THE EVOLUTIONARY CONTEXT OF CHRONIC ALLERGIC CONDITIONS

The Hiwi of Venezuela

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The question of why populations with ecologies that resemble our evolu-tionary past rarely experience allergic conditions such as asthma has intrigued many biomedical scientists. Here we present descriptive data on the ecological context of allergic sensitization among the Hiwi of southwestern Venezuela and suggest reasons for why this and other low-land South American Indian groups do not express the allergic response at levels seen in industrialized contexts. Allergic sensitization among the Hiwi appears to be negligible. This absence occurs in the context of high exposure to macroparasites (mainly hookworm), nutritional stress, fre-quent and prolonged breastfeeding, low indoor allergen deposition, and few hours spent per day indoors. We conclude that seeking unidimen-sional answers to the question of why isolated human groups generally experience few allergic conditions is potentially flawed because allergies are produced by a multifaceted immunoglobulin E (IgE) system that re-sponds in complex ways to the environmental and behavioral exposures we examined. Instead, we propose a general model of physiological trade-offs in energy allocation between production of IgE of undefined specificity and production of allergen-specific IgE. In addition, we con-sider the simultaneous effects that exposures such as nutritional stress, allergen exposure, and breastfeeding may have on these trade-offs.

The question of why populations with ecologies that resemble our evolutionary past rarely experience allergic conditions such as asthma has intrigued many biomedical scientists (Godfrey 1975; Hurtado and Arenas 1996; Nesse and Williams 1995). If we could figure out the reasons for the absence, we may find ways to minimize allergy-related morbidity experienced by millions of people in the industrialized world (Weiss and Stein 1993). This paper proposes a model of energy allocation to IgE-mediated defense against pathogens and toxins, the physiological trade-offs involved, and how composite extrinsic causes might influence the conditions under which these trade-offs are expressed. We then examine descriptive data collected among the Hiwi of southwestern Venezuela and suggest reasons for why this and other lowland South American Indian groups do not express the allergic response at levels seen in industrialized contexts. The data include assessments of allergic sensitization (skin prick tests, number of asthma cases observed), prevalence of endoparasites (stool samples, eosinophilia) and ectoparasites (grooming behavior), nutritional status (hematocrits, seasonal changes in the diet), breastfeeding behavior (prevalence and duration), and indoor allergen exposure (dust mites; time spent "indoors").

Theoretical concepts and empirical results suggest that current approaches seeking unidimensional answers devoid of evolutionary considerations to problems posed by a multifaceted mammalian IgE system are flawed. We propose that, minimally, physiological trade-offs between total IgE and allergen-specific IgE production, and costs associated with safety catches for this defense system, need to be considered in any explanation for why the prevalence of allergic conditions has increased dramatically in our species' recent past while groups like the Hiwi still continue to experience negligible allergic sensitization.

BACKGROUND

The Study Population

Various aspects of the behavioral ecology of Hiwi foragers have been the subject of several publications (see Hill and Hurtado 1989 for review; Hurtado and Hill 1987, 1990; Hurtado et al. 1992). The Hiwi reside and forage in the sparsely inhabited savannas or llanos of Venezuela and

Colombia, about thirty kilometers from the nearest rural town on the Venezuelan side and hundreds of kilometers from the nearest rural town in Colombia. The llanos flood annually and are characterized by extensive grasslands, with belts of gallery forests one to two kilometers in width. The ecological consequence of seasonal flooding is a marked fluctuation in the temporal and spatial distribution of, and in the biomass and productivity of, plants and animals. Close to 90% of the precipitation falls during the months of May through November, followed by a period of severe moisture stress between January and March. In contrast, temperatures are relatively constant throughout the year (Hurtado and Hill 1990). This seasonal variation is associated with long periods of nutritional stress and may be partially responsible for low fertility and high child mortality among Hiwi foragers (Hurtado and Hill 1990; see below).

Isolation

According to informant reports, the Hiwi of Venezuela (for information on the Hiwi of Colombia, see Arcand 1976) initiated occasional and often hostile contact with cattle ranchers in the early 1950s. However, these contacts were sporadic and discontinuous until 1960, when the Hiwi settled on the Capanaparo River under the protection of a local cattle rancher. During the next three decades, the Hiwi settled permanently at two sites on the Capanaparo and had intermittent contact with ranchers, priests and missionaries, government officials, anthropologists, and tourists (Hurtado and Hill 1987). In the wet season (May–November) Hiwi settlements are only accessible by water, and the llanos become quite inhospitable because of dreadfully high levels of insect pests. In contrast, dry season months (December–April) turn the savanna into a hunting and fishing attraction. Even during this seasonal barrage of visitors, social interactions between Hiwi and outsiders are minimal. Instead, the visitors' presence is felt through the depletion of game and fish.

During much of the year the Hiwi reside in the main settlements, but they also break into smaller bush camps for periods of up to four weeks at a time, particularly during the dry season. Main settlements have been moved to places within close proximity (within ten miles) twice since 1962. During some seasons of the year, a few Hiwi men or families may be hired by outsiders to work for wages in a nearby town. However, because the surrounding rural population views the Hiwi as drunkards and thieves, wage earnings are an insignificant component of the economy. This isolation has led to little outmigration, and strong adherence to religious beliefs and traditional dances. In the 1988 dry

season, the Venezuelan Hiwi population consisted of 290 individuals in two distinct groups, one residing in the middle of a dry savanna next to the local Indian services office (188 individuals) and another settled in a gallery forest (102 individuals). This more isolated group of Hiwi is the focus of our investigations.

The "Indoor" Environment

Exposure to indoor allergens is an important etiologic factor in allergic sensitization. "Indoor" space among the Hiwi differs considerably from its counterpart in many other human contexts. Present-day Hiwi live in huts with dirt floors. Half-height walls and roofs built out of tin or palm thatch provide protection from rain and sun. Hammocks, the Hiwi's traditional bedding, are made out of nylon obtained from outsiders or from palm string woven by Hiwi women. Hammocks invariably have very large gaps between the threads ("Venezuelan style"). They are shaken out almost daily and, when not in use, folded out of the way against hut poles. Today's Hiwi huts are a far cry from the well-enclosed dwellings of modern humans. Concrete and/or wooden buildings and houses serve as excellent reservoirs of dust, which in turn favors breeding by living organisms such as mites, the most important source of indoor allergen around the world (van Bronswijk 1981). Allergens, and their sources, are certainly not at risk of confinement to indoor areas among the Hiwi.

Cooking fires are made in adjacent, similarly built rooms or outside the huts. Exposure to smoke occurs primarily in the wet season when termite nests are burnt under hammocks for mosquito control. Even though Hiwi men enjoy smoking cigarettes, minimal contact with outsiders and few wage-earning opportunities keep them from adopting this habit. Consequently, passive smoking has not become an important aspect of Hiwi ecology.

In addition, the Hiwi did not keep pets except for hunting dogs, and no one owned cats. Dogs were kept tied outside the huts, allowed little if any access into living areas, and children were rarely, if ever, allowed to play with them. Lastly, the Hiwi are not at risk of inhabiting "old" dwellings since they rebuild their huts almost every year with numerous repairs and replacement of walls and roofing materials in between, and permanent movement of settlements involving construction of brand new dwellings occurs every twenty or so years.

Population Density and Respiratory Viruses

The risk of respiratory virus transmission increases as population density increases (Sungu and Sanders 1991), and respiratory viruses are a

major risk factor to the onset of wheezy lower respiratory infections and asthma in children (Bardin et al. 1992; Martinez et al. 1995). Population density is extremely low among the Hiwi of Venezuela and surrounding rural population. In 1988, the population density was estimated at 0.024 individuals per hectare (290 individuals divided by 12,058 hectares). Although the Hiwi have been exposed to influenza viruses, they appear to be minimally infected as has been observed in other isolated South American Indian groups (Neel et al. 1964). Gastrointestinal diseases are the leading causes of infant deaths among the Hiwi (unpublished data) as opposed to the common developing country pattern wherein respiratory infections are the highest ranked cause of death from birth to five years of age (see Denny 1995).

Other Health Profiles

The Hiwi have relatively small families for a natural fertility population (see Hill and Hurtado 1995). The mean number of live births for postreproductive women was 5.13 births. Of all offspring born who could have reached 15 years of age, 52% ($n = 64$ births) died before reaching maturity. Consequently, the population has experienced zero population growth in recent decades (Hurtado and Hill 1987). These demographic profiles are indicators of significant nutritional stress. Malnutrition, in turn, influences the IgE levels in parasitized children, which are markers of the allergy phenotype (Hagel et al. 1995).

Diet and Foraging Behavior

Exposure to cow's milk early in life and nutritional status may play a role in the development of allergic sensitization. Although the Hiwi live in close proximity to cattle ranches, cow's milk is not consumed by adults or children, and mothers did not own or use baby bottles at Hiwi settlements. Children are breastfed from infancy to as late as five years of age (see below). Solid foods are introduced early with considerable concomitant consumption of soil; geophagia is very common among Hiwi children.

From samples collected over a full seasonal round, we estimate that 68% of the Hiwi diet comes from game and fish, 27% from total vegetable foods, while only 4% comes from store-bought foods (Hurtado and Hill 1990) yielding fewer than 2,000 calories per capita during the dry and early wet seasons and almost 3,000 calories per capita during the late wet season (November and December). Thus the Hiwi are calorically deprived during most seasons, although at any one point in time 50% or more of energy intake comes from animal protein consumption (Hurtado et al. 1990).

To provide for this daily sustenance, Hiwi adults spend fewer than two hours per day foraging, with females spending slightly more time in this activity than do men. All foraging technology is traditional except for metal digging tools and axes used to gather vegetable resources (Hurtado and Hill 1989). The Hiwi lifestyle is by no means leisurely; foraging involves considerable energy expenditure. In addition, foraging occurs in the context of extraordinary heat stress, a possible reason why the Hiwi allocate few hours per day to foraging (fewer than two hours per day on average; see Hurtado and Hill 1990 for discussion).

In sum, in spite of several decades of contact with outsiders the Hiwi lifestyle has remained virtually unaffected in many areas which are relevant to the expression of chronic allergic disease. The "indoor" environment, as defined in the Euroamerican habitat (van Bronswijk 1981), is virtually nonexistent among the Hiwi. They sleep in hammocks and do not keep pets inside their huts, thus reducing opportunities for indoor allergen deposition and exposure. Low population densities probably keep influenza viruses in check while breastfeeding buffers morbidity when and if exposure does occur. Lastly, nutritional stress is an ongoing problem for Hiwi foragers owing to a reduction in territory size and the onslaught of Venezuelan hunting and fishing *aficionados* to the savannas during the dry season. Since contact, this territorial reduction has been counterbalanced to some extent by greater access to feral cattle, and the adoption of metal digging tools which can increase carbohydrate return rates as shown by experimental data (see Hurtado and Hill 1989).

A THEORETICAL MODEL

In order to understand the absence of allergic sensitization we need to understand the ultimate function of the immunoglobin ε (IgE) system (Profet 1991). Allergic sensitization is here defined as "a spectrum of IgE-mediated immediate-type hypersensitivity reactions that manifest as respiratory reactions (asthma or rhinitis), skin reactions (urticaria, dermatitis), gastrointestinal symptoms, and in their most severe condition, anaphylactic shock" (Hamilton and Adkinson 1992:2169). Of particular interest is the chronic manifestation of these responses in industrialized contexts, which are usually precipitated by exposure of predisposed and sensitized persons to diverse environmental substances that generally do not adversely affect most individuals (e.g., pollen, house dust, mite feces antigens, and cockroach and cat saliva).

A review of the literature on IgE-mediated reactions suggests that this system's activation is multidimensional and complex. It may therefore be premature to propose that unifactorial explanations such as the toxin

(Profet 1991) or parasite (see Moqbel and Pritchard 1990 for review) hypotheses will adequately account for the evolution of this multifaceted system (Nesse and Williams 1995). A more productive approach might be to subsume these potentially complementary explanations under two overarching concepts: *(a)* physiological trade-offs and their implications for the evolution of energy allocation to the IgE-system, one of our many defenses against disease, and *(b)* composite extrinsic conditions, or contexts in which trade-offs fail to, or are likely to, occur.

Physiological Trade-offs

Physiological trade-offs occurring at two levels are relevant to the expression of allergies in modern populations. The first entails competition over resources to produce total serum IgE of undefined specificity versus allergen-specific IgE. The second involves the costs of supporting safety catches that contain defense mechanisms for systems such as IgE-mediated responses.

The IgE system has two important components which appear to compete for energy under some conditions: the production of IgE of several, largely undefined specificities (polyclonal) and the production of allergen-specific IgE. The production of polyclonal IgE is notoriously increased in parasite infestation, and it most probably plays an important role in the defense against these organisms as well as in the protection from potentially mutagenic and carcinogenic substances (Profet 1991 and references therein). After an extensive review of the literature, we were only able to find one study that reports both total serum IgE and allergen-specific IgE as measured in the same individuals. A graph of these data shows that the relationship between the two IgE types is curvilinear (Figure 1). At low levels of total IgE serum, there is a positive relationship between total polyclonal IgE and allergen-specific IgE. However, past a threshold point, which appears to be 1500 IU/ml, there is an inverse relationship between total serum and allergen-specific IgE. Simply put, it appears as though our physiologies are only able to support the production of specific anti-allergen IgE in the absence of strong nonallergenic stimuli (e.g., macroparasites). When the latter push total IgE production over levels past 1500 IU/ml in serum, the production of anti-allergen IgE is dampened. This is a physiological trade-off interpretation of the conventional mast cell saturation hypothesis: competitive stimuli obliterate the specific response (see Hurtado and Arenas 1996 for discussion). IgE levels past 1500 IU/ml are the clinical marker of parasitism. Therefore, in addition to nutritional stress (Hagel et al. 1995), high parasite load is a condition under which allergen-specific IgE (the culprit of present-day allergies) is shut down (Hagel et al. 1995).
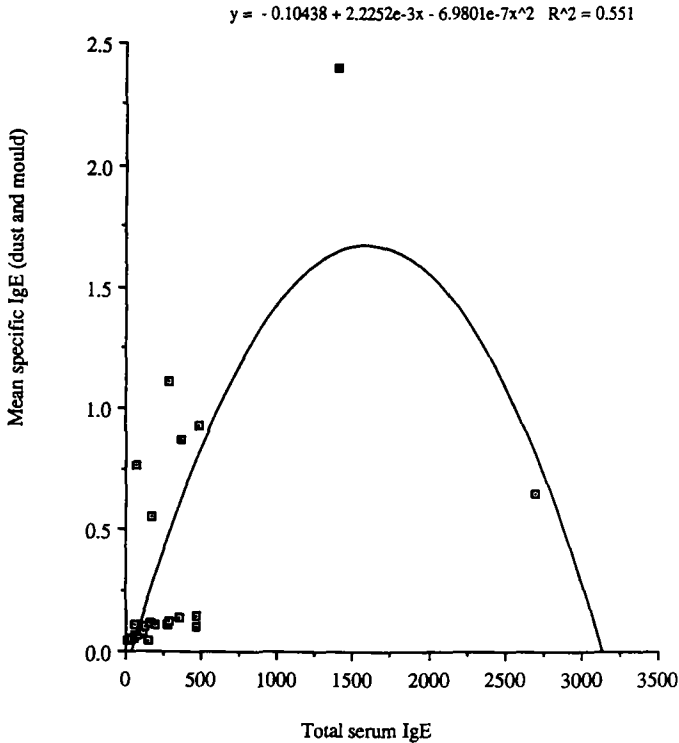
$$y = -0.10438 + 2.2252e\text{-}3x - 6.9801e\text{-}7x^\wedge 2 \quad R^\wedge 2 = 0.551$$

Figure 1. The relationship between total serum IgE and the mean house dust– and mold-specific IgE described for 27 patients, ages 13 to 67 (data published in Lynch et al. 1985:Tab. 1).

While this trade-off hypothesis is useful for understanding the absence of allergic sensitization in some contexts, it does not address the question of why the IgE system appears to produce much "unnecessary" morbidity in the modern world. Again some of the answer may lie in physiological trade-offs. Defense against disease adds two types of cost to an organism's energy budget: the costs of production and maintenance, and the costs of providing a safety catch for the defense system (Janzen 1987). Throughout human history, high IgE levels elicited by multiple and endemic parasitic exposure might have worked to keep them in check. Under such conditions, parasite infestation served as a safety catch to the allergen-specific IgE response by maintaining high levels of total serum, polyclonal IgE. At present, low levels of parasitic infestation in combination with high nutritional levels allow for the unchecked expression of allergen-specific IgE. Because it is so recent, defenses to prevent injuries caused by this part of the immune system have

not been under strong selection. At this point in human history, selection may favor a safety catch for allergen-specific IgE expression if individuals with the *chronic* forms of the allergic phenotype do in fact experience lower survival and/or fertility than the rest of the population.

Whether or not human populations are more or less likely to experience trade-offs between total serum IgE and allergen-specific IgE production is influenced by a composite of extrinsic causes. Figure 2 summarizes relationships between total and allergen-specific IgE levels, parasites, nutritional status, breastfeeding behavior, and indoor exposures.

Composite Causes

By "composite" extrinsic causes we mean factors that occur in packages regardless of their statistical dependence or lack thereof. Throughout most of our history, factors such as parasite load, nutritional stress, breastfeeding, and time spent outdoors were part and parcel of daily life, possibly more frequently than now even though there is little reason to believe that any one of these factors caused any other (with the exception of the variance in nutritional status that is explained by parasite load and vice versa); they simply happened to occur at the same time. Because of their simultaneity these factors have important composite effects on the risk of allergic disease onset via effects on expression of trade-offs between total and allergen-specific IgE (Figure 2).

Parasites elicit a strong total IgE serum defense, which has been well documented in numerous studies (Allen and Maizels 1996). The extent
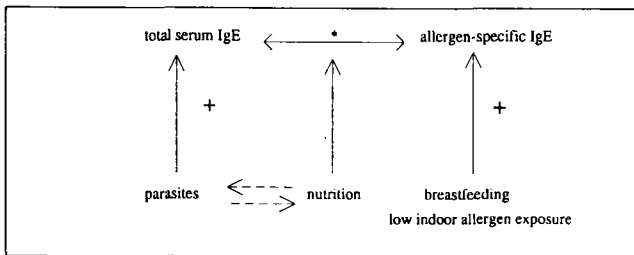
Legend

⟷	trade-offs
*	trade-off occurs at high levels of total IgE mast cell saturation ~ 1500 IU/ml (see Hurtado and Arenas 1996)
⟶	independent variable

Figure 2. The etiology of total and allergen-specific IgE activation: trade-offs and independent variables.

to which this response bestows the expression of allergen-specific IgE depends upon nutritional status. This is for two reasons. First, protein-energy malnutrition often causes very high serum levels of IgE as a result of altered T cell regulation of IgE production (Keusch 1991). Second, poorly nourished individuals are less likely to experience allergic sensitization than are their better nourished counterparts, after controlling for parasitic infestation (Hagel et al. 1995) (Figure 2). This suggests that competition over energy causes a relinquishing of allergen-specific IgE activation at lower levels of total IgE production in nutrient-deprived than in other individuals.

Breastfeeding affects these trade-offs through a reduction in the risk of respiratory viral infection given the same levels of exposure (Victora et al. 1989; de Francisco et al. 1993). Among the Hiwi, the risk of exposure may be low (see above); however, breastfeeding behaviors may minimize morbidity when rare exposures do occur (see Neel et al. 1964), and reductions in morbidity of this sort have been shown to reduce the risk of asthma onset, one of the more troublesome manifestations of allergies in the modern world. In addition, breastfeeding may buffer the effects of protein-energy malnutrition noted earlier that also contribute to IgE-mediated pathologic responses to influenza infections (see Keusch 1991).

Lastly, indoor allergens appear to be trivial components of the Hiwi way of life, and this too reduces the risk of allergen-specific IgE activation.

Among the Hiwi, if chronic allergic conditions fail to occur, as has been noted for other indigenous populations, then this trend needs to be viewed in terms of two contextual explanations:

1. nutritional stress in combination with high parasite load may greatly increase energetic costs incurred by nonspecific IgE activation, leading to a reduction in allergen-specific IgE production (the primary culprit of modern allergies), and
2. breastfeeding behaviors and indoor allergen exposures may decrease risk factors for allergen-specific IgE activation.

These two explanations guide our presentation of data on Hiwi foragers.

METHODS

The Study Site

Medical assessments as well as behavioral and anthropometric data were collected over a three-year period during three separate field sessions: October–December 1985, April 1986, and December 1987–May

1988, representing a total of 192 days in residence at the field site. Behavioral and anthropometric methods are described at length elsewhere (Hurtado and Hill 1987, 1990). Collection of medical data took place during April of 1986 only. Hurtado, Hill, and Arenas coresided with Hiwi families in their huts during the 1985 and 1986 sessions, and in a concrete block house within ten meters of Hiwi huts during the 1988 session. Consequently, in addition to field work time, the investigators spent all other daylight and evening hours in activities such as housekeeping, cooking, child care, and social activities in close interaction with Hiwi women, men, and children.

Skin Prick Tests

The experienced allergist in the team, I. Arenas, completed the skin prick tests on 18 Hiwi individuals ranging between 14 and 35 years of age, and on one atopic and one nonatopic adult Venezuelan nationals. Skin-prick tests were performed with commercially available extracts (Pharmaica: *Dermatophagoides farinae*), pollen (grass, *Pinus*, leguminosae), and molds (aspergillus, penicillum, cladosporium, alternaria) and extracts locally prepared and supplied by Dr. Neil Lynch (house dust, *Ascaris*, and "aeroallergens" or material collected in Venezuela by continuous suction air sampling). Positive reactions were taken as immediate wheal diameters of ≥3 mm. Control prick tests were performed with the extract's diluent (negative control), and with 1% w/v histamine solution, 5% codeine solution, and 1 mg/ml goat anti IgE Fc (positive controls). The solutions used in control tests were also supplied by Dr. Neil Lynch (see Lynch et al. 1985).

Endoparasites

Fecal samples were deposited by 52 Hiwi into vials partially filled with a preservative solution (MIF; Beck and Davies 1981) and transported to the Laboratorio de Alergia, Centro de Microbiologia, Instituto Venezolano de Investigaciones Cientificas (IVIC) in Caracas. Rodriguez examined all samples for the presence of helminth eggs (Barnsley-Pessöa 1963; Beck and Davies 1981).

Ectoparasites, Breastfeeding Behavior, and Time Spent "Indoors"

Our best estimate of ectoparasite load is time spent in grooming and hygiene behaviors among the Hiwi. Grooming rates and time spent "indoors" were calculated from time allocation data gathered during the 1985 and 1988 field sessions ($n = 6,954$ scan samples in 1985 and 4,969 in

1988; see methodological descriptions in Hurtado and Hill 1987). Total number of observations when subjects were observed grooming were divided by the total number of observations made for individuals of different ages and sexes to calculate percent time spent in this activity.

To describe breastfeeding behavior among Hiwi children, nursing rates by age of child were also calculated from time allocation data. In addition, focal follow data were collected on a sample of nine infants and children ranging in age between two months and fifty months of age to calculate the length of interbout suckling intervals as a function of a child's age (see Hurtado and Hill 1987 for description of these methods) over a total of 140 hours of observation (n = 328 intervals; 155 interbout intervals and 173 nursing bout intervals). Random sampling without replacement was used to assign children and data collection times on any given day. Observations were then completed on ten consecutive nursing bouts to avoid statistical problems in the analysis and interpretation of incomplete data on interbout interval and nursing bout interval length (see Wood 1994).

Eosinophilia and Microhematocrits

Blood was drawn by skin puncture. Blood smears prepared in the field were taken to the laboratory for staining (Wright-Giemsa's solution) and for differential leukocyte counts completed by Rodriguez (Miale 1977). Eosinophilia is a percentage that is calculated by counting the number of eosinophils observed for every 100–200 leukocytes. Microhematocrit assessment (percent volume of packed red cells) involved use of heparinized capillary tubes (Red-tips, Fisher Scientific Co.) centrifuged in the field with a portable mechanical device (Vargas Manufacturing Co.). This device was calibrated prior to fieldwork to an Autocrit II electrical centrifuge (Clay Adams) at IVIC laboratories.

"Indoor" Allergens

Arenas collected dust accumulated in three Hiwi hammocks and corresponding hut floors. These samples were handled and visually inspected for house dust acari as described elsewhere (Arenas and Parini 1987).

RESULTS

The Dependent Variable:
Allergic Sensitization

One Hiwi subject tested positive to *Ascaris* and "aeroallergens." The atopic Venezuelan national tested positive to *D. farinae* and molds. All

other subjects tested negative to allergen extracts. Control tests were negative to the extract's diluent and positive to histamine in all subjects. Control tests to codeine and anti-IgE were not uniformly positive. In addition, asthma symptoms were never observed during a total of 434 researcher person-days among the Hiwi, or during three medical examinations conducted by two Venezuelan physicians: I. Arenas, an expert in pediatric asthma, and O. Forness, a cardiologist.

Physiological Trade-offs

Among the Hiwi, high parasite loads and nutritional stress may place this population at levels of total serum IgE higher than the 1500 IU/ml theoretical threshold (Figure 1). The prevalence of *Necator americanus* (hookworm) among males and females of all ages is close to 100%. *Ascaris, Trichuris*, and *Entamoeba* are much less prevalent; both sexes and life stages appear to be similarly affected (Figure 3). Grooming behaviors that serve to eliminate ectoparasites are also quite prevalent, accounting for 5.1% to 6.9% of scan samples, which represents approximately 36 to 50 minutes per day. Differences by life stage are minor (Figure 4a) while differences by sex are more pronounced. Females spent more time grooming (6.9%) than males (4.7%) for an estimated 50 minutes versus 34 minutes per day, respectively (Figure 4b). This difference is probably due to women's time spent in child care, for which grooming and hygiene are important components.

High eosinophilia is consistent with elevated parasite loads among the Hiwi since eosinophils in increased number are part of the classical clinical profile of infestations by helminths such as *Necator, Ascaris*, and *Trichuris* (Miale 1977). Eosinophilia among Hiwi males and females is considerably higher than standard levels established in American populations (Miale 1977) with little if any overlap between the two distributions (Figures 5a and b). These high levels are consistent with parasitic infestation prevalence among the Hiwi.

Nutritional stress is also a key feature of Hiwi ecology. Microhematocrit assessments show that males and females experience values consistently below standards for American populations at all ages (Figures 6a and 6b). Blood loss due to hookworm infestation is likely; a diet that is rich in animal protein but low in calories seems to fail to compensate for this loss (see Background, above; also Layrisse and Martinez 1983).

Other Causes

Among the Hiwi, children of mothers who are not pregnant may be breastfed on demand between birth and five years of age, and interbirth intervals are generally very long. When pregnancies occur while the
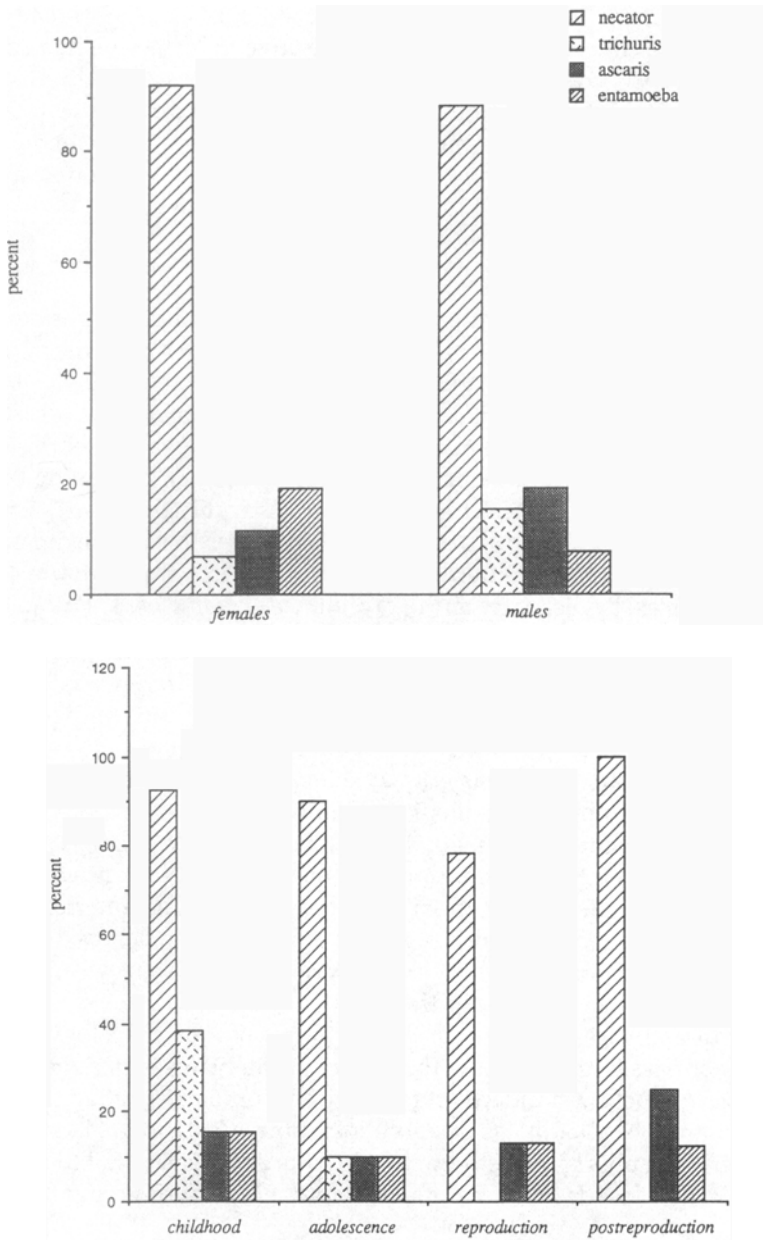
Figure 3.   Prevalence of endoparasites among the Hiwi: *(a)* stratified by sex, *(b)* stratified by developmental stage.
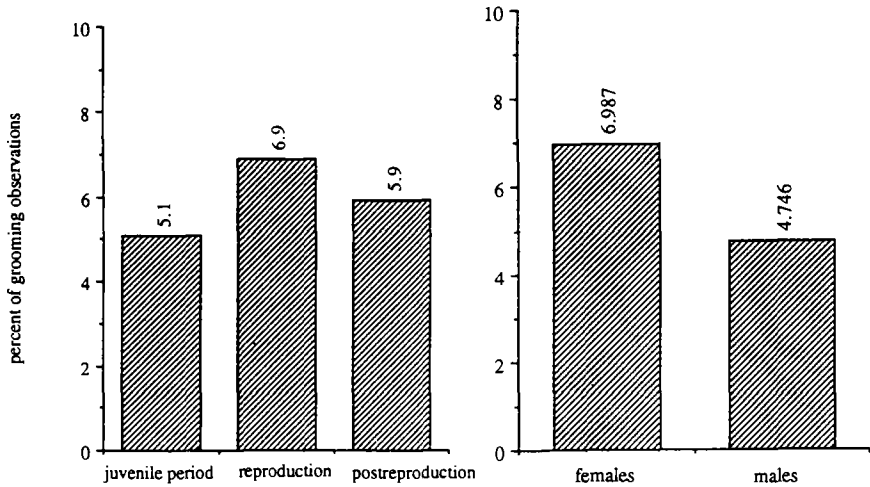
Figure 4. Percent time spent grooming among the Hiwi: *(a)* stratified by developmental stage, *(b)* stratified by sex.

child is still younger than five, abrupt weaning of children as young as one year of age occurs. We estimated changes in breastfeeding behavior by age of the child by dividing the number of scan samples when a child breastfed by the total number of scan samples for that child at different ages (n = 13 boys and 10 girls between birth and six years of age; 2,228 observations). Since children whose age was greater than or equal to six years were not observed breastfeeding, these null data were excluded from the analysis. Percent time spent breastfeeding decreases substantially with the child's age up to five years of age from 6.5% to 0.5% of all observations (n = 2,228). At the same time the mean number of minutes between interbout intervals (defined as time between the end of one suckling period and beginning of another) and the variation around this mean increases considerably with age from 36 minutes for children between birth and one year of age to 111 minutes (almost two hours) for five-year-olds (Figure 7). Thus, Hiwi children up to five years of age breastfeed more frequently than most children in modern contexts without formula or cow's milk supplementation.

While breastfeeding may buffer the effect of respiratory viruses on allergic sensitization among Hiwi children, an allergen-free indoor environment may also minimize its onset. Cockroaches were not seen in any of the Hiwi huts during the entire period of observation. Dust mites were not found in samples of debris collected from hut floors and hammocks. Furthermore, if other allergens do occur inside huts, they are
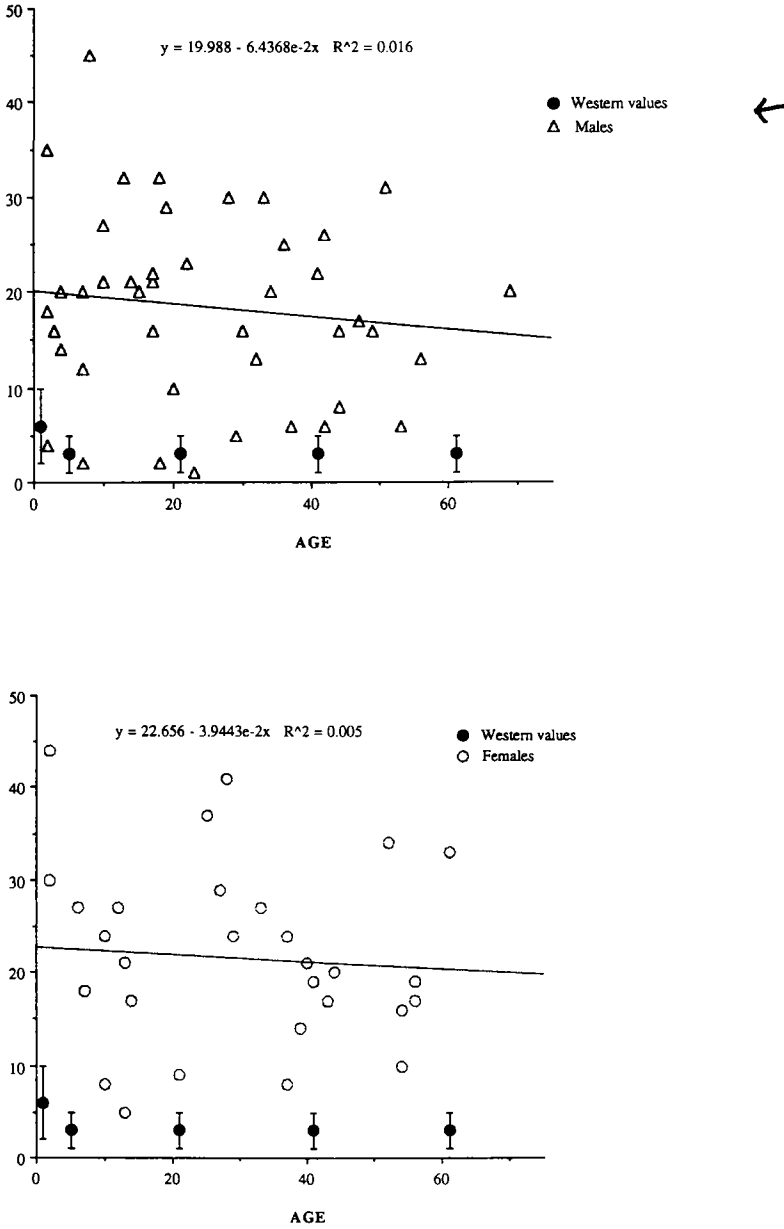
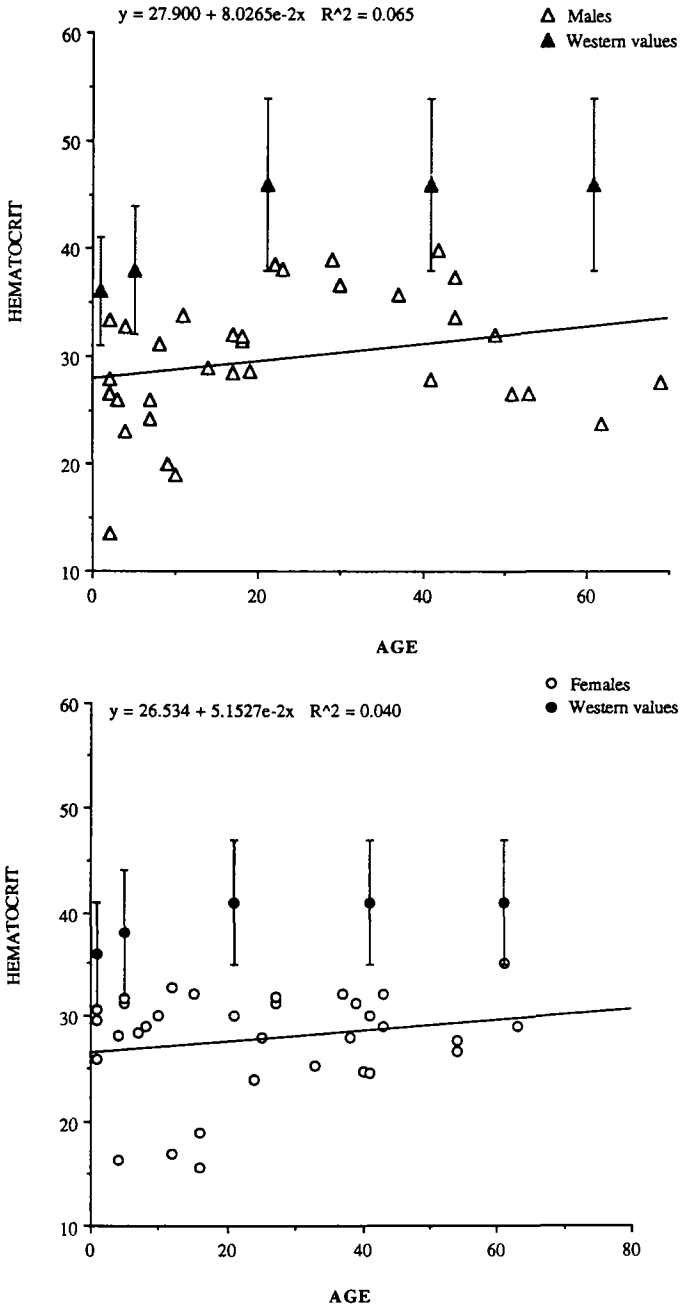Figure 5. Eosinophilia for Hiwi and western samples: (a) Hiwi males, (b) Hiwi females.

Figure 6. Hematocrit levels for Hiwi and western samples: *(a)* Hiwi males, *(b)* Hiwi females.
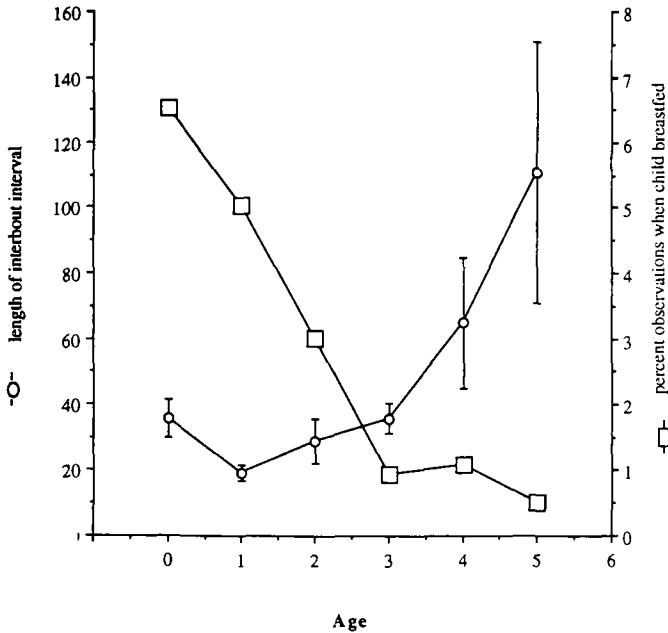
Figure 7. Mean number of minutes between interbout intervals and percent of scan samples when the infant or child was observed breastfeeding as a function of age of the infant or child.

probably diffused frequently by gusty winds and minimal wall protection. In addition, regardless of age or sex, Hiwi individuals spent only 33% of their daylight hours "indoors" (approximately four hours per day)—that is, lying, sitting in hammocks, or working in their huts.

DISCUSSION

Allergic sensitization among the Hiwi appears to be negligible. It may be argued that some of the allergens we tested were foreign to the Hiwi (e.g., the house dust mite, *Dermatophagoides farinae*). That was not the case for most of the allergens. Molds are ubiquitous (Arenas and Riegler-Gohlman 1986) and leguminosae pollen is airborne and widely dispersed in the tropics (Arenas and Alson 1996). Sources of house dust and "aeroallergen" were local. *Ascaris* exposure may still be relevant, in spite of the relatively low *Ascaris* prevalence we found (Figures 3a and b). *All these allergens failed to elicit reactions in 17 out of 18 subjects.*

To our knowledge, skin prick tests have been completed in only a few groups of South American Indians. Among the Waorani, 1% of individu-

als tested positive for allergens while 11% of controls sampled in North Carolina tested positive (Buckley et al. 1985). In another study among the Waorani and Yanomamo, 5.7% and 6.7% tested positive for locally extracted allergens, respectively (Kaplan et al. 1980; Lynch et al. 1983). It is also interesting to note that out of 75,013 medical visits with Indians from various isolated groups of Amazonians over a five-year period, and out of a total population of close to 20,000 individuals that might receive medical care annually, only 900 consultations were asthma related, or 1.02% (Lynch et al. 1983). In contrast, 38% of Indians of multiethnic origin from the Vaupes region tested positive to dust mite allergens and 13% reported asthma symptoms. However, since the levels of acculturation and living conditions for individuals sampled were not described, the data are difficult to interpret (Sanchez Medina 1994). The multiethnic composition of the sample leads us to suspect that these are highly acculturated groups. If we are correct about the acculturation status of these Vaupes Indians, then, sparse data on these and other groups suggest that the onset of chronic allergic conditions may be largely environmental since indigenous groups whose living conditions have changed in the recent past appear to manifest allergen-specific responses at high rates.

An absence of allergic sensitization among Hiwi foragers occurs in the context of several other ecological and behavioral features. The prevalence of macroparasites is very high among the Hiwi and almost universal for *Necator americanus* (hookworm). Given the cross-sectional sampling procedure with single stool specimens per individual, the prevalence is probably higher than the one reported in this study. In spite of these shortcomings, the Hiwi endoparasite profile compares with those of other populations in interesting ways. Hookworm prevalences of 90% or higher have been observed in many South American Indian groups with a range between 10.9% for the Aguaruna of Peru and 97% for the Xavante of Brazil (Table 1). In contrast, the Hiwi show one of the lower prevalences of *Ascaris lumbricoides* (15.4%; range: 3% among the Waorani to 99% among some Yanomamo groups) (Table 1).

Interestingly, the total IgE serum levels measured for the Waorani of Ecuador are some of the highest ever reported in the literature (mean = 9806 IU/ml, Buckley et al. 1985, and 11,975 IU/ml, Kaplan et al. 1980), and this group had a low prevalence of positive skin tests, as noted above (Buckley et al. 1985). The Yanomamo of Venezuela show somewhat higher total IgE levels (13,088 IU/ml, Lynch et al. 1983). In contrast, Indians from the Vaupes who tested positive for allergens had lower total serum IgE levels than the Yanomamo and Waorani (mean = 2930 IU/ml), although not lower than the hypothetical threshold proposed earlier (1500 IU/ml, Figure 1).

Table 1. Parasite Infestation Prevalence in Various American Indian and Rural Populations

Parasites	Hiwi (*)	Xavante Brazil	Xingu Brazil	Kren-Akoroe Brazil	Surui Brazil	Unknown Brazil	Three tribes Brazil	Galibi Brazil	Palikur Brazil	Campa Peru
Helminths										
Ascaris lumbricoides	15.4	70	18	15	53	70	46 to 67	46 to 76	76	28
Trichuris trichiura	11.5	20	n.d.	76	5	91	46 to 100	46 to 100	19	20
Ancylostoma (hookworm)	90	97	81	97	43	95	60 to 96	60 to 96	90	45
Strongyloides sp.	—	5	11	30	33	26	0 to 20	0 to 20	10	11
Enterobius vermicularis	—	2	13	—	—	—	—	—	—	—
Hymenolepis nana	—	—	—	—	—	—	—	—	—	—
Protozoa										
Entamoeba coli	13.5	67	87	24	—	42	20 to 69	20 to 69	14	37
Giardia lamblia	—	7	29	9	3	12	20 to 27	20 to 27	5	—
Entamoeba hystolytica	—	48	61	18	1	23	0 to 29	0 to 29	10	21

Parasites	Aguaruna Peru	Waorani Ecuador	Ticuna Colombia	Choco Colombia	Rio Negro Venezuela	Yanomama Venezuela	Yanomamo Venezuela	Yanomamo Coyove-Teri	Yanomamo Mayoave-Teri	Yanomamo Niyayoave-Teri
Helminths										
Ascaris lumbricoides	62	3	60 to 85	74	52 to 76	89 to 99	73 to 80	71.1	80.4	78.9
Trichuris trichiura	92	2	92 to 95	30	0 to 29	68 to 92	9 to 53	57.9	4.3	9.6
Ancylostoma (hookworm)	93	46	60 to 100	30	6 to 22	76 to 79	39 to 67	63.2	39.1	39.1
Strongyloides sp.	7	—	—	—	0 to 12	3 to 11	0 to 1	2.6	4.6	1.3
Enterobius vermicularis	—	3	—	—	—	—	—	2.6	19.6	8.3
Hymenolepis nana	—	—	—	—	—	—	—	5.3	0	0
Protozoa										
Entamoeba coli	49	51	69	50	16 to 47	91 to 100	70 to 84	68.4	89.1	82.05
Giardia lamblia	11	28	22	—	12 to 52	4 to 5	20	21.1	30.43	19.9
Entamoeba hystolytica	—	20	55	61	—	26 to 77	—	13.2	6.5	25

Source: Salzano 1989
(*) Data from the present study.

Hence, even though we did not determine total serum IgE levels for the Hiwi, negative skin tests, absence of asthma cases, concomitant high parasitic load, and raised eosinophilia lead us to believe that the Hiwi probably have IgE levels close to those reported for groups such as the Yanomamo and the Waorani. Elevated parasite loads may limit production of allergen-specific IgE in favor of total IgE activation. Comparable parasitic load data in other South American Indian groups suggest that similar patterns may occur in other isolated groups scattered throughout the continent.

Elevated parasite loads among the Hiwi are not independent of other factors that also affect the manifestation of allergy. The Hiwi experience considerable nutritional stress as evidenced by microhematocrit levels below the U.S. national standards for both males and females as well as other published data on caloric consumption fluctuations by season of the year. With increasing nutritional stress, allergen-specific IgE activation is dampened (Hagel et al. 1995). Moreover, mothers breastfeed their children frequently at all ages and up to the fifth birthday, which buffers the effects of respiratory viruses, also a risk factor for allergic sensitization. In addition, the risk of indoor allergen deposition is negligible in this population since housing is extremely well-ventilated and rebuilt frequently, and loose-woven hammocks are probably inhospitable to pests such as dust mites. Finally, the Hiwi spend less time indoors in their well-ventilated huts than do Americans, who spend extraordinary amounts of time in well-insulated, allergen-polluted environments. In a sample of 1,000 households surveyed between 1990 and 1991, children between five and twelve years of age spent more than 95% of their daylight hours indoors at home or at school (Silvers et al. 1994).

CONCLUSIONS

Current approaches to the question of why allergic conditions are rare among isolated groups such as indigenous peoples of South America are potentially flawed in seeking unidimensional answers to a problem posed by a multifaceted mammalian IgE-related system. The possibility of physiological trade-offs between energy allocation to the production of total serum IgE of undefined specificity versus the production of allergen-specific IgE needs to be incorporated into these explanations. In addition we need to consider causes whose simultaneous presence may independently affect these trade-offs and the expression of allergen-specific IgE. The physiological trade-off approach proposed here suggests that we may expect to find both positive and negative correlations between parasite load and allergic sensitization, depend-

ing on the ecological context. Under conditions where parasite loads are elevated and nutritional status impaired, a negative relationship might be expected, while a positive relationship might be expected for conditions under which parasite loads are low and nutritional status is high. The simultaneous effect of factors such as breastfeeding behavior, time spent indoors, and indoor allergen densities must also be taken into account.

Lastly, although not least important, over and above these explanations we need to consider the costs of providing a safety catch for defense systems such as IgE-mediated responses (Janzen 1987). Due to the recency of nutritionally enhanced, parasite-free and indoor allergen-laden conditions that favor allergen-specific IgE activation, defenses to keep possessors from being injured by this part of the immune system have not been under strong selection for a long enough period of time. At present it is unclear whether individuals with an "unchecked" allergic phenotype experience higher mortality and lower fertility than the rest of the population. The phenotypic variation of interest is also uncertain. Some individuals may have active IgE systems with concomitant safety catches, and thus be able to avoid allergic morbidity. Others may fail to show allergic morbidity because of defective IgE systems. Given the survival advantage that is conferred by IgE during trauma (DiPiro et al. 1994), heart failure (Sczeklik et al. 1993), and parasitic infestation (Allen and Maizels 1996), we may expect the former to show the highest fitness levels and the latter, the lowest, with atopic individuals at intermediate levels. Clearly, we need to do a great deal more theoretical and basic empirical research that takes into account the evolutionary context of allergic disease.

A. Magdalena Hurtado and Kim Hill collaborate in life history research among South American Indians. Inés Arenas and A. Magdalena Hurtado have worked together on several projects on the evolutionary ecology of childhood asthma and allergic sensitization. Inés' clinical and research experiences in Venezuela over the past three decades have considerably influenced this study among South American Indians as well as others planned for the future. Selva Rodriguez' laboratory skills and many years of experience at IVIC have been invaluable to the project.

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