

2. Konno A, Togawa K, Hishira S. Seasonal variation of sensitivity of nasal mucosa in pollinosis. *Arch Otorhinolaryngol* 1981;232:253-61.
3. Connel JT. Quantitative intranasal pollen challenge. II. Effect of daily pollen challenge, environmental pollen exposure, and placebo challenge on the nasal membrane. *J Allergy* 1968;41:123-39.
4. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticoids. *N Engl J Med* 1987;316:1506-10.
5. Vilsvik JS, Jenssen AO, Walstad R. The effect of beclomethasone dipropionate aerosol on allergen induced nasal stenosis. *Clin Allergy* 1975;5:291-4.
6. Pipkorn U. Budesonide and nasal allergen testing in man. *Allergy* 1982;37:129-34.
7. Walden SM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Antigen-provoked increase in histamine reactivity: observations on mechanisms. *Am Rev Respir Dis* 1991;3:642-8.
8. Andersson M, Andersson P, Pipkorn U. Allergen-induced specific and non-specific nasal reactions. Reciprocal relationship and inhibition by topical glucocorticosteroids. *Acta Otolaryngol (Stockh)* 1989;107:270-7.
9. Pipkorn U. Budesonide and nasal histamine challenge. *Allergy* 1982;37:359-63.

Relationships of bronchial responsiveness assessed by methacholine to serum IgE, lung function, symptoms, and diagnoses in 11-year-old New Zealand children

Benjamin Burrows, MD,^a Malcolm R. Sears, MB, FRACP, FRCPC,^b
Erin M. Flannery,^c G. Peter Herbison, MSc,^d and
M. David Holdaway MD, FRACP^e

Tucson, Ariz., Hamilton, Ontario, Canada, and Dunedin, New Zealand

The relationship of bronchial responsiveness (BR), assessed by methacholine challenge, to serum IgE, baseline ventilatory function, and symptoms or diagnoses suggesting an atopic disorder were examined in 522 11-year-old New Zealand children. BR was assessed by the presence or absence of a PC₂₀ 25 mg/ml or less and by calculating a continuous index of the decline of the FEV₁ during the methacholine test. The latter facilitated multivariate analyses and revealed significant relationships to predictor variables even in those considered "nonresponsive" by PC₂₀ criteria. There was a close relationship of BR to the baseline FEV₁/vital capacity ratio, seen even in patients with known asthma, but this relationship was seen only in subjects with at least moderate levels of serum IgE. There was a less close relation of BR to percent predicted FEV₁, but this persisted even after accounting for the FEV₁/vital capacity ratio and was present regardless of the level of serum IgE. Reported asthma was associated with increased BR independent of all other factors, but other diagnoses and symptoms contributed relatively little to the prediction of BR once the serum IgE and lung function were taken into account. The overall results are compatible with the concept that IgE is a critical factor in the development of bronchial responsiveness in childhood. (J ALLERGY CLIN IMMUNOL 1992;90:376-85.)

Key words: Asthma, bronchial responsiveness, IgE, lung function

From the Respiratory Sciences Center, University of Arizona College of Medicine, Tucson,^a Firestone Regional Chest and Allergy Unit, St. Joseph's Hospital-McMaster University, Hamilton, Ontario,^b the Departments of Medicine,^c Preventive and Social Medicine,^d and Paediatrics and Child Health,^e University of Otago Medical School, Dunedin, New Zealand.

Data collection and processing in New Zealand supported by grants from the Medical Research Council of New Zealand and the Otago Medical Research Foundation.

Data analyses in Arizona supported by a Specialized Center of

Research Grant from the Lung Division, National Heart, Lung, and Blood Institute (HL-14136).

Received for publication Dec. 30, 1991.

Revised May 20, 1992.

Accepted for publication May 20, 1992.

Reprint requests: Benjamin Burrows, MD, Respiratory Sciences Center, University of Arizona College of Medicine, Tucson, AZ 85724.

1/1/39473

An extensive literature has accumulated on factors related to responsiveness to challenge with bronchoconstrictor agents. It has been shown in different population samples that such responsiveness is related to the baseline level of lung function, allergy skin test reactivity, and the presence of a variety of respiratory symptoms or diagnoses.¹⁻¹⁰

We recently reported that bronchial responsiveness (BR) to methacholine in 11-year-old New Zealand school children is critically dependent on the level of serum IgE, and that this relationship remains even after exclusion of children with any history of an atopic disorder.¹¹ However, this previous article did not consider other factors that might determine BR nor how such factors might interact with serum IgE.

In the present report, we examine the relative importance of serum IgE and baseline lung function, as well as symptoms and diagnoses as correlates of BR; interactions among these various factors are examined. In addition to examining BR in terms of the provoking concentration of methacholine inducing a 20% fall in the FEV₁ (PC₂₀ FEV₁), we have calculated an index of the FEV₁ decline during methacholine challenge. This method of expressing responsiveness provides a continuous variable for BR, allowing a wider range of multivariate analyses. In this data set, a different method of calculating this slope appeared preferable to that previously recommended by O'Connor et al.¹²

PATIENTS IN THE STUDY AND METHODS

The population sample is described in more detail in previous reports.^{11,13} In brief, 784 New Zealand school children of European extraction were seen at age 11 years in the course of a multidisciplinary longitudinal study of a cohort of children born at the only maternity hospital in Dunedin, New Zealand, between April 1, 1972, and March 31, 1973. These 784 children (75.6% of the sample originally enrolled at age 3 years) were representative of the full enrolled sample of 1037 3-year-old children and were also representative of the entire birth cohort of 1661 children in regard to major demographic and socioeconomic variables, except that the few children of non-European extraction have been excluded from the present study. Of the 784 children seen, 562 (71.7%) had blood drawn for IgE determination, a prerequisite for inclusion in the current analyses; permission for venipuncture was refused by the remainder. Of the 562 with serum IgE levels, 539 (95.9%) had either a validated abbreviated methacholine challenge previously described or were tested for bronchodilator response to salbutamol.¹⁴

The study was approved by the Ethics Committee of the Otago Medical Board. Written consent for each procedure was obtained from the parent or guardian; for venipuncture it was also obtained verbally from the children.

Comparisons of these 539 cases with the 245 with less complete testing showed no significant differences in sex distribution or in rates of reported asthma, hay fever,

Abbreviations used

BR:	Bronchial responsiveness
IU:	International units
IgE:	Serum immunoglobulin E as IU/ml
IgIGE:	Log 10 IgE
FEV ₁ :	Forced expired volume in 1 second
VC:	Vital capacity
RATIO:	The FEV ₁ /VC expressed as a percent
PC ₂₀ :	The concentration of methacholine inducing a 20% fall in FEV ₁
BRindex:	The log of the % decline in FEV ₁ /log final methacholine concentration as mg/deciliter after adding 10 to eliminate negative values
IgE*loRAT:	An interaction term, IgE × (100 - RATIO).
noAS*IGE:	An interaction term, with constant for IgE in asthma
CI:	Confidence interval
ANOVA:	Analysis of variance
R:	Correlation coefficient
R ² :	Multiple correlation coefficient

wheeze, or a history of eczema. Of the 245 who declined venipuncture or challenge testing, 231 did perform simple spirometry; their mean forced expired volume in one second (FEV₁) and their mean FEV₁ to vital capacity (VC) ratios (FEV₁/VC) showed no significant differences from the 539 cases with both serum IgE levels and methacholine or salbutamol challenge. Thus no important bias was apparent in the group with both IgE and challenge testing.

However, 17 of the 539 studied cases showed moderately severe baseline airflow obstruction (FEV₁/VC <70% or <75% with very recent symptoms), and for safety and ethical reasons they were given only salbutamol. Although these cases did show a significant improvement with a bronchodilator, their methacholine response was not measured and they were therefore not included in subsequent analyses. These 17 subjects were predominantly male (14 of 17), and most had known asthma (10 of 17). The exclusion of these subjects, who were likely to have marked increases in BR, could minimize any possible relationship of BR to sex in the following analyses, which are limited to the 522 children with methacholine tests and with serum IgE measurements.

The baseline characteristics of these 522 subjects are summarized in Table I. In view of its log-normal distribution, the central tendency of serum total IgE is expressed as a geometric mean, and the base 10 log of serum IgE (IgIGE) is used in all statistical analyses. The values of IgE are expressed as International Units (IU) per milliliter.

Predicted values for the FEV₁ based on height and sex were determined in those subjects without wheezing who denied ever having asthma. These values were used to calculate percent predicted values (percent predicted FEV₁) for all subjects. The ratio of the FEV₁ to the total vital capacity (FEV₁/VC) is expressed as a percent and called RATIO.

The methods for determining PC₂₀ and serum IgE are

TABLE I. Characteristics of study population

Total no. of subjects	522
Age	11 yr
Percent males	53.1%
Reported asthma	9.4%
Reported wheezing	17.4%
Reported hay fever	17.6%
Reported eczema	28.4%
Mean height $\pm$ SD (cm)	142.7 $\pm$ 6.31
Mean FEV ₁ $\pm$ SD (L)	2.22 $\pm$ 0.30
Mean percent predicted FEV ₁ $\pm$ SD (%)	99.20 $\pm$ 9.45
Mean FEV ₁ /VC ratio $\pm$ SD (%)	88.74 $\pm$ 5.42
Mean IgIgE $\pm$ SD (IU/ml)	2.04 $\pm$ 0.68
(Geometric mean IgE)	(109.6)

given in previous reports.¹¹ In brief, the challenge consisted of five deep breaths of methacholine in concentrations of 0.025, 0.25, 2.5, and 25.0 mg/ml. The FEV₁ was measured at 30 and 90 seconds after the inhalations, and the challenge was terminated if the FEV₁ fell more than 20%. The validity of this abbreviated challenge compared with a more conventional test has been demonstrated.¹⁴ Since the maximum concentration of methacholine administered was 25 mg/ml, a PC₂₀ FEV₁ could be calculated only in those with a fall in FEV₁ of at least 20% by the end of the test, as occurred in 16.7% of the subjects. The remaining 83.3% are simply considered nonresponsive by this criterion.

To calculate a continuous index of methacholine responsiveness, the log of the slope of the percent decline from the baseline FEV₁ after the last dose of methacholine per unit concentration of methacholine was calculated, approximating the method of O'Connor et al.¹² Fourteen percent of the subjects showed slight negative slopes (i.e., a slight increase in FEV₁ during serial testing), the most negative value being -0.70% per unit concentration. To permit log transformation, negative declines had to be eliminated, requiring that a constant be added to all of the actual slope values; the addition of a constant was also required in the data of O'Connor et al.¹² The slopes were then log transformed, but the distribution of the resulting log percent decline in baseline FEV₁ per unit concentration of methacholine proved to be very skewed toward the high (more reactive) side; there was even a hint of a bimodal distribution on this side. Also, the addition of a constant to the most negative pre-log value resulted in a low outlier value. Use of 1.0 as the constant added to eliminate negative values resulted in a distribution with a skewness index of 3.5.

We therefore tried a different method of calculating slope, dividing the percent decline in baseline FEV₁ after the last methacholine challenge by the log of the last methacholine concentration given. To avoid negative or zero logarithms in the denominator, all concentrations were expressed as milligrams per deciliter. As an example, if the baseline FEV₁ was 3.40 L, the last concentration given was 25 mg/ml (2500 mg/dl), and the FEV₁ after this dose was 3.10 L, the percent decline in baseline FEV₁ would be $100 \times$

$(3.40 - 3.10)/3.40$, or 8.824%. The log of the last concentration expressed in milligrams per deciliter would be 3.398. Thus the calculated slope would be $8.824/3.398$, or 2.597.

As shown in Fig. 1, the derived slopes, although without frank outliers, still showed a very marked skew toward the high side (a skewness index of 2.0), too different from a normal distribution to allow their use in regression analyses. Only when subjects with all risk factors for BR were deleted did the small proportion of subjects remaining show a distribution that was not significantly different from normal when tested by the Kolmogorov-Smirnov goodness-of-fit test. This distribution in "normals" apparently reflected primarily the intrinsic variability in FEV₁ measurements.

To make the overall distribution more normal, the log₁₀ of the slope values (after adding a constant of 10 to eliminate negative numbers) was determined. This transformation reduced the skewness index to 1.0, and the overall distribution more closely resembled a Gaussian one than that shown in Fig. 1. These estimates were used in all subsequent parametric analyses. We consider them only as indexes of bronchial responsiveness (BRindex). Their actual value is not meant to reflect directly the methacholine dose-response curve. The BRindex is introduced only to provide a continuous and relatively normally distributed variable for use in statistical analyses.

"Asthma" was recorded if the parent gave a positive response to the question of whether their child had ever had asthma. Wheezing, whether or not associated with an asthma diagnosis, was recorded separately, as were other conditions including hay fever and eczema. Conditions were considered current and were used in the analyses if they had occurred during the previous 2 years.

The data were collected, processed by computer, and analyzed initially at the University of Otago. The stored computerized data were then transferred to the University of Arizona for further analyses.

The first analyses in the present study consider BR as either present (a PC₂₀ ≤ 25 mg/ml) or absent (i.e., the fall in FEV₁ was $< 20\%$ after the last dose of methacholine). Univariate and multivariate analyses with BRindex as the dependent variable were then carried out.

Statistical methods include simple and trend chi square, analysis of variance (ANOVA), simple correlation, and stepwise multiple regression. All reported *p* values are two tailed.

RESULTS

The relations of several categorical variables to BR (a PC₂₀ ≤ 25 mg/ml) are shown in Table II. Differences in continuous variables in relation to BR are also shown in this table. The significance of differences in categorical variables are determined by chi square, and ANOVA is used for continuous variables. There is no significant relation of responsiveness to gender, but histories of asthma, wheeze, and hay fever are all highly predictive of BR ($p < 0.0001$). Even a history of eczema is related to BR at $p < 0.005$. Responsiveness is also related to a high serum IgE

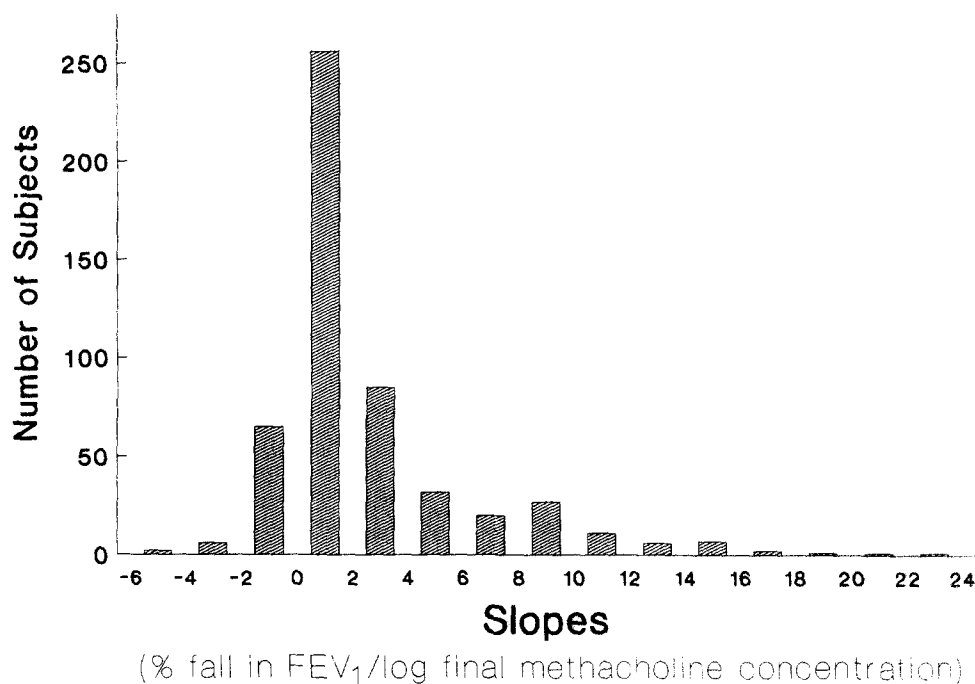


FIG. 1. Distribution of slope values before final log transformation, calculated as indicated under "Methods," in 11-year-old New Zealand children.

TABLE II. Relationships to methacholine response measured by PC₂₀

	No response	Responder (PC ₂₀ ≤ 25)	RR* (95% CI)	p value
(No.)	(435)	(87)		
Males	52.2%	57.5%	1.20 (0.81 - 1.76)	NS
Reported asthma	3.9%	36.8%	5.62 (4.07 - 7.75)	<0.0001
Reported wheeze	10.3%	52.9%	5.31 (3.73 - 7.58)	<0.0001
Reported hay fever	14.0%	35.6%	2.59 (1.78 - 3.77)	<0.0001
Reported eczema	25.7%	41.4%	1.78 (1.22 - 2.61)	<0.005
Mean percent predicted FEV ₁ ± SD (percent predicted)	100.4 ± 8.85	93.3 ± 10.25		<0.0001
Mean FEV ₁ /VC ± SD (%)	89.6 ± 4.98	84.6 ± 5.69		<0.0001
Mean IgE ± SD (IU/ml) (Geometric mean)	1.96 ± 0.67 (90.2)	2.49 ± 0.55 (305.5)		<0.0001

RR, Relative risk of response in those with the finding compared with those without the finding (95% CI); NS, not significant.

level, a low FEV₁, expressed as percent of predicted FEV₁, and a low RATIO, all at $p < 0.0001$. Very few subjects reported only recurrent cough or a diagnosis of "bronchitis," and these variables are not included in any of the analyses.

The univariate relationships of BRindex (i.e., the transformed slopes) to the variables examined in Table

II are shown in Table III. Relationships to the categorical variables are evaluated by ANOVA and to continuous variables by correlation. The univariate relationships to BR with use of BRindex as a criterion are qualitatively similar to those with PC₂₀ reported in Table II.

We were interested in whether lung function vari-

TABLE III. Relationships to methacholine response measured by BRindex

	Mean BRindex $\pm$ SD or correlation coefficient	p value
Comparisons of mean BRindex		
Males	1.09 $\pm$ 0.107	NS
Females	1.08 $\pm$ 0.114	
Without asthma	1.07 $\pm$ 0.093	
With asthma	1.24 $\pm$ 0.145	<0.0001
Without wheeze	1.07 $\pm$ 0.085	<0.0001
With wheeze	1.19 $\pm$ 0.160	
Without hay fever	1.07 $\pm$ 0.098	<0.0001
With hay fever	1.13 $\pm$ 0.147	
Never had eczema	1.07 $\pm$ 0.101	<0.0001
Ever had eczema	1.12 $\pm$ 0.127	
Correlation coefficients versus BRindex		
With percent pre- dicted FEV ₁	-0.307	<0.0001
With FEV ₁ /VC (RATIO)	-0.381	<0.0001
With IgIgE	0.285	<0.0001

ables would show different relationships to BR depending on the level of serum IgE, and whether predictor variables would have different relations to BR in patients with asthma than in nonasthmatic patients. To look for such interactions, we divided the continuous predictor variables IgE, RATIO, and percent predicted FEV₁ into terciles to allow their inclusion as main effects in an ANOVA with BRindex as the dependent variable. The limits for the low, mid, and high terciles of IgE are <50.7 IU, 50.7 < 208 IU, and 208 + IU. For RATIO, these limits are <86.8%, 86.8% < 91.6%, and 91.6 + %. There was a highly significant interaction between IgE and RATIO in predicting BRindex. This reflected an insignificant correlation of BRindex with RATIO in the lowest IgE tercile but correlation coefficients of -0.404 in the mid tercile and of -0.467 in the highest IgE tercile ($p < 0.0001$ for both). To clarify the nature of this interaction, the relationships of the rate of BR (expressed as a measurable PC₂₀) to terciles of RATIO within terciles of IgE are shown in Fig. 2. It is evident that with a low serum IgE there are low rates of responsiveness regardless of the RATIO, but the relationship of rates of BR to RATIO become increasingly strong with increasing IgE level.

An interaction term to represent these relationships, called "IgE * IoRAT", was calculated as follows: IgE * IoRAT = IgE $\times$ (100 - RATIO). The actual RATIO was subtracted from 100 to allow both the IgE term and the RATIO to relate in a positive manner

to BRindex. The correlation coefficient for IgE * IoRAT with BRindex was 0.486. The interaction term explained slightly more of the variance in BRindex than was explained by a combination of separate terms for IgE and RATIO in a multiple regression with BRindex as the dependent variable. The latter gave a multiple correlation coefficient of 0.454. Furthermore, forcing the main effects as well as the interaction term into a multiple regression with BRindex as the dependent variable revealed insignificant correlations with BRindex for both RATIO and IgE ($p = 0.08$ and $p = 0.11$, respectively). No significant interaction with serum IgE was noted in regard to the relation of percent predicted FEV₁ to BRindex.

ANOVA with BRindex as the dependent variable also revealed a significant interaction between terciles of IgE and the presence or absence of an asthma diagnosis. This resulted from the fact that increasing IgE level was associated with an increasing BRindex only in nonasthmatic patients, in whom the correlation of IgE with BRindex showed an $r = 0.228$ ($p < 0.0001$), whereas in patients with asthma the correlation was insignificant. To reflect this, an interaction term "noAS * IgE" was computed by assigning the mean IgE for patients with asthma (2.69) to all those with asthma. Use of this interaction term raised the correlation coefficient for IgE with BRindex in the total sample from 0.289 to 0.318, both highly significant ($p < 0.0001$). Unlike IgE, a low RATIO and low percent predicted FEV₁ were significant predictors of BRindex both in subjects with and without asthma and showed no significant interactions with this diagnosis.

Multiple regressions with BRindex as the dependent variable were then carried out, first with use of only the objective measurements from spirometry and serum IgE. The variables in the final equation when IgE * IoRAT, IgE, RATIO, and percent predicted FEV₁ were all forced to enter the regression are shown in Table IV, A. As can be seen, IgE and RATIO were not significantly predictive of BRindex in the presence of the interaction term, and although they will be included among the independent variables, they will not be forced to enter the regressions in subsequent analyses. When the four measurements were entered stepwise, the interaction term IgE * IoRAT entered first, and the main effects of IgE and RATIO showed partial correlations that had p values so high that they did not enter ($p = 0.45$ for RATIO and $p = 0.84$ for IgE). However, percent predicted FEV₁ did enter at a highly significant level ($p < 0.0001$) and raised the correlation coefficient (R) from 0.486 for the interaction term alone to a multiple R of 0.513.

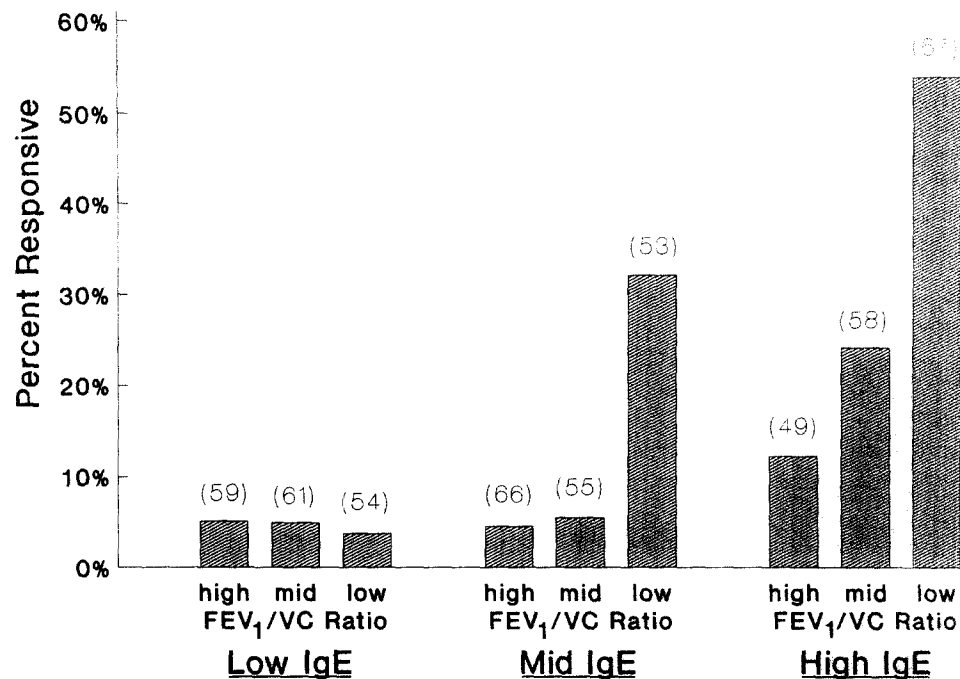


FIG. 2. Frequency of methacholine responsiveness ($PC_{20} \leq 25$ mg/ml) in relation to tertiles of FEV_1/VC ratio within tertiles of serum IgE level (see text for limits of tertiles). There is no significant relationship of responsiveness to the ratio in subjects with IgE levels in the lower third of the total sample, but trend chi squares indicate significant increases in responsiveness with lower values of the ratio in the mid-range IgE group and the high IgE tertile ($p < 0.0001$ in both). The number of subjects in each of the subgroups is indicated in parentheses above the bars.

TABLE IV. Results of multiple regressions with BRindex as the dependent variable

Variable	Coefficient $\pm$ SE in final equation	p in final equation	Multiple R after entry
A. Forcing all spirometric variables and serum IgE into the equation			
IgE*IoRAT	0.00513 $\pm$ 0.00151	<0.0001	
Percent predicted FEV_1	0.00214 $\pm$ 0.000474	<0.0001	
IgIgE	-0.0174 $\pm$ 0.0145	NS	
RATIO	0.00482 $\pm$ 0.00252	NS	0.519
B. Including all variables in the study in a stepwise regression			
IgE*IoRAT	0.00224 $\pm$ 0.000298	<0.0001	0.486
Asthma	0.1108 $\pm$ 0.0146	<0.0001	0.568
Percent predicted FEV_1	-0.00204 $\pm$ 0.000434	<0.0001	0.591
Hay fever	0.0225 $\pm$ 0.0106	<0.05	0.596
Eczema	0.0185 $\pm$ 0.00879	<0.05	0.601
(Sex, IgIgE, RATIO, Wheeze, and noAS*IgE did not enter)			

The results of a stepwise multiple regression when all of the variables in the study were allowed to enter are shown in Table IV, B. The IgE * IoRAT interaction term had a slightly higher correlation with BRindex than asthma and entered the regression first. As seen in Table IV, B, asthma then entered followed

by percent predicted FEV_1 , and these three variables account for 35% of the variance in BRindex. Statistically significant relationships to hay fever and eczema persisted, but these variables explained little of the remaining variance in BRindex.

Since asthma was a highly predictive variable, and

TABLE V. Results of stepwise multiple regressions with BRindex as the dependent variable, excluding asthma

Variable	Coefficient $\pm$ Sd in final equation	p in final equation	Multiple R after entry
A. Deleting Asthma and noAS*IgE as predictor variables			
IgE*IoRAT	0.00252 $\pm$ 0.000313	<0.0001	0.486
Wheeze	0.0555 $\pm$ 0.0122	<0.0001	0.526
Percent predicted FEV ₁	-0.00202 $\pm$ 0.000452	<0.0001	0.549
Hay fever	0.0242 $\pm$ 0.0113	<0.05	0.555
(Sex, RATIO, IgIgE, and Eczema did not enter)			
B. Limiting analysis to nonasthmatics (N = 473)			
IgE*IoRAT	0.00220 $\pm$ 0.000301	<0.0001	0.396
Percent predicted FEV ₁	-0.00209 $\pm$ 0.000431	<0.0001	0.442
Hay fever	0.0287 $\pm$ 0.0109	<0.01	0.457
Eczema	0.0186 $\pm$ 0.00870	<0.05	0.465
(Sex, IgIgE, RATIO, and wheeze did not enter)			

since relationships might differ in subjects with and without this diagnosis, the regressions were also carried out without allowing asthma to enter the regression and separately in subjects without the disease. When the total sample was studied without including asthma or its interaction term as variables (Table V, A), wheeze entered after IgE * RATIO, apparently acting as a surrogate for asthma; 54% of those with wheeze had an asthma diagnosis. The percent predicted FEV₁ then entered followed by hay fever, but hay fever showed only a weak relationship to BRindex after the other factors were taken into account.

When analyses were limited to nonasthmatic patients, reducing the overall variance in BRindex, almost all of the other variables related to BRindex in the total series (Table III) remained significantly related to it in univariate analyses. In a stepwise multiple regression (Table V, B), IgE * IoRAT and percent predicted FEV₁ were the most significant predictors and entered the regression first. Hay fever and eczema then entered, but explained little of the remaining variance in BRindex.

In the 49 patients with asthma, the only significant correlations with BRindex were with the RATIO ($r = -0.455$, $p = 0.001$), and IgE * IoRAT ($r = 0.342$, $p < 0.02$). In a multiple regression, only RATIO entered; none of the other variables considered in Tables IV and V were significant after accounting for RATIO. The relationship of BR to RATIO in patients with asthma is depicted in Fig. 3. Despite the small number of subjects, the trend for BR to decrease with increasing FEV₁/VC is significant at $p < 0.01$.

From the above analyses, one cannot tell whether the use of the continuous variable BRindex adds to

simple measurement of the PC₂₀ in evaluating the methacholine response. When the correlations of BRindex with the variables used above were examined in the 435 subjects whose FEV₁ failed to decline by 20% during the methacholine test and who would have been grouped together as "nonreactive" by the PC₂₀, highly significant relationships were found for IgE * IoRAT ($r = 0.204$, $p < 0.0001$) and RATIO ($r = -0.181$, $p < 0.0002$). BRindex was also related to percent predicted FEV₁ ($p < 0.01$), eczema ($p < 0.01$), and asthma ($p < 0.02$), and, for the first time in any of the analyses, it was significantly higher in males than in females ($p < 0.05$). In a stepwise multiple regression with BRindex as the dependent variable in these nonreactors, IgE * IoRAT entered first, followed by eczema. The overall regression yielded an R^2 of 0.231 ($p < 0.0001$). Thus some additional information was added by use of a continuous variable when attempting to predict the overall response to methacholine.

DISCUSSION

Some features of this study limit the interpretation of the analyses. As noted under "Methods," more boys than girls were excluded from methacholine challenge. The exclusion of a disproportionate number of males with low ventilatory function may account for the failure of sex to be a significant predictor of methacholine responsiveness in most of our analyses. Despite the selection bias, boys in the final sample still had significantly lower FEV₁/VC ratios than girls, but the correlations of BRindex with RATIO and percent predicted FEV₁ were not different in the two sexes, and no interactions between sex and spirometric variables in predicting BRindex could be identified. Sev-

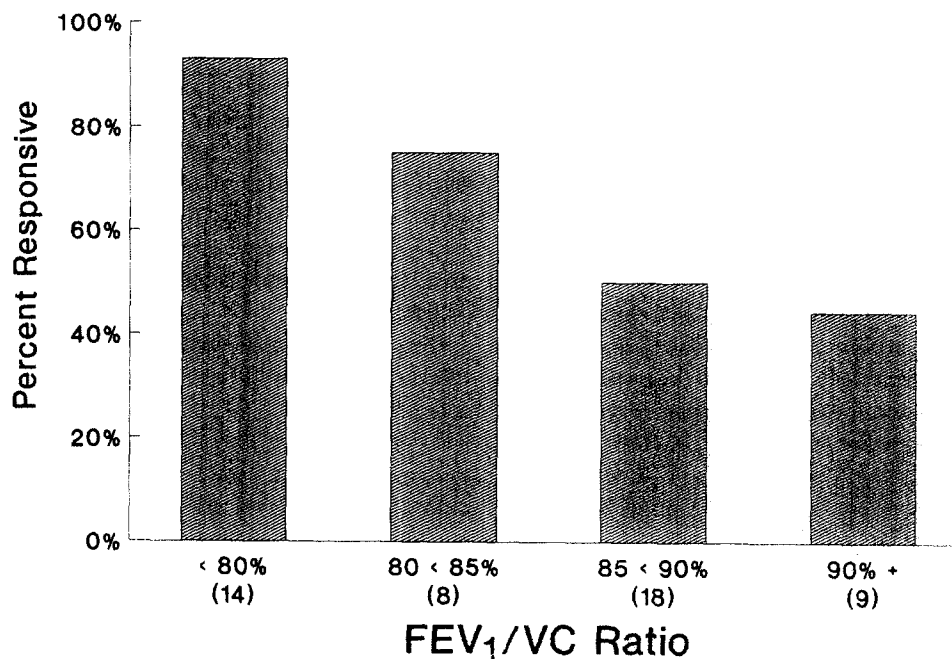


FIG. 3. Relationship of rates of methacholine responsiveness ($PC_{20} \leq 25$ mg/ml) to the FEV₁/VC ratio in subjects with asthma. The number of patients with asthma at risk in each ratio group are shown in parentheses. The trend for responsiveness to increase with decreasing FEV₁/VC ratios is significant at $p < 0.01$.

eral other studies have suggested a higher overall frequency of responsiveness in boys, as reviewed by Weiss et al.¹⁵

The accuracy of diagnoses obtained by questionnaire alone must also be considered. We cannot exclude the possibility that some of the cases reported as having "asthma" may not have met strict clinical criteria for the disease. Also, some of the "nonasthmatic patients," who reported wheezing may have a mild form of the disease. The same types of diagnostic inaccuracies exist for "hay fever." The problem may be the greatest in regard to reported "eczema." In view of the very high frequency of reports of this diagnosis in the study population, we doubt that all these cases represent the type of infantile eczema that characterizes the atopic child. However, no accepted epidemiologic criteria exist for identifying any of these disorders. Most important, any misclassification would tend to decrease rather than accentuate the relationships demonstrated in this report.

In regard to expressing methacholine responsiveness as a continuous variable, when we attempted to imitate the method of O'Connor et al.¹² the distribution of the log of the percent fall in FEV₁ per unit concentration was discontinuous and outlier values were present. The distribution, though still markedly skewed toward high values, appeared more reasonable

when we used the percent decline in FEV₁ at the last concentration of methacholine administered divided by the log of that concentration, expressing the latter as milligrams per deciliter to avoid negative log values. To decrease the marked skew in the distribution of the data, we then log converted these calculated slopes to create a reasonably normal distribution of an index of the decline in FEV₁ with methacholine challenge. As noted in the "Methods" section, this BRindex is not meant to convey any direct measure of the dose-response curve to methacholine. It is used solely as a statistical convenience to facilitate multivariate analyses in this data set. How applicable it would be to other data sets is uncertain.

In any case, we agree with Peat et al.¹⁰ that the use of some type of continuous variable to express the overall response to methacholine appears to be highly desirable in epidemiologic research. It not only facilitates multivariate analyses, but, at least in present data, there are highly significant relationships of explanatory variables to the calculated BRindex even in subjects who would be included together as nonreactive based on PC_{20} criteria.

In view of the very wide variability in BR and its capacity to change over time within individuals, we were surprised that a multiple R higher than 0.6 could be obtained by any combination of predictor variables.

However, as much as 36% of the variance in responsiveness could be explained only if a term for asthma was included as a predictor. Even more of the variability might have been explained if the state of activity of asthma at the time of testing could have been evaluated, since even among patients with asthma the degree of BR is known to vary markedly in relation to both the state of activity and the severity of the disease.

To some extent including asthma as a variable involves circular reasoning because clinical manifestations of BR are probably the major determinants of an asthma diagnosis. If asthma and clinical symptoms related to asthma are not included, the highest multiple correlation coefficient we were able to demonstrate was 0.519, with a combination of serum IgE and spirometric variables.

Except for an asthma diagnosis, respiratory symptoms contributed relatively little to the prediction of BR once the serum IgE level and level of lung function were taken into account. In some other studies, it is difficult to determine the extent to which symptoms that appear closely related to BR are simply serving as surrogates for IgE and low lung function. In the present study wheeze, hay fever and eczema, as well as asthma were all significantly related to IgE and $\text{IgE} \times \text{IoRAT}$. Wheeze, as well as asthma, was significantly related to a low BRindex and a low percent predicted FEV_1 . Present findings suggest that the wheeze relationship to BR depends largely on the high frequency of asthma in wheezy subjects. When patients with asthma were excluded, wheeze did not even enter the regression predicting BRindex (Table V, B).

In contrast to some reported studies on clinical series,¹⁶ a significant relationship of BR to lung function existed among patients with asthma, and this was much more evident when the FEV_1/VC ratio was used as an index of function rather than the percent predicted FEV_1 . In children, the ratio appears to be a more reliable indicator of an airway abnormality. This type of relationship is probably more easily demonstrated in a community population such as ours, where there is wide variability in both the activity and the severity of the disease, than in clinic patients. It is unclear whether the relationship exists because lung function serves as an indicator of the activity and severity of the disease or whether it results more directly from the implied changes in airway geometry with a low RATIO. In contrast to lung function, serum IgE level did not predict the severity of BR among patients with asthma. It simply identified those subjects most likely to have the diagnosis.

Perhaps the most interesting observation was the highly significant interaction of serum IgE level and

the FEV_1/VC ratio in predicting responsiveness. Decreased RATIO was associated with increased methacholine responsiveness only when at least moderate levels of IgE were present. We have previously noted that BR is rare and that asthma diagnoses do not occur at all in this population sample when the serum IgE level is <32 IU.¹¹ Those findings and present results are compatible with the concept that, at least in children, IgE is of critical importance in the development of BR.

Despite the clear interaction of RATIO with serum IgE, no significant interaction was noted with the percent predicted FEV_1 itself. The fact that this variable was consistently related to BRindex in all of the analyses may be explained, at least in part, by the more direct mathematical relationship of the level of the FEV_1 to a slope that is calculated in terms of percent of the baseline FEV_1 value. A low percent predicted FEV_1 consistently added to the prediction of BRindex after the RATIO was taken into account, including its interaction term with IgE.

All of the analyses in the present report consider BR as the dependent variable and inherently assume that lung function is one of its determinants rather than vice versa. In fact, cause and effect cannot be determined from the type of cross-sectional data being studied. It is possible that BR is one of the mechanisms that leads to a low FEV_1/VC ratio. If so, however, IgE would still remain a critical determinant of BR. In present data, the direct relationship of IgE to lung function is very weak and barely significant for the RATIO ($p < 0.05$). If the RATIO is used as the dependent variable in a multiple regression, BRindex, sex, and wheeze, are all highly significant predictors. Small, but statistically significant additional relationships to the RATIO are seen with hay fever and asthma. Serum IgE is not significantly related to RATIO once BRindex is taken into account. Thus if IgE is a major factor in determining lung function, its effect would appear to be a result of its relationship to BR.

At least in children, before other factors such as smoking may independently lower function, the following scenario appears compatible with the data: there is an early development of an IgE related (presumably allergic) inflammatory reaction in the airway that leads to both BR and, directly or indirectly, to a reduction in baseline function. The FEV_1/VC ratio may be an indicator of the degree of activity of the inflammatory process leading to BR as well as increasing BR more directly by the alterations in the geometry of the airway that it implies. With this scenario, the independent inheritance of a tendency to BR or some deficiency in lung function would not be

essential for the development of severe BR and clinical asthma. This scenario would be compatible with the observation that early exposure to house dust mite is a predictor of subsequent asthma in childhood,¹⁷ possibly initiating the airway inflammatory response in susceptible children.

Although this is an attractive hypothesis, from present data no way exists to disprove the possibility that low lung function and/or a tendency to BR are determined separately from IgE and simply increase the likelihood that an IgE-related reaction in the airway would result in measurable airway responsiveness.

The authors thank M. D. Lebowitz, PhD, F. D. Martinez, MD, and Duane Sherrill, PhD, for their helpful suggestions in regard to this report and to acknowledge the assistance in data processing provided by M. G. Cline, MS.

REFERENCES

1. Cockcroft DW, Murdoch KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26-9.
2. Mortagy AG, Howell JB, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. *BMJ* 1986;293:525-9.
3. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian school children. II. Relative importance of associated factors. *Clin Allergy* 1987;17:283-90.
4. Salome CS, Peat JK, Britton WJ, Woolcock AJ. Bronchial responsiveness in two populations of Australian school children. I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;17:271-81.
5. Sparrow D, O'Connor G, Colton T, Barry CL, Weiss ST. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The normative aging study. *Am Rev Respir Dis* 1987;135:1255-60.
6. Burney PG, Britton JR, Chinn S, et al. Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987;42:38-44.
7. Rijcken B, Schouten JP, Weiss ST, van der Lende R. The association of airways responsiveness to respiratory symptom prevalence and to pulmonary function in a random population sample. *Bull Eur Physiopathol Respir* 1987;23:391-4.
8. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. Relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;19:419-24.
9. Clifford RD, Howell JB, Radford M. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of school children. *Arch Dis Child* 1989;64:1133-9.
10. Peat JK, Salome CM, Berry G, Woolcock AJ. Relation of dose-response slope to respiratory symptoms in a population of Australian school children. *Am Rev Respir Dis* 1991;144:663-7.
11. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067-71.
12. O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose-response curves to methacholine: an approach suitable for population studies. *Am Rev Respir Dis* 1987;136:1412-7.
13. Silva PA. The Dunedin Multidisciplinary Health and Development Study: a 15-year longitudinal study. *Pediatr Perinatal Epidemiol* 1990;4:96-127.
14. Sears MR, Jones DT, Holdaway MD, et al. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986;41:283-9.
15. Weiss ST, O'Connor GT, Sparrow D. The role of allergy and airways responsiveness in the natural history of chronic airflow obstruction (CAO). In: Weiss ST, O'Connor GT, Sparrow D, eds. *Airways responsiveness and atopy in the development of chronic lung disease*. New York: Raven Press, 1989:194-6.
16. Rubinfeld AR, Pain CF. Relationship between bronchial reactivity, airway caliber, and severity of asthma. *Am Rev Respir Dis* 1977;115:381-7.
17. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.

Bound volumes available to subscribers

Bound volumes of THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY are available to subscribers (only) for the 1992 issues from the Publisher, at a cost of \$54.00 for domestic, \$75.78 for Canadian, and \$72.00 for international subscribers for Vol. 89 (January-June) and Vol. 90 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone (800) 325-4177, ext. 4351, or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.