

This report describes a study in an area of great interest and some controversy in allergic diseases—the effects of concurrent parasitic infection on IgE responses to environmental allergens. Although, as pointed out by the authors, a number of important study design aspects could not be included, we recognize that these omissions are understandable in the light of the great difficulties in carrying out such an investigation in a problematic low-income area of South America during a time of great societal upheaval in the country.

Burton Zweiman, MD

Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum

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It is well known that helminthic infection can cause a polyclonal stimulation of the synthesis of IgE, which is dependent on interleukin-4 (IL-4) production, and it has been suggested that this can modulate the expression of allergic reactivity in tropical populations. We evaluated the effect of regular anthelmintic treatment, for a period of 22 months, on certain aspects of the allergic reactivity of children in a slum area of Caracas, Venezuela, where helminths are endemic. The treatment (Oxantel-Pyrantel; Quantrel) effectively eliminated intestinal helminthic infection and resulted in a significant decrease in the initially elevated total serum IgE levels. IL-4 was detectable in the serum, and a significant reduction in IL-4 was also observed after treatment. In contrast, both the immediate-hypersensitivity skin-test reactivity and serum levels of specific IgE antibody against environmental allergens were markedly increased in the treated children. In a group of children who were also evaluated in the same slum, but who declined treatment, a substantial increase in helminthic infection occurred, which was related to an acute deterioration of the socioeconomic conditions of Venezuela over the course of our study period. This was paralleled by a considerable increase in total IgE levels in these children and a decrease in the skin-test reactivities and specific IgE levels. The application of Prausnitz-Küstner passive transfer tests and analysis of specific IgE antibody levels indicated that the polyclonal stimulation of IgE synthesis by helminthic parasites results in mast cell Fcε receptor saturation and suppression of specific IgE antibody synthesis. This inhibition of allergic reactivity is reversible by anthelmintic treatment. (J ALLERGY CLIN IMMUNOL 1993;92:404-11.)

Key words: Allergy, parasites, helminthic infection, IgE, socioeconomic level, anthelmintic treatment

Considerable uncertainty exists regarding the prevalence of allergic disease in tropical populations and the possible influence of helminthic infection on this.¹⁻⁴ Studies in animal models⁵ and

Abbreviations used

IL-4: interleukin 4
P-K: Prausnitz-Küstner test
PRU: Phadebas RAST units

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comparative studies of populations with varying degrees of helminthic infection⁶⁻¹³ have indicated that these parasites can cause a nonspecific polyclonal stimulation of IgE synthesis, which is dependent on interleukin-4 (IL-4) production.¹⁴⁻¹⁶ This augmented synthesis of IgE can, under appropriate circumstances, increase allergic reactivity.¹⁷⁻¹⁹ However, when excessive, it has been suggested to actually be suppressive.⁷⁻¹³ The mechanism of this inhibition could be via a saturation of

mast cell Fcε receptors²⁰⁻²⁴ and/or an inhibition of specific IgE synthesis by the polyclonal response.^{9, 25}

Because direct evaluation of the influence of helminthic infection on IgE production and allergic reactivity cannot be undertaken in human beings, in the present study we approached the problem from the reverse direction; we determined the effect of elimination of these parasites in a group of children who had endemic helminthiasis. Previous studies on the effect of antiparasite treatment on serum IgE levels have given variable results.²⁶⁻²⁹ Because these were generally short-term evaluations, in this study we treated the children for a prolonged period (22 months).

METHODS

Study population and protocol

A group of 375 children between the ages of 5 and 15 years was examined; the children were from a well-defined and delimited slum area of Caracas, Venezuela (Barrio Los Erasos), in which we have been working for the past 12 years. The children were evaluated with the tests described below after the written authorization of their legal representatives had been obtained and under the medical supervision of the José Manuel de los Ríos Children's Hospital, which operates a pediatric clinic within the slum area. The study was approved by the ethical committees of the Institute of Biomedicine and the Children's Hospital and was ratified by both the National Council for Scientific and Technological Investigation and the Humanistic and Scientific Development Council of the Central University of Venezuela. It was also conducted with the cooperation and active participation of the community leaders of the slum area.

All of the children were then offered antiparasite treatment, and in agreement with the community leaders, participation in the treatment protocol was entirely voluntary. One hundred seven of the children (mean age $\pm$ SD, 8.4 ± 2.4 years old) were treated for 22 months and then reevaluated. Because of particular sociocultural conditions in the slum area, a placebo group was not included in this study. However, at the end of the study period, 80 of the children who were evaluated initially (mean age $\pm$ SD, 8.9 ± 2.7 years old) but who did not elect to or were unable to participate in the treatment protocol were reevaluated in parallel with the treated group. These subjects served as an untreated control group. Because of the voluntary nature of the study, an unintentional concentration of children of a lower socioeconomic level occurred in the treated group. Thus at the beginning of the study, 62% of the children who were subsequently treated were in officially defined³⁰ "critical poverty," and the remaining 38% were in the somewhat better situation of "poverty," compared with 45% and 55%, respectively for the untreated group (data not presented). It is relevant to remark here that our study coincided with an acute deterioration in socioeconomic

conditions, which was accompanied by the outbreak of the most violent social unrest in the recent history of Venezuela and which resulted in a great increase in the degree of poverty in the slum.³¹ By the end of the study, 87% of the untreated group were in "critical poverty."

The children of the treated group were given the wide-spectrum anthelmintic combination Oxantel-Pyranterel (Quantrel; Pfizer Inc., New York, N.Y.) on a monthly basis at a dose of 20 mg/kg of body weight for a period of 22 months. They were regularly examined by the medical personnel of the dispensary during this protocol, and no evidence of untoward effects of the treatment was noted. If after any feces examination, intestinal protozoal infections were detected (e.g., *Amoeba* or *Giardia* spp.), these were appropriately treated, but this was not done on a regular basis. Because a placebo-controlled study was not acceptable to the leaders of the community, tests subject to reader bias (particularly skin tests) were performed by a person who was unaware of the treatment status of the subjects. Technical personnel who were not directly involved with the study protocol participated in the different laboratory tests. Because the clinical evaluation of the children was performed by the same medical practitioner who was responsible for the welfare of the children and thus was not "blinded," these data were not included in the analysis.

Skin tests

Immediate-hypersensitivity prick tests were performed with allergenic extracts prepared and partially purified in our laboratory²⁸; extracts included house dust, mixtures of common molds, mixtures of whole-body extracts of common insects, animal epithelia, and an extract of *Ascaris lumbricoides*. The wheal diameters were measured after 20 minutes, and results were considered positive when wheal diameters were 3 mm or larger, in the absence of significant reactivity of the diluent control. Control prick tests were also performed with 1% histamine, 5% codeine, and 1 mg/ml anti-IgE. The anti-IgE was a 0.005 mol/L potassium phosphate eluate of a diethylaminoethyl cellulose chromatography of a rabbit antiserum, which was prepared in 1982 and stored at -70°C , for use in all of our subsequent studies of the allergic reactivity of the different socioeconomic sectors of the Venezuelan population.²⁵ The anti-IgE was membrane-filtered and bacteriologically checked before use and has been periodically quality-tested in the persons responsible for the study over the years of its use, with no evident adverse affects.

In persons with negative skin test results to the inhalant allergens, Prausnitz-Küstner (P-K) passive transfer tests were performed with a serum pool rich in IgE antibody (RAST class 4) against *Dermatophagoides* species. This pool had been collected in 1981 from children of a high socioeconomic level, centrifuged twice at 100,000 g for 5 hours, membrane-filtered, bacteriologically tested, and stored at -70°C . It was shown to be negative for hepatitis B antigen and anti-human immunodeficiency virus antibodies; the lat-

TABLE 1. Prevalence of helminthic infection (percent)*

	Untreated		Treated	
	Beginning	End	Beginning	End
Total helminths	43	70	68	5
<i>Ascaris lumbricoides</i>	27	67	48	3
<i>Trichuris trichuria</i>	24	35	36	2

*Prevalence (percent) of infection by any helminth, *Ascaris* or *Trichuris*, at the beginning and end of the 22-month study period, in the untreated group and in the group that received regular anthelmintic treatment.

ter was evaluated by two independent laboratories. The P-K serum has been periodically tested in the persons responsible for the study, with no evident side effects.

Serum IgE antibody

Total serum IgE levels were measured by the Paper Radioimmunosorbent Test (Phadebas; Pharmacia, Uppsala, Sweden), and specific antibody levels were determined by RAST, taking into account the possible existence of nonspecific adsorption, as previously described.^{28, 32} The RAST with local allergens was standardized with the Phadebas test, and the results were expressed as Phadebas RAST units (PRU) per milliliter. According to the recommendations of the manufacturer and our experience in the use of the RAST in the Allergy Clinic of the Instituto de Biomedicina,³³ values equal to or greater than 0.35 PRU/ml (level 1 on the Phadebas scale) were considered to indicate the presence of significant concentrations of IgE antibody, and values equal to or greater than 0.70 PRU/ml (level 2) were considered to be indicative of "clinically relevant" levels of specific antibody.

Serum IL-4

Serum levels of IL-4 were measured with the commercial Intertest-4 kit (Genzyme, Cambridge, Mass.) in 20 treated children who showed high initial levels and substantial decreases of total IgE after treatment.

Feces examination

Samples of three successive evacuations were collected into a preservative solution consisting of 40% tincture of thimerosal, 5% formaldehyde, and 1% glycerol; these were examined microscopically within a period of 2 weeks. We should note here that, probably because of our medical intervention in the slum area over the past years, the intensity of infection was moderate and not over-dispersed.

Eosinophilia

Because of social unrest in Venezuela at certain points in our study, it was not possible to perform absolute eosinophil counts on fresh blood samples for some of the study subjects. However, peripheral blood eosinophilia was also determined by preparing air-dried

smears that were stored and then stained with Wright's stain and counted differentially.

Statistical analysis

The total and specific IgE levels were normalized by log-transformation, and the geometric mean (plus 1 SD) was presented. Analysis of variance was performed, and the statistics presented were determined by the paired Student's *t* test for within-group (before treatment vs after treatment) comparisons, and the unpaired test was used for between-group comparisons (treated vs untreated). Different proportions between groups were analyzed by the chi square test.

RESULTS

Helminthic infection

In Table I it can be seen that at the beginning of the study, the prevalence of intestinal helminths was high in the group of children who were subsequently treated but was significantly ($p < 0.001$) lower in the group of children who did not participate in the treatment protocol.

At the end of the study, the treated group was found to be virtually free of intestinal helminthic infection. In fact, sequential feces examinations performed during the course of the study revealed that treatment was almost completely effective by the second month, and only occasional infections occurred in this group for the rest of the study period (data not presented). In contrast, the prevalence of infection rose dramatically ($p < 0.001$) in the untreated group (Table I).

Total IgE levels and eosinophilia

Table II shows that at the beginning of the study, the total serum IgE levels were high in both groups, but these were significantly ($p < 0.005$) greater in the children who were later treated, compared with those who were not treated. This pattern was inverted by the end of the study, when the levels in the untreated group had risen substantially ($p < 0.001$) but had fallen signifi-

TABLE II. Total IgE and blood eosinophilia

	Untreated		Treated	
	Beginning	End	Beginning	End
Total IgE* (IU/ml)	1649 (4073)	3697 (7513)	2543 (6140)	1124 (2454)
Eosinophil count†				
Absolute cells/ml $\times 10^{-6}$	0.69 $\pm$ 0.39	0.78 $\pm$ 0.29	0.84 $\pm$ 0.44	0.45 $\pm$ 0.34
Differential (%)	10.5 $\pm$ 6.6	12.0 $\pm$ 4.3	12.3 $\pm$ 7.3	5.7 $\pm$ 3.3

*Geometric mean (plus 1 SD).

†Mean $\pm$ SD. Differential counts were performed on the entire group. The number of subjects for absolute counts were, in order across the table: 75, 46, 86, 86.

TABLE III. Skin test positivity (percent)

	Untreated		Treated	
	Beginning	End	Beginning	End
House dust	26	16	17	68
<i>Ascaris lumbricoides</i>	32	49	47	83
Histamine	90	98	98	96
Codeine	92	97	93	100
anti-IgE	80	83	83	100
P-K*	46	34	52	79

*P-K positivity of persons with negative results of skin tests with environmental allergens. Number of subjects, across the table: 56, 61, 84, 33.

cantly ($p < 0.001$) in the group that received treatment. Stratified cohort analysis revealed that the changes that occurred in total IgE levels were independent of age. For example, the starting level in 8-year-olds (the mean age at the beginning of the study) was 2377 IU/ml, and in 10-year-olds (the mean age at the end of the study) the starting level was 2600 IU/ml.

Peripheral blood eosinophilia was elevated in both groups at the beginning of the study and was significantly ($p < 0.001$) reduced by treatment (Table II).

Serum IL-4

Serum IL-4 levels were measured in 20 selected children who showed both initially elevated IgE and then substantial posttreatment reductions (from geometric mean values of 3420 to 845 IU/ml). Despite the fact that the absolute levels of this interleukin in serum are low, a significant ($p < 0.001$) decrease was observed between the beginning and end of the treatment period: 2.5 ± 0.7 ng/ml versus 0.7 ± 0.25 ng/ml.

Skin-test reactivity

The data presented in Table III reveal that the immediate-hypersensitivity skin-test reactivity to-

ward common environmental allergens, such as house dust, was greatly increased ($p < 0.001$) after treatment. Comparable results were obtained for other common allergens tested; for example, in the treated group the positivity toward mixed molds rose from 11% to 23% ($p < 0.025$) and from 18% to 31% ($p < 0.025$) for mixed insect extracts (data not presented). The initial positivity of the untreated group tended to be higher than that of the treated group, but it decreased during the course of the study.

In regard to skin-test reactivity toward *Ascaris* extract, the most notable change was a substantial increase ($p < 0.005$) in positivity in the treated group.

The positivities to the control skin tests, histamine, codeine, and anti-IgE were effectively normal in both groups throughout the study.

The P-K positivity in the children who had negative skin test results to environmental allergens at the beginning of the study was relatively low, compared with normal Venezuelan children of a higher socioeconomic level who rarely have helminthic infection (100% P-K positive¹³). A striking increase in P-K positivity ($p < 0.01$) occurred in the treated group, whereas that of the untreated group tended to decrease.

TABLE IV. Specific IgE antibody

	Untreated		Treated	
	Beginning	End	Beginning	End
House dust				
≥ Level 1 (%)*	88	72	78	81
≥ Level 2 (%)	39	25	32	63
GM (+ 1 SD)†	0.68	0.52	0.52	0.82
PRU/ml	(0.81)	(0.72)	(0.62)	(1.07)
<i>Ascaris lumbricoides</i>				
≥ Level 1 (%)	80	86	71	95
≥ Level 2 (%)	37	41	46	72
GM (+ 1 SD)	0.71	0.56	0.56	0.76
PRU/ml	(0.95)	(0.78)	(0.66)	(0.93)

GM, Geometric mean.

*Percent of group with results above RAST level 1 (0.35 PRU/ml) or level 2 (0.70 PRU/ml).

†Geometric mean (plus 1 SD) of specific IgE levels.

Specific IgE antibody

The levels of IgE antibody against house dust are presented in Table IV. At the beginning of the study a very high proportion of both groups had positive results at RAST level 1 (≥ 0.35 PRU/ml). By the end of the study, a substantial ($p < 0.001$) increase had occurred in the percentage of treated subjects with positive results at RAST level 2 (≥ 0.70 PRU/ml), whereas this tended to decrease in the untreated group. These differences were also reflected by the mean IgE antibody levels, in which an evident increase ($p < 0.001$) occurred in the treated group, compared with a decrease ($p < 0.01$) in the untreated group. An essentially similar pattern was found for anti-*Ascaris* antibody (Table IV).

DISCUSSION

The main objective of this study was to investigate the possible influence of intestinal helminthic infection on the allergic reactivity of human beings. This was achieved by the most direct and ethically acceptable means available, which was the evaluation of a group of children in a slum where these parasites are endemic and then keeping them free of infection by means of a prolonged period of regular anthelmintic treatment. For this purpose we performed initial tests on a large group of subjects in a well-defined slum area of Caracas, Venezuela, and then offered them all the opportunity to enter the treatment protocol. We were able to maintain 107 of these children on a monthly regimen of Oxantel-Pyrantel for 22

months, after which time they were reevaluated, and found to be virtually free of intestinal helminthic infection. In fact, the great majority of the children were completely free of parasites by the second month of treatment, and thereafter only occasional infections were detected. In parallel, we were able to reexamine 80 subjects of the original group, who for various reasons did not wish or were unable to participate in the treatment program. This latter group served therefore as an untreated control group. Various aspects must, however, be considered regarding these two groups of children. First, because of the strictly voluntary nature of participation in this study, the socioeconomic status of the children who sought treatment was generally lower than those who did not, and this was reflected by a significantly higher initial prevalence of helminthic infection in the treated group. Second, because of an acute aggravation of the socioeconomic conditions in Venezuela during the course of our study, the level of poverty of the children increased dramatically, and consequently, a substantial increase in the prevalence of helminthic infection in the untreated group occurred.³¹

These differences were reflected in the total serum IgE levels of the children; at the beginning of the study these were elevated in both groups but were significantly higher in the group that was subsequently treated, compared with the group that was not. The IgE levels then fell significantly as a consequence of the treatment protocol, whereas a striking elevation occurred in the un-

treated children. Taking into account this increase in the control subjects, which presumably would have also occurred in the treated children had they not participated in the study, the anthelmintic treatment effectively reduced the total IgE levels by at least fivefold in the period of 22 months. Despite the fact that the control group was not strictly comparable to the treated group, the validity of the within-group comparisons (before treatment vs after treatment) is confirmed by stratified cohort analysis, which demonstrates that the changes detected in IgE levels are independent of age, which is the major uncontrolled variable in this study. Thus although indirect, these results provide quantitative evidence that helminthic infection in human beings causes an elevation in serum IgE levels. This confirms the conclusions of numerous comparative studies on different population groups, which had varying degrees of helminthiasis,⁶⁻¹³ and also those of more direct animal experiments.⁵ In addition, these results demonstrate that the potentiation of IgE synthesis is, at least to some extent, reversible. The reason the IgE levels did not fall to "normal" values may be that the treated children have had polyparasitism essentially since birth, and so a period of 22 months is probably too short a time for the immunologic system to revert to a normal state. In addition, although treatment with Oxantel-Pyrantel is effective against adult helminths, it does not prevent contact with eggs and larvae of these organisms, which must occur constantly in the conditions of endemicity under which these children live. Likewise, this treatment is not necessarily effective against systemic helminthic infections, such as toxocariasis, which also occur in such children.³⁴ As would be expected from its close relationship with helminthic infection,³⁵ blood eosinophilia was also significantly reduced in the treated children.

It has been demonstrated that the synthesis of IgE is dependent on IL-4 production and that this is particularly evident in hyperimmunoglobulinemia E states in general and in helminthic infection in particular.¹⁴⁻¹⁶ In the present study we selected a subgroup of treated patients who showed substantial reductions in IgE levels and found that although the absolute values of IL-4 in serum were relatively low, a significant decrease also occurred in the levels of this interleukin.

With respect to immediate-hypersensitivity skin-test reactivity toward common inhalant aller-

gens, our results are consistent with the concept of a suppression caused by the elevated total IgE levels that are stimulated by helminthic infection.²⁰⁻²⁴ Thus at the beginning of our study skin-test positivity tended to be lower in the group that had the higher IgE levels, that is, the one that was subsequently treated. In contrast, by the end of the study period, the positivity in the treated group had become very high, whereas it decreased in the control group, which became more infected during this time. In concordance with these changes, the positivity in P-K passive transfer tests was markedly increased in the treated group, thus reaffirming the relationship between elevated total IgE levels and mast cell Fcε receptor blockade and also indicating the reversibility of this relationship.

Further evidence for the existence of mast cell saturation caused by elevated total IgE levels is provided by the fact that at the beginning of the study, the positivity for specific IgE antibody against environmental allergens was far higher than the corresponding skin-test reactivity in both groups, particularly when RAST level 1 (≥ 0.35 PRU/ml) was considered to be positive. This very high positivity for detectable IgE antibody is probably due to the polyclonal stimulation of IgE synthesis that is caused by helminthic infection¹⁷⁻¹⁹ and that tends to result in discrete increases in the production of a very wide range of different IgE specificities.^{9, 25} This could also explain the particularly significant result obtained in the treated group, which at first appears contradictory; although the total IgE levels are reduced, the specific IgE levels against common inhalant allergens are in fact substantially augmented, both in terms of mean levels and in the proportion of the children who had positive results at RAST level 2 (≥ 0.70 PRU/ml). We propose that low-level contact with helminths, such as in the case of the treated children, causes a stimulation of IgE synthesis that is less widely polyclonal, and thus the response against allergens that are continually present in the environment is actually enhanced. This, coupled with decreased mast cell saturation, is the probable cause of the exceptionally high skin-test positivity to environmental allergens found after treatment. Another finding in our study, which might be considered unexpected, is that in the treated group both the skin-test positivity and specific IgE antibody against *Ascaris* antigens also increased substantially, despite the

elimination of the parasites. This may have occurred because the same changes that affect the response to common inhalant allergens also apply to the parasite antigens. In addition, the uninterrupted exposure of the treated children to eggs and larvae of the helminths could provide a stimulus for a specific IgE antibody response, possibly in the absence of polyclonal potentiation induced by the adult organisms.

The results of this study indicate that helminthic infection does indeed increase IgE synthesis and that this increase, when moderate, can enhance allergic reactivity; however, when it is excessive, it can actually be suppressive through both a saturation of mast cell Fcε receptors and an inhibition of specific IgE synthesis. We are currently undertaking long-term follow-up studies of the children treated in this study to determine whether the changes that we observed will have repercussions on the clinical expression of allergic disease.

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