

IgE, parasites and asthma in Tanzanian children

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Summary

Two rural Tanzanian primary schools were surveyed to test the hypothesis that parasitic infestation prevents the development of asthma. 242 pupils were interviewed to determine the prevalence of pupils with recurrent episodes of wheezing. The nineteen pupils so discovered had more exercise-induced bronchial lability than equivalently exercised controls. More girls (12·8%) than boys (3·3%) had asthma. In one school, 77% of the controls had faecal parasites, mainly *Ascaris* spp., and in the other school 55% of the controls had *Schistosoma haematobium* in their urine. Parasites were found in similar proportions in the asthmatics. The mean serum IgE for the whole population was 3174 u/ml with no demonstrable difference between the asthmatics and controls. There was no difference in immediate cutaneous hypersensitivity to twenty-two allergens between the asthmatics and controls. These findings suggest that parasitic infestation does not prevent the development of asthma.

Introduction

Circulating levels of immunoglobulin E (IgE) are commonly elevated in patients with allergic asthma (Johansson, 1967) and in subjects with parasitic infestation (Johansson, Mellbin & Vahlquist, 1968). Asthma has been reported to be uncommon among the rural population of tropical areas where parasitic infestations are prevalent (Anderson, 1974; Godfrey, 1975), and it has been postulated that parasites may prevent asthma (Preston, 1970; Stanworth, 1971; Bazara, Orgel & Hamburger, 1973).

There is *in vitro* evidence to support this hypothesis: allergen-specific IgE antibodies have been identified in clinically non-atopic rural Africans (Merrett, Merrett & Cookson, 1976), and IgE-rich serum can block the release of mediators from previously sensitized chopped human lung tissue (Godfrey & Gradidge, 1976). Furthermore, the Prausnitz–Küstner (P–K) test is blocked when reaginic serum is first incubated with myelomatous IgE serum (Stanworth *et al.*, 1967). Mast cell blockade after saturation of IgE receptors is also suggested by animal experiments (Jarrett, Orr & Riley, 1971; Ohman & Block, 1972). The observation that patients with IgE

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myelomata cannot be passively sensitized (Ogawa *et al.*, 1971) also suggests the mechanism of mast cell blockade.

However, no study to date has been reported in which all the variables of parasite infestation, demonstrated asthma, skin hypersensitivity and serum IgE were examined in the majority of subjects in a community-based study. We now report such a study, based on two different village schools (Kwamsisi and Ubiri) in the Tanga province of Northern Tanzania.

Materials and methods

A pilot survey in June 1975 examined five primary schools in Northern Tanzania and demonstrated that the majority of children in Kwamsisi primary school had *Schistosoma haematobium* infestation while the majority of those in Ubiri primary school had *Ascaris* spp. infestation. The two schools were selected because of their contrasting locations. Ubiri is situated at an altitude of 2,000 m and so malaria is absent, unlike the low-lying (500 m) Kwamsisi where the disease is endemic. Accordingly, the pupils from these two schools were surveyed in order to test the mast cell blockade theory. The prevalence of asthma in the two communities was unknown before the present survey.

We examined whole classes of children and screened a total of 242 pupils (114 Kwamsisi and 128 Ubiri). A history of asthma was elicited by Swahili-speaking staff, all of whom had considerable medical experience. Asthma was diagnosed when there had recently been recurrent episodes of wheeze and breathlessness.

Peak expiratory flow rates (PEFR) were recorded, using peak flow gauges (Airmed Ltd). All children were taught the technique and performed the manoeuvre under expert surveillance. To test for exercise-induced bronchial lability, 6 min of continuous free-range running was carried out under supervision. PEFR was recorded by noting the best three of five blows: the highest consistent result was used. PEFR was recorded before exercise, and every 2 min after exercise until 16 min had elapsed.

The percentage fall in PEFR was calculated:

$$\text{percentage fall} = 100 \times \frac{(\text{pre-exercise PEFR} - \text{lowest post-exercise PEFR})}{\text{pre-exercise PEFR}}$$

The heart rate was recorded immediately before and after the exercise.

Immediate hypersensitivity skin-testing was carried out, using twenty-two standard (Bencard) antigens, two carbolsaline controls and a histamine (0.05%) control. Positive results were recorded when the diameter of the weal present 15 min after pricking the skin was greater than the mean of the two carbolsaline controls.

Faeces were examined by direct smear stained with iodine, and parasite counts were performed. Urinary schistosomiasis was identified by the quantitative filtration method (Bradley, 1965).

Total serum IgE was measured by a conventional inhibitory radioimmunoassay (RIA) using a solid-phase second antibody to separate the 'antibody-bound' from the 'free' IgE fraction (Merrett & Pantin, 1975). The assay was made less sensitive to accommodate the high IgE levels expected in African children—the range was 120–25,000 u/ml IgE, using a sample dilution of 1/20 in 50% chicken serum. Within assay, precision was 7.1% around 1500 u/ml IgE, 5.7% around 7000 u/ml IgE and 4.7% around 18,000 u/ml IgE. Serum IgE values were computed using a cubic equation

fitted to the standard calibration curve, and geometric means are quoted since values followed an almost normal distribution when plotted logarithmically.

Unless otherwise quoted, all statistical results are derived from χ^2 tests.

Results

The age, sex and prevalence of asthma in these two primary schools are shown in Table 1. There was no significant difference in the age, sex or asthma distribution between the Kwamsisi and Ubiri populations, but there was a significant ($P < 0.05$) excess of asthma in the female population. There was a higher proportion of female asthmatic patients in both population groups. There was no significant difference in the prevalence of parasitic infestations between the sexes.

Table 1. Age, sex and diagnosis

Group	Age		Male	Female	Total
	Mean	$\pm$ s.d.			
Asthma	12.3	1.79	4	15*	19
Normal	12.5	1.91	116	102	223†
Total	12.5	1.91	120	117	242

* Excess of females in the asthmatics significant at $P < 0.05$.

† Includes five normal subjects in whom sex was not recorded.

The diagnosis of asthma made from the clinical history correlated significantly with an increased incidence of exercise-induced bronchial lability (Table 2). Both asthmatics and control pupils had exercise of equivalent severity, as shown by their similar heart rate changes.

Table 3 lists the proportions of the asthmatic and control groups with positive reactions to the allergens. There were no significant differences in the median sizes of the reactions to individual allergens, nor in the median size of the largest positive reaction in the asthmatics (1 mm) and controls (1.5 mm). A significantly higher proportion of both asthmatic (Wilcoxon's sum of ranks test) and control (χ^2 test) children from Ubiri gave positive reactions when compared with the equivalent Kwamsisi children ($P < 0.05$). The control subjects from Ubiri had more positive reactions to *D. Pteronyssinus* ($P < 0.05$), cockroach ($P < 0.05$), maize pollen ($P < 0.01$), *S. Roseus* ($P < 0.01$), house dust ($P < 0.01$) and meats ($P < 0.05$) than the normal subjects from

Table 2. Exercise-induced bronchial lability

Group	No. of subjects	Fall in PEFR (%)		Rise in HR*	
		Mean	$\pm$ s.d.	Mean	$\pm$ s.d.
Asthma	15	9.4	1.4†	32.9	6.2
Normal	35	0.9	1.4†	41.6	4.0

* Heart rate. † Significant at $P < 0.01$.

Table 3. Percentage of positive immediate hypersensitivity reactions

Allergens	Asthmatics	Controls
<i>D. farinae</i> (2800)	36	40
A ₁ mixed dust and animal hair (3200)	42	46
<i>D. pteronyssinus</i> (2801)	32	42
A ₂ animal hairs (3300)	37	43
Cockroach (2702)	16	38
Maize pollen (4921)	32	46
<i>Aspergillus fumigatus</i> (2000)	36	35
Mixed threshings (6317)	31	39
B ₂ grass pollens (4100)	38	31
B ₃ tree pollens (4200)	38	32
<i>S. roseus</i> (1804)	16	38
<i>C. albicans</i> (2003)	25	42
<i>P. betae</i> (1802)	25	31
M ₁ moulds (1100)	31	30
M ₂ moulds (1200)	21	32
M ₃ moulds (1300)	38	16
Mezquit pollen (4949)	25	34
House dust (3201)	42	37
Mixed yeast (5902)	8	25
Meats (5400)	32	32
Milk (5202)	26	25
Egg (5201)	8	12
Median proportion positive	9	31
Total number tested	19	223

Allergen numbers refer to the Bencard catalogue.

Kwamsisi. More controls from Kwamsisi (53%) than from Ubiri (18%) reacted to *Phoma betae* ($P<0.05$). More asthmatics (70%) from Ubiri than Kwamsisi (11%) reacted to house dust ($P<0.05$).

Parasites were present in the faeces of 77% of the control subjects in Ubiri and 45% of the Kwamsisi controls ($P<0.001$); *Schistosoma haematobium* was present in the urine of 55% of the Kwamsisi controls and 12% of the Ubiri controls ($P<0.001$). This had been anticipated from the pilot study. The nature of the parasites and their distribution between the asthmatic and non-asthmatic groups in the two locales is indicated in Table 4. There was no significant difference in the proportions of asthmatic and non-asthmatic subjects who had parasites, no matter how the populations were compared. There was no demonstrable correlation between the presence of parasites in the faeces and/or urine and the size and number of the immediate hypersensitivity skin reactions.

The geometric mean serum IgE in the whole population (216 samples) was 3174 u/ml (log 3.5016 with a standard deviation of 0.483). There was no significant difference between the mean values for Kwamsisi (3589 u/ml) and Ubiri (2851 u/ml). Although there was a significantly lower ($P<0.05$; *t*-test) total serum IgE in the female Kwamsisi population when compared with the male Kwamsisi, there was no significant difference in the overall series (male mean 3614 u/ml; female mean 2729 u/ml). There was no significant difference between the mean value for the total serum IgE

Table 4. Percentage of patients with parasites

Parasite and location	In Kwamsisi		In Ubiri		In total	
	Asthmatics	Normals	Asthmatics	Normals	Asthmatics	Normals
Faeces						
No. of samples examined	5	71	9	104	14	175
<i>Ascaris</i> spp.	0	24	67	65	43	49
Hookworm	20	20	22	25	21	23
<i>S. Mansoni</i>	0	0	0	2	0	1
<i>Trichiuris</i> spp.	0	1	0	1	0	1
<i>Taenia</i> spp.	0	0	0	1	0	1
<i>Entamoeba coli</i>	0	7	11	10	7	9
<i>Enterobius</i> spp.	0	0	0	3	0	2
<i>Strongyloides</i> spp.	0	7	22	7	14	9
<i>Dicroelium</i> spp.	0	0	0	1	0	1
Any faecal parasite	20	45	78	77	57	64
Urine						
No. of samples examined	7	87	1	50	8	137
<i>Schistosoma haematobium</i>	29	54	0	14	25	37

in the asthmatic population (2851 u/ml; seventeen samples) and the mean value in the non-asthmatic population (3206 u/ml; 195 samples).

No significant difference between the total serum IgE concentrations was observed, even when the asthmatic subjects were matched for age, sex and domicile with non-asthmatic subjects and compared. There was a significant positive correlation ($P < 0.05$) of the serum IgE with the presence of atopy (defined as having a skin reaction equal to, or greater than, 2 mm) only when the mean serum IgE for those with more than two such reactions was compared with the others (2965 vs 5248 u/ml). Table 5 attempts

Table 5. Quantitative parasite counts and total serum IgE

Parasite counts	Geometric mean total serum IgE (units/ml)	No. of blood samples
Faeces		
<i>Ascaris</i> (eggs/HP field)		
0	3020	53
≤ 9	3289	38
> 9	3656	34
Urine		
<i>Schistosoma haematobium</i> (eggs/5 ml urine)		
0	3483	29
≤ 14	2118	20
> 14	3148	10

to relate the quantitative parasite loads for *Ascaris* spp. and *Schistosoma haematobium* to the total serum IgE's of the subjects. There was no significant correlation between parasite loads and total serum IgE.

Discussion

This study has established that parasitic infestation and asthma can co-exist in tropical communities. We found no evidence for the hypothesis that parasitic infestation prevents asthma.

Parasites stimulate the excessive production of IgE (Jarrett, 1976). Preston (1970) postulated that this excess IgE will so effectively dilute allergen-specific IgE antibodies as to prevent them occupying adjacent mast cell receptor sites, and so degranulation of the cell will be inhibited and no effector substances released to cause positive prick tests or asthma in the lungs. Therefore, in parasite-prevalent areas this hypothesis predicts a low incidence of asthma and skin sensitivity, and this would be associated with excessively high total IgE levels. Asthma should be only rarely encountered and, compared to controls, such cases would be associated with lesser parasite infestations and a greater skin sensitivity.

Prevalence of asthma

The diagnosis of asthma was confirmed by there being a significantly greater prevalence of exercise-induced bronchial lability (Silverman & Anderson, 1972) in our asthmatics when compared with control subjects. Our prevalence of asthma of 7.8% (19/242) is certainly comparable to that reported in Melbourne (11%) (Williams & McNichol, 1969), Aberdeen (4.8%) (Dawson *et al.*, 1969) and Birmingham (2.3%) (Morrison-Smith, Harding & Cumming, 1971), but is higher than that reported from other rural tropical paediatric groups. Surveys of 132 children in rural Gambia (Godfrey, 1975) and 122 children in New Guinea (Anderson, 1974) did not reveal any cases of asthma. Childhood asthma prevalences of 2.4 and 1.1% have been reported for Nigeria (Sofowora, 1970) and Barbados (Pearson, 1973) respectively.

A very interesting feature of our survey is that the male/female ratio of asthma was 0.3/1. This increased female/male ratio was true for both Ubiri and Kwamsisi, two quite different communities. Thus, asthma is significantly more common in our females, whereas in other reports published there has usually been a preponderance of male asthmatics. (For example, male/female ratios of 2.3/1 (Williams & McNichol, 1969), 2.2/1 (Dawson *et al.*, 1969), 1/1 (Pearson, 1973) and 1.4/1 (Anderson, 1974)).

In a survey of asthma and wheezy bronchitis in British children (Davis, 1976), 15.3% of boys were found to wheeze compared to 7% of girls. However, similar numbers of girls and boys were atopic subjects (Pepys, 1973). Clearly, the sex-linked mechanism governing the manifestation of asthma merits further study.

Prevalence of skin sensitivity

Our immediate hypersensitivity skin tests have demonstrated a similar reactivity in the controls to that observed in the asthmatic children, but the Kwamsisi children are significantly less reactive than the Ubiri children. There are no community-based surveys of immediate hypersensitivity in tropical children in which rural asthmatic and non-asthmatic children are compared. A 1% prevalence of positive skin reactions was found in urban and rural non-asthmatic schoolchildren in the Gambia (Godfrey,

1975). The surveys in the tropics show that a greater proportion of positive skin reactions occur in urban adult asthmatics than control non-asthmatic populations (Anderson, 1974; Godfrey, 1975; Warrell *et al.*, 1975; Cookson & Makoni, 1975).

Total IgE levels

Circulating IgE concentrations are often elevated in both parasite infestations and in allergic diseases, and so asthma surveys conducted in parasite-endemic areas can provide conflicting results as to whether it is the allergic subjects, or the controls, who have the higher IgE concentrations in the serum. Our geometric mean IgE concentrations were certainly higher than the 21 u/ml reported for a normal European population (Nye *et al.*, 1975), but there was not the significant difference between the asthmatic and control that has been observed to be typical of European populations (Johansson, 1967; Havnen *et al.*, 1973). Higher serum IgE concentrations have been found in asthmatic and atopic adult subjects in New Guinea (Grove & Forbes, 1975; Turner, Baldo & Anderson, 1975), but in the Gambia (Godfrey, 1975) no significant difference was found between adult asthmatics and controls when their serum IgE concentrations were compared. We found some suggestion of a sex-linked difference in IgE concentrations similar to that previously reported for adult asthmatics (Burr *et al.*, 1975).

Many parasites are known to stimulate the production of IgE in animals (Jarrett, 1973). A survey of pre-school children in Ethiopia showed that those infested with parasites had a significantly higher serum IgE concentration than the uninfested (Johansson *et al.*, 1968). In addition, one group living in a community home where efforts had been made to lower the level of parasite infestation over 2 years showed a significant lowering of the mean serum IgE over that period. Parasite loads have been reported to be significantly lower in atopic, compared with non-atopic, villagers in New Guinea (Grove, Burston & Forbes, 1974). Our results do not demonstrate any difference in total serum IgE when children are separated into infested and non-infested groups (Table 5), nor did we demonstrate a lower parasite load in the atopic versus the non-atopic population. Other authors (Turner *et al.*, 1975) have failed to find any correlation between parasite loads and total serum IgE.

Co-existence of asthma and parasites

We have been able to confirm only one prediction made by the mast cell blockade theory: namely, that circulating IgE concentrations are high in children living in a parasite-endemic area of East Africa. We found, in agreement with other authors (Warrell *et al.*, 1975; Turner *et al.*, 1975; Rees *et al.*, 1974) who worked with adults, that there was no difference in the prevalence of parasite infestations between asthmatic and control subjects. Recently, some preliminary communications (Lasch, 1976; Kok & Robinson, 1976) have also reported parasite infestations in asthmatic children in the tropics.

It may be possible to reconcile the fact that parasites stimulate IgE production with the present observation that they do not prevent the development of allergic disease. In experimental rats, if exposure to parasites occurs *after* exposure to any allergen, there is no change in skin hypersensitivity to that allergen (Jarrett & Stewart, 1973). There is an increase in the specific IgE to that allergen, as well as in the parasite-specific IgE. If the parasitic infestation in our populations normally occurs after exposure to the usual aero-allergens, there should not be any difference in the pre-

valence of skin or pulmonary hypersensitivity when the parasitized population is compared with an unparasitized population.

Parasitic infestation normally occurs in the tropics after 6 months of age (Jelliffe, 1970). Significant allergen exposure in the United Kingdom has been postulated to start by 3 months of age (Soothill *et al.*, 1976). It is unlikely that allergen exposure would be later in rural Africa. Presumably, then, our children's parasitic infestations did not prevent asthma because allergen exposure occurred prior to infestation. It would be surprising if this was not also true for other tropical locales, and it would suggest that the parasite prevention of asthma—although theoretically or experimentally possible—is unlikely to occur in practice. If, indeed, there is a low prevalence of asthma in the tropics, it seems that other explanations than mast cell blockade should be sought.

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