children with a high index of atopy. These findings provide evidence that the relationship between atopy and BHR is complex. It appears that, within the atopic population, the type of allergen to which the individual is sensitized, the quantity of aeroallergen present in the environment and the degree of atopy, as measured by the number and size of the skin reactions, are all factors that may interact to increase the risk of BHR.

Acknowledgments

We extend our thanks to both Dr Malcolm Hudson of Macquarie University, NSW

and Ms Concetta Rizzo of Abacus Research Consultants for statistical consultation and assistance with multivariate analyses.

This study was supported by the Asthma Foundation of NSW, Australia.

References

- 1 Coca A, Cook RA. On the classification of the pneumonia of hypersensitivity. *J Immunol* 1923; 8:163-71.
- 2 Burrows B, Lebowitz MD, Barbee RA. Respiratory disorders and allergy skin-test reactions. *Ann Intern Med* 1976; 134:9.
- 3 Kreukniet J, Pijper MM. Response to inhaled histamine and to inhaled allergens in atopic patients. *Respiration* 1973; 30:345-59.
- 4 Cockcroft DW, Murdoch KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984; 53:26-9.
- 5 Witt CS, Stuckey MS, Woolcock AJ, Dawkins RL. Positive allergy prick tests associated with bronchial histamine responsiveness in an unselected population. *J Allergy Clin Immunol* 1986; 77:698-702.
- 6 Platts-Mills TAE, Heymann PW, Chapman MD, Mitchell EB. Bronchial hyper-reactivity and allergen exposure. *Prog Respir Res* 1985; 19:276-84.
- 7 Bryant DH, Burns MW. The relationship between bronchial histamine reactivity and atopic status. *Clin Allergy* 1976; 6:373-81.
- 8 Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977; 7:503-13.
- 9 Britton WJ, Woolcock AJ, Peat JK, Sedgwick CJ, Lloyd DM, Leeder SR. Prevalence of bronchial hyperresponsiveness in children: the relationship between asthma and skin reactivity to allergens in two communities. *Int J Epidemiol* 1986; 15:202-9.
- 10 Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987; 17:271-81.
- 11 Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. II. Relative importance of associated factors. *Clin Allergy* 1987; 17:283-90.
- 12 Katelaris C, Baldo BA, Howden MEH, Matthews PA, Walls RS. Investigation of the involvement of *Echium plantagineum* (Patterson's curse) in seasonal allergy. *Allergy* 1982; 37:21-8.
- 13 Green WF, Woolcock AJ, Stuckey M, Sedgwick CM, Leeder SR. House dust mites and skin tests in different Australian localities. *Aust NZ J Med* 1986; 16:639-43.
- 14 Fleiss JL. Statistical methods for rates and proportions. Wiley series in probability and mathematical statistics. New York: John Wiley and Sons, Inc., 1973.
- 15 Baker RJ, Nelder JA. GLIM manual (release 3). Oxford: Numerical Algorithms Group, 1978.
- 16 Stenius B, Wide L, Seymour WM. Clinical significance of total IgE and of specific IgE to *Dermatophagoides* spp., grass pollen and other common allergens. II. Relationship to clinical manifestations. *Clin Allergy* 1972; 2:303-6.
- 17 Altounyan R. Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. In: Disodium Cromoglycate in Allergic Airways Disease. Pepys J, Frankland AW, eds. London: Butterworths, 1970:47-53.
- 18 Boulet L-P, Cartier A, Thompson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in non-allergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983; 71:399-406.
- 19 McNicol KN, Williams HE. Spectrum of asthma in children. II: Allergic components. *Br Med J* 1973; 4:12-6.
- 20 Godfrey RC, Griffiths M. The prevalence of immediate positive skin tests to *Dermatophagoides pteronyssinus* and grass pollen in schoolchildren. *Clin Allergy* 1976; 6:79-82.
- 21 Welty C, Weiss ST, Tager IB, Munoz A, Becker C, Speizer FE, Ingram, RH Jr. The relationship of airways responsiveness to cold air, cigarette smoking, and atopy to respiratory symptoms and pulmonary function in adults. *Am Rev Respir Dis* 1984; 130:198-203.
- 22 Vedal S, Chang-Yeung M, Ashley MJ, Enarson D, Lam SC. Does a family history of allergy predict immediate skin test reactivity? *Can Med Assoc J* 1985; 132:34-7.
- 23 Zeiger RS. Atopy in infancy and early childhood: natural history and role of skin testing (editorial). *J Allergy Clin Immunol* 1985; 75:633-9.

- 24 Van Asperen PP, Kemp AS, Mellis CM. A prospective study of the clinical manifestations of atopic disease in infancy. *Acta Paediatr Scand* 1984; 73:80-5.
- 25 Sibbald B, Turner-Warwick M. Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. *Thorax* 1979; 34:332-7.

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.