

Precipitating factors in respiratory allergic disease in Indonesian children

K. J. TURNER, SUMARMO* and C. MATONDANG-SIAHAAN*

Clinical Immunology Unit, Department of Microbiology, University of Western Australia, and Princess Margaret Hospital, Subiaco, W.A., and * Department of Child Health, University of Indonesia, Jakarta, Indonesia

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Summary

Skin test results and IgE antibody levels measured by RAST indicate that hypersensitivity to house dust mite (*D. pteronyssinus*) is a major feature of asthma and allergic rhinitis in Indonesian children. Total serum IgE levels were higher in the allergic than in control children. 60% (twenty-one out of thirty-five) of the asthmatic children and 56% (five out of nine) of the children with allergic rhinitis had IgE antibodies to the helminth *Ascaris lumbricoides* compared with none out of four control children. A tendency was found for high IgE antibody levels to *D. pteronyssinus* to occur in association with low IgE antibody levels to *A. lumbricoides* and vice versa.

Introduction

It is not clear what role, if any, helminthic infections play in the aetiology of allergic respiratory disease. *Ascaris*, *Strongyloides* or hookworm infections have been implicated in the causation of bronchial asthma in some reports (Tullis, 1970; Chacko, 1970; Mantle & Pepys, 1974), while others have found that the association of intestinal parasites and bronchial asthma is fortuitous (Farzan, 1970; Cheah & Kan, 1972; Turner, Baldo & Anderson, 1975). Finally, the low prevalence of asthma and hay fever in areas of the world where parasitism is endemic has led to the suggestion that some factor associated with parasitic infection may block or inactivate immediate hypersensitivity reactions (Godfrey, 1975).

Notwithstanding this potential influence of helminthic infections, bronchial asthma in the tropics, as elsewhere, appears to have a multifactorial aetiology. Multiple sensitivities are common, although sensitivity to house dust and house dust mite (*Dermatophagoides pteronyssinus*) appears to be the commonest form of allergy (Sofowora, 1970; Pearson, 1973; Anderson, 1974; Mantle and Pepys, 1974). An interesting feature of Anderson's study (1974) in New Guinea was the fact that in children and adolescents asthma was extremely uncommon, with no case being identified in a community study at Lufa and the youngest case at Goroka Hospital being 10 years of age. No explanation was offered for the late age of onset of the disease when compared with European countries.

Correspondence: Dr K. J. Turner, Clinical Immunology Unit, Princess Margaret Hospital, Subiaco, Western Australia.

This paper describes the features of asthma and related allergic diseases as seen at the Dr Cipto Mangunkusomo Hospital, Jakarta, situated at a similar latitude to that of Lufa in Papua New Guinea.

Materials and methods

Subjects

The patients in this study were referred mostly by paediatricians to the Outpatient Clinic of the Subdivision of Allergy, Departments of Medicine and Child Health, University of Jakarta. Most of the children (forty-four out of fifty-three) were from families with medium to high socio-economic status and all were less than 14 years of age. They comprised the groups shown in Table 1.

Table 1. Distribution and age of Indonesian children in respective allergic categories

Allergic state	Group	Number	Mean age (years)	Age range (years)
Asthmatic	1	36	6.8	2-13
Allergic rhinitis	2	9	6.7	4-9
Other allergies	3	5	6.3	4-8
None	4	4	4	3-5

Twenty-five of the asthmatic group had one or more of the following allergic conditions: allergic rhinitis, urticaria and eczema; and seven of the group with allergic rhinitis had, in addition, urticaria, chronic cough or flexma dermatitis; and the five subjects in group 3 had eczema, angioneurotic oedema, stomatitis or chronic cough.

Four of the subjects in group 1 suffered from protein-calorie malnutrition, but all the children in the other groups were normally nourished and were in good health.

Skin tests

All of the subjects in groups 1 to 3 were skin (prick) tested with the following extracts (Bencard): house dust, *Dermatophagoides pteronyssinus*, feathers, milk and *Aspergillus fumigatus*; and the following mould extracts: group A13, group M10 and group M11. Reactions were read on a scale of 1+ to 3+, 20 min after challenge with allergen.

Serum samples

Blood samples were taken at least 5 days after drug (antihistamine and corticosteroid) therapy had been discontinued, and before hyposensitization had been initiated. The blood samples were allowed to clot and the serum transported by air to Perth where it was stored at -20°C until required for analysis.

Serum IgE was measured by the paper radioimmunosorbent test (Phadebas IgE PRIST) method and IgE antibodies to *D. pteronyssinus*, rye grass pollen (*Lolium perenne*), milk proteins, *A. fumigatus* and *Ascaris lumbricoides* by the radioallergo-sorbent test (RAST). Commercial reagents (Phadebas) were used for all assays except *A. lumbricoides*, extracts of which were coupled to CNBr-activated paper discs as

Table 2. Number of subjects skin test-positive to various allergen extracts

Group	House dust	<i>D. pteronyssinus</i>	Feathers	Milk	<i>A. fumigatus</i>	Percentage skin test-positive		
						Group A13 moulds	Group M10 moulds	Group M11 moulds
(1) Asthmatic	53	50	47	18	15	24	15	15
(2) Allergic rhinitis	22	44	33	11	0	11	0	0
(3) Other allergens	50	50	25	25	25	0	0	0
(4) Normal controls	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

n.d. = Not done.

Table 3. Total serum IgE and IgE antibodies in Indonesian children

Group	Total IgE (u/ml)		Percentage RAST-positive ($\geq 2\%$ radiation bound)				
	Geometric mean	Range					
			<i>D. pteronyssinus</i>	<i>Lolium perenne</i>	Milk	<i>A. fumigatus</i>	<i>A. lumbricoides</i>
(1) Asthmatic	891	54-9000	43	14	0	11	60
(2) Allergic rhinitis	933	202-3750	22	11	0	0	56
(3) Other allergies	479	128-1340	50	0	0	0	25
(4) Normal controls	295	240-300	0	0	0	0	0

Total IgE: group 1 vs group 2, not significant; group 1 vs group 3, not significant; group 1 vs group 4, significant ($P < 0.05$).

previously described (Turner et al., 1975). The RAST was considered positive if the ^{125}I -labelled anti-IgE bound to the test discs was at least 2% of that added to the assay tubes. The RAST scores are therefore expressed as 'percentage radiation bound'.

Results

House dust, *D. pteronyssinus* and feathers proved to be the major allergens to which subjects with asthma (group 1), allergic rhinitis (group 2) or any one of the remaining allergic diseases represented in group 3 yielded positive skin reactions on prick testing with the eight allergen extracts (Table 2). Overall, fourteen (41%) of group 1, five (55%) of group 2 and two (50%) of group 3 failed to give positive skin tests to any of the allergens tested.

43% of the sera from subjects in group 1 (asthmatics) were positive by RAST to *D. pteronyssinus* (Table 3), confirming the skin test results that mites represent the major inhalant allergens triggering asthma in Indonesian children. The incidence of RAST-positive scores to *D. pteronyssinus* was low in the group with allergic rhinitis (22%) and high (50%) in the group with other allergic states, although the number of subjects in this latter group was too small to permit valid comparisons. High levels of IgE antibodies to *D. pteronyssinus* were found only in group 1 (asthmatics), and while the arithmetic mean RAST score for group 1 ($9.1 \pm 14.2\%$ radiation bound) was higher than that for both the allergic rhinitis patients (1.3 ± 1.4) and controls (0.42 ± 0.37), the large standard deviations precluded these differences from reaching statistical significance (Fig. 1). All of the subjects in groups 1 to 3 showed a low incidence of serum RAST-positive scores to milk and *A. fumigatus* antigens, again confirming the skin test results. The incidence of IgE antibodies to rye grass (*Lolium perenne*) antigens

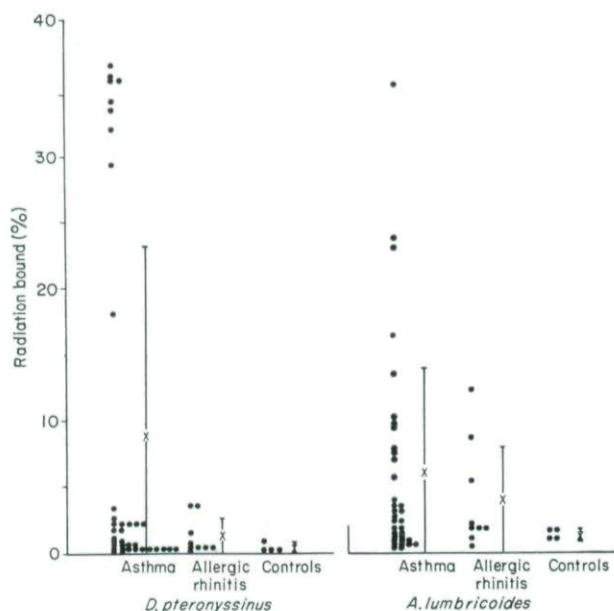


Fig. 1. RAST scores (percentage radiation bound) to *D. pteronyssinus* and *A. lumbricoides* in control Indonesian subjects and patients with asthma and allergic rhinitis. Arithmetic mean levels ($\times$) $\pm$ one standard deviation (bars) are shown for each group.

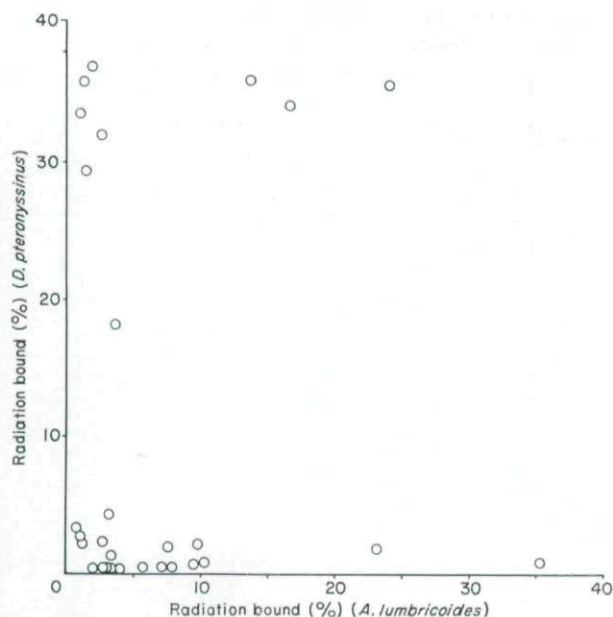


Fig. 2. Corresponding RAST scores (percentage radiation bound) to extracts of *D. pteronyssinus* and *A. lumbricoides* in each serum sample from Indonesian asthmatic children.

was low in all three groups of allergic children. None of the sera from the four normal children had significant levels of IgE antibodies to any of the antigens tested.

The size of the skin test to *D. pteronyssinus* did not correlate with the magnitude of the RAST scores for groups 1 and 2. However, positive skin tests correlated with positive RAST and negative skin tests with negative RAST overall to a level of 77%.

Over 50% of the subjects in groups 1 and 2 had IgE antibodies to the helminth *A. lumbricoides*. Of the four malnourished children, all of whom were in group 1, two had the highest levels of IgE antibodies to *Ascaris* (35% and 24% radiation bound) in this group, and two had no significant titres (1.2% and 0.7% radiation bound). There was a tendency for high antibody levels to *D. pteronyssinus* to correlate with low levels to *A. lumbricoides* and vice versa in group 1 (Fig. 2). Only three children (Nos 32, 29 and 18), all in the older age group, had high levels of IgE antibodies to both *D. pteronyssinus* and *A. lumbricoides* (Table 4). Of the fourteen patients in group 1 with positive ($\geq 2\%$ radiation bound) RAST scores to *D. pteronyssinus*, eight were also positive to *A. lumbricoides*, but of the twenty-one who were positive to *A. lumbricoides*, only eight were also positive to *D. pteronyssinus*. The prevalence of high IgE antibody levels ($> 10\%$ radiation bound) to *Ascaris* was higher (four out of nine, 44%) in the children from low socio-economic groups than in the children (three out of forty-four, 7%) from middle to high socio-economic groups.

When the skin test and RAST results were combined, it was found that fourteen out of forty-four (32%) of the children in groups 1 and 2 were negative to both skin testing and RAST using all of the allergens except *A. lumbricoides*. Of this fourteen, seven (50%) were RAST-positive to the parasite, leaving a total of seven out of forty-four (16%) of asthmatic and/or allergic rhinitis patients with clinical symptoms of hypersensitivity unconfirmed by serological or *in vivo* investigation.

Table 4. IgE antibodies* (percentage radiation bound) to *D. pteronyssinus* and *A. lumbricoides* in Indonesian asthmatic children (group 1)

Sample numbers	<i>D. pteronyssinus</i>	<i>A. lumbricoides</i>	Age (years)	Sex
32	36	24	13	M
29	36	14	13	M
20	36	1.9	9	F
5	36	1.3	4	F
18	34	17	11	F
11	34	1.0	10	F
12	32	2.6	4	M
27	29	1.5	12	M
38	18	3.6	7	M
41	3.4	0.8	5.5	M
8	2.7	1.0	4	F
15	2.3	2.7	9	M
6	2.2	1.2	3	M
26	2.2	9.8	7	F
14	2.0	7.6	3.5	F
2	1.0	35	8	F
10	1.9	23	10.5	M
7	0.8	10	12	M
9	0.7	9.5	9	F
3	0.5	7.9	9	F
1	0.5	7.1	9	F
17	0.5	5.8	10	F
35	0.3	4.0	6	M
40	1.3	3.4	6	M
37	0.4	3.2	8	F
55	0.4	3.1	9	M
23	0.4	2.8	2	F
54	0.4	2.0	7	F

* The Table reports only those samples which were RAST positive ($\geq 2\%$ radiation bound) to *D. pteronyssinus* and/or *A. lumbricoides*.

Table 5. IgE antibodies (percentage radiation bound) as a function of age for Indonesian asthmatic (group 1) and/or allergic rhinitis (group 2) children

Age (years)	Number	RAST-positive ($\geq 2\%$ radiation bound)*			
		<i>Lolium perenne</i>	<i>D. pteronyssinus</i>	<i>A. fumigatus</i>	<i>A. lumbricoides</i>
2	2	0	0	0	1
3-4	12	0	6 (50)	0	3 (25)
5-6	6	0	1 (17)	0	3 (50)
7-8	7	1 (14)	3 (43)	1 (14)	7 (100)
9-10	13	3 (23)	3 (23)	0	11 (85)
11-13	3	1 (33)	3 (100)	2 (67)	3 (100)

* Percentages in parentheses.

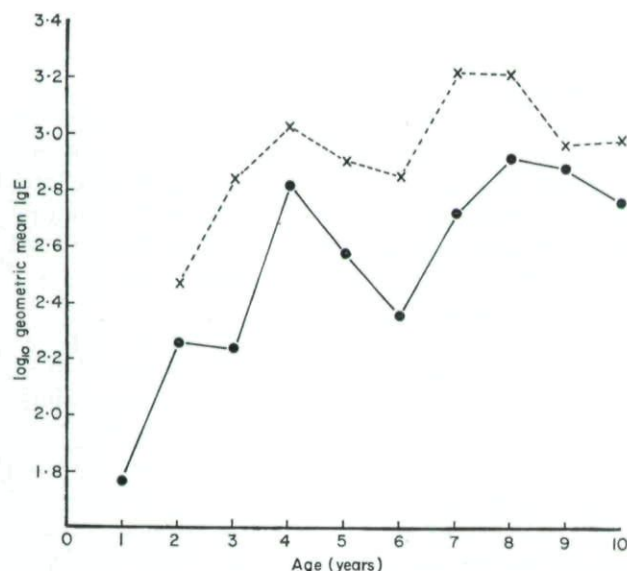


Fig. 3. Geometric mean total serum IgE levels as a function of age for the combined groups 1 and 2 (asthmatics and allergic rhinitis patients) Indonesian subjects (x) and for a corresponding group of patients resident in Perth, Western Australia (●).

The number of children in the combined groups 1 and 2 whose sera were positive by RAST to *Ascaris* was maximal at the age of 7–8 years and thereafter remained at a high level (Table 5). In contrast, the number who had significant titres of IgE antibodies to *D. pteronyssinus* followed a triphasic distribution with peak values occurring at 3–4, 7–8 and 11–13 years of age.

Total serum IgE levels were higher in the three groups of allergic subjects than in the controls (Table 3). No significant differences were found between the allergic groups (1, 2 and 3), but the geometric mean IgE levels for groups 1 and 2 were significantly ($P < 0.05$) higher than that for the normal subjects (group 4). Geometric mean serum IgE levels followed a biphasic distribution with age for Indonesian children in the combined groups 1 and 2, with peak values occurring at the age of 4 and 7–8 years (Fig. 3). This distribution essentially matched that for a similar group of children resident in Perth, Western Australia, although the IgE levels at each age group were lower than those for the Indonesian children.

Discussion

Hypersensitivity to the house dust mite (*D. pteronyssinus*) is a major factor in the aetiology of asthma, allergic rhinitis and related allergic disorders amongst Indonesian children, as it is in most other areas of the world. Skin test results also indicated that a high percentage of the asthmatic children in particular were sensitized to extracts of feathers. While the magnitude of the skin test results to *D. pteronyssinus* did not correlate with the magnitude of RAST scores, as occasionally reported by others (Norman, 1975; Henderson, Larson & Gleich, 1975), good agreement (77%) was obtained between the positive skin tests and positive RAST, and negative skin tests and negative RAST. Nonetheless, this correlation was lower than has been found in

similar studies undertaken in Perth with asthmatic children, all of whom had case histories of hypersensitivity to *D. pteronyssinus* (Turner & Hobday, unpublished observations). The latter study established a 93% correlation figure for these parameters. The lower correlation figure obtained with the Indonesian children does not appear to be explained on the basis that high serum IgE levels potentiated by a concurrent parasitic infection inhibit skin test reactions (Editorial, 1976), as only three out of forty-three patients in groups 1 and 2 had negative skin tests with significant serum levels of IgE antibodies to *D. pteronyssinus*. Moreover, these children had relatively low total serum IgE (660, 760 and 800 u/ml) and correspondingly low IgE antibody levels (3.6, 2.3 and 2.0% radiation bound respectively).

This study fails to confirm the observation of Abbassy *et al.* (1974) that malnourished children are unable to develop positive skin tests, since two out of the three malnourished children who were skin-tested gave positive reactions to at least three different allergen extracts.

The geometric mean serum IgE level for Indonesian asthmatic (group 1) and allergic rhinitis (group 2) patients was significantly higher than that found for corresponding Perth children of the same age range. It is well documented that intestinal parasitic infections stimulate IgE production and that in humans (Turner, Feddema & Quinn, unpublished), as in animal models (Ogilvie & Jones, 1973), much of the IgE lacks specificity for the parasite antigens. On this basis, it might be anticipated that the incidence of allergic disease would be higher in tropical areas, where parasitism is endemic, than in more temperate climates. However, the converse is generally found (Godfrey, 1975; Anderson, 1974; Woolcock & Blackburn, 1967; Fourie, personal communication), suggesting an inverse relationship between the incidence of parasitism and allergic disease. Godfrey & Gradidge (1976) postulated that the high levels of parasite-stimulated IgE with undetermined specificity may saturate mast cell receptors and inhibit sufficient binding of specific IgE to allow histamine release upon subsequent challenge with allergen. This model might account for the low incidence of allergic disease in tropical areas. However, competition for mast cell receptor sites does not appear to be a factor of major importance in this study, as the patients with the highest serum IgE levels (9000, 7200 and 3100 u/ml) were skin test-positive to a range of allergens, including *D. pteronyssinus*, and had high levels of serum IgE antibodies to both *D. pteronyssinus* and *A. lumbricoides*. This suggests that specific (e.g. *D. pteronyssinus*) IgE antibodies have a greater capacity to bind to mast cells than do the parasite-stimulated 'non-specific' IgE molecules. The observation that IgE-rich serum from West Indians, when mixed with that from a pollen-sensitive subject, failed to inhibit sensitization of lung mast cells for subsequent allergic histamine release when exposed to pollens (Godfrey & Gradidge, 1976) lends support to our concept of differential binding capacity or avidity of IgE molecules. What is of particular relevance in the experiment of Godfrey & Gradidge (1976) is that the ratio of total IgE in the West Indian (parasitized?) serum to that of the pollen-sensitive subject was 50:1.

It is not clear what contribution, if any, infection with *A. lumbricoides* makes towards the incidence of asthma in Indonesia. Tullis (1970) and Chacko (1970) reported a marked correlation between the manifestations of bronchial asthma and the presence of intestinal parasites, notably hookworm and *Ascaris*. However, this association has not been confirmed by other workers (Van Dellen & Thompson, 1971; Turner *et al.*, 1975) in studies concerned primarily with adults. The high incidence of

IgE antibodies to *Ascaris* in the asthmatic group of Indonesian children and the absence of these antibodies in the controls suggests that *Ascaris* may be a contributing factor in children. These comparisons may not be valid, as *Ascaris*-specific IgE antibodies predominate in the older children and the four normal children, all of whom lacked antibodies to *Ascaris*, were aged 3–5 years. Similar studies based on faecal egg counts (Kurniawan *et al.*, 1976) have shown that the prevalence or the intensity of infection with *A. lumbricoides* and *T. trichiura* was highest in the younger age group (5–9 years), while the prevalence for hookworm infection was highest in adults (25–34 years). Only two out of eleven asthmatic children in this age range had significant levels of IgE antibodies to *Ascaris*. The tendency for high IgE antibody levels to *D. pteronyssinus* to occur in association with low IgE antibody levels to *A. lumbricoides* and vice versa (Table 4, Fig. 2) suggests that a mechanism of antigenic competition may be operable. On this basis, the induction of a vigorous antibody response to the parasite may inhibit the capacity of the subject to respond to stimulation of mites or other airborne allergens. However, such a mechanism cannot be absolute as three of the asthmatic children (Nos 32, 18 and 29) developed high titres of IgE antibodies to both allergen extracts. Nonetheless, if antigenic competition is exerting an influence, it provides further evidence for *Ascaris* being a triggering factor in childhood asthma, particularly in those children who were negative by both skin test and RAST to all allergens except *Ascaris*. It may also be relevant in this context that the capacity to produce IgE antibodies to *D. pteronyssinus* appears to develop at an earlier age of the child than the capacity to produce corresponding antibodies to *Ascaris*. However, the limited number of subjects in this study may impair the validity of this comparison.

This differentiation between IgE antibodies to mites and *Ascaris* may equally well be associated with environmental factors, as it is likely that the predominantly mite-positive *Ascaris*-negative patients lived in a more affluent society, where parasitism would be less prevalent. Conversely, the predominantly *Ascaris*-positive, mite-negative group might live in less hygienic surroundings, in dwellings which lacked adequate facilities for the proliferation of mites. Faecal egg counts (Kurniawan *et al.*, 1976) have established in other Indonesian subjects both increasing prevalence and intensity of parasitic infection with low socio-economic status. In the absence of detailed information on environmental factors, interpretation of the joint role of *Ascaris* and mites in asthma amongst Indonesian children remains in the realm of speculation.

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