

Sensitivity and specificity of histamine PC₂₀ determination in a random selection of young college students

Donald W. Cockcroft, MD, FRCP(C), Karen Y. Murdock, BSCN,
Barbara A. Berscheid, BA, and Brenda P. Gore

Saskatoon, Saskatchewan, Canada

Histamine provocative concentration causing a 20% drop in FEV₁ (PC₂₀) was measured in 500, randomly selected, young (20 to 29 years) university students. Participation was 500/619, or 81%. In this population, by a research assistant-administered questionnaire, we identified 17 subjects with current asthma, 16 with asthma only on allergen exposure, 19 with past (more than 1 year ago) asthma, 158 with rhinitis (77 atopic and 81 nonatopic subjects), and 290 subjects with neither asthma nor rhinitis. Histamine airway hyperresponsiveness (PC₂₀ ≤ 8 mg/ml) was observed in 58 subjects and included the 17 subjects with current asthma, 6/16 with asthma only on allergen exposure, 2/19 subjects with previous asthma, 20/158 with rhinitis, and 13/290 subjects with neither asthma nor rhinitis. With "current symptomatic asthma" as the diagnosis and PC₂₀ ≤ 8 mg/ml as the positive test, the sensitivity was 100%, the specificity was 93%, and the negative predictive value was 100%; the positive predictive value (for current symptoms of asthma) was only 29%. The strength of this test with a cutoff of 8 mg/ml is the high sensitivity, indicating that a PC₂₀ > 8 mg/ml is likely to indicate that current asthma is not present. The weakness is the failure to predict current symptoms of asthma. As the cutoff is lowered, for example, to PC₂₀, 1 mg/ml, the sensitivity falls to <50% and the positive predictive value approaches 100%. These data indicate that a PC₂₀ > 8 (or 16) mg/ml rules out current asthma in most instances, whereas a PC₂₀ < 1 mg/ml is almost diagnostic of current asthma. Values between 1 and 8 mg/ml are intermediate in these regards. (J ALLERGY CLIN IMMUNOL 1992;89:23-30.)

Key words: Airway responsiveness, sensitivity, specificity, histamine inhalation

Airway hyperresponsiveness to nonsensitizing stimuli, such as histamine or methacholine, is a characteristic feature of subjects with current asthma.¹ Mild airway hyperresponsiveness is also found in some subjects with rhinitis^{2, 3} and in a small number of normal (no asthma and no rhinitis) subjects.^{2, 4} We have developed and standardized a method for measuring airway responsiveness to histamine and methacholine.² The current investigation describes the re-

Abbreviations used

- PC₂₀: Provocative concentration causing a 20% drop in FEV₁
Q: Question on American Thoracic Society Adult Questionnaire

From the Royal University Hospital, Saskatoon, Saskatchewan, Canada.

Supported by Medical Research Council of Canada Grant No. MA7051.

Received for publication Nov. 15, 1990.

Revised March 27, 1991.

Accepted for publication May 10, 1991.

Reprint requests: D. W. Cockcroft, MD, University Hospital, Saskatoon, Saskatchewan, Canada S7N 0X0.

1/1/32748

sults of airway responsiveness to inhaled histamine performed by this method in a random selection of 500 young university students. Special reference is made to descriptive characteristics of responsive versus nonresponsive populations and to assessment of sensitivity and specificity of determinations versus current symptoms of asthma recorded by a research assistant-administered questionnaire. The unimodal distribution of histamine airway responsiveness⁵ and relationship of histamine airway responsiveness to atopy⁶ has previously been reported in portions

(N = 300 and N = 400, respectively) of the same population.

METHODS

Subjects

Five hundred university students were selected from a computer-generated list of students enrolled at the University of Saskatchewan. The list contained an equal number of male and female white students, aged 20 to 29 years. To study 500 subjects (253 female and 247 male subjects), we had to contact by telephone 619 subjects from the list; this represents a participation rate of 81% of contacted individuals. The investigation was approved by the President's Ethics Committee of the University of Saskatchewan, and signed informed consent was obtained.

Histamine inhalation test

Airway responsiveness to inhaled histamine was assessed as previously described.^{2,7} Aerosols were generated with a Wright nebulizer calibrated to deliver an output of 0.13 ml/min. Aerosols were inhaled for 2-minute periods of quiet tidal breathing. The FEV₁ was initially measured in triplicate, isotonic, nonbuffered saline was inhaled for 2 minutes through the open mouth with the nose clipped, and the FEV₁ was repeated once at 30 and 90 seconds. After this procedure, doubling concentrations of histamine from 0.03 to 8 mg/ml, dissolved in isotonic saline, were inhaled for 2 minutes at 5-minute intervals. The FEV₁ was repeated at 30 and 90 seconds, and, if this were necessary, 180 seconds after each inhalation. The test was continued until the FEV₁, measured from the lowest postsaline to the lowest posthistamine value, had fallen $\geq 20\%$ or until the highest concentration had been administered. The PC₂₀ was then interpolated by a linear interpolation formula of the last two data points.⁸

Questionnaire

The American Thoracic Society Adult Questionnaire on Respiratory Disease⁹ was administered by one of us to each subject. The complete questionnaire was used as well as modifications to include increased descriptions of causes of wheezing (under question 10), temporal relationship of symptoms to the tests, and supplemental questions regarding the presence, duration, and perceived cause(s) of rhinitis. Based on this standardized questionnaire, the following definitions were made: Asthma was considered to be present if there was a positive response to Q20C (asthma diagnosed by a physician), Q10A3 (wheezing on most days or nights), or Q11C (two or more episodes of wheezing resulting in shortness of breath). Asthma was also considered to be present if there was a positive response to Q10A2 (wheezing apart from a cold) only when such wheezing occurred on response to an allergen to which the subject had a positive skin test. Wheezing caused by respiratory tract infections (Q10A1) and other wheezing apart from a respiratory tract infection (Q10A2) were not considered diagnostic of asthma. The population with asthma was divided into three groups. Subjects with *current asthma* were subjects who

had symptoms at least within the past week, subjects with past asthma were subjects who had not had symptoms within the previous year, and subjects who had symptoms within the past year but not within the past week proved to be subjects with seasonal allergic asthma or subjects with asthma exclusively related to allergen exposure. Perennial rhinitis was arbitrarily defined as rhinorrhea or nasal congestion for 3 months of the year for 2 consecutive years analogous to the definition of chronic bronchitis. Rhinitis was also considered to be present if there were acute nose and eye symptoms on response to exposure to a relevant allergen as confirmed by skin test. Arbitrarily, subjects with perennial rhinitis were considered to have allergic rhinitis if they had one or more positive skin tests and to have nonallergic rhinitis if their skin test battery was negative (see below). A search was made for other respiratory diseases.

Skin tests

Allergy prick skin tests were performed with a standard battery of a control and seven allergens. The allergens used were *Dermatophagoides farinae*, 1:100; mixed tree pollen, 1:20; mixed grass pollen, 1:20; mixed weed pollen, 1:20; mixed grain dust, 1:10; mixed animal danders (equal proportions of cat, 1:10; dog, 1:10; and horse, 1:10); and mixed molds (equal proportions of *Alternaria*, 1:20; *Aspergillus* mix, 1:20; and *Cladosporium*, 1:20), purchased from Hollister-Stier Canada Ltd., Rexdale, Ontario. The wheal size was recorded at 10 minutes and was scored from +1 to +4 if the wheal size was larger than any wheal produced by the control skin test. Subjects were considered atopic if they had one or more single positive response to any of the seven allergen extracts tested.

Study design

Subjects were contacted by telephone and requested to participate in the study. Subjects who were unwilling to participate in the study were questioned as to the reason for their decision. A brief telephone questionnaire regarding allergies and asthma was administered to these subjects. The remainder of the subjects was brought into the laboratory. The questionnaire and skin tests were performed. Spirometry was measured with a Godart water spirometer (Godart, Bilthoven, The Netherlands). The histamine inhalation test was then done with a shortened technique starting with diluent, then 1 mg/ml for subjects in whom there was no suspicion of asthma, and with longer protocols for subjects in whom there was suspicion of asthma. Such a shortened protocol is routinely used in our laboratory.

Analysis

Continuous data were analyzed with the Student's *t* test¹⁰ and noncontinuous data (prevalence of positive histamine tests among subjects with or without various positive responses on the questionnaire, such as prevalence of asthma, atopy, wheeze, etc.) with the chi-square test.¹¹ Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the test were assessed at various arbitrary "cut points" with the standard 2 by 2 contingency

table in which "disease" versus "no disease" is tabulated versus "positive test" and "negative test."¹² The reference disease was current symptomatic asthma as defined from the questionnaire. The defined "nondisease" was all subjects who neither now nor ever had had asthma, and, in a second analysis, all subjects (regardless of past history) without current asthma symptoms.

RESULTS

These anthropometric data of the 500 subjects are presented in Table I. The FEV₁ was normal (>80% of predicted¹³) in 499 of the 500 subjects and was 79% in the other subjects. Atopy was observed in 199 of 499 subjects (38.3%); one subject refused to have skin tests but consented to the remainder of the investigations.

Asthma was diagnosed in 52 subjects (10.4%). This number included 17 subjects with current symptomatic asthma (3.4%), 16 with seasonal asthma (3.2%), and 19 subjects with a past history of asthma (3.8%); 42 of these 52 subjects (81%) were atopic. Rhinitis without asthma was observed in 158 subjects (77 atopic and 81 nonatopic subjects) or 31.6% of the population. The remaining 290 subjects or 58% of the population had, by history, neither asthma nor rhinitis. There was no other chronic or recurrent respiratory condition. There were 361 lifelong nonsmokers, 45 exsmokers, and 94 current smokers. The mean smoking consumption of the 139 smokers was 2.44 ± 1.87 pack years. Chronic phlegm production for more than 3 months of the year for 2 consecutive years (Q7E-2 years), the definition of *chronic bronchitis*, was present in 26 individuals or 5.2% of the population. Thirteen of these subjects (50%) were smokers.

Airway hyperresponsiveness (histamine PC₂₀ ≤ 8 mg/ml, based on previous investigations of selected subjects²) was present in 11.6% (58/500) of the population. This included 100% of subjects with current symptomatic asthma, 38% of subjects with seasonal asthma, and 11% of subjects with past asthma (for a total of 48% of the entire population with asthma), 14% of atopic subjects with rhinitis, 11% of nonatopic subjects with rhinitis (13% of all subjects with rhinitis), and 4.5% of subjects with neither asthma nor rhinitis (Table II). Distribution of PC₂₀ values is illustrated in Fig. 1.

Descriptive statistics are presented in Table III; chi-squared values are used only to rank and compare strength of the relationships. The prevalence of airway hyperresponsiveness was not significantly increased in smokers or in subjects with cough, sputum, or dyspnea or recent reported respiratory infection. Airway hyperresponsiveness was more common among subjects reporting wheeze, physician-documented

TABLE I. Anthropometric data

	M	F
No.	247	253
Height (cm)	177.8 ± 6.7	164.5 ± 6.1
FEV ₁ (L)	4.74 ± 0.59	3.51 ± 0.42
(% predicted)	105.7 ± 11.4	106.7 ± 10.4

TABLE II. Prevalence of airway hyperresponsiveness

Disease	No.	PC ₂₀ ≤ 8 mg/ml	%
Asthma			
Current	17	17	100
Seasonal	16	6	38
Past	19	2	11
Total	52	25	48
Rhinitis			
Atopic	77	11	14
Nonatopic	81	9	11
Total	158	20	13
Normal subjects			
No asthma or rhinitis	290	13	4.5
Total	500	58	11.6

asthma, asthma by our definitions, subjects with rhinitis, with rhinitis but not asthma, and with atopy. The relationships were particularly strong for asthma, atopy, wheeze, and rhinitis (which includes many subjects with asthma). The mean percent predicted FEV₁ was $96.3\% \pm 10.6\%$ in the hyperresponsive individuals and $107.6\% \pm 10.7\%$ ($p < 0.001$) in the normoresponsive individuals.

Sensitivity/specificity data are tabulated for the 17 subjects with current symptomatic asthma versus the 448 subjects who had never had a history of asthma (Table IV). Sensitivity and negative predictive values were both 100%, and specificity and accuracy were both approximately 93%; however, the positive predictive value, that is, the percentage of subjects with positive tests who claimed to have current symptoms of asthma, was only 34%. Similar results are obtained by observing subjects with current asthma versus the entire remaining 483 members of the population, although positive predictive value is even lower (29%). For subjects with current asthma versus subjects with no asthma ever ($N = 448$), as the histamine PC₂₀ "cut point" is reduced in a stepwise fashion from 8 to 1 mg/ml, the sensitivity gradually falls from 100% to 41%, the positive predictive value rises to almost

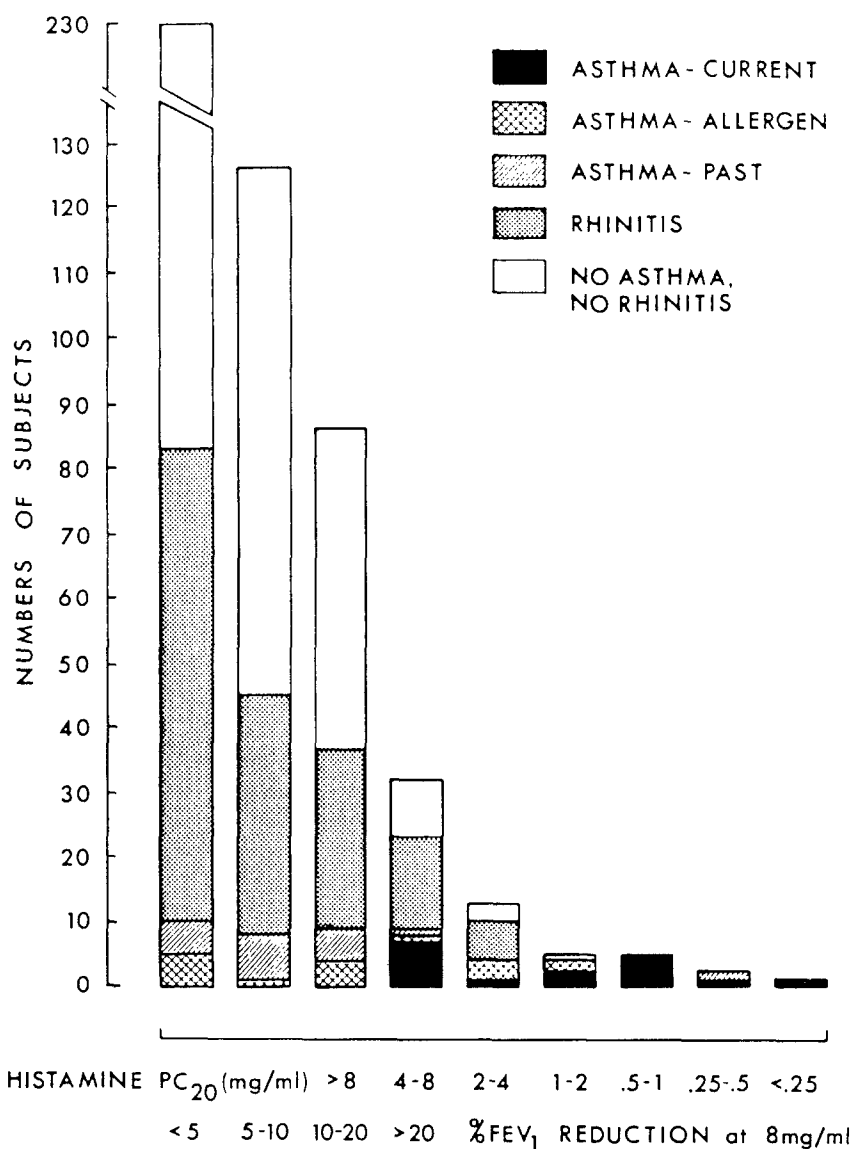


FIG. 1. Population distribution of PC₂₀ values in 500 randomly selected subjects. PC₂₀ values >8 mg/ml are divided into subjects with a 10% to 20% FEV₁ fall with 8 mg/ml (PC₂₀ between 8 and 16), subjects with a 5% to 10% FEV₁ fall with 8 mg/ml (PC₂₀ extrapolated to between 16 and 32), and subjects with <5% FEV₁ fall with 8 mg/ml.

90% at 2 mg/ml and 100% at 1 mg/ml (Fig. 2), the specificity reaches 100% at 1 mg/ml, and the negative predictive value falls slightly to <98%. For current asthma versus the 483 with no current asthma, similar results are observed. However, positive predictive value is only about 70% at 2 mg/ml and 86% at 1 mg/ml.

DISCUSSION

These data confirm that the 8 mg/ml cut point, arbitrarily chosen, retrospectively, from selected subjects,² has a high sensitivity and negative predictive value for current symptoms of asthma as recorded on

questionnaire. However, it is relatively insensitive to allergen-induced asthmatic symptoms within the past year but for more than 1 week previously. A PC₂₀ ≤8 mg/ml was a poor predictor (<30%) of current symptoms. Lowering the cut point, as would be expected, reduces the sensitivity and negative predictive values while it increases specificity and the positive predictive value; the latter reached 90% at 2 and 100% at 1 mg/ml in this population.

In this study, questionnaire-recorded symptoms, asked and recorded by one of us, were used as the "gold standard" for the diagnosis of asthma in those subjects with normal lung functions. We recognize the

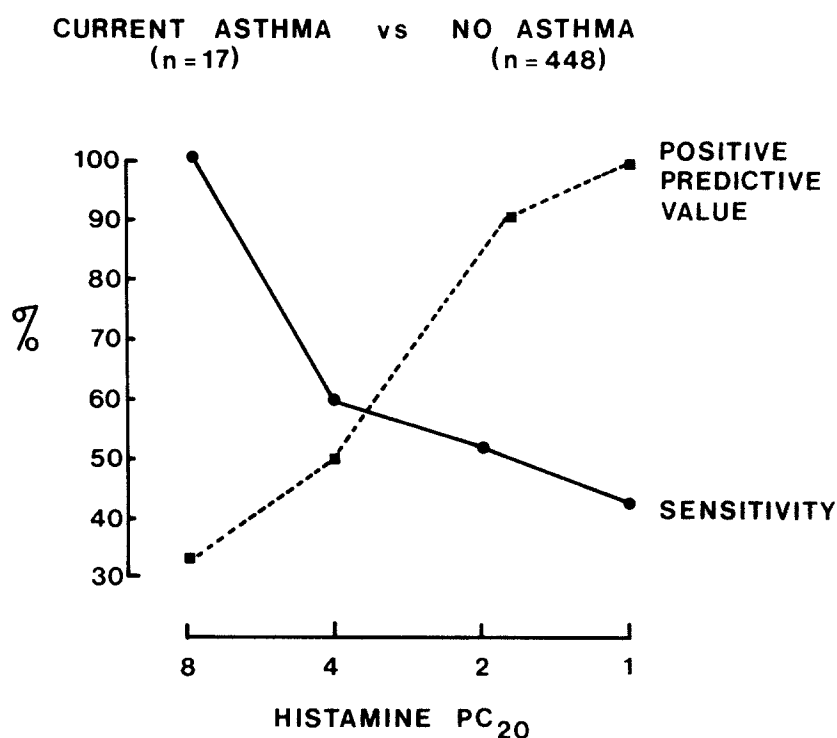


FIG. 2. Sensitivity and positive predicted value on y axis for four arbitrary cut point values of PC₂₀ (PC₂₀ ≤ value) on x axis for current symptoms of asthma (N = 17) versus no asthma ever (N = 448) as the reference population.

TABLE III.

Rank	Characteristic	PC ₂₀ <8 mg/ml/ characteristic present	%	PC ₂₀ <8 mg/ml/ characteristic absent	%	χ ² (uncorrected for multiple comparison)	p
1	Asthma (our definition)	25/52*	48	33/448†	7.4	76	<0.001
2	Wheeze (Q10A2)	35/106	33	23/394	5.8	60	<0.001
3	Asthma (Q20C)	16/31	52	42/453	9.3	52	<0.001
4	Rhinitis (total)	40/203	20	18/297	6.1	22	<0.001
5	Atopy	38/191	20	20/308	6.5	21	<0.001
6	Rhinitis (without asthma)	20/158	13	13/290	4.5	10	
7	Family history of asthma (Q28C)	7/30	23	51/470	11	4.2	
8	Smoking	11/139	7.9	47/361	13	2.6	
9	Male	24/245	9.7	34/253	13	1.6	
10	Cough (Q7E)	4/24	17	54/476	11	0.6	
11	Sputum (Q8E)	3/26	12	53/474	11	0.0001	
12	Dyspnea (Q13A1B)	1/2	50	57/498	11	---	
13	URTI <1 wk	1/42	2.3	---	---	---	
14	URTI <4 wk	7/126	5.6	51/374	14	6	

URTI, Upper respiratory tract infection.

*With asthma, PC₂₀ ≤ 8/total number (e.g., 25 of 52 with asthma had PC₂₀ ≤ 8).

†Without asthma, PC₂₀ ≤ 8/total number (e.g., 33 of 448 without asthma had PC₂₀ ≤ 8).

weakness of this, since symptoms (and even “doctor-diagnosed asthma”) are neither sensitive nor specific for asthma. However, in the absence of any physiological abnormality, the (questionnaire-recorded) symp-

oms are the only available means to arrive at a diagnosis for the purposes of addressing PC₂₀ sensitivity. The test, of course, cannot be used to validate itself. The definition, although it is expanded slightly, was

TABLE IV

	PC ₂₀ ≤8 mg/ml	PC ₂₀ >8 mg/ml	Total
Current asthma	17	0	17
No asthma	33	415	448
Total	50	415	465

Sensitivity: 100 times 17/17, 100%; specificity: 100 times 415/448, 92.6%; positive predictive value: 100 times 17/50, 34%; and negative predictive value: 100 times 415/415, 100%.

clearly defined before the tests. The additional questions appear to have improved sensitivity versus "doctor-diagnosed asthma" (Table III). The added questions plus the meticulous questionnaire completion by research assistants likely make these subjects' clinical characteristics, particularly the temporal relationship between last symptoms and the test, better defined than in many population studies.

This study was done, as in our original methods description,² with unbuffered isotonic saline as the diluent. Since pH affects the response,¹⁴ we now use phosphate-buffered saline and adjust the pH of solutions to 7.4.¹⁵ The unbuffered PC₂₀ of 8 mg/ml corresponds, approximately, with a buffered PC₂₀ of 10 to 12 mg/ml.¹⁴ For this reason, and because of the continuous distribution of PC₂₀ with its reproducibility $\leq \pm 0.5$ doubling concentration, we recognize a "grey area" of borderline hyperresponsiveness between 8 and 16 mg/ml.¹⁶ Thus a PC₂₀ >8 to 16 mg/ml virtually rules out current (i.e., within days) symptomatic asthma, whereas a PC₂₀ <1 to 2 mg/ml is usually associated with asthma symptoms. PC₂₀ values between these values are in the range of *mild* airway hyperresponsiveness and are intermediate in these regards.

The population in this study was selected both because of its availability and in an attempt to minimize confounding problems associated with age and smoking. Histamine airway hyperresponsiveness is observed in subjects with (usually smoking-induced) chronic airflow limitation; a number of features suggest that different mechanisms may be involved. Increased prevalence of airway hyperresponsiveness with age and cigarette-smoking history likely relate to increased prevalence of resting airflow obstruction. These confounding factors were successfully avoided in this population; sensitivity, in particular, might be expected to be reduced in an older population. The possibility of a selection bias toward more healthy individuals cannot be excluded; subjects with severe asthma may well not attend university or may move away from our cold climate.

In a random population, the high prevalence of sub-

jects with mild airway hyperresponsiveness not reporting symptoms on a questionnaire has been observed in other studies.^{17, 18} There may be several explanations. One possibility is that these individuals do not encounter a strong enough stimulus in their day-to-day activities to provoke bronchoconstriction. This is particularly likely for sedentary individuals who do little exercise. However, like subjects with symptomatic asthma,¹⁹ both children²⁰ and adults²¹ with asymptomatic mild airway hyperresponsiveness do appear to have variable airflow obstruction, as assessed by diurnal peak flow variability. Therefore, alternative explanations would include both the failure to perceive airflow obstruction and the failure to recognize airflow obstruction as abnormal. Subjects with $\geq 20\%$ FEV₁ fall after histamine often spontaneously volunteered that airflow obstruction was associated with symptoms similar to sensations that occurred during (after) exercise but that these sensations had not been recognized as "abnormal." This was not examined, prospectively, in a standardized way; however, this is one way in which future population studies could be improved.

To our knowledge, there are no other published sensitivity/specificity data of histamine or methacholine responsiveness in a randomly selected healthy population. Previous examinations of sensitivity and specificity of airway responsiveness (including an attempt to apply this from our data on selected subjects²²) have used selected populations in which the proportion of subjects with current asthma: normal subjects was overrepresented, being 1:2²³ or 1:1²⁴ versus our study with a population with current asthma/without asthma ratio of 1:26 (Table IV). When the test is defined arbitrarily and retrospectively to have near 100% sensitivity, the specificity in these selected populations ranged from 60% to 80%.^{23, 24} These values, especially positive and negative predictive values, are dependent on the denominators in each group (i.e., the prevalence of disease and of nondisease). As the number of normal subjects or subjects without asthma are increased (to represent the proportion observed in a random population), the specificity will improve to >90% as presented here; however, the 4.5% positive tests in subjects denying symptoms ("false positives") cause this larger population to yield much lower positive predictive values.

Unfortunately, such data cannot be readily completely extrapolated to a clinical setting. The use of histamine or methacholine responsiveness as a diagnostic test is usually limited to subjects with respiratory symptoms, often atypical or nondiagnostic. In such a selected population, expected to have a higher prevalence of asthma, the positive predictive value

should be higher. These data may be used with some certainty to state that a PC₂₀ above a certain value (e.g., >16 mg/ml) is inconsistent with current symptoms being caused by asthma (as it is currently defined). However, a positive test in subjects with symptoms must be interpreted with caution. This is because there is not, in subjects with normal spirometry, an independent "test" for asthma that can be used as a validation. Although the positive predictive value in subjects with symptoms should be much better than in subjects without symptoms, in the absence of a confirmatory test, the coexistence of symptoms and airway hyperresponsiveness does not prove cause and effect. Response to specific treatment may be useful,²⁵ but, when the response is evaluated by symptoms, it is likely only slightly less subjective than the symptoms themselves. Variable airflow obstruction can be confirmed by peak flow monitoring,^{19,21} but this procedure is probably only an alternate way to measure airway responsiveness and not truly "independent." Despite these weaknesses, it is useful to assume at least the possibility of cause and effect, when nondiagnostic symptoms and airway hyperresponsiveness coexist, and to use this finding as an objective basis for a trial of therapy.²⁶

The prevalence of airway hyperresponsiveness and descriptive relationships presented in Table III are similar to other random populations of adults.^{17,27} This relationship of airway hyperresponsiveness to asthma, wheeze, and atopy has been noted^{17,27} with the latter relationship being particularly strong in pediatric populations.^{28,30} There has been a lack of a relationship to smoking in young populations,^{17,27} but this relationship appears in older populations,^{17,27} perhaps as lung function on smokers deteriorates.³¹ Other population studies,^{17,27} as well as studies on selected individuals,³² have also failed to document a significant relationship between recent reported respiratory tract infections, despite the observations of histamine airway hyperresponsiveness (measured by specific airway resistance) in normal subjects with recent presumed viral respiratory infections.³³ The relationship between PC₂₀ <8 mg/ml and recent reported respiratory infection in our study was actually in the opposite direction to that expected, although, when the relationship is corrected for multiple comparisons, it would not be significant. Also surprising was the relatively weak relationship of a family history of asthma to airway hyperresponsiveness.

In summary, these data confirm the arbitrary cut point of 8 mg/ml (increased to 16 mg/ml as a "grey area") for the tidal breathing method of measuring airway hyperresponsiveness as highly sensitive for current asthma symptoms in a random selection of

young, largely nonsmoking, college students. Specificity (93%) and positive predictive value (<30%) are low. If the cut point is lowered to 1 or 2 mg/ml, the specificity and positive predictive value for symptoms approach 100%, whereas the sensitivity falls to <50%. Values between 1 and 16 mg/ml are intermediate. The test performance, particularly positive predictive value, would be expected to improve in populations in which the prevalence of disease is higher, that is, in subjects with nondiagnostic symptoms. However, as yet, there remains no "independent" test to confirm the diagnostic accuracy of the PC₂₀.

We thank Jacquie Bramley for assistance in preparing this manuscript.

REFERENCES

1. Hargreave FE, Ryan G, Thomson NC, et al. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J ALLERGY CLIN IMMUNOL* 1981;68:347-55.
2. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
3. Townley RG, McGeady S, Bewtra A. The effect of beta adrenergic blockade on bronchial sensitivity to acetyl-beta-methacholine in normal and allergic rhinitis subjects. *J ALLERGY CLIN IMMUNOL* 1976;57:358-66.
4. Malo J-L, Pineau L, Cartier A, Martin RR. Reference values of the provocative concentrations of methacholine that cause 6% and 20% changes in forced expiratory volume in one second in a normal population. *Am Rev Respir Dis* 1983;128:8-11.
5. Cockcroft DW, Berscheid BA, Murdock KY. Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population. *Chest* 1983;83:751-4.
6. Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26-9.
7. Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;33:705-10.
8. Cockcroft DW, Murdock KY, Mink JT. Determination of histamine PC₂₀: comparison of linear and logarithmic interpolation. *Chest* 1983;84:505-6.
9. Ferris BG. Epidemiology standardization project: adult questionnaire. *Am Rev Respir Dis* 1978;118(suppl):10-27.
10. Steel RDG, Torrie JH. Principles and procedures of statistics: a biometrical approach. 2nd ed. New York: McGraw-Hill, 1980:102.
11. Steel RDG, Torrie JH. Principles and procedures of statistics: a biometrical approach. 2nd ed. New York: McGraw-Hill, 1980:495-520.
12. Department of Clinical Epidemiology and Biostatistics. Clinical epidemiology rounds: interpretation of diagnostic data. 2. How to do it with a simple table (part A). *Can Med Assoc J* 1983;129:559-64.
13. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971;103:57-67.
14. Cockcroft DW, Berscheid BA. Effect of pH on bronchial response to inhaled histamine. *Thorax* 1982;37:133-6.

15. Cockcroft DW. Measurement of airway responsiveness to inhaled histamine or methacholine: method of continuous aerosol generation and tidal breathing inhalation. In: Hargreave FE, Woolcock AJ, eds. *Airway responsiveness: measurement and interpretation*. Mississauga, Ontario: Astra Pharmaceuticals Canada Ltd., 1985:22-8.
16. Woolcock AJ. Expression of results of airway responsiveness. In: Hargreave FE, Woolcock AJ, eds. *Airway responsiveness: measurement and interpretation*. Mississauga, Ontario: Astra Pharmaceuticals Canada Ltd., 1985:80-5.
17. Woolcock AJ, Peat JK, Salome CM, et al. Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. *Thorax* 1987;42:361-8.
18. Pattemore PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. *Am Rev Respir Dis* 1990;142:549-54.
19. Ryan G, Latimer KM, Dolovich J, Hargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax* 1982;37:423-9.
20. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J ALLERGY CLIN IMMUNOL* 1985;75:573-7.
21. Gibson PG, Mattoli S, Sears MR, Dolovich J, Hargreave FE. Variable airflow obstruction in asymptomatic children with methacholine airway hyperresponsiveness. *Clin Invest Med* 1988;11:C105.
22. Britton J. Is hyperreactivity the same as asthma? *Eur Respir J* 1988;1:478-9.
23. Hopp R, Bewtra AK, Nair NM, Townley RG. Specificity and sensitivity of methacholine inhalation challenge in normal and asthmatic children. *J ALLERGY CLIN IMMUNOL* 1984;74:154-8.
24. Popa V, Singleton J. Provocation dose and discriminant analysis in histamine bronchoprovocation: are the current predictive data satisfactory? *Chest* 1988;94:466-75.
25. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981;123:413-7.
26. Cockcroft DW, Hargreave FE. Airway hyperresponsiveness: relevance of random population data to clinical usefulness. *Am Rev Respir Dis* 1990;142:497-500.
27. Burney PFJ, 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.
28. Witt C, Stuckey MS, Woolcock AJ, Dawkins RC. Positive allergy prick skin tests associated with bronchial histamine responsiveness in an unselected population. *J ALLERGY CLIN IMMUNOL* 1986;77:698-702.
29. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian school children. III. Effect of exposure to environmental allergens. *Clin Allergy* 1987;17:291-300.
30. Peat JK, Salome CM, Sedgwick CS, Kerrebijn J, Woolcock AJ. A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian school-children. *Clin Exp Allergy* 1989;19:299-306.
31. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39:912-8.
32. Jenkins CR, Breslin ABX. Upper respiratory tract infections and airway reactivity in normal and asthmatic subjects. *Am Rev Respir Dis* 1984;130:879-83.
33. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976;113:131-9.

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.