
Airway hyperresponsiveness and the clinical diagnosis of asthma: Histamine or history?

Like many diseases, asthma is easy to describe but hard to define. Published definitions of asthma tend not to specify clear definitive criteria,^{1, 2} as for example Scadding's² "disease characterized by wide variations over short periods of time in resistance to flow in intrapulmonary airways." Although clearly evocative of asthma, this definition is, in fact, a description, since it does not specify how wide the variations in airflow should be or in how short a period they should occur. In clinical practice most physicians diagnose asthma from a clinical history, complemented by serial measurements of airflow made before, during, and after a trial of asthma therapy.³ Many would argue that these measures are so important to the assessment of the patient that there is no requirement for a quick diagnostic test to bypass the process. However, a standardized diagnosis is essential to all involved in the conduct or interpretation of clinical or epidemiologic research into asthma, and this need has stimulated the search for appropriate methods. Fifteen years ago, Cockcroft et al.⁴ described a histamine-challenge method with clinical survey data that suggested that a provocative concentration causing a 20% fall in FEV₁ value of 8 mg/ml or less might be diagnostic of asthma. In the present issue of this JOURNAL, Cockcroft et al.⁵ present the results of a larger survey and a virtually identical conclusion. Should we now accept that hyperresponsiveness to histamine is diagnostic of asthma?

Since Cockcroft et al.⁴ first described their bronchial-challenge method, there has been substantial progress in our understanding of bronchial hyperresponsiveness. To a great extent this understanding has originated from studies of asthma epidemiology in which logistic constraints make the need for a simple objective diagnostic test for asthma particularly acute. Epidemiologic studies have tended to use other more rapid methods of bronchial challenge than the method according to Cockcroft et al.,⁴ for example,

that of Yan et al.,⁶ and many investigators have used methacholine rather than histamine. However, these methods produce results that are comparable in principle if not in precise detail.⁷⁻⁹ Therefore, it is reasonable to set aside methodologic differences in an overview of the epidemiology and clinical associations of hyperresponsiveness.

Clinical and epidemiologic studies have consistently identified the main predictor of hyperresponsiveness to be atopy.^{4, 10-16} Hyperresponsiveness is also related to age, being particularly prevalent in infants and young children,^{17, 18} less frequent with increasing age to early adult life,^{13, 15} and perhaps more prevalent again in middle and older ages.^{11, 19} The relation with cigarette smoking is difficult to discern, being subject to selection bias as well as possible causal effects. Hence, the finding that young smokers demonstrate less hyperresponsiveness than nonsmokers²⁰ may be due to a tendency for hyperresponsive individuals not to smoke; however, older smokers are generally more likely to be hyperresponsive than nonsmokers.^{11, 12, 14, 21-25} Hyperresponsiveness is also increased independently from smoking in inverse relation to baseline airway caliber.^{16, 21, 23, 25, 26} There appears to be little relation between hyperresponsiveness and sex,^{11, 13} although at least one study has suggested a slight increase in responsiveness in adult female smokers.¹⁶ There is evidence from many studies that age, smoking, atopy, and airway caliber interact in their effects on hyperresponsiveness,^{11, 13, 14, 19, 21, 22} but the nature of these interactions is likely to be complex, and no single study has yet addressed their full extent. In relation to morbidity, hyperresponsiveness is strongly associated with symptoms of wheeze, cough, chronic sputum production, breathlessness, nocturnal waking with dyspnea, chest tightness on exposure to allergens, and episodes of bronchitis.^{12, 15, 25-37} The association between hyperresponsiveness and self-reported or clinically diagnosed asthma and the relation with severity of disease is well recognized.^{4, 9, 12, 15, 27-30} Hyperresponsiveness is also found more frequently among patients with other airway diseases, particularly chronic bronchitis and chronic airflow obstruction,^{31, 32, 38-43} rhinitis and cough,⁴⁴⁻⁴⁶ and other chronic lung disease.⁴⁷⁻⁴⁹

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The relevance of these clinical associations to the use of hyperresponsiveness as a diagnostic test for asthma has been reviewed previously,⁵⁰ but the main point is self-evident. Hyperresponsiveness is not only characteristic of asthma but is also associated with most other causes of chronic respiratory tract symptoms, including chronic bronchitis, chronic airflow obstruction, cigarette smoking, and atopy. Therefore, in relation to hyperresponsiveness as a diagnostic test for asthma, the question we should be asking is not just whether hyperresponsiveness distinguishes asthma from normality but whether hyperresponsiveness can discriminate between asthma and other causes of respiratory symptoms. Other investigators who have addressed this question have reported serious reservations on the ability of hyperresponsiveness to discriminate.^{31, 32, 36, 37} Does the study⁵ in this issue of the JOURNAL shed any new light?

In this study, Cockcroft et al.⁵ report data from a healthy young population with a low proportion of cigarette smokers. The selection of a sample so unrepresentative of either clinical or general community populations is justified as a means of "successfully avoiding" confounding by age, smoking, and other obstructive airway diseases. The result is, however, that the authors are unable to address the issue of whether hyperresponsiveness discriminates asthma from other causes of chronic respiratory symptoms; they can only assess the ability of hyperresponsiveness to distinguish asthma from normality. In this respect the present study adds little to the clinical survey of 15 years ago. The estimates of sensitivity and specificity for asthma are very similar in both studies but are probably less reliable in the present study,⁵ since they are based on a smaller number of symptomatic subjects. The predictive value of the test in the present population is much as might be expected from the original sensitivity and specificity applied to a population with a low prevalence of asthma⁵¹ and is such that more than two thirds of test-positive individuals do not, in fact, have current asthma. The authors argue that positive predictive value will be higher in clinical populations in which the prevalence of asthma will be higher. This is true but not the point; what matters is not so much the absolute predictive value of the test but how much this differs from the probability of disease before the test was performed. For example, a test with a positive predictive value of 90% would appear at first sight to be potentially very helpful, but not if this were the case only when the prior probability (or prevalence) of disease is 80% and the remainder of the population consists only of unequivocally normal individuals. What the clinician needs to know is how the test will perform in the

clinical populations he or she observes. From what is known of the other clinical associations of hyperresponsiveness, it is likely that specificity, and therefore positive predictive value, will be substantially lower in clinical populations than in the present study.

An important additional consideration is that of what exactly the hyperresponsiveness test is able to predict. In this study, asthma has been defined in terms of responses to an interview on respiratory symptoms, without any of the objective evidence usually collected in the process of clinical diagnosis. The authors are therefore using a complex inhalation challenge to predict responses to questions which require a few seconds to ask. If the ultimate aim is to ascertain the answers to these questions, surely the simplest approach is to ask the questions. In epidemiology, this can be achieved by questionnaire; in clinical medicine, information like this is obtained from a clinical history.

In any disease, diagnostic tests are only useful in clinical terms if they hasten the path from the initial consultation to the instigation of appropriate therapy. Since there is no evidence that asthma can be prevented or that the prognosis of asthma is improved by currently available therapies, there is presently no justification for screening to identify asymptomatic individuals at risk from asthma. Relief of morbidity is the principal objective of asthma diagnosis, and a therapeutic trial of bronchodilators and steroids is essential to this process.³ If this is to be offered at some stage to all individuals presenting with symptoms potentially caused by asthma, there is little, if any, practical advantage to be obtained in clinical medicine from trying to predict the outcome by measuring airway responsiveness. As argued previously,⁵² the main application of measurement of responsiveness is probably in the use of a negative test to reassure the physician or patient that asthma is an unlikely cause of symptoms, when conventional means of diagnosis and assessment have failed.

For epidemiologic studies, the problem of asthma definition remains. When it is possible, the use of standardized questionnaires, or at least of questions already used in other studies, is to be encouraged so that responses from different studies can be compared directly. However, international linguistic and cultural differences limit the validity of questionnaire comparisons,^{53, 54} requiring an objective index. One possibility that is gaining increasing interest is to assess airflow variability more directly in population studies with serial measurements of peak expiratory flow rate. However, these methods are still in the early stages of development and standardization.^{32, 55, 56} For the clinician who needs to diagnose asthma in individuals

and to assess and prescribe the best therapy for that individual, a standard clinical history complemented by measurements of airflow and an assessment of therapy remain essential. Histamine-challenge tests are no substitute for traditional clinical skills.

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REFERENCES

1. American Thoracic Society. Definitions and classifications of chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1962;85:762-8.
2. Scadding JG. Definition and clinical categories of asthma. In: Clark TJH, Gordfrey S, eds. *Asthma*. 2nd ed. London: Chapman & Hall, 1983.
3. Clark TJH. Asthma: an overview. In: Brewis RAL, Gibson GJ, Geddes DM, eds. *Respiratory medicine*. London: Bailliere Tindall, 1990.
4. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
5. Cockcroft DW, Murdock KY, Berscheid BA, Gore SP. Sensitivity and specificity of histamine PC₂₀ determination in a random selection of young college students. *J ALLERGY CLIN IMMUNOL* 1992;89:23-30.
6. Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;38:760-5.
7. Britton JR, Mortagy A, Tattersfield AE. Histamine challenge testing: comparison of three methods. *Thorax* 1986;41:128-32.
8. 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.
9. Higgins BG, Britton JR, Chinn S, et al. Comparison of histamine and methacholine for use in bronchial challenge tests in community studies. *Thorax* 1988;43:605-10.
10. Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26-9.
11. Burney PGJ, 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.
12. Woolcock AJ, Peat JK, Salome CM, et al. Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. *Thorax* 1987;42:361-8.
13. Crane J, O'Donnell TV, Prior IA, Waite DA. The relationships between atopy, bronchial hyperresponsiveness, and a family history of asthma: a cross-sectional study of migrant Tokelauan children in New Zealand. *J ALLERGY CLIN IMMUNOL* 1989;84:768-72.
14. O'Connor GT, Sparrow D, Segal MR, Weiss ST. Smoking, atopy, and methacholine airway responsiveness among middle-aged and elderly men. *Am Rev Respir Dis* 1989;140:1540-6.
15. Peat JK, Salome CM, Sedgwick CS, Kerrebijn J, Woolcock AJ. A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian schoolchildren. *Clin Exp Allergy* 1989;19:299-306.
16. Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. *Am Rev Respir Dis* 1991;143:317-22.
17. Lesouëf PN, Geelhoed GC, Turner DJ, Morgan SEG, Landau LI. Response of normal infants to inhaled histamine. *Am Rev Respir Dis* 1989;139:62-6.
18. Montgomery GL, Tepper RS. Changes in airway reactivity with age in normal infants and young children. *Am Rev Respir Dis* 1990;142:1372-6.
19. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The association of airway responsiveness to respiratory symptom prevalence and to pulmonary function in a random population sample. *Bull Eur Physiopathol Respir* 1987;23:391-4.
20. Cockcroft DW, Berscheid BA, Murdock KY. Bronchial response to inhaled histamine in asymptomatic young smokers. *Eur J Respir Dis* 1983;64:207-11.
21. Sparrow D, O'Connor GT, Rosner B, Segal MR, Weiss ST. The influence of age and level of pulmonary function on non-specific airway responsiveness. *Am Rev Respir Dis* 1991;143:978-82.
22. Gerrard JW, Cockcroft DW, Mink JT, Cotton DJ, Poonawala R, Dosman JA. Increased nonspecific bronchial reactivity in cigarette smokers with normal lung function. *Am Rev Respir Dis* 1980;122:577-81.
23. Taylor RG, Joyce H, Gross E, Holland F, Pride NB. Bronchial reactivity to inhaled histamine and annual rate of decline in FEV₁ in male smokers and ex-smokers. *Thorax* 1985;40:9-16.
24. Cerveri I, Bruschi C, Zoia C, et al. Smoking habit and bronchial reactivity in normal subjects. *Am Rev Respir Dis* 1989;140:191-6.
25. 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. *Am Rev Respir Dis* 1987;135:1255-60.
26. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship between airway responsiveness to histamine and pulmonary function level in a random population sample. *Am Rev Respir Dis* 1988;137:826-32.
27. Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;286:1256-8.
28. Sears MR, Jones DT, Holdaway MD, et al. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986;41:283-9.
29. Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;17:271-81.
30. Pattemore PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. Ethnic differences in prevalence of asthma symptoms and bronchial hyperresponsiveness in New Zealand schoolchildren. *Thorax* 1989;44:168-76.
31. Enarson DA, Vedal S, Schulzer M, Dybuncio A, Chan-Yeung M. Asthma, asthma-like symptoms, chronic bronchitis, and the degree of bronchial hyperresponsiveness in epidemiological surveys. *Am Rev Respir Dis* 1987;136:613-7.
32. Brand PLP, Postma DS, Kerstjens HAM, Koëter GH. Relationship of airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variations in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:916-21.
33. Mortagy AK, Howell JBL, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. *Br Med J* 1986;293:525-9.
34. Clifford RD, Howell JB, Radford M, Hoigate ST. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989;64:1133-9.
35. Burney PGJ, Chinn S, Britton JR, Tattersfield AE, Papacosta

- AO. What symptoms predict the bronchial response to histamine? *Int J Epidemiol* 1989;18:165-73.
36. Rijcken B, Schouten JP, Weiss ST, Meinesz AF, De Vries K, van der Lende R. The distribution of bronchial responsiveness to histamine in symptomatic and asymptomatic subjects. *Am Rev Respir Dis* 1989;140:615-23.
37. 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.
38. Klein RC, Salvaggio JE. Nonspecificity of the bronchoconstricting effect of histamine and acetyl-beta-methylcholine in patients with obstructive airway disease. *J ALLERGY* 1966;37:158-68.
39. Barter CE, Campbell AH. Relationship of constitutional factors and cigarette smoking to decrease in 1-second forced expiratory volume. *Am Rev Respir Dis* 1976;113:305-14.
40. Ramsdell JW, Nachtwey FJ, Moser KM. Bronchial hyperreactivity in chronic obstructive bronchitis. *Am Rev Respir Dis* 1982;128:829-32.
41. 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.
42. Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985;132:25-9.
43. Parker DR, O'Connor GT, Sparrow D, Segal MR, Weiss ST. The relationship on nonspecific airway responsiveness and atopy to the rate of decline of lung function. *Am Rev Respir Dis* 1990;141:589-94.
44. Stevens WJ, Vermeire PA. Bronchial responsiveness to histamine and allergen in patients with asthma, rhinitis cough. *Eur J Respir Dis* 1980;61:203-12.
45. Townley RG, Dennis M, Itkin IH. Comparative action of acetyl-beta-methylcholine, histamine, and pollen antigens in subjects with hay fever and patients with bronchial asthma. *J ALLERGY* 1965;36:121-37.
46. Cockcroft DW, Berscheid BA, Murdock KY. Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population. *Chest* 1983;5:751-4.
47. Varpela E, Laitinen LA, Keskinen H, Korhola O. Asthma, allergy, and bronchial hyperreactivity to histamine in patients with bronchiectasis. *Clin Allergy* 1978;8:273-80.
48. Van Asperen P, Mellis CM. Bronchial reactivity in cystic fibrosis with normal pulmonary function. *Am J Dis Child* 1981;135:815-9.
49. Northway WH Jr, Moss RB, Carlisle KB, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 1990;323:1793-9.
50. Britton JR, Tattersfield AE. Does measurement of bronchial hyperreactivity help in the clinical diagnosis of asthma? *Eur J Respir Dis* 1986;68:233-8.
51. Britton JR. Is hyperreactivity the same as asthma? *Eur Respir J* 1988;1:478-9.
52. Cockcroft DW, Hargreave FE. Airway hyperresponsiveness. Relevance of random population data to clinical usefulness. *Am Rev Respir Dis* 1990;142:497-500.
53. Burney P, Chinn S. Developing a new questionnaire for measuring the prevalence and distribution of asthma. *Chest* 1991;6:79-83.
54. Burney PGJ, Laitinen LA, Perdrizet S, et al. Validity and repeatability of the IUATLD (1984) bronchial symptoms questionnaire: an international comparison. *Eur Respir J* 1989;2:940-5.
55. Higgins BG, Britton JR, Chinn S, et al. The distribution of peak expiratory flow variability in a population sample. *Am Rev Respir Dis* 1989;140:1368-72.
56. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. *Am Rev Respir Dis* 1991;14:323-30.