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THE EVOLUTIONARY ECOLOGY  
OF CHILDHOOD ASTHMA

A. MAGDALENA HURTADO  
I. ARENAS DE HURTADO  
ROBERT SAPIEN  
KIM HILL

National practice guidelines provide the following definition of childhood asthma:

a lung disease with the following characteristics: 1. airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; 2. airway inflammation; and 3. increased airway hyperresponsiveness to a variety of stimuli (U. S. Department of Health and Human Services 1991: 1)

A disproportionate increase in childhood asthma morbidity and mortality over the past 2 decades in spite of pharmacotherapeutic improvements is known in the epidemiological literature as the "asthma paradox" (Page 1991). This, and other questions in epidemiology (Magana and Clark 1995; Markides and Coreil 1986; Tambyraja 1991) may not seem paradoxical when viewed from an evolutionary perspective (Ewald 1994; Hill 1993; Nesse and Williams 1995; Profet 1991). In contrast to epidemiology, modern evolutionary theory seeks to explain and predict the timing of biological events. The objective of evolutionary explanations of disease is to understand why throughout history human diseases have caused considerable morbidity and mortality under some conditions and little if any harm under others (Ewald 1994). In epidemiology, on the other hand, there is no consensus on what constitutes a unifying body of principles for explaining the distribution of disease in human populations (Koopman and Weed 1990), even though one of its most important tenets is the significance of theory for assigning causality to statistical associations (Rothman 1986). "Theory" usually refers to hypotheses informed by published statistical trends as opposed to deductively derived propositions, and methodological rigor informs research design (Kleinbaum et al. 1982). In most instances, explanations are devoid of evolutionary principles, a

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paradoxical oversight for a field that seeks to explain biological phenomena.

Here we propose a theoretical framework for the study of the natural history of childhood asthma informed by life history theory, the overarching body of principles in evolutionary ecology (Roth 1992; Stearns 1992). The application of life history principles is new to epidemiology, biological and medical anthropology, and evolutionary medicine (Nesse and Williams 1995). This chapter starts with an overview of fundamental information about the natural history of childhood asthma: a definition of this disease phenotype followed by a chronological discussion of the contexts in which asthma occurs, its phylogenetic history, its emergence in human evolution, and its distribution in contemporary populations. Recent advances in immunology are key to understanding the asthma phenotype and its expression in contemporary human populations. It has been known for some time that immunological pathways responsible for asthma are ancient features of the class Mammalia (Moqbel 1992). In human history these pathways served to contain and expel macro-parasites such as helminths, whereas in contemporary populations they cause atopy, a condition in which people with genetic predispositions to allergy upon exposure to ubiquitous biological or chemical substances that are inhaled or ingested produce significantly greater quantities of the immunoglobulin E (IgE) than the average individual (Pope et al. 1993). IgE in turn sets off a complex network of physiological events (Sutton and Gould 1993), leading to allergy symptoms such as inflammation of the skin (eczema), lung (bronchoconstriction, wheeze, and asthma), upper respiratory tract (rhinitis), and intestinal tissues (diarrhea and vomiting) (Barnes et al. 1992) and their more severe anaphylactic end products. Anaphylaxis refers to severe allergic reactions that involve respiratory compromise and cardiovascular collapse or shock.

Although the bulk of the evidence suggests that IgE-mediated defenses against parasites are adaptive (Moqbel 1992 and references therein), research in contemporary human populations have yet to demonstrate that asthma renders a fitness advantage to those who suffer from the condition (see discussion below). While we wait for the evidence, it would perhaps be wise for clinical practice guidelines (U. S. Department of Health and Human Services 1991) to consider that the IgE network has evolved for good reasons. As long as we do not understand its full range of functions and their impact on fitness, primary emphasis should be given to patient care strategies that effectively alter the environmental conditions under which the IgE network produces *asthma among patients at risk of the condition and/or at risk of its sequelae*. The more frequently used and invasive pharmacotherapeutic treatment (U. S. Department of Health and Human Services 1991), with as yet unknown long-term side effects, should then be subsumed to this preventive scheme. A preventive environmental approach would provide all children at risk of asthma morbidity and their parents an opportunity to assess the effectiveness of environmental changes and to adopt those changes when appropriate. Such oppor-

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tunities are only available to the fortunate few who are in the care of health care providers knowledgeable of environmental control solutions and who believe in their effectiveness.

Although clinical practice guidelines for asthma care provide considerable direction to providers, the guidelines' primary focus is on medical algorithms to guide decisions about drug prescriptions, in what quantities, and what to do when they fail to work (U.S. Department of Health and Human Services 1991). No equivalent algorithms are included for screening children at risk of asthma onset (mainly, those born to families with a history of asthma), for determining which environmental changes might work for the patient, for prescribing to parents suitable changes, and for monitoring their effectiveness through time. In lieu of algorithms, general descriptions of environmental controls in asthma care are published in the guidelines (U.S. Department of Health and Human Services 1991). These descriptions make the erroneous assumptions that physicians have the time and know how to translate general information about indoor allergens, where they are found, and how to reduce their densities into protocols tailored to each child (there is considerable variation in the substances to which children are allergic and that trigger asthma attacks). Even if physicians were to devise such protocols, general descriptions also erroneously assume that patients will comply to their prescriptions or recommendations. Like the asthma phenotype, parental behavior is under selection pressure favoring decisions which optimally allocate resources among behavioral alternatives and in response to environmental cues; in childhood asthma these cues include perceived or actual net benefits incurred from spending effort and time on drug and environmental therapies. Given the haphazard nature of clinical practice in childhood asthma (Asthma Zero Mortality Coalition 1995), parents are probably prescribed ineffective treatments more often than not and are thus more likely to experience costs rather than benefits associated with prescribed treatment for their asthmatic children. If we expect parents to adopt environmental controls in combination with drug therapy, algorithms in the guidelines should help ensure that parents adhere to corresponding behavioral changes in the home.

Sound management of asthma in the home is unlikely to occur as long as existing clinical practice guidelines do not translate environmental and pharmacotherapeutic treatments into algorithms that tailor prescribed treatment to the patient's risk profile and to the daily contexts in which care takes place. National health-policy decisions are partially responsible: only a tiny fraction of funds allocated to asthma research by the National Institutes of Health is spent on areas most akin to this translation process. In addition, U.S. health insurance companies and health maintenance organizations do not pay for indoor allergen assessment costs. If we continue to ignore the natural history of childhood asthma as well as social and political obstacles to sensible treatment, natural selection processes rather than judicious clinical practice will determine the levels of morbidity and mortality experienced by children with asthma in present and future generations.

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## Background

The incidence (i.e., instantaneous increase or decrease in the number of new cases as measured longitudinally) and prevalence (i.e., proportion of cases as measured cross-sectionally) of asthma-related morbidity and mortality among children has increased at alarming rates in many parts of the world over the past 2 decades. At the same time, drug clinical trials have demonstrated considerable improvement in the efficacy of combined use of bronchodilator and anti-inflammatory metered-dose inhalers or pharmacotherapeutic management of asthma symptoms, although for the most part effectiveness in natural settings has not been determined. These improvements in pharmacotherapeutics are not compensating for what appears to be a worldwide childhood asthma epidemic. In this section we discuss epidemiological trends, the asthma paradox, and national practice guidelines designed by experts in response to this paradox.

### The Epidemiological Entity

Rates of childhood asthma increased dramatically over the past decade throughout the world. In the United States, prevalence per 1000 persons between birth and 21 years of age increased from 38 to 51 cases from 1980 to 1990 (4.3% prevalence in children from birth to 17 years of age; *1988 National Health Interview Survey*; Halfon and Newacheck 1993). Throughout the decade children and adolescents experienced higher prevalence rates than individuals over 20 years of age (U.S. Department of Health and Human Services 1991). Moreover, hospitalizations rates due to asthma increased substantially between 1979 and 1987, and most of this increase was accounted for by pediatric patients under 15 years of age (U.S. Department of Health and Human Services 1991). Analysis of National Health Interview Survey data indicate that childhood asthma afflicted 2.7 million children under 18 years of age in 1988 and that the costs associated with the condition were substantial. Of these children with asthma, 30% experienced some limitation of activity, accounting for 10.1 million days missed from school and 200,000 hospitalizations (Taylor and Newacheck 1992). In 1990, national health-care related asthma expenditures (including adult asthma) were estimated at \$6.2 billion, or nearly 1% of all U.S. health care costs (Mortality and Morbidity Weekly Report 1992; Sullivan and Weiss 1993).

In keeping with national trends, a rise in the use of asthma-related health care was observed among Native Americans a population showing negligible rates of asthma when compared to whites up to the early 1970s (Cerrard et al. 1976). Between 1979 and 1989, asthma-related hospital admissions on U.S. Indian reservations increased an average of 2.6% per year, with the highest increase (3.7%) in children between birth and 4 years of age. In contrast, hospitalization rates for all causes declined by 1% per year over the same time period for the same age group (Hishanick et al. 1994). In addition, the lifetime prevalence of childhood asthma was estimated at 12.3% as measured by pa-

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rental reports of physician diagnoses for children between 3 and 13 years of age in one Pueblo Indian group (Clark et al. 1995).

Similar trends have been documented in many countries. In various regions of the United Kingdom, lifetime prevalence rates of asthma among children and adolescents increased from 3.1% to 12% between 1964 and 1988. Hospital admissions registered for the entire country increased from 34 to 76.3 per 10,000 among 0–4 year olds between 1980 and 1985 (Wells 1994). The annual percent increase in childhood asthma prevalence from 1956 to 1989 in England, New Zealand, Switzerland, France, Taiwan, Sweden, and Finland ranged between 1.3% and 12.4% (Burney 1992). Finally, a study conducted in Costa Rica in the early 1990s found a 23.4% lifetime prevalence rate of asthma among children between 5 and 17 years of age in a sample of 2682 children (Soto-Quiros et al. 1994).

This universal increase in childhood asthma prevalence is paralleled by several other consistent findings across continents. Prevalence rates are invariably higher in urban than in rural areas (Gambia, Venezuela, Finland; Godfrey 1975; Lynch et al. 1984; Poysa et al. 1991). A most striking finding is the almost complete absence of asthma among isolated Amerindian groups such as the Waorani of Ecuador, the Yanomamo and Hiwi of Venezuela (see below; Hurtado et al. 1996a; Kaplan et al. 1980; Lynch et al. 1983). In addition, higher prevalence rates of asthma are reported for low socioeconomic status populations than for middle or upper classes (Evans 1992; Gottlieb et al. 1995; Weiss et al. 1992; Willies-Jacob et al. 1993).

#### The Asthma Paradox and National Practice Guidelines

Demonstrations of efficacy in drug clinical trials (Hatoum et al. 1994) has led to the widespread assumption in the asthma literature that most patients whose doctors follow national practice guidelines and who in turn abide by their physicians' prescribed treatments should be able to lead active lives and to avoid hospitalizations and near deaths (Taylor and Newacheck 1992; U.S. Department of Health and Human Services 1991). However, a majority of patients with asthma report more disability, missed school and/or work days than clinical trials would lead us to expect (LeSon and Gershwin 1995; Page 1991). In response to this problem, the National Institutes of Health recently supported an initiative by the National Asthma Education Program (NAEP) to develop and disseminate national practice guidelines; that is, preformed recommendations issued for the purpose of influencing decisions affecting patients in clinical practice (Eddy 1990). In 1991 the NAEP published the "Guidelines for the Diagnosis and Management of Asthma" (GDMA; U.S. Department of Health and Human Services 1991) to guide medical decisions in clinics and hospitals attending children and adults with asthma throughout the United States. Given their salience in asthma treatment at the national level, we discuss here the therapeutic strategies supported by the guidelines.

Algorithms are important tools in ensuring that human error is minimized in clinical decisions (Lawler 1995). Here we use the term "algorithm" to refer

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to questionnaires, charts, tables, or other information-gathering aids that prompt health care providers or patients to record one or more criteria (e.g., oxygen saturation) at critical or ongoing junctures in care (e.g., to decide whether or not to discharge a patient, seek emergency care, or discontinue use of bronchodilators) to help ensure that the best decision is made given the circumstances of the particular patient and health condition. Only 4 out of the 10 chapters in the GDMA provide detailed algorithms. The entire sample of 13 algorithms in turn help inform pharmacotherapeutic decisions. In contrast, the rationale for environmental control and patient education measures is described in prose that is of little use to the general practitioner and nurses for whom the guidelines are intended (U.S. Department of Health and Human Services 1991: xi).

Some specific examples of algorithms published in the guidelines are the "algorithm for diagnosing asthma" (U.S. Department of Health and Human Services 1991: 9), which describes the interpretation of health outcomes in patients with asthma after use of bronchodilators and anti-inflammatory agents as the basis for establishing a diagnosis of asthma. A diagnosis is ruled out if symptoms do not subside after presumed compliant use of these agents. Other important criteria such as assessment of allergies and the allergens to which a child is exposed are *not* included. Similarly, "classification of asthma by severity of disease" (U.S. Department of Health and Human Services 1991:10) lists symptomatological criteria for establishing a diagnosis of severity. Symptoms are incorrectly assumed to have high sensitivity (i.e., proportion of those who truly have asthma who are accurately classified as asthmatic) and high specificity (i.e., proportion of those who truly do not have asthma who are accurately classified as not having the condition) for establishing severity.

To the contrary, use of symptoms to assign severity puts patients at risk of considerable misclassification because asthma symptoms are as much a function of true disease severity (differences in the extent of bronchial hypersensitivity upon exposure to an allergen to which a patient is sensitized) as they are a function of patient noncompliance (Alessandro et al. 1994), access to health care (Halfon and Newacheck 1993), and total exposure to allergenic substances (total number of allergens multiplied by allergen density). Consequently, in the worst-case scenario, a well-managed child (i.e., a patient with a good physician who is compliant to treatment, whose home is allergen-free, and who reports few exacerbations and few if any school days lost) whose true disease status is severe is likely to be classified as a mild case, whereas a poorly managed patient (i.e., a patient inadequately cared for and/or who is noncompliant) whose true disease status is mild will be classified as moderate or severe case according to the algorithm. In reality, a large proportion of asthmatics who are admitted to emergency rooms and who die are reported as mild cases. In one study, researchers reported that 22% of all patients who died of asthma at a hospital had been assigned mild severity, while in another study mild cases accounted for 29% of all patients with asthma attending an emergency room clinic, followed by moderate (52%) and severe cases (19%) (Matsuse et al. 1995). Interestingly, the severe cases were the least represented. Misclas-

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sification of severity probably occurs often because general practitioners and emergency room doctors who treat most children with asthma (Mortality and Morbidity Weekly Report 1992) do not routinely conduct bronchoprovocation tests, a more objective assessment of severity, in which patients inhale methacholine or other substances at incrementally higher doses causing bronchoconstriction only in individuals with asthma.

Algorithms for home and hospital management of chronic asthma and acute exacerbations also emphasize pharmacotherapeutics in lieu of a more well-rounded preventive approach. The "weekly asthma symptom and peak flow diary" (U.S. Department of Health and Human Services 1991:53) includes a chart on which patients record their peak flows and symptoms in the mornings and afternoons, but no room is provided for recording the timing of respiratory infections (viral or bacterial), environmental exposures, including the number of hours spent indoors, and at what locations, and whether the patient has followed the prescribed regimen. This is unfortunate because neither patient or physician are encouraged to identify on an ongoing basis the conditions under which children are at highest risk of respiratory problems. Instead, the weekly diary is used to inform decisions about altering drug dosage and types of drugs prescribed to the patient. The "family guide for managing a child's asthma episode" (U.S. Department of Health and Human Services 1991:55) includes a detailed series of pharmacotherapeutic decisions to follow when a child's condition begins to deteriorate; no such detail is given to inform decisions about what to do when a child's environment and family functioning begins to deteriorate. The "correct use of a metered-dose inhaler" (United States Department of Health and Human Services 1991:57) is also a detailed set of steps that helps children and parents learn the most efficacious pharmacotherapeutic inhaling techniques. This contrasts with one list with vague descriptions of allergen reduction recommendations such as "encase the mattress in an airtight cover" (What is an airtight cover? Do physicians provide them? How often should the cover be changed?), "use chemical agents to kill mites" (Should all parents do this, including those of children who are not allergic to mites? How often should these be used? How should the effects of the chemical agents be measured to determine whether or not they work?) (U.S. Department of Health and Human Services 1991:66).

Finally, charts for the management of pediatric asthma (chronic, moderate, and severe asthma), and "acute exacerbations of asthma in children: home management and emergency department management" describe detailed lung function indicators (mainly, peak expiratory flow) that should be used to guide decision making about pharmacologic therapy; which medications to prescribe for daily use and during asthma attacks, how often they should be administered, what beneficial outcomes to expect from drug therapy and what to do when these fail (U.S. Department of Health and Human Services 1991: 80, 82, 105, 107, 108). No equivalent algorithms are provided with precise measures of environmental (allergen exposure) and behavioral (poor access to medical care, noncompliance) risk factors for patients and physicians to make decisions about what environmental controls to implement in the home, what

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behavioral changes to teach or adopt, and how to proceed when these fail to produce the expected outcomes. Thus, the GDMA algorithms fare poorly in a preventive scheme because primary prevention would require the removal of environmental causes and changes in the pertinent parental and patient behaviors before onset or recurrence of adverse health events.

The GDMA reflect and sanction a universal emphasis on pharmacotherapy in the clinical care of children with asthma at several institutional levels. Government-endorsed patient education programs, although well studied and widely disseminated, are considered to be secondary rather than central to clinical care in pediatric asthma (U.S. Department of Health and Human Services 1984). These programs provide fundamental background information on asthma physiology, symptoms, and their control. However, once again, they do not provide algorithms that guide decisions about which environmental and behavioral instructions are most appropriate for each family. Furthermore, the National Institutes of Health spends a small portion of its asthma-related funds on research to enhance preventive, family-centered approaches to asthma management. In 1995 half of these funds were allocated to research immunological mechanisms (figure 5.1). The remainder was distributed among epidemiology, educational interventions, drug clinical trials, genetic studies, and research center activities. A small percentage of the total funds (6%) were in turn allocated to apparently less important areas such as assessments of environmental control interventions, development of medical curricula, patient noncompliance, methodological improvement, and family functioning (figure 5.1). Interestingly, it appears that none of these include research on physician noncompliance to national practice guidelines: in a sample of 990 physicians surveyed in 1994, only 22% of physicians reported use of therapeutic protocols for moderate and severe asthma that are consistent with the GDMA (Asthma Zero Mortality Coalition 1995). In keeping with these trends most health maintenance organizations and insurance companies in the United States today ignore the significance of environmental controls for patients with asthma; these agencies do not pay for indoor allergen assessments, purchases of mattress and pillow covers, carpet and bedding chemical treatments, vacuum cleaner filters, and other allergen reduction costs.

In summary, pharmacotherapeutic improvements may be failing to contain childhood asthma epidemics because they relieve symptoms but do not eliminate the causes of such epidemics. Simply put, better drugs may only help solve the asthma paradox when subsumed to a preventive plan of action that includes effective environmental control and behavioral management strategies. Although national practice guidelines acknowledge the significance of these causes, they de facto endorse exclusive use of pharmacotherapeutic agents by only providing easy-to-use algorithms for this form of therapy and by omitting environmental control and behavioral equivalents. Whether these omissions are warranted depends on an as yet unanswered biostatistical question: How much of the variance in childhood asthma morbidity and mortality is explained by pharmacotherapeutic therapies relative to environmental and

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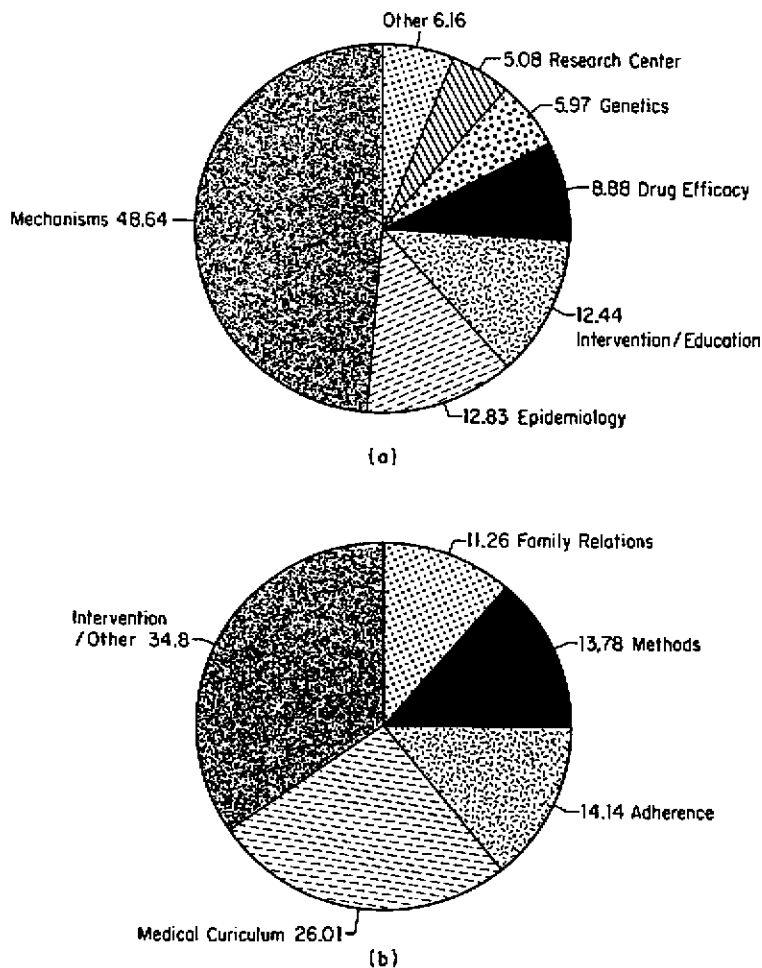


Figure 5.1. National Institutes of Health research funding for the fiscal year January 1, 1995 to December 30, 1995. (a) percentage of funds by category; (b) percentage of funds accounting for the "other" category. (Source: National Institutes of Health 1997.)

behavioral causes? The guidelines reviewed here make the implicit assumption that inadequate or minimal adoption of pharmacotherapeutic therapies account for most of the variance. In the absence of data, we can and should reformulate and approach the question from a deductive rather than from a biostatistical standpoint only: whether the omissions of environmental and behavioral factors in the guidelines are justified in light of epidemiological evidence and immunological insights into the etiology of childhood asthma and its place in human evolutionary history.

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### An Evolutionary View of Childhood Asthma

Informed by the theory of natural selection, life history principles explain the diversity of the life course across populations. Particularly relevant to the life course are the timing and probability of births and deaths, which are in turn determined in large part by disease, a physiological state leading to deviations from a culturally expected state of good health for a given age or sex. Within this framework, diseases are viewed as phenotypes whose manifestations are determined in part by ecology (i.e., environmental factors). The genotypes coding for these phenotypes are in turn subject to selective pressures depending upon the extent to which timing of deaths or disability (early as opposed to later in the life course) affect frequency of conceptions, live births, and viability of offspring.

Here we define asthma as a disease phenotype—the expression of heritable asthma genotypes (*Clinical and Experimental Allergy* 1995) in interaction with the environment during the course of growth and development (Stearns 1992). Two environmental exposures are key to understanding the distribution of childhood asthma in human populations: parasites and indoor allergens (Mogel 1992). The timing of exposure to parasites and allergens across the life course are also significant; the probability that the asthma phenotype will be expressed in an individual is negatively associated with the age at which a child is exposed to inhalant allergens (Sporik et al. 1990). Furthermore, experimental studies with rats show that exposure to inhalant allergens before exposure to helminths is positively associated with the probability of developing allergic disease (Orr and Blair 1969; Turner et al. 1982).

The high prevalence of asthma phenotypes at the present time indicates that associated genotypes have been favored by natural selection throughout human evolution. By this we mean that asthma genotypes and their phenotypic expression have for millennia increased the probability of survival or births or both among its bearers over people without it. To examine this proposition we need to determine whether these genotypes are new only to humans or ancient features that we share with other orders in Mammalia. We then examine the relevant “reaction norms,” or the expression of the phenotype as a function of environmental exposures such as parasites and inhalant allergens in past and present human environments (Stearns 1992). This chronological discussion of the phenotype helps us understand why asthma is a common condition in contemporary human populations and how likely it is that it will be prevalent in future generations. In particular, we present a trade-offs model of parental care behavior and the ways in which these behaviors might interact with levels of inhalant allergen exposure on morbidity and mortality of children with asthma. The extent to which parents can and do minimize the effect of childhood asthma on fertility and mortality before and/or during their offsprings’ reproductive years has implications for the maintenance of asthma genotypes and thus the persistence of childhood asthma epidemics in future generations.

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### Immunological Phenotypes

Asthma is referred to as an atopic disease, a condition in which people with genetic predispositions to allergy upon exposure to ubiquitous biological or chemical substances that are inhaled or ingested produce significantly greater quantities of IgE than the average individual (Pope et al. 1993 see page 190). Interestingly, infestation of human hosts by helminths (parasitic metazoan parasites) is also associated with elevated levels of circulating IgE, and this response in turn predisposes individuals to asthma and allergy, although parasitic infection under other conditions seems to prevent asthma and allergies (Pritchard 1992). It is therefore possible that the genotypes involved in parasitic defense and asthma are similar, but that, whereas the former provides a clear fitness advantage, it is unclear whether asthma is adaptive. For the purposes of our discussion, the asthma phenotype refers to morbidity and mortality proximately caused by the mast cell IgE-mediated reaction to allergens in the lung (Pope et al. 1993).

The immunological principle linking parasite load to asthma is the concept of *mast cell saturation*. IgE circulates in serum (total serum IgE) at varying levels (range: 0.05 IU/ml–46850 IU/ml) (Haus et al. 1988; Hochreutener et al. 1991). A portion of the IgE reacts specifically with identifiable environmental antigens (allergen-specific IgE) (Bazaraal et al. 1973). IgE binds to mast cells in tissue and to basophilic leukocytes and sensitizes these cells to discharge pharmacologically active mediators when they are subsequently exposed to antigens to which the IgE is specifically reactive (Bazaraal et al. 1973). These IgE complexes are responsible for the development and maintenance of the inflammatory response in asthma and its concomitant spasms of bronchial smooth muscle fibers and nonspecific bronchial hyperactivity (Ishizaka 1973). However, under some conditions, animal and human mast cells become saturated and fail to express the allergen-specific response—as, for example, when all or most available receptors are occupied by IgE directed to nonallergen antigens, as may be the case in parasite infestation (Godfrey 1975 and references therein). Among individuals heavily parasitized by helminths, who also tend to be free of asthma and show high total IgE levels, it has been demonstrated that allergic reactions of the skin are not expressed. This has been interpreted to mean that although specific antiallergen IgE may be present in those individuals, it does not react functionally in the presence of high loads of unrelated IgE (Lynch et al. 1993). However, occasional parasitic infestation may activate allergen-specific production via a nonspecific stimulation of IgE synthesis. In this case total IgE synthesis could be large enough to substantially stimulate rather than inhibit allergen-specific IgE production (Hagel et al. 1993).

### Genotypes

Although our understanding of the immunological mechanisms associated with the asthma phenotype has improved considerably over the past 2 de-

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cedes, the genetics of asthma continue to remain elusive (Doull et al. 1996; Sanford et al. 1995). Total serum IgE production appears to be controlled by a dominant atopy gene unlinked to HLA class II, whereas allergen-specific IgE production is unequivocally linked to the HLA class II molecules. The releasability of inflammation mediators mediated by IgE production is controlled by poorly understood genetic coding.

In spite of our poor understanding of the genetics of asthma, it is nevertheless clear that childhood asthma is heritable (Pope et al. 1993). After controlling for other factors, children whose parents have allergies experience the highest incidence of asthma (*Clinical and Experimental Allergy* 1995; Luoma 1984). One study found that children whose mothers or fathers had a history of asthma were almost three times as likely to develop asthma up to the age of 7 (Jenkins et al. 1993). Two studies of histories of asthma in twins found that monozygotic pairs have a higher concordance of asthma onset (59%, 43%) than do dizygotic pairs (24%, 25%) (Nieminen et al. 1991; Sarafino and Goldfeder 1995; see also Akasawa et al. 1991), regardless of whether twins are reared together or apart (Hanson et al. 1991).

Differences in childhood asthma prevalence across ethnic groups have been attributed to genetics as well. Puerto Rican children with asthma have significantly larger numbers of the variant S or Z in  $\alpha_1$ -antitrypsin than do nonasthmatic controls (Hurtado 1995 and refs therein). In 1984, this ethnic group, with considerably more African admixture than other Hispanics in the United States, was reported in a national survey as having higher lifetime prevalence rates of asthma than Mexican Americans, the group with substantial Amerindian admixture (21% versus 4%, respectively) (Hurtado 1995). Similarly, in a national sample of self-reports of asthma collected from 1976 to 1990, African Americans reported higher lifetime prevalence rates of asthma than did non-Hispanic whites (9.2% versus 6.2%) (Hurtado 1995; Turkeltaub and Gergen 1991; see also Gaddy et al. 1993; Grundbacher and Massie 1985). African Americans have been found to produce IgE at significantly higher levels than non-Hispanic whites in the United States (Grundbacher and Massie 1985), but the extent to which these differences are genetically determined has yet to be determined.

#### Is the Immunological Phenotype Fixed at Higher Taxonomic Levels?

The immunological mechanisms associated with asthma are ancient features of Mammalia. Immunoglobulin E is fixed at this taxonomic level, sharing a common ancestor, IgY, with other nonmammalian vertebrates (Warr et al. 1995). IgE and IgG evolved from IgY in mammals as two separate antibodies that had fulfilled two distinct immunological functions in their IgY ancestor. In mammals IgE is a major low molecular weight serum antibody that mediates allergic reactions; IgG defends tissues from systemic infections and neutralizes viruses. Upon divergence of immunoglobulin functions sometime in the phylogenetic history of mammals, IgE became a quantitatively minor isotype

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(0.002% of total serum immunoglobulin), probably downregulated due to its life-threatening anaphylactic (i.e., allergic reactions resulting in respiratory compromise and/or cardiovascular collapse) side effects, and IgG assumed the role of the major serum antibody in mammals (80% of total serum immunoglobulin). IgG downregulates IgE production by mechanisms yet to be fully identified and is often referred to as a *blocking antibody*. Immunotherapy (allergy shots) stimulates the production of IgG to ensure this blocking action; IgG interferes with anaphylactic reactions through direct competition for antigens (i.e., foreign molecules bearing sites to which antibodies bind) (Durham 1995; Hussain et al. 1992). It has been proposed that IgE and IgG became mutually distinct in mammals and not in other animals in order to prevent maternal anaphylaxis from damaging the embryo, and thus IgE must behave independently in protecting the fetus from the onslaught of the maternal immune system in mammals (Ionov 1985). More definitive insights into the evolutionary reasons for bifurcation may someday shed light on the evolution of asthma.

#### How Does the Distribution of Asthma in Humans Compare to Other Mammals?

Although IgE is ubiquitous in Mammalia, chronic wheezing is rarely seen in noncaptive animals. However, data on zoo animals, pets, and experimental breeds suggest that asthma can be easily induced under some conditions. Halpern et al. (1989) reported a 12-year history of respiratory tract allergic disease in a 25-year-old, 70-kg female chimpanzee. The symptoms were controlled with treatment. This animal had strong positive skin reactions to grass, weed, and tree allergens but not to mold or mite antigens (Halpern et al. 1989). At least one case of atopic dermatitis in gorillas living in captivity has been reported (Hog and Schindera 1989). Feline asthma syndrome was identified in 29 cats, and treated effectively with prednisone, a commonly used steroid in human asthma treatment (Corcoran et al. 1995). Finally, the asthma phenotype or its immunological correlates have been experimentally induced in several species of mice, rats, guinea pigs, rabbits, sheep, dogs, horses, baboons, and rhesus monkeys (Breen et al. 1987; Karol 1994; Patterson and Harris 1993; Wegner et al. 1993). To our knowledge, asthma-induced deaths in these species have not been reported, although IgE mediated reactions have been induced in laboratories (Karol 1994).

#### What Might Be the Adaptive Function of the Asthma Trait?

The term "adaptive" has many definitions in evolutionary biology (Stearns 1992). Here we use a less mathematically rigorous meaning: a presumed change in a phenotype that occurs in response to a specific environmental signal that results in improvement in growth, survival, and/or fertility. More mathematically rigorous definitions include precise and valid measures of age-

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specific fertility and mortality for individuals bearing alternative phenotypes (e.g., "has asthma," "does not have asthma") under specified environmental conditions (e.g., "parasitized," "not parasitized") to measure the effects of the phenotypic expression on fitness in different contexts of interest (Stearns 1992). It would be advantageous for us to know whether individuals bearing the asthma phenotype have higher survivorship rates and/or fertility than do others in populations with endemic parasite infestation. For example, some studies show a strong negative correlation between asthma and worm load (Venge and Shaw 1989). However, these short-term observations tell us little about the fitness profiles of individuals (i.e., age-specific fertility and survival rates) necessary to determine whether asthma is truly adaptive.

Total serum IgE levels have been shown to increase and provide a survival advantage in the face of multiple and massive endo- and ectoparasitic infestation (Abdel Fattah et al. 1994; Hagan et al. 1991; Kigoni et al. 1986; Matsuda et al. 1990). Because parasitic infestations are naturally hyperendemic in all species including humans, it is possible that asthma is a problem arising in recent times and one that is limited to mammals who have drastically reduced their exposure to parasites over the past century (Bazaraal et al. 1973). Thus, it appears that the asthma phenotype is in part a cost that humans have incurred for getting ahead in the host-pathogen arms race in human history, if only momentarily. Similar inferences apply to diseases such as diabetes, one of the costs of having superabundant nutrient supplies, particularly carbohydrate and fats, in the modern world (Eaton et al. 1988, Sapolsky 1994 and references therein).

Total serum IgE also appears to play a role in other debilitating or life-threatening conditions: risk of sudden cardiac death (IgE depresses clot formation) (Szczeklik et al. 1993); development of cancerous tumors (IgE decreases tumor growth and incidence); and risk of death during traumatic injury (IgE is inversely associated with organ failure and mortality in trauma patients) (DiPiro et al. 1994); onset of *Staphylococcus aureus* related infections in persons unable to produce other immunoglobulins (Nesse and Williams 1995); and containment of inhalant and ingested toxins of all sorts (Profet 1991), which in turn may reduce the risk of developing cancer (Profet 1991 and references therein).

#### What Are Some Examples of Reaction Norms for the Phenotypic Expression of Childhood Asthma?

The mast cell saturation principle provides the foundation for understanding reaction norms between parasite load, exposure to allergens, and the expression of asthma. One way to learn about these reaction norms is to examine the relationship between total serum IgE levels (as determined by parasite load) and allergen-specific IgE (a strong correlate of asthma prevalence) (see figure 5.2). The mast cell saturation principle would lead us to predict an inverse relationship between parasite-induced total IgE and allergen-specific IgE; as total IgE serum levels increase, mast cells become saturated, impeding

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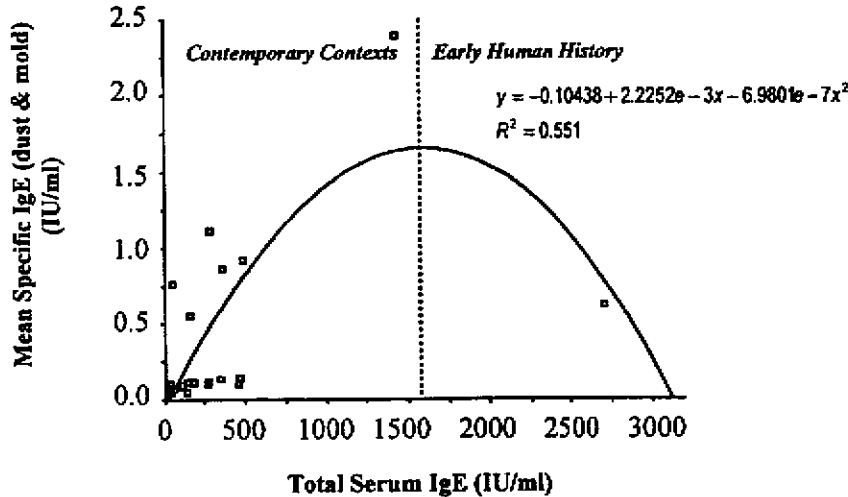


Figure 5.2. The relationship between total blood serum IgE levels and the mean house dust and mold-specific IgE levels for 27 patients, ages 13–67 (data from Lynch et al. 1985: table 1).

allergen-specific IgE from accessing receptor sites. The relationship between IgEs, however, is more complex: effective inhibition of allergen-specific IgE may only occur at high levels of parasite load exposure and not at intermediate levels. At intermediate levels, serum IgE synthesis could be large enough to substantially increase total serum IgE levels, but not large enough to block mast cell activation of allergen-specific IgE levels (Hagel et al. 1993). Figure 5.2 illustrates this complexity: allergen-specific IgE is positively associated with total IgE up to a point (~1500 IU/ml), but beyond that point it appears to be negatively correlated.

The reaction norm between parasite load (as measured by total serum IgE) and the expression of the allergic response (as measured by allergen-specific IgE) (figure 5.2) provides insight into the epidemiology of childhood asthma in present and past environments. Research on isolated Amerindian groups support the proposition that thresholds >1500 IU/ml total IgE may be typical of our evolutionary past. Loads of helminth infestation in remote South American Indian populations are extremely high, ranging between 60% and 98% prevalence for individuals of all ages (population prevalence rates are positively associated with worm count or load per individual; see Bundy and Medley 1992: figure 2.7). These estimates may be our best guess of what parasite prevalence was throughout human history (Salzano 1990). Not surprisingly, total IgE levels in these populations are the highest ever measured in extant populations (11,975 and 13,088 IU/ml among the Waorani and various Venezuelan Amazon groups, respectively, see table 5.1), and asthma rates are extremely low or nonexistent (Hurtado, Arenas and Hill 1996; Kaplan et al. 1980; Lynch et al. 1983). Other extant populations residing in rural areas also

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Table 5.1 Total serum IgE and childhood asthma in diverse populations

Population	Age group	Mean total serum IgE (IU/ml)	% Positive skin test	Asthma prevalence	Allergen <sup>a</sup>	Sample size	Reference
South American Indians							
Waarani	Adults	11,975	5.67	n.d.	V	227	Kaplan et al. (1980)
Amazonas groups, Venezuela	Adults	13,088	6.70	1.02 <sup>b</sup>	V	49	Lynch et al. (1983)
Rhodesia							
Rural	Adults	1,613	6.00	n.d. <sup>c</sup>	DF	100	Merrett et al. (1976)
Gambia							
Rural	Children	962	0.01	0	V	131	Godfrey (1975)
Urban	All ages	368	0.01	0.008 <sup>d</sup>	V	191	Godfrey (1975)
United States, Mexicans							
Parasite infested	Adults	2,219	n.d.	n.d.	n.d.	20	Bazaraal et al. (1973)
No parasite infestation	Adults	458	n.d.	n.d.	n.d.	12	Bazaraal et al. (1973)
Java laborers							
Low parasite load	Adults	2,193	n.d.	n.d.	n.d.	15	Noerjasin (1973)
High parasite load	Adults	5,460	n.d.	n.d.	n.d.	21	Noerjasin (1973)
Mestizos, Venezuela							
Rural	All ages	975	6.42	6.00	D(2)	327	Lynch et al. (1984)
Urban	All ages	745	14.53	25.00	D(2)	475	Lynch et al. (1984)
Urban, Venezuela							
Pre-parasite treatment	Children	2,543	17	n.d.	HD	86	Lynch et al. (1993)
Post-parasite treatment	Children	1,124	68	n.d.	HD	86	Lynch et al. (1993)
No treatment, beginning of study	Children	1,649	26	n.d.	HD	75	Lynch et al. (1993)
No treatment, end of study	Children	3,697	12	n.d.	HD	46	Lynch et al. (1993)
Medium-high SES	Children	557	42	n.d.	HD	391	Hägel et al. (1993)
Low SES	Children	1,870	23	n.d.	HD	455	Hägel et al. (1993)
Rural	Children	3,140	8	n.d.	HD	319	Hägel et al. (1993)

<sup>a</sup>DF, dust mite species *Dermatophagoides farinae*; V, various; D(2), two species of *Dermatophagoides*; HD, house dust.

<sup>b</sup>Estimate based on 75,013 medical consultations among Venezuelan Amazonian Indians over a 5-year period.

<sup>c</sup>n.d., no data.

<sup>d</sup>No systematic data were collected: 44 individuals with asthma were referred to the investigators. In contrast, only 1 person with asthma was reported in a population of 1200 rural residents.

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show IgE levels above the 1500 IU level, high parasite load, and low rates of asthma and/or low percentage of positive skin tests (rural Rhodesia, rural Gambia, rural mestizos, urban poor; table 5.1). Finally, Venezuelan children of higher socioeconomic status are less parasitized and show lower total IgE levels than do their lower socioeconomic status counterparts (table 5.1).

Parasite load per se may not only play a role in inhibiting allergen-specific IgE production among South American Indian groups but also the *timing* of exposure in growth and development may be critical. Extensive exposure to helminths before exposure to inhalant allergens early in life may greatly dampen the expression of allergies in humans as has been shown in the rat (Orr and Blair 1969; Turner et al. 1982). Among the less acculturated South American Indian groups, children become infested with parasites at a very young age (Santos et al. 1995). However, they are exposed to few if any indoor allergens because they live in well-ventilated huts and use traditional bedding that is a poor breeding site for dust mites and cockroaches (Hurtado et al. 1996a). As groups adopt less ventilated housing (concrete block shelters and homes with machine-made wooden boards), Western bedding such as mattresses and blankets, and spend more time indoors (National Research Council 1991; Spengler and Sexton 1983), the risk of exposure to high levels of indoor allergens soon after birth increases. Moreover, in contemporary urban centers with a high prevalence of childhood asthma, children are not only chronically exposed to indoor allergens throughout infancy and the school-age years but may also be intermittently, although minimally, exposed to helminth infestation (Bosman et al. 1991; Kappus et al. 1994). Lastly, acculturation and urban residence leads to an increase in the probability of helminth infestation, however slight, *after exposure* to indoor allergens.

Hence, decreases in parasite load and adoption of insulated housing and Western bedding in recent human history help explain why total IgE levels <1500 IU/ml are characteristic of populations residing in metropolitan areas throughout the world today (Hetman et al. 1988; Yadav et al. 1994). Within this lower range (figure 5.2), elevated total IgE is an important and consistent predictor of asthma in children. Total serum IgE levels are strongly associated with a history of asthma, whereas no asthma is present in subjects with the lowest IgE levels (Burrows et al. 1989; Criqui et al. 1990). Among children diagnosed with asthma, those with elevated IgE levels (>500 IU/ml in older children and 100 IU/ml in infants) experience higher asthma-related morbidity than children with lower total IgE serum levels (Maruo et al. 1990). Finally, total IgE predicts the onset of asthma but not the onset of other atopy-related phenotypes such as allergic rhinitis (DiPiro et al. 1994).

Throughout the world today, children living in poverty are more likely than their affluent counterparts to develop asthma (Evans 1992; Gottlieb et al. 1995; Halfon and Newacheck 1993; Weiss et al. 1992) and to have elevated allergen-specific IgE and total serum IgE (but <1500 IU/ml) (Berciano et al. 1987; Pollart et al. 1989; Willies-Jacob et al. 1993). Although both high and low socioeconomic status individuals find themselves at the contemporary lower end of the distribution (see figure 5.2), socioeconomic status is associated negatively

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with total IgE production. This is possibly because exposures or factors that elevate total IgE occur more frequently and at higher levels in low than in high socioeconomic status families. Factors of primary interest are intermittent exposure to parasites, respiratory viruses and/or chronic exposure to indoor and outdoor allergens (Bardin et al. 1992; Sporik et al. 1990), and the number of hours that children spend indoors (Silvers et al. 1994).

Public health programs have eliminated exposure to helminths in high socioeconomic status communities but failed to do so entirely, if at all, in low socioeconomic status areas (Stephenson 1987). Low socioeconomic status families are therefore faced with the synergistic effects of parasite and indoor allergen exposure on childhood asthma (Hagel et al. 1993). The co-occurrence of parasite infestation and allergens and the incidence of asthma has been studied in depth by Lynch and co-workers in Venezuela (but see Hagel et al. 1993; Moqbel 1992). The implications of this work may be far reaching and extremely relevant to U.S. populations: Puerto Ricans show both higher rates of childhood asthma (Hurtado 1995) and hookworm infestation (Maldonado 1993) than any other ethnic group in the United States. This raises the possibility that parasitism may also play a role in asthma among African Americans residing in low socioeconomic status neighborhoods.

In addition to parasite exposure, low socioeconomic status children experience respiratory viral infections at significantly higher rates than do their more affluent counterparts (Margolis et al. 1992; McConnochie et al. 1995; Porro et al. 1992). Viruses are major culprits of asthma exacerbations in children and adults (Bardin et al. 1992), and they do so through stimulation of IgE production (Weiss and Stein 1993). Prospective studies have shown that 28% of subjects with undetectable IgE to respiratory syncytial virus had subsequent wheezing (an important asthma symptom), whereas 70% with elevated IgE to respiratory syncytial virus wheezed (Welliver et al. 1986). Another study found a strong relationship between infection with parainfluenza 3 virus and respiratory syncytial virus and the subsequent development of allergy symptoms coupled with significant elevations in total IgE within 3 months of infection (Frick 1986).

Children of low socioeconomic status families are also at higher risk of indoor and outdoor allergen exposure than are children of high socioeconomic status. This is true of all the major allergens currently under extensive investigation throughout the world: dust mite, cockroach, animal dander and cigarette smoke (Barnes and Brenner 1996; Malveaux and Fletcher-Vincent 1995; Pattermore et al. 1989). Exposure to dust mites is of particular concern; Sporik et al. (1990) found a positive dose-response relationship between the age at which children were exposed to dust mites above a critical threshold and the probability of developing asthma before adolescence. The relationship between exposure to the other major indoor allergens and the incidence of asthma in children is less well understood; nevertheless, correlational (i.e., cross-sectional) studies clearly indicate that levels of cockroach, cigarette smoke, and animal dander are strongly associated with the prevalence of asthma in children (Etzel 1995). Synergistic effects between indoor allergens

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and inhalant pollutants (e.g., nitrogen dioxide; Infante-Rivard 1993; ozone: Bethel 1984; Biagini et al. 1986; Peden et al. 1995), known to be more densely distributed in low socioeconomic status areas (Bryant and Mohai 1992), may further increase the risk of developing asthma among children residing in these areas. Cellular responses to allergens such as dust mites among children sensitized to this allergen are significantly more pronounced in the presence of ozone than in its absence (Biagini et al. 1986; Peden et al. 1995).

The impact of indoor allergens on the onset of asthma among children living in poverty is further exacerbated by the number of hours that children spend indoors (National Research Council 1991). Children of low socioeconomic status tend to spend more hours per day watching television and are less active than children of high socioeconomic status families (Evers and Hooper 1995; Rosenfeld 1992; Wolf et al. 1993). Under such conditions, the percentage of time spent indoors by children between 5 and 12 years of age may exceed the national average of 60% ( $n = 1000$  households; Silvers et al. 1994).

In summary, part of the solution to the asthma paradox involves an appreciation for the relationship between levels of parasite infestation and the timing and extent of allergen exposure during early human development. It appears that in more recent human history, ample opportunities for IgE stimulation occur below levels necessary to saturate and impede the expression of allergen-specific IgE. These opportunities in turn are more ubiquitous in disadvantaged populations and they tend to occur together; e.g., children exposed to high levels of cockroach allergen are also more likely to be exposed to ozone and nitrogen oxygen, cigarette smoke, and to spend more time indoors.

### How Does the Evolutionary Biology of Asthma Interact with Human Parental Care Strategies?

Environmental factors associated with an increase in the frequency of childhood asthma cases are mediated by parental care behaviors. Table 5.2 illustrates how little we know about these behaviors. In contrast to biology and anthropology (Clutton-Brock 1991; Hrdy 1992), pediatrics curricula do not include the study of parental care behaviors, even though the evolutionary ecology of parental decisions is key to understanding the distribution of childhood diseases in human populations. This relevance is evident because most forms of investment necessary to ensure a productive life in children is primarily under the control of parents. The role of ecology and curvilinear relationships are as important for understanding the etiology of parental care as is true for understanding the IgE network. Parents face difficult trade-offs between allocating time and effort to activities that are beneficial to the child with asthma but are also mutually exclusive (e.g., ensuring allergen-free environments versus directly monitoring pulmonary function; administering medication versus providing other direct forms of care) (table 5.2). These

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Table 5.2 Behavioral changes associated with medication and environmental control protocols

Prescribed treatment <sup>a</sup>	Behavioral changes associated with the prescribed treatment	Actual treatment or actual behavioral changes
Pharmacological agents Purchase, administer medication, and report adverse effects	Income expenditures to purchase medication, transportation (gas, bus, taxi) to go to pharmacy Time spent traveling to pharmacy, waiting for the prescription to be filled, etc. Time spent calling the provider to talk about adverse effects, waiting for the return call, etc. Activities foregone in order to purchase and administer the medication (leisure, work, etc.)	? ? ?
Monitor signs and symptoms and peak expiratory flow rate Environmental control Encase mattress in an airtight cover	Time spent convincing children to use the peak flow meter for measurement on a regular basis	? ?
Wash the bedding in water of 130° weekly Remove carpets from the bedroom	Income expenditure to purchase of cover Time expenditure to time to find a store that sells the cover, time to actually purchase the right cover (e.g., waiting in line, exchange) Time expenditure	? ? ?
	Income expenditure to pay for cleaning or adding a new floor Time expenditure to find professional to remove the carpet, time to monitor workers	? ?

<sup>a</sup>Source of prescribed treatment examples: Guidelines for the diagnoses and treatment of asthma (U.S. Department of Health and Human Services 1991).

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trade-offs can be hypothetically described to shed light on the reasons that, even though parents may agree with physicians about ideal health goals for their children with asthma, they are not in a good position to attain those goals. Parents seek those goals in a constrained environment; health care officials, on the other hand may naively assume that parents can attain unconstrained optimal levels by simply taking home drug prescriptions and asthma management recommendations.

#### A Hypothetical Model of Parental Care Decisions

A hypothetical optimization graph of the relationship between maternal time and child health outcomes helps us identify the behavioral causal pathway that links environmental constraints such as allergen exposure and levels of education with health outcomes among children with asthma (see also Hurtado et al. 1996c). In this thought experiment, only families with one child who has asthma are considered. We then consider the options available to mothers over a 12-hour period; these options are stratified by differences in educational levels (figure 5.3). We plot on the x axes of figures 5.3a and the goods obtained from working outside the home and from providing care in terms of income and health insults avoided (e.g., accidents, infections, malnutrition). Income yields food, shelter, clothing, and medical care. Direct care protects children from experiencing health insults of a diverse nature. In asthma care, health insults of relevance include morbidity (e.g., school days lost) and near deaths that can be avoided by monitoring environmental triggers, respiratory function and planning daily and weekly environmental control and medication use schedules. Good care depends entirely on parental ability to predict symptoms and attacks based on information about changes in the child's exposure to triggers and lung function (peak expiratory flow). Parents must be able to identify and avoid triggers such as respiratory viruses and indoor allergens and implement preventive measures to avoid school absences and severe asthma attacks and assure participation in leisure activities (table 5.2). Parental inability to behave effectively and in a timely manner is one of the most important predictors of asthma mortality in children (Robertson et al. 1990; Sears et al. 1986).

At this point we describe differences in hypothetical budget constraints (figure 5.3c, d) that might characterize the ecologies of less and more educated mothers. In our example, if less and more educated women were to spend all their time in child care, they would avoid a maximum of 65 and 35 health insults, respectively, over a 12-hour period (y axis). We chose these numbers to reflect published findings showing that women who are less educated are also more likely to be of low socioeconomic status (Grogger and Bronars 1993) and more likely to reside in homes and areas with high allergen density. In contrast, if less educated mothers were to spend all their daylight hours working outside the home, they would obtain a maximum of \$48 over a 12-hour period (\$4 per hour), while more educated mothers would obtain a maximum of \$240 dollars over the same time period (\$20 dollars per hour) (x-axis). These

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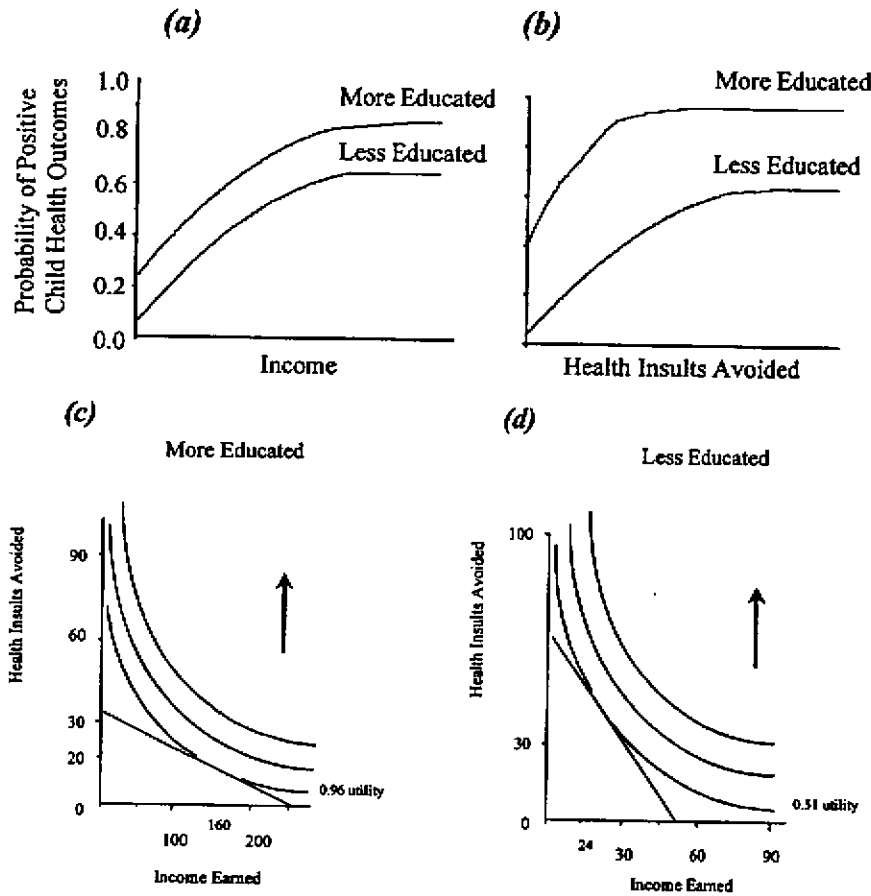


Figure 5.3. Qualitative optimization model of trade-offs women face between working outside the home and providing child care for more and less educated mothers. (a) Relationship between the number of health insults avoided by providing child care and the probability of positive child health outcomes. (b) Relationship between income earned and the probability of positive child health outcomes. (c,d) Optimal combination of time expenditures for more and less educated mothers, respectively.

numbers also reflect a common wage difference in the United States today. The budget constraint lines connect the maximum amount of goods that would be obtained if women spent all their time in one activity or another; these show that even though mothers may want to both avoid the maximum number of health insults per day and to earn the maximum income per day possible, they can only choose from a limited set of combinations.

Which combination should a mother choose? The answer depends on the effect of income earned and health insults avoided on the probability of positive child health outcomes. Monotonically decreasing returns curves are used

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to describe these relationships (figure 5.3a, b). For both types of goods (income and health insults avoided), the baseline probability of positive health outcomes among children with asthma is higher for more educated than for less educated mothers. This is because on average infants and young children of less educated mothers experience higher co-morbidity unrelated to asthma than their more educated counterparts (Scholl et al. 1987). Moreover, more educated women are likely to hold jobs that include health benefits. Furthermore, it is also hypothesized that the marginal child health returns are higher and reach a point of diminishing returns sooner among more educated than among less educated women because skills and knowledge greatly increase parental ability to implement medical information (targeted to educated individuals in the first place). Consequently, we propose that more educated mothers are able to attain higher levels of child health utility (defined in our example as the probability of positive child health outcome) than are less educated mothers at all levels of income earned and health insults avoided through child care.

For both sets of women, the public health, medical, and parental ideal of 100% probability of positive child health outcome is not an option; this is because they cannot both earn the maximum income and avoid the maximum number of health insults on a given day (figs 5.3c, d). Instead mothers must choose among realistic possibilities, and preferably choose the one that yields the highest utility among alternatives (i.e., the optimal solution). In our example, less educated women can attain a maximum of 56% probability of positive child health outcomes, and they can only realize this maximum if they choose to earn \$24 per day and to avoid 30 health insults (6 hours working outside the home, 6 hours in child care). More educated women, on the other hand, can attain a maximum of 96% probability of positive child health outcome, and they can only realize this maximum if they choose to earn \$160 per day and avoid 20 health insults per day (8 hours working outside the home, 4 hours in child care). This thought experiment raises questions relevant to the asthma paradox: are ecological constraints on behavioral options the reason rates of parental and patient compliance with prescribed asthma medication are so dismally low (Range: 14.5–66%; Alessandro et al. 1994; Coutts et al. 1992; Gibson et al. 1995; Pachter and Weller 1993; Rand and Wise 1994; Schoni 1993; Warner 1995; Wood et al. 1985)?

#### What Are the Life History and Parental Care Implications for Fitness of the Asthma Phenotype?

The behavioral trade-offs that parents of diverse socioeconomic status face in the care of children with asthma may have fitness implications: if low socioeconomic status parents provide less care than wealthier parents, then their children will be at risk of morbidity and mortality at higher rates than the rest of the population. Research findings are consistent with this proposition. Children of low socioeconomic status who have asthma experience more days lost from school, more hospitalizations, more deaths due to poorly-managed

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asthma attacks at home, more psychological problems, and lower grades in school than their more well-to-do counterparts (Fowler et al. 1992; MacLean et al. 1992). From the published data, it is not clear whether these short-term effects result in lower fitness, for which sex, and at what levels of asthma severity. We know that asthma tends to delay puberty, marriage (Kokkonen 1995), and employment (Sibbald et al. 1992), but effects on age-specific mortality and fertility have not been measured. Predictions about increases in the prevalence of asthma in future generations depend on knowing something about life expectancy at reproductive age and subsequent fertility among asthmatics. Is this highly heritable phenotype (Neiminen et al. 1991) under directional, neutral, or negative selection in contemporary populations?

### Conclusions

An appreciation for the evolutionary etiology of childhood asthma leads us to conclude that there is little incongruity to the asthma paradox. There are probably good evolutionary reasons that childhood asthma is prevalent in contemporary populations: it may be a consequence of an active IgE network favored by natural selection to provide defense against ubiquitous and endemic parasites throughout human history. But this is only part of the story; IgE-mediated mechanisms may also provide a survival advantage in heart disease, bacterial respiratory infection, cancer, and injury. However, whether childhood asthma is an *adaptive* consequence is an important empirical question: does asthma provide a survival or fertility advantage to individuals growing up in contemporary allergen-infested environments? We need more than qualitative arguments to test this proposition and show that children with asthma experience increased survivorship and fertility as adults when compared to children free of chronic conditions.

For as long as we do not fully understand the range of functions of the IgE system, it may be prudent for clinical practice guidelines to focus on environmental controls with pharmacotherapy as a complementary, albeit fundamental, aspect and the parental care behaviors that are key to their effective implementation. At the present time, national practice guidelines do not provide such practical algorithms. Instead, practitioners are given ample instruction on how to tailor medication prescriptions to individual patients and on ways to evaluate the effectiveness of their decisions. Excessive dependence on pharmacotherapeutics for asthma management *de facto* assumes that the benefits from drug intake can in fact counteract incremental increases in allergen exposure. As is true in most biological systems, there is probably a threshold point at which the morbidity caused by additional exposure to allergens cannot be relieved by further increments in drug therapy. Are some populations of children living at that threshold or beyond it? If so, a call for guidelines with a focus on environmental and behavioral changes would be easy to justify. In the meantime, we should perhaps consider the possibility that many children in contemporary populations may be at that threshold.

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## THE EVOLUTIONARY ECOLOGY OF CHILDHOOD ASTHMA 125

To assess the usefulness of an evolutionary approach to medical problems in childhood asthma, we propose several areas of research that focus on the development, implementation, and evaluation of detailed algorithms and their use in clinical practice. These algorithms are information-gathering aids that longitudinally assess (1) allergic sensitization (including total IgE levels) in children at risk of asthma (as determined by family history) or that have been diagnosed as having asthma using bronchoprovocation tests; (2) allergen exposure levels relevant to the child's sensitization profile (e.g., if the child is allergic to dust mites, measure levels of dust mite allergen in the home) with corresponding environmental control measures; (3) parental ability to provide the care necessary to attain effectiveness and parental noncompliance with specific courses of action to follow when parents are unable to comply or choose not to comply; (4) the effectiveness of these algorithms (i.e., computer-based data-tracking procedures that are user friendly for general practitioners and nurses); and (5) the cost effectiveness and quality of life outcomes of interventions outlined in items 1-4 as compared to existing pharmacotherapeutic-based interventions. Research findings on these clinically based algorithms with proven effectiveness should then be translated into home-based algorithms. This transfer could be made possible by developing technologies that allow parents to monitor allergen exposure in the home, at school, and other places where children spend most of their time (i.e., cheap and easy-to-use kits) and by instituting health insurance mechanisms for reimbursement of environmental control-related costs (e.g., installation of adequate heating, ventilation, and air conditioning systems; purchase of high-efficiency particulate-arresting [HEPA] air filters; elimination of carpeting; purchase of nonallergenic bedding, mattresses, and pillow covers).

An evolutionary approach to public health problems in childhood asthma also helps inform a basic science research agenda in epidemiology and immunology. Three areas of research largely neglected to date seem especially promising to undertake in developing nations, among U.S. ethnic groups with the highest prevalence rates of asthma (African Americans and Puerto Ricans), and among groups showing a recent rise in asthma prevalence (American Indians): (1) the relationship between parasite exposure, allergen exposure, and the onset of allergic sensitization between birth and adolescence; (2) changes in the timing, sequence, and levels of allergen and parasite exposure early in life among populations in the process of adopting more insulated housing and Western bedding; (3) the relationship between levels and forms of parental investment and the survivorship and fertility of adults who as children had asthma as compared to those free of chronic childhood conditions; and (4) The effect of allergen exposure levels on the efficacy of pharmacotherapy.

In addition, basic research on more immunologically precise definitions of "asthma phenotypes" is equally timely. Given the critical role of IgG in blocking IgE-mediated inflammation, it may be the case that a rise in total IgE levels among children with asthma could be entirely a function of IgG responses. If so, definitions of asthma phenotypes should be based on IgE- and IgG-informed criteria. Among individuals exposed to the same level of allergens and having

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the same levels of total serum IgE, IgG may successfully keep in check over-activation of IgE in some (no asthma), in others this may be accomplished intermittently (true mild asthma), while still in others this may not be accomplished at all (true moderate to severe asthma). The reasons IgG fails to provide its blocking function in some individuals and under some conditions needs to be investigated. One possible reason might be that total IgE production increases under conditions where IgG is being used to fight other concurrent problems such as bacterial infections, and the differences in the expression of asthma that we observe reflect these physiological trade-offs. Future research projects guided by evolutionary principles should help resolve some of these uncertainties.

Finally, current pediatric asthma management guidelines would be considerably strengthened by a prevention addendum that includes health care delivery decision-making algorithms for providers and home care algorithms for parents of children who have asthma. These algorithms will help providers recommend lifestyle changes that are within reach to families and ensure that parents and patients make the necessary medication use and environmental control-related behavioral adjustments at home and at school as allergen exposures change and as the severity of the condition waxes and wanes.

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— +1

758