
Genetic-environmental interactions in asthma and allergy: a study in a closed population exposed to different environments

Einat Yaari, MD, MHA*; Ziv Susser, MD†; Amnon Lahad, MD, MPH‡ Yaron Nesher, MD*; Sylvia Kachalsky, PhD‡; Asher Tal, MD§; and Eitan Kerem, MD*

Background: Asthma and allergy are common chronic diseases caused by genetic and environmental factors.

Objective: To study the effect of different environments on the prevalence of both diseases in an isolated founder population that resettled in different geographic and environmental areas (namely, the genetically homogeneous population that immigrated to Israel from Cochin, India, 50 years ago).

Methods: Respiratory and allergy symptoms were recorded by a questionnaire. The relative contribution of genetic factors on asthma and allergy was established by comparing Cochin with non-Cochin Jews living in the Jerusalem mountains; the relative contribution of the environment was determined by comparing mountain Cochin Jews with those living in the desert. The study was conducted from January to October 2004.

Results: A total of 983 individuals (481 mountain Cochins, 353 desert Cochins, and 149 non-Cochins) were studied. The overall prevalence of asthma in Cochins was 23.7%; and of allergy, 29.5%. The rate of asthma and/or allergy in Cochins in the mountains was significantly higher than in control non-Cochins. The rates of both asthma and allergy among Cochin Jews in the mountains were significantly higher than those among Cochin Jews in the desert, the former because of a higher prevalence of allergic asthma. The rates of nonallergic asthma and allergy without asthma were similar in both environments.

Conclusions: Two different asthma and allergy phenotypes were detected that share a distinct genetic background but differ in the environmental influences. Allergic asthma is strongly determined by both genetic and environmental factors, whereas nonallergic asthma or atopy without asthma is determined mainly by genetic factors and is less influenced by environmental factors.

Ann Allergy Asthma Immunol. 2009;102:233–237.

INTRODUCTION

Asthma is characterized by an inflammatory airway disease associated with intermittent respiratory symptoms leading to reversible airflow obstruction and bronchial hyperresponsiveness. It forms part of the spectrum of atopic diseases, involving activation of T cells to produce a range of cytokines that induce the synthesis of IgE and recruitment of mast cells, basophils, and eosinophils that mediate secretion. Asthma and atopy are common, with a reported prevalence of 10% to 25% in different populations.^{1,2}

Both asthma and atopy show a strong genetic component that follows a complex mode of inheritance, involving interactions between exogenous environmental factors and genetically determined endogenous factors with complex genetic inheritance.^{3–10} The mechanisms responsible for inheriting

asthma and atopy are not yet completely understood because of the influence of the environment on disease expression.^{10–14}

Closed populations are ideal for studying the genetics of asthma and other complex diseases.^{15–18} Isolated inbred populations with a high prevalence of asthma or allergy that are exposed to different environments may allow analysis of the relative contribution of both environmental and genetic factors that influence the disease phenotype. The Israeli population includes many previously isolated subpopulations originating from different ethnic groups that immigrated after many centuries of isolation, such as the Jews of Cochin, who exhibit a high prevalence of asthma and atopy. They are named for Cochin, the capital of Kerala in southwest India, and are thought to originate from a small number of Jewish travelers who arrived in Cochin, nearly 2000 years ago; they remained isolated from other Jewish communities inside or outside India. After their immigration to Israel in 1954, they settled in agricultural communities in different parts of the country with extremely dissimilar environments and until recently continued to intermarry. Today, approximately a third of the 7,000 to 8,000 Cochin Jews are still living in those communities. This gave rise to the unique opportunity to study the interaction between the genetic and environmen-

Affiliations: * Department of Pediatrics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; † Department of Family Medicine, Hebrew University Hadassah Medical School, Jerusalem, Israel; ‡ Linkagene Ltd, Lod, Israel; § Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University, Be'er Sheva, Israel.

Disclosures: Authors have nothing to disclose.

Funding Sources: This study was funded by a grant from the Dana Foundation, New York, New York.

Received for publication November 13, 2008; Received in revised form December 7, 2008; Accepted for publication January 2, 2009.

tal factors that underline the development of allergy and asthma.

Controlling for the environmental or genetic factors allows the study of the relative contribution of each factor in the pathogenesis of asthma and allergy.

METHODS

The study protocol and informed consent were approved by the Hadassah-Hebrew University Medical Center Institutional Committee for Human Studies. The study was conducted from January to October 2004.

Population and Environment

All participating Cochin Jews in this study can trace their ancestry and all are related, descending from the same family tree. The participants of this study live in 2 different geographic areas in Israel: the Jerusalem Mountains (20 km west of Jerusalem, 400 m above sea level), which have a typical Mediterranean climate and flora; and the Negev desert (170 m above sea level). The Jerusalem mountain population is distributed over several villages within a radius of 5 km of a small town with 30,000 citizens. Most Cochin Jews work in either this town or Jerusalem. Approximately 20% of households grow chickens and olive trees. The population in the Negev desert is located in 1 village 15 km southeast of Be'er Sheva (population, 155,000), where most of the Negev Cochin Jews work. Approximately 30% of households grow flowers. Chickens and olive trees are considered major allergens in the mountains. Green house flowers were grown by the Negev Cochin Jews for commercial purposes in the past; however, because of the increased onset of asthma in this population, the for-profit production was discontinued.

Data Collection

Attempts were made to reach all the inhabitants of these villages. After explaining the aim of the study and with the assistance of the local health care professionals, all inhabitants were personally approached in their homes to ensure a higher level of participation. All participants were asked to answer a standard questionnaire, presented by research physicians (E.Y., Z.S., and Y.N.), not the family physician or a research nurse. Parents answered the questionnaire for their children. The participation level was more than 50%; no data of nonparticipating inhabitants are available. A participant was considered to be of Cochin origin only if both parents and all 4 grandparents were from Cochin. All other individuals were not considered to be of Cochin origin. The different groups were studied in parallel.

Questionnaire

Medical histories were obtained by using a standard questionnaire translated into Hebrew.¹⁸ The questionnaire recorded the presence of respiratory symptoms, such as cough, sputum, and wheezing; the presence of other chest disorders, including recent upper respiratory tract infection; allergic history; asthmatic attacks, including onset, offset, confirmation by a physician, prevalence, severity, and precipitating

factors; other illnesses; smoking history; and all medications used within the previous 3 months. A physician-confirmed asthmatic attack was the principal criterion for a diagnosis of asthma. Wherever possible, we obtained details of the family pedigree.

Disease Classifications

Asthma

Asthma was classified based on 1 of the following: (1) physician's diagnosis (except if made when the patient was >60 years), (2) documented recurrent episodes of wheezing and/or cough and/or shortness of breath associated with defined triggers or in atopic individuals, (3) individuals responding to bronchodilators, or (4) individuals experiencing cough, wheeze, sputum production, or breathlessness with atopy who were younger than 40 years. All asthmatic patients had to have a negative history of smoking.

Respiratory symptoms were classified based on those with respiratory symptoms who did not meet the criteria for asthma. Allergy included patients with a history of recurrent and episodic nasal itching and ocular discharge, irritation, or atopic eczema. Allergic asthma included individuals with both asthma and allergy.

Data Analysis

To determine the relative contribution of genetic factors, we compared the rate of asthma and allergy among the Cochin population living in the Jerusalem mountain area with the rate of a heterogeneous population of Jews of non-Cochin origin living in the same villages or in the same area (within a 2-km radius). The inhabitants of these villages have a similar socioeconomic level, standard of living, and occupations. All the villages in the area have been observed for many years by the same medical staff, ensuring a higher reliability of medical diagnosis.

To determine the relative contribution of the environment, we compared the rate of asthma and allergy among the Cochin population living in the Jerusalem mountain area with the rate of those living in the desert area.

Statistical Analysis

The different groups (Cochin/non-Cochin and desert/mountain) were compared using the *t* test for continuous variables and the χ^2 test for categorical variables; all statistical tests were 2-tailed. Logistic regression was used to control for age and sex, which are potential confounders. Data analysis was performed with SPSS for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

The study population included 834 individuals (50.7% females), composing 71% of the total village population, who were Cochin Jews according to our definition and who completed the questionnaire. A total of 481 subjects lived in the Jerusalem mountain area and 353 lived in the desert. Their mean (SD) age was 32.7 (20.9) years (median, 31 years;

range, 1–92 years), with an abnormal age distribution showing 2 peaks, at age 10 to 15 years and 40 to 45 years.

Overall, among the Cochin Jewish population, the prevalence of asthma was 23.7%; and of allergy, 29.5% (Table 1). There was no sex difference in the prevalence of asthma (males, 25.3%; females, 22.2%). Ninety-eight individuals (11.8%) reported a smoking history (20.0% males and 4.1% females, $P < .001$) and were not included; 99 individuals (11.9%) reported respiratory symptoms that were not classified as asthma according to our criteria. The mean (SD) age at onset of asthma was lower for the total Cochin study population compared with non-Cochin controls (23.6 [2.5] years vs 38.1 [4.9] years; $P = .02$). In the desert, 58% developed asthma before the age of 5 years compared with only 31% in the mountains ($P = .002$). Because a higher rate of allergic asthma was detected in the mountain area (results given later), our results suggest that prolonged exposure to allergens is necessary to develop allergic asthma.

As indicated in Table 1, the prevalence of allergic asthma (defined as individuals with both asthma and allergy) was significantly higher than that of nonallergic asthma (defined as individuals with asthma who did not have symptoms of allergy) (14.0% vs 9.7%; $P > .001$).

Asthma and Allergy Prevalence Among Cochin and Non-Cochin Jews: The Contribution of Genetic Factors

To determine if the Cochin Jews show an increased prevalence of asthma and allergy, they were compared with non-Cochin Jews ($n = 149$) living in the Jerusalem mountain area. The rate of asthma among the Cochin Jews in this area was 27.4%, significantly higher than that of 8.7% among the control non-Cochin Jews; the odds ratio (OR) was 3.4 (95% confidence interval [CI], 2.1–5.7; $P < .001$), using logistic regression, controlled for age and sex. The increased rates of asthma among Cochin Jews were mainly due to a higher prevalence of allergic asthma (18.7% vs 4.7%; OR, 3.9; 95% CI, 2.0–7.7; $P < .001$). The rate of nonallergic asthma was 9.7% compared with 4.0% among non-Cochin Jews (OR, 2.2; 95% CI, 1.0–4.8; $P = .08$) (Table 1).

Similarly, the allergy rate was significantly higher among Cochin Jews compared with non-Cochin Jews (34.5% vs 6.7%; OR, 6.99; 95% CI, 3.95–12.30; $P < .001$). The rate of allergy without asthma was 15.8% among Cochin Jews compared with 2.0% among non-Cochin Jews (OR, 10.2; 95% CI, 3.2–32.7; $P < .001$). Overall, 43.2% of Cochin Jews in this area experienced allergy and/or asthma, significantly more than the 10.7% of non-Cochin Jews (OR, 5.96; 95% CI, 3.7–9.5; $P < .001$). All results are controlled for age and sex.

Asthma and Allergy Prevalence Among Cochin Jews Living in Different Areas: The Relative Contribution of Environmental Factors

The rate of asthma among the Cochin Jews living in the Jerusalem mountain area was significantly higher than that of Cochin Jews living in the desert (27.4% vs 18.7%; OR, 1.7; 95% CI, 1.3–2.2; $P = .003$). The increased rates were mainly because of the higher prevalence of allergic asthma: 18.7% in the Jerusalem mountain area compared with 7.6% in the desert (OR, 2.7; 9% CI, 1.9–4.0; $P < .001$). The rate of nonallergic asthma was similar for both environments (ie, 8.7% vs 11.0%; OR, 1.3; 95% CI, 0.90–1.98; $P = .26$) (Table 1).

The rate of allergy among Cochin Jews living in the Jerusalem mountains was 34.5%, significantly higher compared with 22.7% among Cochin Jews living in the desert (OR, 1.78; 95% CI, 1.36–2.32; $P < .001$). The rate of allergy without asthma was similar for both environments: 15.8% in the Jerusalem mountains and 15.0% in the desert (OR, 1.05; 95% CI, 0.72–1.55; $P = .76$).

Overall, 43.2% of Cochin Jews living in the Jerusalem mountains experienced allergy and/or asthma, significantly more than the 33.7% of Cochin Jews living in the desert (OR, 1.50; 95% CI, 1.18–1.90; $P = .006$). All results are controlled for age and sex.

DISCUSSION

Both asthma and atopy show a strong genetic component that follows a complex mode of inheritance, involving interac-

Table 1. Prevalence of Asthma and Allergy Phenotypes Among Cochin and Non-Cochin Jews Living in Different Geographic Areas^a

Variable	Cochin group				Non-Cochins living in Jerusalem mountains (n=149)	
	Total (N=834)	P value ^b	Those living in the desert (n=353)	P value ^c	Those living in Jerusalem mountains (n=481)	
Age, mean (SD), y	31.6 (20.3)	.002	31.1 (20.3)	.49	32.1 (20.3)	38.3 (23.6)
Asthma total	198 (23.7)	<.001	66 (18.7)	.003	132 (27.4)	13 (8.7)
Nonallergic asthma	81 (9.7)	.02	39 (11.0)	.26	42 (8.7)	6 (4.0)
Allergic asthma	117 (14.0)	.002	27 (7.6)	.001	90 (18.7)	7 (4.7)
Allergy total	246 (29.5)	<.001	80 (22.7)	.001	166 (34.5)	10 (6.7)
Allergy with no asthma	129 (15.5)	<.001	53 (15.0)	.76	76 (15.8)	3 (2.0)
Allergy and/or asthma	327 (39.2)	<.001	119 (33.7)	.005	208 (43.2)	16 (10.7)

^a Data are given as number (percentage) of each group unless otherwise indicated.

^b Comparison between total Cochins and non-Cochins living in the Jerusalem mountain area.

^c Comparison between Cochins living in the desert and Cochins living in the Jerusalem mountain area.

tions between exogenous environmental factors and genetically determined endogenous factors with complex genetic inheritance.³⁻¹⁰ By controlling for the environment and comparing the rates of asthma and allergy among Cochin Jews with Jews of different ethnic origins who lived in the same environment, we found a 3.4-fold increased risk for asthma and a 6.99-fold increased risk for allergy in Cochin Jews. These figures may determine the relative contribution of the genetic factors for asthma and allergy in this population. It is unclear if this value is similar in other populations. Lebowitz et al¹⁹ examined the genetic background for asthma in 344 families in Arizona. In families in which neither parent had asthma, 6% of the children had the disease; in those with 1 asthmatic parent, 20% of the children had asthma; and in families with 2 parents who had asthma, 60% of the children were asthmatic.¹⁹ Using data from monozygotic and dizygotic twins, estimates of heritability of asthma liability have been reported to be as high as 60% to 70%.^{20,21}

Asthma is generally divided into 2 major phenotypes, allergic asthma and nonallergic asthma, which was confirmed by our study. Although both types may share common immunopathologic mechanisms, nonallergic asthma was constantly shown to have a highly distinct phenotype.^{24,25} Patients with allergic and nonallergic asthma differ by many biological parameters (eg, C-reactive protein levels,²⁶ responsiveness to cold air,²⁷ patterns of T-cell activation, and cytokine production²⁸). By controlling for the genetic factor and comparing Cochin Jews who live in the mountains with those who live in the desert, we found that the prevalence of allergic asthma was much higher among individuals living in the mountains (OR, 2.7), whereas the prevalence of nonallergic asthma was comparable in both environments (OR, 1.3). Similar results were found for nonasthmatic allergy. This indicates that both nonallergic asthma and allergy without asthma are distinct phenotypes, defined mostly by genetic factors, and are less environmentally dependent.

Sensitizing allergens in the desert may be different from those in the mountains. Although the allergen *Alternaria* was shown to play a major role in the development of asthma in children raised in a desert environment,²⁹ horticulture and air conditioning are changing the environment, and allergens such as house dust mite and local pollens are more common risk factors for asthma and allergy in desert climates.^{30,31} In desert countries, the prevalence of asthma and allergy is increasing and approaches that of temperate climate areas. In countries such as Kuwait, Qatar, and Saudi Arabia, asthma used to be rare; however, its incidence is rapidly increasing. Urbanization, increased use of air conditioners, sandstorms, and pollens from imported plants are all thought to be contributing factors.³²⁻³⁴ In our study, the desert environment lowered the probability for allergic asthma from 18.7% to 7.6%, but did not influence nonallergic asthma and/or nonasthmatic allergy.

The situation in which a closed population has changed its environment and resettled in 2 different climatic areas is unique. The different reactions to these environments can

be attributed to the environmental component because we assume that all individuals share the same genetic components. The different climate does not influence the nonallergic phenotype.

The older members of the Cochin population do not recall asthma cases while living in India and confirmed that it developed only years after settling in Israel. Similarly, in immigrants to Australia from southeast Asian countries during the past 20 years an increase in asthma and allergic disease was observed. Epidemiologic data showed that the prevalence rates of asthma and allergic disease increased with the duration of residence in Australia; after 10 years, up to 60% of southeast Asian immigrants developed hay fever while 15% showed symptoms of asthma, suggesting that the environment plays an important role in the pathogenesis of asthma and allergy. With respect to nonallergic asthma, the prevalence was similar in the different environments.³⁵ This suggests that even nonallergic asthma, although genetically determined, may require an external trigger. Although sensitization to inhalant allergens, such as house dust mite and grass pollen, is apparently important, other yet undefined local factors are likely to contribute significantly to the overall increase in prevalence.

Another result of our study is the finding that genetics exerts a strong impact on allergy, which was already implicated at the beginning of the 20th century, after the observations that allergic subjects had a significantly higher incidence of family histories of disease compared with controls. Follow-up studies have shown that if 1 parent has allergies, a child has a 33% chance of developing allergies and if 2 parents are allergic the chance increases to 70%.²² Analysis of several hundred pairs of twins clearly showed that quantifiable traits associated with allergic diseases, such as total serum IgE levels, skin test results, and methacholine sensitivity in the lungs, show intrapair correlation coefficients 2-fold higher for monozygotic than dizygotic twins.²³ Comparing the rates of allergic asthma of Cochin Jews with those of non-Cochin Jews exposed to a similar environment showed a 3.9-fold increased risk for allergic asthma and a 2.4-fold increased risk for nonallergic asthma in Cochin Jews. Likewise, the relative risk for allergy development without asthma was 10.2-fold higher among Cochin Jews. These results point to a clear genetic impact on the development of asthma and allergy in this population and define the relative effect of the genetic factor. Further studies in different populations are needed to define the relative risk of genetic factors on the development of asthma and allergy.

This study has several limitations, mainly the definitions of asthma and allergy that were based on subjective report and not objective evidence. Also, no information is available for nonresponders.

The results of this study demonstrate 2 different asthma and allergy phenotypes that have distinct genetic backgrounds and different environmental influences. The results show that allergic asthma is strongly determined by both genetic and environmental factors and that nonallergic

asthma or atopy without asthma is determined mainly by genetic factors and is less influenced by environmental factors. Studies using large or closed populations to identify genetic markers for asthma or allergy should, therefore, classify the patients according to the different phenotypes before performing statistical analysis.

ACKNOWLEDGMENTS

We thank Arthur Slutsky, MD, St Michael's Hospital, and Noe Zamel, MD, Toronto General Hospital, Toronto, Ontario, Canada, for their support of the initiation of this study; A. Karni, MD, I. Moran, MD, and J. Shabi, MD, for their care of the patients; and R. Cayam, MD, for helpful comments.

REFERENCES

1. Beasley R, Ellwood P, Asher I. International patterns of the prevalence of pediatric asthma: the ISAAC program. *Pediatr Clin North Am*. 2003;50:539–553.
2. Rees J. ABC of asthma prevalence. *BMJ*. 2005;20:443–445.
3. von Mutius E. Environmental factors influencing the development and progression of pediatric asthma. *J Allergy Clin Immunol*. 2002;109(suppl):S525–S532.
4. von Mutius E, Martinez FD, Fritsch C, et al. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med*. 1994;149(pt 1):358–364.
5. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355:2226–2235.
6. Alfvén T, Braun-Fahrlander C, Brunekreef B, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle: the PARSIFAL study. *Allergy*. 2006;61:414–421.
7. Custovic A, Simpson A. Environmental allergen exposure, sensitization and asthma: from whole populations to individuals at risk. *Thorax*. 2004;59:825–827.
8. Carroll W. Asthma genetics: pitfalls and triumphs. *Paediatr Respir Rev*. 2005;6:68–74.
9. Blumenthal MN. Genetics of asthma and allergy. *Allergy Asthma Proc*. 2000;21:55–59.
10. Hall IP. The genetics of asthma: candidate gene approaches: gene-environmental interactions. *Clin Exp Allergy*. 1998;28(suppl 1):74–76.
11. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun*. 2006;7:95–100.
12. Castro-Giner F, Kauffmann F, de Cid R, Kogevinas M. Gene-environment interactions in asthma. *Occup Environ Med*. 2006;63:776–786, 761.
13. Cookson W. The alliance of genes and environment in asthma and allergy. *Nature*. 1999;402(suppl):B5–B11.
14. Marks GB. Environmental factors and gene-environment interactions in the aetiology of asthma. *Clin Exp Pharmacol Physiol*. 2006;33:285–289.
15. Ober C, Cox NJ. The genetics of asthma: mapping genes for complex traits in founder populations. *Clin Exp Allergy*. 1998;28(suppl 1):101–105; discussion, 108–110.
16. Ober C, Cox NJ, Abney M, et al. Genome-wide search for asthma susceptibility loci in a founder population: the Collaborative Study on the Genetics of Asthma. *Hum Mol Genet*. 1998;7:1393–1398.
17. Ober C, Tsalenko A, Parry R, et al. A second-generation genome wide screen for asthma-susceptibility alleles in a founder population. *Am J Hum Genet*. 2000;67:1154–1162.
18. Zamel N, McClean PA, Sandell PR, et al; University of Toronto Genetics of Asthma Research Group. Asthma on Tristan da Cunha: looking for the genetic link. *Am J Respir Crit Care Med*. 1996;153(pt 1):1902–1906.
19. Lebowitz MD, Barbee R, Burrows B. Family concordance of IgE, atopy, and disease. *J Allergy Clin Immunol*. 1984;73:259–264.
20. Duffy DL, Martin NG, Battistutta D, et al. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis*. 1990;142:1351–1358.
21. Koppelman GH, Los H, Postma DS. Genetic and environment in asthma: the answer of twin studies. *Eur Respir J*. 1999;13:2–4.
22. Coca AF, Cooke R. On the classification of the phenomenon of hyper-sensitiveness. *J Immunol*. 1923;8:163–182.
23. Hopp RJ, Bewtra AK, Watt GD, et al. Genetic analysis of allergic disease in twins. *J Allergy Clin Immunol*. 1984;73:265–270.
24. Romanet-Manent S, Charpin D, Magnan A, et al. Allergic vs nonallergic asthma: what makes the difference? *Allergy*. 2002;57:607–613.
25. Jayaratnam A, Corrigan CJ, Lee TH. The continuing enigma of non-atopic asthma. *Clin Exp Allergy*. 2005;35:835–837.
26. Olafsdottir IS, Gislason T, Thjodleifsson B, et al. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax*. 2005;60:451–454.
27. Ludviksdottir D, Janson C, Björnsson E, et al. Different airway responsiveness profiles in atopic asthma, nonatopic asthma, and Sjögren's syndrome. *Allergy*. 2000;55:259–265.
28. Walker C, Bode E, Boer L, et al. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis*. 1992;145:109–115.
29. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med*. 1997;155:1356–1361.
30. Dowaisan A, Al Ali S, Khan M, et al. Sensitization to aeroallergens among patients with allergic rhinitis in a desert environment. *Ann Allergy Asthma Immunol*. 2000;84:433–438.
31. Ezeamuzie CI, Thomson MS, Al Ali S, et al. Asthma in the desert: spectrum of the sensitizing aeroallergens. *Allergy*. 2000;55:157–162.
32. Strannegard IL, Strannegard O. Asthma and serum IgE levels in children in a desert country. *Int Arch Allergy Appl Immunol*. 1987;82:553–554.
33. Bener A, al-Jawadi TQ, Ozkaragoz F, et al. Bronchial asthma and wheeze in a desert country. *Indian J Pediatr*. 1993;60:791–797.
34. Sattar HA, Mobayed H, al-Mohammed AA, et al. The pattern of indoor and outdoor respiratory allergens in asthmatic adult patients in a humid and desert newly developed country. *Allerg Immunol (Paris)*. 2003;35:300–305.
35. Leung RC, Carlin JB, Burdon JG, et al. Asthma, allergy and atopy in Asian immigrants in Melbourne. *Med J Aust*. 1994;161:418–425.

Requests for reprints should be addressed to:
Eitan Kerem, MD
Department of Pediatrics
Hadassah-Hebrew University Medical Center
Mount Scopus
91240 Jerusalem, Israel
E-mail: kerem@hadassah.org.il