

Skin reactivity to inhalant allergens, total serum IgE levels, and bronchial responsiveness to methacholine are increased in parents of nonatopic asthmatic children

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Background: Family studies suggest that asthma has an increased familial occurrence, but the hypothesis of a genetic predisposition to IgE response and bronchial hyperresponsiveness (BHR) on the expression of nonatopic asthma is controversial.

Objective: The aim of this study was to evaluate familial predisposition to IgE response and BHR on expression of nonatopic asthma.

Methods: One hundred four parents of nonatopic asthmatic children, 154 parents of atopic asthmatic children, 78 parents of atopic nonasthmatic control children, and 80 parents of nonatopic control children provided questionnaire data and underwent allergy skin prick tests with 10 inhalant allergens and methacholine bronchial provocation tests. Total serum IgE levels were determined in 352 parents (134 with atopic asthmatic children, 87 with nonatopic asthmatic children, 65 with atopic control children, and 66 with nonatopic control children).

Results: Prevalence of asthma, based on questionnaire data and on BHR to methacholine, was higher among parents of nonatopic asthmatic children (10.6%) and atopic asthmatic children (9.1%) than among those of nonatopic control children (1.3%). BHR to methacholine was higher among parents of nonatopic asthmatic children (19.2%) and atopic asthmatic children (16.2%) than among those of atopic and nonatopic control children (5.1% and 1.3%, respectively). The percentage of positive skin test responses to 10 inhalant allergens was higher among parents of atopic asthmatic children (43.9%), nonatopic asthmatic children (39.4%), and atopic control children (38.5%) than among those of nonatopic control children (23.7%). Geometric means (IU/mL $\pm$ SEM) of total serum IgE were higher among parents of atopic and nonatopic control

children than among those of nonatopic control children (2.11 ± 0.05 vs 2.20 ± 0.06 vs 2.09 ± 0.07 vs 1.92 ± 0.06).

Conclusion: Nonatopic asthma runs in families. The prevalence of positive skin test responses to inhalant allergens, BHR to methacholine, and total serum IgE levels is higher among the parents of nonatopic and atopic asthmatic children than among those of nonatopic control children. (*J Allergy Clin Immunol* 1999;104:311-6.)

Key words: Nonatopic, asthma, skin reactivity, bronchial responsiveness, total serum IgE

Asthma is associated with eosinophil-rich inflammation of the bronchial mucosa.¹ IgE-mediated release of mediators from sensitized cells is believed to play a role in the pathogenesis of this inflammation because exposure of sensitized atopic asthmatic subjects to allergens causes immediate and late bronchoconstriction, as well as bronchial hyperresponsiveness (BHR),² whereas removal of such subjects from allergen exposure ameliorates the disease.³ However, some patients with asthma are not demonstrably atopic, and therefore it has been suggested that atopic and nonatopic variations of the disease may exist.⁴

Subjects with nonatopic (so-called "intrinsic") asthma have negative skin test responses to common inhalant allergens. It is uncertain whether these patients represent asthma with a different mechanism or similar immunopathology with allergy to an as yet undetected allergen. It has been shown in epidemiologic study⁵ that, irrespective of atopic status, total serum IgE concentrations relate closely to the prevalence of self-reported asthma, suggesting that IgE-mediated mechanisms may play a role in nonatopic asthma despite the fact that these patients have no detectable allergen-specific IgE. Moreover, recent reports^{6,7} that there were increased numbers of cells expressing the high-affinity IgE receptor and an increase in expression of IL-4 and IL-5 mRNA and protein in bronchial biopsy specimens from atopic and nonatopic asthmatic subjects suggest that IgE-mediated mechanisms may participate in the pathogenesis of both atopic and nonatopic asthma.

Atopic and nonatopic asthmatic subjects have been shown to differ in their personal and family history of allergy and their age of onset.⁸⁻¹⁰ These differences suggest that the 2 forms of asthma may be genetically distinct. A number of studies¹¹⁻¹³ showed that the risk of

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Abbreviations used

BHR: Bronchial hyperresponsiveness
 DRS: Slope of dose-response curve
 MBPT: Methacholine bronchial provocation test
 SPT: Skin prick test

asthma in offspring was higher when one or both parents had asthma than when neither parent was affected. Family and twin studies,^{14,15} however, suggest that regardless of its clinical presentation, asthma has an increased familial occurrence.

BHR and IgE response are intermediate phenotypes in the development of asthma.¹⁶ Compared with normal subjects, the bronchi of asthmatic individuals tend to have both a decreased stimulus threshold and an increased response for bronchoconstriction. Family studies^{17,18} have shown that there is an increased prevalence of BHR among the relatives of asthmatic subjects compared with nonasthmatic individuals. It has been shown that there is a close association between atopic status and the presence of asthma⁵ and between the atopic status of asthmatic patients and the risk of asthma in their relatives.^{9,14} However, there have been few studies dealing with familial influence of IgE response and BHR on the expression of nonatopic asthma.

To evaluate familial aggregation of nonatopic asthma, IgE response, and bronchial responsiveness, the prevalence of asthma, BHR to methacholine, skin response to inhalant allergens, and total serum IgE levels were measured in parents of nonatopic and atopic asthmatic children and atopic and nonatopic control children.

METHODS

Probands were recruited consecutively in 1996 from children between 6 and 14 years of age who were attending the pediatric clinic at Seoul National University Children's Hospital. Asthmatic children had a history of episodic wheezing or breathlessness and showed reversible airway obstruction on treatment with a bronchodilator (more than 15% of predictive value of FEV₁) or BHR to methacholine (PC₂₀ methacholine <12 mg/mL). None of the nonasthmatic control subjects who visited the clinic because of problems unrelated to allergy had a clinical history of asthma, allergic rhinitis, and atopic dermatitis, and physical examination and spirometry had been normal at the time of the clinic visits. Skin prick tests (SPTs) to 10 inhalant allergens common in Korea were performed on all the children to evaluate atopic status. Atopy was defined as a positive reaction (allergic/histamine ratio ≥ 1.0) to 1 or more of the 10 inhalant allergens.

Both natural parents of these probands (77 atopic asthmatic children, 54 nonatopic asthmatic children, 40 atopic control children, and 41 nonatopic control children) were asked if they would participate in the study. Two fathers and 2 mothers of nonatopic asthmatic children, 1 parent of an atopic control child, and 1 parent of a nonatopic control child declined to participate. Parents provided questionnaire data, underwent methacholine bronchial provocation tests (MBPTs) and SPTs with 10 common inhalant allergens, and gave blood specimens for the measurement of total serum IgE. The study protocol was approved by the hospital ethics committee.

All the parents responded to a questionnaire, which was developed from the Respiratory Disease Questionnaires of the American Thoracic Societies.¹⁹ The questionnaire was translated into Korean

and contained questions regarding demographic data, smoking history, and medical history, with a focus on asthmatic symptoms (paroxysmal cough, wheezing, nocturnal dyspnea, and dyspnea at rest) and chronic nasal symptoms (sneezing, watery rhinorrhea, nasal itching, and nasal obstruction). The parents were assumed to have symptoms of asthma or rhinitis if they had experienced 2 or more asthmatic or chronic nasal symptoms.

All of the parents underwent MBPTs. At the time of the study, all had been free of acute respiratory tract infection for 4 weeks, and subjects who required medications were required to stop using bronchodilators or other medications for 3 days and topical corticosteroids or cromolyn for 7 days before the test. FEV₁ was measured with a computerized spirometer (Multispiro-SX, Irvine, Calif), and the largest value of triplicate FEV₁ was adopted. MBPTs were carried out by using the modified method of Chai et al.²⁰ Concentrations of 1.25, 2.5, 6.25, 12.5, and 25 mg/mL methacholine were prepared by dilution with buffered saline. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Md) was used to deliver the aerosol generated by a DeVilbiss 646 nebulizer. Subjects inhaled 5 breaths of increasing concentrations of methacholine until FEV₁ fell by more than 20% of its basal value or the highest concentration was reached. The largest value of triplicate FEV₁ at 90 or 180 seconds after each inhalation was adopted for analysis. If PC₂₀ was less than 25 mg/mL, a subject was considered to have BHR to methacholine. The slope of the dose-response curve (DRS), defined as the percentage fall in FEV₁ at the last dose divided by the log of the total dose (mg/mL) administered, was calculated for a continuous index of bronchial responsiveness to methacholine.²¹ A diagnosis of asthma was made if parents indicated asthmatic symptoms on the questionnaire and showed BHR to methacholine.

All the parents underwent SPTs with a panel of 10 allergens (Bencard Co) common in Korea. None of the subjects had received antihistamines orally for 3 days preceding the study. The panel included house dust mite (*Dermatophagoides pteronyssinus*, *D farinae*), cat fur, mold (*Aspergillus* spp, *Alternaria* spp), pollen (tree pollen mixture, grass pollen mixture, mugwort, and ragweed), and cockroach allergens. A positive control of histamine (1 mg/mL), along with a negative diluent control, was included in all tests. After 15 minutes, the mean diameter of a wheal formed by the allergen was compared with that formed by histamine. If the former was the same or larger than the latter (A/H ratio ≥ 1.0), the reaction was deemed to be positive. The skin index was defined as the total number of allergens to which each subject had a positive response.²² A diagnosis of allergic rhinitis was made if parents indicated the presence of rhinitic symptoms on the questionnaire and had a positive SPT response to 1 or more of 10 inhalant allergens.

Total serum IgE levels were determined by ELISA in 175 probands (64 atopic asthmatic children, 46 nonatopic asthmatic children, 33 atopic control children, and 32 nonatopic control children) and 352 parents (134 parents of atopic asthmatic children, 87 parents of nonatopic asthmatic children, 65 parents of atopic control children, and 66 parents of nonatopic control children). Polypropylene 96-well microtiter plates were precoated overnight at 4°C with mouse monoclonal anti-human IgE (Sigma Chemical, St Louis, Mo) in carbonate buffer of 1:3000 titer and washed 3 times with 10 mmol/L PBS containing Tween-20 (0.05% Tween-20/PBS, pH 7.4). After washing, 3% BSA (Sigma) in 0.05% Tween-20/PBS was added, and the plate was incubated for 1 hour to eradicate any non-specific background reaction. This was followed by 3 washes with 0.05% Tween-20/PBS, and 100 μ L of serum diluted 10-fold was added to each well in duplicate for a 2-hour incubation period. After another 3 washes, peroxidase-conjugated anti-human IgE (optimally diluted at 1:1000 in 0.1% BSA/0.05% Tween-20/PBS) was added to each well and incubated for 1 hour at room temperature. After 5

TABLE I. Clinical characteristics of probands

	Asthmatic subjects		Control subjects	
	Atopic	Nonatopic	Atopic	Nonatopic
No.	77	54	39	40
Sex (M/F)	42/35	30/24	23/16	24/16
Age, y (mean [range])	8.9 (6-14)	9.0 (6-14)	9.0 (7-14)	9.1 (7-14)
Log IgE, IU/mL (mean $\pm$ SEM)	2.57 $\pm$ 0.06*	2.01 $\pm$ 0.07†	2.56 $\pm$ 0.06*	1.51 $\pm$ 0.13

* $P < .01$ compared with nonatopic asthmatic and control subjects.

† $P < .01$ compared with nonatopic control subjects.

TABLE II. Prevalence of asthma and allergic rhinitis in parents

	Parents of asthmatic children		Parents of control children	
	Atopic	Nonatopic	Atopic	Nonatopic
No.	154	104	78	80
Fathers	77	52	39	40
Mothers	77	52	39	40
Age, y (mean [range])	36.4 (30-49)	36.5 (29-52)	37.2 (26-55)	37.5 (27-58)
Fathers	37.7 (32-49)	37.8 (31-52)	38.2 (29-55)	38.4 (29-58)
Mothers	35.2 (30-47)	35.3 (29-50)	35.6 (26-51)	35.7 (27-55)
Smokers (%)	32.4	32.6	29.4	38.7
Fathers	63.6	65.3	58.9	70.0
Mothers	1.3	0	0	7.5
Asthmatic symptoms	22 (14.3%)*	21 (20.2%)*	6 (7.7%)	7 (8.8%)
Fathers	10 (13.0%)*	10 (19.2%)*	3 (7.7%)	2 (5.0%)
Mothers	12 (15.9%)*	11 (21.2%)*	3 (7.7%)	5 (12.5%)
Asthma	14 (9.1%)*	11 (10.6%)*	4 (5.1%)	1 (1.3%)
Fathers	5 (6.5%)*	7 (13.5%)*	1 (2.6%)	1 (2.6%)
Mothers	9 (11.9%)*	4 (7.7%)*	3 (7.7%)*	0
Rhinitic symptoms	53 (34.4%)*	24 (23.1%)	18 (23.1%)	12 (15%)
Fathers	24 (31.2%)*	12 (23.1%)	8 (20.5%)	8 (20%)
Mothers	29 (37.7%)*	12 (23.1%)	10 (25.6%)	4 (10%)
Allergic rhinitis	34 (22.4%)*	13 (13%)*	8 (10.5%)*	3 (3.8%)
Fathers	15 (20%)*	8 (16%)*	5 (13.2%)*	2 (5.1%)*
Mothers	19 (24.7%)*	5 (9.6%)*	3 (7.8%)*	1 (2.5%)*

Symptoms of asthma or rhinitis were defined as the presence of 2 or more asthmatic or chronic nasal symptoms on a questionnaire. Asthma was defined as positive asthmatic symptoms and BHR to methacholine. Allergic rhinitis was defined as positive rhinitic symptoms and positive skin responses to 1 or more inhalant allergens.

* $P < .05$ compared with nonatopic control subjects.

† $P < .01$ compared with nonatopic control subjects.

‡ $P < .05$ compared with atopic asthmatic subjects.

washes, 100 μ L of *o*-phenylenediamine dihydrochloride (Sigma) was added to each well. The plate was incubated at 37°C for 1 hour, and the reaction was terminated by the addition of 100 μ L of 3 mol/L H₂SO₄. Optical density was determined at 490 nm in a Ceres 900 ELISA microtiter plate reader (Bio-Tek Instruments). Each sample was assayed in duplicate, and the mean of the results for each sample was taken. The minimum level of detection was 4 IU/mL. The coefficient of variation between assays was 13%.

Statistical analysis

Results were expressed as means $\pm$ SEM unless otherwise indicated. The chi-square test and ANOVA with unpaired *t* tests were used to assess differences between the groups. Correlation between continuous variables was assessed by a simple regression test. A *P* value of .05 or less was regarded as significant.

RESULTS

Two hundred ten probands and their 420 natural parents participated in the study. The probands were divided

into 4 groups (77 atopic asthmatic children, 54 nonatopic asthmatic children, 39 atopic control children, and 40 nonatopic control children) according to whether asthma and positive SPT responses to common inhalant allergens were present. Table I summarizes the clinical characteristics of the probands. For the probands, mean age and sex ratio did not differ among the 4 groups. Geometric mean (IU/mL) of total serum IgE levels was higher among atopic asthmatic subjects and control subjects than among nonatopic asthmatic subjects and control subjects, but they were higher among nonatopic asthmatic subjects than among nonatopic control subjects (2.57 $\pm$ 0.06 vs 2.01 $\pm$ 0.07 vs 2.56 $\pm$ 0.06 vs 1.51 $\pm$ 0.13).

Table II summarizes the clinical characteristics of the parents. Parents of atopic and nonatopic asthmatic children and atopic and nonatopic control children consisted of 77 fathers and 77 mothers with a mean age of 36.4 years (range, 30 to 49 years), 52 fathers and 52 mothers

TABLE III. Bronchial responsiveness to methacholine, skin reactivity to inhalant allergens, and total serum IgE levels in parents

	Parents of asthmatic subjects		Parents of control subjects	
	Atopic (n = 154)	Nonatopic (n = 104)	Atopic (n = 78)	Nonatopic (n = 80)
Basal FEV ₁ (% pred)	94.4 ± 0.8	94.9 ± 0.9	97.0 ± 1.6	94.6 ± 1.2
Fathers	94.3 ± 1.2	94.6 ± 1.4	98.9 ± 2.3	94.7 ± 1.7
Mothers	94.5 ± 0.9	95.1 ± 1.1	95.5 ± 1.9	94.8 ± 1.6
BHR	25 (16.2%)*	23 (22.1%)*	4 (5.1%)	1 (1.3%)
Fathers	12 (15.6%)*	11 (21.2%)*	1 (2.7%)	1 (2.5%)
Mothers	13 (16.9%)†	12 (23.0%)†	3 (7.7%)	0
DRS	8.95 ± 2.42†	9.40 ± 0.52†	4.06 ± 0.48	1.94 ± 0.38
Fathers	10.65 ± 4.79	8.96 ± 0.71	3.68 ± 0.64	2.25 ± 0.59
Mothers	7.25 ± 0.75*	9.84 ± 0.76‡	4.44 ± 0.71†	1.62 ± 0.47
Positive skin responses	66 (42.9%)†	41 (39.4%)†	30 (38.5%)†	19 (23.7%)
Fathers	38 (49.4%)†	22 (42.3%)	18 (46.2%)	10 (25.0%)
Mothers	28 (36.4%)	19 (36.5%)	12 (30.8%)	9 (22.5%)
Log IgE, IU/mL (mean ± SEM)	2.11 ± 0.05†	2.20 ± 0.06†	2.09 ± 0.07	1.92 ± 0.06
Fathers	2.19 ± 0.06	2.38 ± 0.08†	2.30 ± 0.09	2.13 ± 0.06
Mothers	2.02 ± 0.06†	2.03 ± 0.07†	1.88 ± 0.08	1.73 ± 0.07

BHR is defined as a PC₂₀ of less than 25 mg/mL; DRS is defined as a percent fall of FEV₁ divided by log of total concentration of methacholine (mg/mL).

**P* < .05 compared with parents of atopic and nonatopic control subjects.

†*P* < .05 compared with parents of nonatopic control subjects.

‡*P* < .05 compared with parents of atopic asthmatic subjects and atopic and nonatopic control subjects.

with a mean age of 36.5 years (range, 29 to 52 years), 39 fathers and 39 mothers with mean age of 37.2 years (range, 26 to 55 years), and 40 fathers and 40 mothers with a mean age of 37.5 years (range, 27 to 58 years), respectively. Smoking history of the parents was not statistically different among the 4 groups (32.4% vs 32.6% vs 29.4% vs 38.7%). With regard to asthmatic symptoms on the questionnaire, the prevalence was higher among parents of atopic (14.3% [22 of 154]) and nonatopic asthmatic children (20.2% [21 of 104]) than among those of nonatopic control children (8.8% [7 of 80]). The prevalence of asthma, based on positive asthmatic symptoms and on BHR to methacholine, was higher among the parents of atopic (9.1% [14 of 154]) and nonatopic asthmatic children (10.6% [11 of 104]) than among those of nonatopic control children (1.3% [1 of 80]). The prevalence of allergic rhinitis, based on positive rhinitic symptoms and on positive skin responses to allergens, was higher among the parents of atopic (22.4% [34 of 154]) and nonatopic asthmatic children (13% [13 of 104]) than among those of nonatopic control children (3.8% [3 of 80]).

Bronchial responsiveness to methacholine, skin response to inhalant allergens, and total serum IgE levels in the parents are shown in Table III. Basal FEV₁ (percent of predicted value) before the MBPTs did not differ among the 4 groups (94.4% ± 0.8% vs 94.9% ± 0.9% vs 97.0% ± 1.6% vs 94.6% ± 1.2%). The prevalence of BHR was higher among parents of atopic (16.2% [25 of 154]) and nonatopic asthmatic children (22.1% [23 of 104]) than among those of atopic (5.1% [4 of 78]) and nonatopic control children (1.3% [1 of 80]). A similar trend was observed among fathers (15.6% [12 of 77] vs 21.2% [11 of 52] vs 2.7% [1 of 39] vs 2.5% [1 of 40]) and mothers (16.9% [13 of 77] vs 23.0% [12 of 52] vs 7.7% [3 of 39] vs 0%) of the 4 groups. DRS (%/mg/mL) was

higher among parents of atopic (8.95 ± 2.42) and nonatopic asthmatic children (9.40 ± 0.52) than among those of nonatopic control children (1.94 ± 0.38). This figure was marked in the mothers (7.25 ± 0.75 vs 9.84 ± 0.76 vs 1.62 ± 0.47; *P* < .05), although a similar trend was observed in the fathers (10.65 ± 4.79 vs 8.96 ± 0.71 vs 2.25 ± 0.59; *P* > .05).

The prevalence of positive skin responses to inhalant allergens was higher among parents of atopic (42.9% [66 of 154]) and nonatopic asthmatic children (39.4% [41 of 104]) and parents of atopic control children (38.5% [30 of 78]) than among those of nonatopic control children (23.7% [19 of 80]). This trend was more marked among the fathers (42.9% [38 of 77] vs 42.3% [22 of 52] vs 46.2% [18 of 39] vs 25.0% [10 of 40]; *P* < .05) than among the mothers (36.4% [28 of 77] vs 36.5% [19 of 52] vs 30.8% [12 of 39] vs 22.5% [9 of 40]; *P* > .05).

Geometric means (IU/mL) of total serum IgE were higher among parents of atopic and nonatopic asthmatic children than among those of nonatopic control children (2.11 ± 0.06 vs 2.20 ± 0.06 vs 1.92 ± 0.06). When the data for fathers and mothers were analyzed separately, the trend was similar among the fathers (2.19 ± 0.06 vs 2.38 ± 0.08 vs 2.30 ± 0.09 vs 2.13 ± 0.06) and among the mothers (2.02 ± 0.06 vs 2.03 ± 0.07 vs 1.88 ± 0.08 vs 1.73 ± 0.07) of the 4 groups. There was a significant correlation between skin index and geometric value of total serum IgE (correlation coefficient: 0.466, *P* < .001) in the parents.

DISCUSSION

We have found that the prevalence of asthma and allergic rhinitis was higher among parents of nonatopic and atopic asthmatic children than among those of nonatopic

control children. The prevalence of BHR to methacholine was higher among parents of asthmatic children than among those of nonasthmatic control children, irrespective of the atopic status of the probands. The prevalence of positive SPT responses to inhalant allergens was higher among the parents of atopic asthmatic, nonatopic asthmatic, and atopic control children than among those of nonatopic control children, and total serum IgE levels were also higher among parents of atopic and nonatopic asthmatic children than among those of nonatopic control children.

Rackerman²³ suggested in 1918 that asthma can be classified as “intrinsic” (nonatopic) and “extrinsic” (atopic). Atopic asthma is common in children,^{24,25} but many adults and some children have negative skin test responses.²⁶ Danish children with nonatopic asthma were reported to show more hyperinflation, more hospital admissions caused by asthma and/or pneumonia, more elevated serum IgG and IgM, a higher likelihood of bacterial airway infection, and more progression of their disease despite treatment with corticosteroids.²⁶ Atopic and nonatopic asthmatic subjects have been shown to differ in their personal and family history of allergy and their age at onset.⁸⁻¹⁰ Such differences suggest that these 2 forms of asthma may be genetically distinct.

The absence of unambiguous criteria for the diagnosis of asthma is a major obstacle in elucidating the genetic basis of the disease. Although it is generally accepted that episodic wheezing and breathlessness are the principal symptoms of asthma, patients vary so widely in their clinical presentation that it is difficult to find a set of diagnostic criteria that is both comprehensive and exclusive. There have been numerous attempts to develop comprehensive definitions during the last 35 years.^{19,27,28} Although the current definition of asthma now emphasizes the importance of inflammatory mechanisms, this is not often helpful for early diagnosis or for the differentiation of asthma from other closely related conditions.²⁸ Because one uniform phenotype defining asthma may not exist, investigators have used different subjective or more objective definitions for asthma that include a reported diagnosis of asthma before presentation to the physician,⁵ questionnaire data,²⁹ presence of BHR,³⁰ or a combination of the above.³¹ All of these various approaches make it difficult to compare results of different family studies. Because reliance on only subjective information, however, causes limitations such as lack of sensitivity and specificity in the diagnosis of asthma, objective assessment of asthma phenotype is important. In this study diagnosis of asthma was based on questionnaire data and on the presence of BHR in the parents.

It was not until the middle of this century that there was convincing evidence to show that the prevalence of asthma was significantly higher in the relatives of asthmatic patients than in the relatives of a matched group of nonasthmatic subjects.³² A number of studies¹¹⁻¹³ then followed supporting these findings and showing also that the risk of asthma in offspring was higher when one or both parents were asthmatic than when neither parent was

affected. Up to now, however, few studies had provided conclusive evidence that nonatopic asthma runs in families. Sibbald et al³³ claimed that only atopic asthma had a hereditary basis because they observed a higher prevalence of asthma among relatives of atopic than nonatopic asthmatic subjects in the family study. However, because their study did not include a nonasthmatic group, the possibility of familial transmission of nonatopic asthma could not be dismissed. In subsequent studies including a control group,^{14,34} a higher prevalence of asthma was reported among relatives of nonatopic and atopic asthmatic subjects than among those of control subjects. This study also showed that the prevalence of asthma was higher among parents of nonatopic and atopic asthmatic children than among those of nonatopic nonasthmatic control children. This finding suggests that asthma has an increased familial occurrence, irrespective of atopic status.

BHR is a cardinal feature of asthma and may precede the expression of asthma.³⁵ A decrease of FEV₁ greater than 20% is generally accepted as a discriminating end point to separate the normal and hyperresponsive groups; the index PD₂₀ or PC₂₀ are current measures of the bronchial provocation test. Other methods of expressing bronchial responsiveness include DRS²¹ and the bronchial responsiveness index (BRindex), defined as the log of the slope of the percent decline from baseline FEV₁ after the last dose per unit dose of methacholine.³⁶ These latter 2 methods may be more useful in epidemiologic studies because a value can be calculated for the entire sample, even if a subject does not experience a 20% drop in FEV₁. In this study bronchial responsiveness to methacholine was evaluated by a quantitative parameter, DRS, and a qualitative parameter, positive bronchial response to methacholine.

Twin studies³⁷ have suggested that BHR is under strong genetic control. Family studies^{17,18} have shown that there is an increased prevalence of BHR among the relatives of asthmatic subjects compared with nonasthmatic individuals. However, familial predisposition to BHR is controversial on the expression of nonatopic asthma. This study showed that the prevalence of positive bronchial responsiveness and DRS was higher among parents of asthmatic subjects than among those of nonasthmatic subjects, irrespective of atopic status of the probands. This finding suggests that BHR has a familial predisposition on the expression of both atopic and nonatopic asthma.

Nonatopic asthma is considered to be a distinct pathogenetic variant of asthma because, unlike atopic asthma, patients with the disease have negative SPT responses to common inhalant allergens. However, Burrows et al⁵ seriously challenged the concept of intrinsic or nonatopic asthma by reporting that even in adults with negative SPT responses, the prevalence of asthma was closely related to the serum IgE level standardized for age and sex. The finding that serum IgE levels was higher among the atopic and nonatopic asthmatic children than among the nonatopic control children in this study supports the above report, although the value was higher among the

atopic asthmatic subjects than among the nonatopic asthmatic subjects. Furthermore, recent studies^{6,7} have demonstrated that, as compared with nonatopic and nonasthmatic control subjects, bronchial mucosal biopsy specimens from atopic and nonatopic asthmatic subjects had increased numbers of cells expressing the high-affinity IgE receptor and of cells expressing IL-4 and IL-5 mRNA and protein. These findings suggest that asthma is almost always associated with an IgE-related reaction, even if atopy is not detected by skin tests. Pepys⁹ and Sibbald et al¹⁴ showed that there was a close association between the atopic status of asthmatic patients and the risk of asthma in their relatives. However, genetic predisposition to IgE response on the expression of nonatopic asthma has yet to be elucidated. This study showed that skin response to inhalant allergens and total serum IgE levels was higher among the parents of nonatopic and atopic asthmatic children than among those of nonatopic control children. This finding suggests that familial influence of IgE response to allergens has an important role on the development of asthma, irrespective of atopic status.

In conclusion, this study suggests that nonatopic asthma runs in families and IgE response and BHR have a familial predisposition on the expression of nonatopic asthma.

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