

Original articles

Incidence of atopic disease in a tropical environment: Partial independence from intestinal helminthiasis

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The reported incidence of atopic disease in the tropical environment, albeit somewhat controversial, has often been very low. This has been postulated to be due to an inhibitory influence of intestinal helminthiasis, although the predominantly rural nature of the populations studied might also be an important factor to consider. We evaluated two tropical groups in Venezuela that were basically comparable, both being highly parasitized but one of which was urban and the other rural. The apparent incidence of allergic conditions in the urban group was, in fact, comparable to that in temperate countries, whereas that of the rural subjects was markedly lower. A similar difference was found in skin test positivity to common inhalant allergens, although reactivity to Ascaris extract was comparably high between the two groups, and total serum IgE and eosinophil levels were uniformly elevated. Our results suggest that the incidence of atopic disease in the tropical environment may depend not only on the intensity of helminthiasis suffered but also on factors related to the urban-rural situation. (J ALLERGY CLIN IMMUNOL 73:229-233, 1984.)

The incidence of atopic disease in the tropical environment has been the subject of controversy.^{1, 2} A number of reports have described a very low prevalence of allergic conditions, particularly in rural populations.^{1, 3-7} It is, however, difficult to draw definitive conclusions from independent studies applying diverse methodologies to distinct racial and social groups.¹ In addition, although the reportedly low incidence of atopic disease in the tropics has frequently

been attributed to a blocking or inhibitory effect of intestinal helminthiasis,^{4, 5, 7-9} the possible importance of other factors, which could be environmental, social, or nutritional (particularly related to the rural situation), should not be overlooked.

In order to better characterize the effect of these influences, we evaluated two Venezuelan populations that were fundamentally comparable and highly parasitized but that differed by being either urban or rural.

MATERIAL AND METHODS

Survey protocol

The subjects under study were evaluated by direct questioning to establish their socioeconomic status and general clinical history. A history of allergy was elaborated by a medically qualified specialist, following a protocol employed previously,¹⁰ taking into account the generally low level of education and medical awareness of the study groups. Physical examination was also performed when it was considered necessary. Individuals were classified as atopic only when symptoms that could reasonably be con-

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TABLE I. Frequency of atopic disease

Disease	Urban	Rural
Total questioned	431	336
Rhinitis	82	32
Asthma	25	6
Atopic dermatitis	14	12
Urticaria	12	9
"Atopic"*	102	41

*Individuals suffering at least one atopic condition.

sidered as allergic were suffered repetitively during the previous 3 to 5 yr. The occurrence therefore of rhinitis, asthma, dermatitis, and urticaria was established with emphasis on atopic etiology. Subjects with mixed symptomatology were scored for each separate disease type. Because of difficulties encountered in the definition of gastrointestinal symptoms of allergic disease in the study populations, these were not included in the present analysis. The application of similar criteria resulted in an overall prevalence rate of 29.0% in 138 individuals from temperate climates.¹⁰

Study populations

A total of 475 urban individuals (54% female) from a number of different marginal zones of Caracas, Venezuela (latitude 10° N), were examined; the mean ($\pm$ SD) age was 13.8 ± 10.4 yr. Rural subjects (336, 53% male; 15.5 ± 13.1 yr) from various areas of the country were evaluated either in their location or on presentation in Caracas (general pediatric patients, their accompanying family members, etc.). Although strict age-matching between these groups was not possible, particular care was taken to maintain comparable sex ratios and age structures. Apart from low socioeconomic level and residence (urban or rural), sex and age were the only selective criteria deliberately adopted. Minor differences in distribution were observed when the two populations were stratified according to age (5 to 9 yr, 10 to 19 yr, and 20 to 40 yr) and sex; the maximum variation detected between the two social groups was in men 20 to 40 yr (13.0% of the urban total compared to 17.8% of the rural $p > 0.05$). Young women, 10 to 19 yr old constituted the largest single sex/age group in both cases (26.9% and 24.1%, respectively).

When heights and body weights were considered in relation to sex and age, no consistent or marked differences were noted between the two populations.

Skin tests

Prick skin tests were performed with partially purified extracts prepared from local environmental allergens^{10, 11} and *Ascaris lumbricoides*. The materials tested were selected to provide the widest possible range of allergens: house dust from four different climatic localities of Venezuela, two species of *Dermatophagoides*, five of the most common moulds, six common insects, epithelia from eight animal species, 23 foods, and an extract prepared from the

TABLE II. Skin test reactivity

	Urban	Rural
No. tested	475	327
No. positive		
House dust	103	28
<i>Dermatophagoides</i> sp.	69	21
Moulds	10	6
Insects	24	7
Animal epithelia	14	6
Foods	15	10
Aeroallergens	8	4
<i>Ascaris lumbricoides</i>	120	88
Total positive*		
Excluding <i>Ascaris</i>	128	34
Including <i>Ascaris</i>	189	107

*Number of individuals with at least one positive skin test.

material obtained from 2 yr continuous suction sampling of air (referred to as "aeroallergens"). The extracts were fractionally precipitated with ammonium sulfate, Sephadex G-25 (Pharmacia, Uppsala, Sweden), chromatographed and standardized to 1500 PNU/ml prior to use.^{10, 11} Immediate hypersensitivity wheal diameters that were clearly greater than the diluent (50% saline, 50% glycerol; 0.4% phenol) control were taken as positive, and this was usually >3 mm.

The overall skin test positivity of 138 individuals from temperate climates to their appropriate local allergens was 37.0% when similar testing methods were used.¹⁰

Total serum IgE levels

These were measured by the paper disc technique of Ceska and Lundkvist¹² and standardized against the commercial Phadebas (Pharmacia) test. Because of the extremely high levels of IgE in the study populations, sera were assayed in duplicate after dilution to 1:200 and 1:1000.

Eosinophilia

Dried blood smears were stained with Wright's solution. Because of the generally high eosinophilia of the study populations, a total count of 200 leukocytes provided a reliable measurement in most cases.

Intestinal helminthiasis

At least three feces samples, collected into preservative solution,¹³ were examined for each subject. Concentration by Zn SO₄ flotation was applied when necessary, and in some cases egg counts were performed.¹³

Statistical methods

The data were analyzed by the application of the χ^2 test (Yates correction used when necessary) and Student's t test (after testing for normal distribution). IgE values were normalized by logarithmic (base 10) transformation for statistical analysis.

TABLE III. Total serum IgE and eosinophil count

	Urban	Rural
Log IgE (log IU/ml)	2.872 $\pm$ 0.690 (155)	2.989 $\pm$ 0.997 (110)
Eosinophils (%)	10.0 $\pm$ 7.1 (87)	12.3 $\pm$ 9.6 (24)

Values are mean $\pm$ S.D.; number tested in parentheses.

RESULTS

Atopic disease

The overall frequency of atopic disease, determined by direct interrogation, was significantly lower ($p < 0.001$) in the rural group (12.2%) than the urban group (23.7%) (Table I). This difference was observed for rhinitis (9.5% vs. 19.0%; $p < 0.001$) and asthma (1.8% vs. 5.8%; $p < 0.01$), but not for either atopic dermatitis or urticaria.

Skin test reactivity

The overall frequency of positive skin tests to common (nonparasitic) allergens was significantly lower ($p < 0.001$) in the rural group (10.4%) than the urban group (26.9%) (Table II). This difference was particularly evident with the two extracts that were most frequently positive: house dust (8.6% vs. 21.7%; $p < 0.001$) and *Dermatophagoides* (6.4% vs. 14.5%; $p < 0.001$). The frequency of positivity to *Ascaris* extracts was, however, very high, and not significantly different between the two populations (26.9% vs. 25.3%). The total skin test positivity was, in fact, little different (32.7% vs. 39.8%). The wheal diameters of positive reactions to house dust were generally small but tended to be greater, although not statistically significantly so, in the urban compared to the rural group (5.3 ± 3.8 mm and 4.1 ± 4.0 mm $p > 0.05$, respectively). Positive wheal diameters to *Ascaris* were essentially identical between the two populations (6.0 ± 3.1 mm and 6.3 ± 3.2 mm).

Total serum IgE

The total IgE levels in sera of both study populations were very high (Table III). The geometric mean concentrations were 745 IU/ml in the urban population and 975 in the rural group, this difference not being statistically significant.

Eosinophilia

The percentage of eosinophils, relative to the remainder of the white blood cells, was very high in both the urban and rural groups (Table III).

TABLE IV. Intestinal helminthiasis

	Urban	Rural
No. tested	193	76
No. positive		
<i>Ascaris lumbricoides</i>	208	42
<i>Trichuris trichiura</i>	38	25
<i>Necator americanus</i>	5	16
Total positive*	256	59

*Individuals suffering at least one helminthic infection.

Intestinal parasitosis

An extremely high proportion of the serially collected fecal samples examined were found to contain eggs of intestinal helminths in both the urban group (80.5%) and rural group (77.6%) (Table IV). Ascariasis was the most common affliction, particularly in the urban population (71.0% vs. 55.3% [$p < 0.005$] positive, respectively). The frequencies of *Trichuris* and *Necator* infection were significantly lower in the urban group (13.0% and 1.7%, respectively) than the rural population (32.9% and 21.0% $p < 0.001$).

Although quantitative egg counts were not feasible for the entire study population, the concentration of *Ascaris* eggs was determined in 36 and 21 randomly selected positive samples from the urban and rural groups, respectively. The range of egg concentrations was very wide, and although somewhat higher levels were detected in the urban group ($16,300 \pm 22,800$ /gm of feces) than in the rural population ($12,000 \pm 19,400$), this difference was not statistically significant.

DISCUSSION

The incidence of atopic disease in the tropical environment has been reported to be very low.^{1, 3-7} This has been attributed to an effect of intestinal helminthiasis.⁸ This could occur via a mechanism of competitive inhibition at the level of the mast cell Fc_ϵ receptor¹⁴ caused by the polyclonal increase of IgE synthesis induced by such infections.^{4, 5, 7, 9} Recent results suggest, however, that the mast cells of heavily parasitized individuals are not necessarily saturated with IgE.¹⁵ Alternatively, helminths might exert a more direct suppression of the allergic response, either by diminishing the synthesis of IgE antibody against common environmental allergens¹ or, conceivably, by inhibiting mast cell degranulation.¹⁶ However, since the tropical populations previously studied have been largely rural in nature, the possible influence of environmental, social, nutritional, and other factors^{1, 6, 17, 18} should also be considered.

We examined two comparable but separate tropical populations in Venezuela, both heavily parasitized but one being purely rural and the other urban. The majority of the latter was actually of rural origin but had been established in poorly serviced marginal zones of Caracas, Venezuela, for at least a generation.¹⁹

The apparent frequency of atopic conditions, determined by direct medical interrogation, was significantly higher in the urban than the rural environment. This difference was detected for the respiratory, but not the cutaneous, manifestations of allergic disease. The urban subjects actually suffered allergic conditions in proportions comparable with populations in temperate climates.^{1, 10} It is, of course, recognized that the data obtained in the establishment of allergic histories are inherently subjective. In fact in many studies the allergic history is established by questionnaire,¹ and this can be misleading in tropical populations where the level of education is low.

In order to provide an independent assessment of allergic reactivity, prick testing was also performed. A similar difference also occurred in the frequency of skin test positivity to common inhalant allergens. The higher responsiveness of the urban group was particularly evident with the two most frequently reactive extracts: house dust and *Dermatophagoides*.

Although some differences in the pattern of intestinal helminthiasis suffered by these groups were detected, the overall intensity and type of infection experienced was similar, ascariasis being predominant. The total serum IgE concentrations and eosinophil count in these two populations were comparably elevated, and this was almost certainly caused by their helminthic infections.^{10, 20, 21}

Thus despite the need for further investigation, our results do not suggest that the diminished allergic reactivity of the rural population is due to more intense helminthic infection and consequently greater mast cell inactivation caused by saturation by IgE. This is in agreement with the conclusions of Larrick et al.¹⁵ We should remark here that we have also compared the skin test results in these groups with the serum levels of specific-IgE antibody. As, however, the interpretation of these studies is complicated by a number of considerations, they will be presented in detail subsequently. Suffice it to mention here that such individuals possess significantly greater quantities of IgE antibody against environmental allergens than the skin test results would suggest. We have also obtained similar results in a study of the allergic reactivity of Amerindians of the Venezuelan sector of the Amazon basin.²²

Another point of particular importance demon-

strated by our results is that in contrast to the inhalant allergens, *Ascaris* extract provoked immediate skin reactions in substantial (and comparable) proportions of both study groups. Further evaluation is required concerning the relationship of such reactivity to allergic disease, as considerable uncertainty surrounds this point.²³ The data presented here suggest, in fact, that the occurrence of allergic disease can not be directly related to the existence of immediate hypersensitivity reactivity to *Ascaris*. It should be noted here that testing with *Ascaris* extract probably also reveals the existence of reactivity to a variety of helminths, due to the immunologic cross-reactivity between these organisms.²⁴

Furthermore, our results underline the particular importance of using allergens that are appropriate to the tropical environment, rather than those that are of significance mainly in temperate climates⁷ and thus would stimulate few skin responses in tropical populations.²

Although in temperate climates few noteworthy differences have been found in allergic reactivity between urban and rural groups,¹ various studies of tropical populations have detected higher frequencies of atopic diseases in the urban situation.^{1, 2, 4-6, 10} This difference has usually been attributed, however, to the blocking effect of a presumably more intense parasitic infestation in the rural individuals.^{4, 5} It has, however, previously been remarked,² and demonstrated by our results, that tropical urban populations are not necessarily free of intestinal helminthiasis. As described in this study we have examined two parasitized groups that differ in their environment (urban vs. rural) and, in combination with a previous report,¹⁰ can compare two groups in the same environment (urban) but with different degrees of parasitosis (high and low socioeconomic levels). Our results suggest that although parasitosis has a modulatory effect that depends on its intensity, other influences apparently also operate on the expression of the atopic state in the tropical environment. It can be postulated that certain factors^{1, 6, 17, 18} may be accentuating in the city (allergenic diet, atmospheric pollution, stress, etc.) and ameliorating in the country (prolonged breast feeding, open housing, etc.). The present study was not designed to identify all the determinants capable of modulating the allergic response in tropical populations. This, in fact, forms the basis of current investigation, in which a variety of social, cultural, and nutritional criteria are being compared between the urban and rural groups.

The net result of all these influences is that tropical urban populations can suffer allergic conditions at an equal or higher¹⁰ rate (depending on their low or high

socioeconomic level) than those in temperate climates whereas tropical rural groups exhibit low prevalence figures.

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REFERENCES

1. Turner KJ: The conflicting role of parasitic infections in modulating the prevalence of asthma. *Papua New Guinea Med J* 21:86, 1978
2. Grove DI: What is the relationship between asthma and worms? *Allergy* 37:139, 1982
3. Anderson HR: The epidemiological and allergic features of asthma in the New Guinea highlands. *Clin Allergy* 4:171, 1974
4. Godfrey RC: Asthma and IgE levels in rural and urban communities of the Gambia. *Clin Allergy* 5:201, 1975
5. Merrett TG, Merrett J, Cookson JB: Allergy and parasites: the measurement of total and specific IgE levels in urban and rural communities in Rhodesia. *Clin Allergy* 6:131, 1976
6. Van Niekerk CH, Weinberg EG, Shore SC, Heese H, Van Schalkwyk DJ: Prevalence of asthma: a comparative study of urban and rural Xhosa children. *Clin Allergy* 9:319, 1979
7. Kaplan JE, Larrick JW, Yost JA: Hyperimmunoglobulinemia E in the Waorani, an isolated Amerindian population. *Am J Trop Med Hyg* 29:1012, 1980
8. Preston PJ: The biology of the atopic response. *R Nav Med Serv* 61:229, 1970
9. Godfrey RC, Gradidge CF: Allergic sensitization of human lung fragments prevented by saturation of IgE binding sites. *Nature* 259:484, 1976
10. Lynch NR, Di Prisco-Fuenmayer MC: High allergic reactivity in a tropical environment. *Clin Allergy* (in press)
11. Hurtado JC, Lynch NR: Humoural and cellular immune responses of atopic individuals in a tropical environment. *J Clin Lab Immunol* 11:75, 1983
12. Ceska M, Lundkvist U: A new simple radioimmunoassay method for the determination of IgE. *Immunochemistry* 9:1021, 1972
13. Brown HW: *Basic clinical parasitology*, ed 4. New York, Appleton-Century-Crofts
14. Stanworth DR, Humphrey JH, Bennich H, Johansson SGO: Specific inhibition of the Prausnitz-Kustner reaction by an atypical human myeloma protein. *Lancet* 2:330, 1967
15. Larrick JW, Buckley CE, Machamer CE, Schlagel GD, Yost JA, Blessing-Moore J, Levy D: Does hyperimmunoglobulinemia E protect tropical populations from allergic disease? *J ALLERGY CLIN IMMUNOL* 71:184, 1983
16. Mazingue C, Camus D, Dessaint JP, Capron M, Capron A: *In vitro* and *in vivo* inhibition of mast cell degranulation by a factor from *Schistosoma mansoni*. *Int Arch Allergy Appl Immunol* 63:178, 1980
17. Report of a meeting on allergic diseases. *Clin Allergy* 10:1, 1980
18. Marsh DG, Meyers DA, Bias WB: The epidemiology and genetics of atopic allergy. *N Engl J Med* 305:1551, 1981
19. Dehollain PA, Perez-Schael I: Venezuela desnutrada. Caracas, 1980, Equinoccio Editorial U.S.B.
20. Johansson SGO, Mellbin T, Vahlquist B: Immunoglobulin levels in Ethiopian preschool children with special reference to high concentrations of immunoglobulin E (IgND). *Lancet* 1:1118, 1968
21. Merino F, Arends T: High levels of IgE in apparently normal Venezuelan populations. *Invest Clin* 16:122, 1975
22. Lynch NR, López RI, Isturiz G, Tenias-Salazar E: Allergic reactivity and helminthic infection in Amerindians of the Amazon basin. *Int Arch Allergy Appl Immunol* 72:369, 1983
23. Aderele WI, Oduwole O: Skin sensitivity reactions in Nigerian children with bronchial asthma. *Trans R Soc Trop Med Hyg* 75:675, 1981
24. Turner KJ, Fisher EH, Mc Williams AS: Homology between roundworm (*Ascaris*) and hookworm (*N. americanus*) antigens detected by human IgE antibodies. *Aust J Exp Biol Med Sci* 58:249, 1980