firm scientific basis. Most epileptic patients can be controlled without side-effects or signs and symptoms of toxicity. However, the clinician may sometimes find it necessary to deviate from accepted principles to gain control in the exceptional case.

REFERENCES


Ascaris lumbricoides and Allergic Asthma

A New Perspective

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SUMMARY

Infestation of humans with the parasite Ascaris lumbricoides may induce high total serum IgE levels, but the influence of this immunogenic response on allergic asthma has not been defined. In this study, the specific anti-parasitic IgE-mediated response as determined by skin-prick testing was related to the incidence of allergic asthma in Ascaris-infested patients. A limited number

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— 17% of the non-allergic controls and 51% of the allergic asthmatics — had a clinically detectable immunogenic response to the parasite. The predicted incidence of asthma was significantly higher than the observed incidence in the subjects in whom the Ascaris skin test was positive. This was not found in subjects in whom the Ascaris skin test was negative. Inhalation of Ascaris antigen induced asthmatic reactions in 7 of 8 patients who were Ascaris-positive on skin testing, but not in the negative controls. The groups of patients who respond immunologically to parasite infestation need to be defined, as they may be predisposed to allergic diseases such as asthma.

the stools of 90% of the asthmatics studied by Tullis' led him to conclude that there was a marked correlation between the manifestations of bronchial asthma and the presence of intestinal parasites. However, Van Dellen et al. were unable to reproduce these results.

Extremely high serum IgE levels have been recorded in Ascaris-infested patients. A direct relationship between these levels and the incidence of asthma has, however, not been established. The answer to the question whether all Ascaris-infested patients have parasite-specific IgE responses may resolve the Ascaris-asthma controversy.

Burger found in 1968 that Ascaris and Trichuris infestation has a 95.7% prevalence among Coloured schoolchildren in the Western Cape. The warm climate, high humidity and sandy soil of this region produce ideal conditions for development of the ova. Allergic asthma and hay fever are also extremely common diseases in the local population.

In this study, a clinical measurement of the Ascaris immunogenic response was related to parasite infestation in allergic asthmatics and in non-allergic patients. Skin-prick testing and bronchial provocation were used to assess the immunogenic reactivity of patients to this antigen. Results of these in vivo determinations of parasite hypersensitivity were employed in an attempt to determine whether this factor is associated with allergic asthma.

PATIENTS AND METHODS

Coloured patients from the Western Cape, between the ages of 12 and 44 years, who attended the allergy clinic of the Tygerberg Hospital with asthma and in some cases with concomitant hay fever, were studied. This age group was chosen so as to study the maximum number of allergic asthmatics and the minimum with chronic obstructive pulmonary disease. Age-matched patients with no allergy symptoms and from the same region, who had been admitted to the medical wards for other reasons, were used as controls. A full history of allergy was taken from every patient and special note was made of the last date on which worms had been passed. Patients were clinically examined and stools were collected from co-operative patients and examined for the presence of parasites. Skin-prick tests were performed, with antigen extracts of 15 common airborne allergens obtained from the Bencard Company, in 85 clinically non-allergic subjects and in 109 allergic asthmatics. Tests were also done with a 6% Ascaris extract, obtained from the same company, in the two groups. Skin reactions of 3 mm diameter and larger were interpreted as positive. The size of skin indurations was graded by two trained staff members, according to a routine procedure. Ascaris-positive and Ascaris-negative subgroups were defined by means of the skin-prick reaction.

Bronchial Provocation with Ascaris lumbricoides Antigen

All patients who participated in this part of the study were younger than 35 years. Eight Ascaris-positive patients, 7 of whom were allergic asthmatics, were contrasted with 6 Ascaris-negative asthmatics, who served as controls. Five of the 8 positive and 3 of the 6 negative patients had ova in their stools at the time of the study, or were aware of having passed worms a few weeks before, or immediately after, bronchial provocation. The bronchial response after provocation was determined by the method described by Vermaak et al. and Bunn et al. Patients recorded maximal expiratory flow volume curves on a Coleman dry spirometer. Flow and volume signals were relayed to an oscilloscope from which the flow volume curve was photographed. The area below the flow volume curve was planimetered and expressed as a percentage of the control pre-inhalation value. These determinations were done at 15-minute intervals for the first 1½ hours after antigen inhalation and then hourly for another 6 hours, the last determination being at 24 hours. Asthmatics on treatment took no medication for 12 hours before bronchial provocation.

As a control prior to provocation with Ascaris antigen, patients inhaled saline for 5 minutes, and the lung response was determined at similar time intervals over an 8-hour period. The mean change was determined for each individual the day after saline had been inhaled. One standard deviation of this value was obtained and expressed as a percentage of the mean, and a value termed 'significant percentage change' was calculated in this way for each individual. Reactions were defined as an immediate response or a delayed response when the change in the area below the flow volume curve was greater than the significant percentage change at two points or more during the first 2 hours after inhalation (immediate response) and at two points or more 4 hours after inhalation (delayed response).

A 0.0006% Ascaris solution was used for an initial 1-minute period and two subsequent 2-minute periods of bronchial provocation, and if this evoked no bronchial response the antigen concentration was increased 10-fold. The concentration was increased if necessary until a 5-minute period of provocation with a 0.06% antigen solution had been completed; 6 controls, subjects who were Ascaris-negative on skin testing, also inhaled a 0.06% solution for 5 minutes.

Bronchial Provocation with Non-Ascaris Antigen

The asthmatic response to non-Ascaris antigen was tested by provocation in 3 of the 6 asthmatics who were Ascaris-negative on skin testing and in 1 of the 8 asthmatics who were positive. Antigen extracts employed in the negative controls included feathers, grass pollen and house-dust mite (Bencard Company), while bronchial provocation was conducted with a house dust extract in the positive subject.

RESULTS

Correlation between Stool and Ascaris Skin Test Results

Skin test and stool results for allergic and non-allergic patients were as follows, taking into account the fact that cross-reactivity exists between Ascaris antigen and IgE
produced against *T. trichiura*. Patients who had *Trichuris* ova in their stools along with *Ascaris* ova, or *Trichuris* only, were thus included as positive on stool testing.

Fifty-one of 123 allergic asthmatics (41.5%) were positive on skin testing and 57 (46.3%) had positive stools. In the non-allergic group, 13 of 71 patients (18.3%) were positive on skin testing and 24 (33.8%) had positive stools.

Results of a correlation between stool and skin test results for non-allergic patients were as follows: in the group with negative stools, 9 of 47 patients (19%) had skin reactions and 20 of 24 (83%) were negative. In the group with positive stools, 9 of 47 patients (19%) had positive skin tests and 38 (81%) were negative on both stool and skin testing.

In allergic asthmatics, 29 of 57 (51%) patients were positive on both stool and skin testing, while 28 of 57 (49%) had positive stools but were negative on skin testing. In the allergic asthmatic group with negative stools, 22 of 66 (33%) were positive on skin testing and 44 of 66 (67%) were negative on both stool and skin testing. A statistical correlation was found between stool and skin test results in allergic asthmatics (*P*<0.05), but not in the non-allergic group.

**Predicted and Observed Incidences of Asthma**

The predicted and observed incidences of asthma were calculated for a group of 194 control non-allergic and allergic asthmatic patients (Fig. 1).

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**Fig. 1.** Predicted and observed incidences of allergic asthma in patients exposed to *Ascaris lumbricoides*.

The predicted incidence of asthma for the whole group was 64%. The patients who were *Ascaris*-negative on stool and skin testing had an observed incidence of asthma of 54%. An incidence of 58% was recorded in the group with positive stools but negative skin test results. In a group with negative stools but positive skin test results the incidence was 71%. An observed incidence of 88% was recorded in the group who were positive on both skin and stool testing. This was significantly higher than the predicted incidence of asthma for the whole group (*P*<0.01). The observed incidence of asthma in all *Ascaris*-positive patients was also significantly higher than the incidence in the patients with negative skin test responses (*P*<0.001).

**Bronchial Provocation in Ascaris-Positive and -Negative Asthmatics**

The asthmatic response after inhalation of *Ascaris* antigen in a patient who was *Ascaris*-positive on skin testing is shown in Fig. 2. An immediate asthmatic response, indicated by a decrease in the area below the flow volume curve (vertical axis), was recorded within 15 minutes of antigen inhalation. This was followed by a delayed response which reached maximum intensity 6½ hours after the onset of the asthmatic reaction.

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**Fig. 2.** Bronchial provocation with *Ascaris* antigen in an asthmatic in whom the *Ascaris* skin test was positive.

Results of bronchial provocation in 8 subjects who were positive on skin testing and 6 who were negative were as follows: asthmatic responses were recorded in 7 of the 8 positive patients. The maximum antigen concentration employed to induce a bronchial response was 0.06%, for 4 minutes. Immediate and delayed responses were recorded in 3, a delayed response alone in 1 and early responses alone in 3 patients. No asthmatic response was recorded in 1 of the *Ascaris*-positive and in the 6 *Ascaris*-negative asthmatics.

**Bronchial Provocation with Non-Ascaris Antigen**

Immediate and delayed asthmatic responses to common inhaled allergens were recorded in all 3 patients who were *Ascaris*-negative on skin testing and in the 1 patient who was positive (Fig. 3).

**DISCUSSION**

The relatively low incidence of allergic asthma among rural Blacks living in areas where parasitic infestation is endemic induced the hypothesis that parasite-specific IgE saturates binding sites on mast cells, thereby pre-
vent IgE specific for common inhaled allergens from making contact with these cells in the respiratory tract; this interesting concept led to a suggestion in a leading article in The Lancet that allergic asthmatics should deliberately be exposed to parasites which enhance anti-parasite IgE synthesis.

The presence of functional or mast cell-bound IgE has not previously been related to allergic asthma. The prevalence of asthma in subjects who have IgE-mediated, anti-Ascaris skin responses suggests that their mast cells participate actively in the asthmatic response, despite the absence of Ascaris-specific IgE (Fig. 1). The close correlation found in this study between results of Ascaris skin tests and bronchial provocation in 7 of 8 positive and 6 negative subjects has also been reported for common inhaled allergens.

Our data demonstrate the presence of Ascaris-specific IgE on the bronchial mast cells of subjects who were Ascaris-positive on skin testing. Clinically, the asthma occurring in positive and negative subjects did not differ in intensity, and the presence of parasite-specific IgE on bronchial mast cells did not prevent acute asthmatic episodes in the Ascaris-positive group. A clear biphasic asthmatic reaction followed inhalation of a house dust antigen extract in 1 subject who was positive to Ascaris and to house dust antigens on skin testing (Fig. 3). These data provide evidence of an Ascaris-specific immunogenic response in the bronchi of patients who suffer from acute asthma, and contradict the hypothesis of a protective role for the parasite-specific IgE.

Only 17% of the clinically non-allergic and 51% of the allergic, parasite-infested subjects had positive, Ascaris-specific immunogenic responses. The absence of a clinically demonstrable immunogenic response to Ascaris antigen in 49% of the allergic and parasite-infested asthmatics needs to be considered when studying the relationship between parasite infestation and asthma. Our data suggest that a direct relationship between parasite infestation and allergic asthma exists only in individuals in whom clinical or laboratory evidence of a parasite-specific immunogenic response can be demonstrated. The similarity of the predicted and observed incidences of asthma in parasite-infested subjects who were Ascaris-negative on skin testing supports this concept (Fig. 1).

No correlation was found in this study between an anti-Ascaris immunogenic response and presence of parasite ova in the stools of clinically non-allergic controls. The absence of an immunogenic response in 83% of the non-allergic patients with Ascaris-positive stools may relate to a genetic inability of this group to produce anti-Ascaris IgE. The positive skin tests in 19% of the non-allergic and 33% of the allergic patients with negative stools may be due to the fact that they had previously employed an IgE-mediated immunogenic response to rid their gastrointestinal tracts of parasites, leaving them with anti-parasite IgE on their mast cells, while the non-responders, who were negative on skin testing, retained their parasites in the gut. Animal experiments have provided evidence in support of such an immunogenic mechanism for enhanced clearance of parasites. Similar evidence exists in humans. The reason for the absence of an immunogenic response in 49% of the allergic asthmatics who were parasite-infested is not entirely clear. The importance of considering both the anti-parasite immunogenic response and stool findings when studying the relationship between Ascaris and asthma is clearly shown by these data. Identification of asthmatic patients with positive immunogenic responses to Ascaris, especially those who also suffer active infestation, is essential in areas of endemic infestation and may be of great therapeutic importance in controlling asthmatic symptoms.

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