

Bronchial Histamine Challenge in the Diagnosis of Asthma

The Predictive Value of Changes in Airway Resistance Determined by the Interrupter Method

F. MADSEN, N.-H. HOLSTEIN-RATHLOU, L. FRØLUND, B. WEEKE and U. G. SVENDSEN

Medical Dept. TA, Allergy Unit, State University Hospital, Copenhagen, Denmark

The predictive value of a bronchial challenge with histamine was determined in a prospective survey on a population with a high prevalence of asthma (0.62). Without knowledge of the bronchial responsiveness 133 patients were classified as asthmatics (83) or non-asthmatics (50) according to variation in peak expiratory flow rate and medical history. Response to challenge was determined by the interrupter method, and the concentration of histamine inducing a 40 % increase in resistance to breathing ($PC_{40}-R_t$) was calculated from the log dose response curve. When defining a positive test as a test giving $PC_{40}-R_t$ -values below 2.00 mg/ml, the predictive value of a positive test was 0.75 and the predictive value of a negative test was 0.72. By decreasing the limit for a positive test to 0.25 mg/ml the corresponding predictive value was increased to 0.91. When further increasing the limit to 4.00 mg/ml the predictive value of a negative test in the diagnosis of asthma was increased to 0.81. The interrupter technique is suitable for diagnostic purposes in the detection and exclusion of bronchial asthma.

Key words: bronchial asthma; bronchial challenge; interrupter method; predictive value.

Accepted for publication 16 November 1985

CLINICAL ASPECTS

Careful monitoring of lung function, perhaps for months or years, in patients without obstruction or with few attacks is necessary to detect or exclude bronchial asthma. In this study $PC_{40}-R_t$ has been found useful for detection or exclusion of bronchial asthma in patients without severe bronchial obstruction.

Bronchial hyperreactivity is a characteristic feature of bronchial asthma (27), and bronchial challenge (BC) has been used as a laboratory test for the diagnosis of bronchial asthma and for the assessment of the severity of asthma (4). Bronchial challenge has also been found of value in the investigation of the protective effects of drugs (23) and in the study of occupational airway diseases (6). Highly standardized methods for bronchial histamine challenge have been developed through standardization of the factors known to modify the response to inhaled nonspecific bronchoconstrictor agents (28). Standardization of BC has been per-

formed in an attempt to reduce the variation in the results due to the method applied. The method developed by Cockcroft et al. (4) has been shown to be highly reproducible (13, 16, 26) and able to distinguish asthmatics from non-asthmatics (8). Unfortunately, the method is time-consuming and the performance of a maximal forced expiratory manoeuvre (deep inspiration) may alter the bronchomotor tone (21) and demands full cooperation of the patients. More sensitive measurements of responses to challenge could shorten the test, especially if it could be measured simultaneously with inhalation of aerosols. The

specific airway conductance (sGaw) has been found four times as sensitive as the first second forced expiratory volume (FEV₁) in BC (3). sGaw is determined by means of a body plethysmograph. Alternative methods to determine airway resistance during BC are desirable, and the aim of the present study was to examine the predictive value of BC, using the resistance to breathing determined by the interrupter method (R_i) in differentiating asthmatics from non-asthmatics in a population with a high prevalence of asthma.

MATERIAL AND METHODS

Two hundred and ninety-eight patients referred from other hospitals or general practitioners to the outpatient department of allergy were consecutively offered BC in a prospective clinical survey (Table 1). The patients were referred for further diagnostic procedures and treatment of potential allergic diseases. Prior to the challenge the patients were excluded: if they refused BC, were unable to perform BC due to neuromuscular disorders, continued their bronchodilating medication, were infected, continued smoking, or were pregnant (Table 1). The remaining 221 patients then had BC performed after informed consent was obtained. Fifty-seven patients were excluded because of an FEV₁ below 60 % of the predicted (2) when challenged, 21 patients were excluded as they had received too high start concentration of histamine chloride, thus making interpolation unsafe. In 10 patients severe dyspnoea and coughing without a 40 % increase in R_i was the reason for termination of the provocation (Table 1). FEV₁ was registered and in these 10 patients the fall amounted to more than 20 % of the post-saline FEV₁-value. The remaining 133 patients were then included for the final analyses, and anthropometric data are given in Table 1. All patients completed a Danish translation of a British Medical Research Council questionnaire on respiratory symptoms (25) supplemented with questions about systemic allergic symptoms and allergic symptoms from eyes, nose, lungs, skin and digestive system (9). Anteroposterior and left lateral chest roentgenograms were without infiltrates and hilar lymphnode enlargement.

Classification of study population into asthmatic and non-asthmatics

It has not yet been possible to achieve agreement on an operational definition of bronchial asthma, but the following definition proposed by Scadding (27) has become widely accepted: "Asthma is a disease characterized by wide variations over short periods of time in resistance to flow in intrapulmonary airways". Like other diseases, asthma must initially be defined in qualitative terms. Practical application of the definition entails the adoption of quantitative factors. What magnitude of variability over what period of time? In this study "short periods of time" were defined as periods of less than 2 weeks duration, since then reversibility during a steroid reversibility test would be detected too. As limits for "wide variations in resistance to airflow" we have used a change in PEF of at least 15 % (30) of the predicted (11). At least two reproducible peak flow measurements in the morning (7–9 a.m.), in the evening (10–12 p.m.) and during attacks of breathlessness were obtained by means of a Mini Wright peak flow meter (Airmed, Harlow, England). Patients

Table 1
Selection of study population

	No. patients	No. patients
Referred to the clinic		298
Refused challenge	5	
Neuromuscular disorders	10	
Unable to abstain from bronchodilators	36	
Airway infections	4	
Smoking	20	
Pregnancy	2	
	77	77
Bronchial challenge performed in FEV ₁ 60 % of predicted	57	221
Received too high start concentration of histamine	21	
Severe dyspnoea before R _i had increased 40 %	10	
	88	88
Included for final analysis		133

receiving bronchodilators in addition determined PEF before and 15 min after nebulized bronchodilator.

At the first visit to the clinic, spirometry was performed in all patients on their usual medication, before and 15 min after inhalation of 0.5 mg salbutamol (Ventoline®). If bronchial obstruction persisted and FEV_1 was below 60 % of the predicted (2) the patients received 30 mg methylprednisolone every day for 2 weeks and spirometry was repeated. Before and after this reversibility test PEF was determined. The PEF-determination were also used for the assessment of fluctuation in resistance to airflow. Some patients only exhibit fluctuations in PEF after a specific allergen exposition, thus presenting a normal lung function ($FEV_1 > 75$ % of the predicted) and no fluctuation in PEF, and some patients do not show fluctuations in PEF owing to their treatment. Thus, patients with a normal spirometry without detectable changes in PEF are also included as having bronchial asthma (anamnesic bronchial asthma), if they gave a positive answer to the following two questions (25):

- 1) Have you ever had attacks of shortness of breath with or without wheezing?
- 2) Is/was your breathing absolutely normal between attacks?

Analyses of questionnaires and diary cards with PEF readings were performed without knowledge of bronchial responsiveness to histamine and clinical diagnosis. As a result of these analyses the patients were classified as asthmatics if they showed a variation in PEF of more than 15 % of the predicted PEF (11) or had anamnestic asthma.

We also divided the patients into the following five therapeutic groups according to their present medication, which was registered immediately before the BC:

- 1) Patients not receiving any kind of anti-asthmatic medication,
- 2) patients using β_2 -adrenergic agonists only,
- 3) patients using bronchodilators inclusive β_2 -adrenergic agonists,

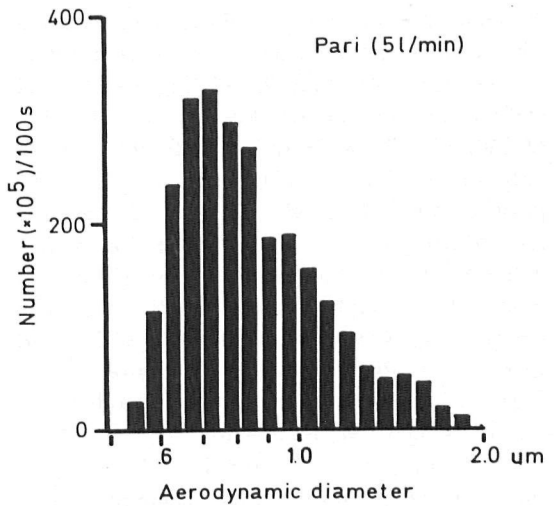


Fig. 1. Particle size of NaCl aerosol delivered by the Pari nebulizer (relative distribution of the aerodynamic diameters of the dry particles).

- 4) patients using inhaled steroids and bronchodilators,
- 5) patients using systemic and inhaled steroids and bronchodilators.

Bronchial challenge

According to our standard procedure the challenge was not performed if the patients had had respiratory tract infections within 2 months or had been smoking within 4 h prior to the planned challenge. The patients were not allowed to use antihistaminics for 72 h before challenge, sustained release methylxanthines for 48 h, plain methylxanthines, ipratropin, sodium cromoglycate or oral β_2 -agonists for 12 h, nebulized β_2 -adrenergic agonists for 8 h before BC. Local and systemic steroids were continued unchanged.

BC was performed using tidal volume breathing of aerosols delivered by a Pari nebulizer with mouthpiece (Paul Ritzau, Pariwerk, W. Germany). The nose was clipped and the output of the nebulizer was determined by calibration of the actual set up (28). The nebulizer was filled with 2.00 ml saline and weighed before and after 2 min tidal breathing. When driven by compressed air at a flow of 5.0 l/min the output was 221 mg/min (191–251) (median of

10 determinations). Under these conditions the aerodynamic diameter of the dry particles varies between 0.5 μm and 2 μm (Fig. 1). Aerosol composition was analysed during nebulization of both saline and histamine acid chloride, and only minor differences between aerosol composition were observed. The aerosol was analysed during 100 s sampling. The aerosol was delivered directly into a Kr-85 neutralizer (TSI model 3054) coupled to a diffusion dryer. The dry particles were led to a mixing chamber and in two steps diluted 1:10⁴ (TSI Diluter 3302). Particles were then analysed in an aerodynamic particle sizer (TSI, APS 300).

Inhalations were performed for 2 min with intervals of 5 min. After isotonic saline, unbuffered histamine chloride (HC) was used in doubling concentrations from 0.03 mg/ml to 16.00 mg/ml. For patients with a baseline FEV₁ above 80 % of the predicted the following modifications were used (28): patients without need for medication started by inhaling HC 2.00 mg/ml. Start concentration 0.25 mg/ml was used if patients only used bronchodilators and 0.125 mg/ml if they used steroids. The challenge was continued until an HC-dose was reached inducing at least a 40 % increase in the post-saline R_t (threshold dose) measured 60 s after termination of the inhalation. Thereafter the provocative concentration of HC (PC₄₀) resulting in a 40 % increase in R_t was determined by linear interpolation between the last two test points on the log dose response curve. Interpolation between R_t-saline and R_t-threshold dose was never performed. Values below 0.03 mg/ml and above 16.00 mg/ml were reported as 0.03 and 16.00 mg/ml, respectively.

Determination of R_t was performed by the interrupter method (1, 16, 22, 24) (APTA, Eric Jaeger, Wurtzburg, W. Germany) 60 s after termination of the inhalation. The APTA (now Bronchoscreen) has a combined provocation-measuring head. In the present study we only used flow interruption during expiration. R_t was determined using the formula:

$$R_t = (P_{\text{alv}}/P_m - 1) \times R_{\text{ref}}$$

where the pressure in the alveolar compartment (P_{alv}) is obtained indirectly by measuring the mouth pressure after closing the shutter. P_m is the pressure measured during free flow. R_{ref} is a fixed serial resistance. The shutter was triggered by an exhaled volume of 180 ml and opened after 100 ms closure. The triggering volume was determined by integrating the signal from a low resistance Lilly pneumotach which had a linearity of $\pm 2\%$ at a flow below 12 l/s. The pressure was determined by a differential transducer (MicroSwitch PK 87636, Honnywell).

Before each challenge the interrupter was calibrated. A vent produced an airflow of 105 l/min, which was led through the shutter, and a calibrating resistance (0.10 kPa l⁻¹ × s) and the determined R_t had to be within $\pm 10\%$ of the reference resistance. Under these conditions the repeatability of R_t is high. For replicated measurements on the same subjects the within-group standard deviation was 0.03 kPa l⁻¹ × s, and the variation was independent of the magnitude of the measurement. Volumes are reported at ambient temperature, atmospheric pressure and saturated with water vapour.

Statistical analysis

Results are reported as median with the range in parentheses. Differences between groups were analysed by the Mann Whitney test (2 α = 0.05) (5). Calculation of diagnostic specificity and sensitivity was done by means of Bayes' theorem (33, 34):

$$P(A/C) = \frac{P(A) \times P(C/A)}{P(A) \times P(C/A) + P(\bar{A}) \times P(C/\bar{A})}$$

$$P(\bar{A}/\bar{C}) = \frac{P(\bar{A}) \times P(\bar{C}/\bar{A})}{P(\bar{A}) \times P(\bar{C}/\bar{A}) + P(A) \times P(\bar{C}/A)}$$

C = positive challenge

$\bar{C}$ = negative challenge

P(A) = probability of having asthma = prevalence

P($\bar{A}$) = probability of not having asthma = 1-prevalence

P(C/A) = probability of a positive challenge if having asthma

$P(C/\bar{A})$ = probability of a positive challenge if not having asthma

$P(A/C)$ = probability of having asthma if the BC is positive = diagnostic specificity = the predictive value of a positive test

$P(\bar{A}/\bar{C})$ = probability of not having asthma if BC is negative = diagnostic sensitivity = the predictive value of a negative test.

RESULTS

The lowest pre-challenge R_t was found in the patients receiving systemic steroids and the lowest FEV₁ per cent predicted was found in the groups "all bronchodilators" and "systemic steroids", but it should be noted that these groups contain only few patients (Table 2). PEF was measured for 45 days (14–91). Fig. 2 shows the PC₄₀-values in the five therapeutic groups. Table 3 shows the probability of having bronchial asthma according to our definition: if PC₄₀ was below a value between 16.00 mg/ml and 0.03 mg/ml. It is noted that 100 % is not reach-

ed and P_{pos} has a maximum for PC₄₀ < 0.25 mg/ml. The 95 % confidence interval for the probabilities is indicated in Table 3. The predictive value of a negative challenge has a maximum for PC₄₀ > 4 mg/ml (Table 3), and the fall in P_{pos} with a further increase in PC₄₀ is probably due to the small number of patients with a PC₄₀-value above 4 mg/ml ($n = 16$).

To discriminate between asthmatics and non-asthmatics the single optimal PC₄₀-value is 2.00 mg/ml resulting in a P_{pos} - and a P_{neg} -value of 75–72 %. P_{pos} is not increased by inhaling concentrations below 0.25 mg/ml and P_{neg} is not increased by inhaling concentrations above 4.00 mg/ml. Two thirds of the patients were classified as asthmatics, since variation in PEF was larger than 15 % of the predicted and correspondingly one third was classified as anamnestic asthmatics.

DISCUSSION

If the widely accepted definition stated by Scadding is accepted, bronchial asthma can only be confirmed through monitoring of pulmonary

Table 2

Number of patients (n), males/females (M/F), age (years), height (cm), FEV₁ in per cent of predicted (FEV₁ % pred.), R_t baseline (kPa l⁻¹ s), PC₄₀- R_t (mg/ml histamine), PEF % predicted. Range is given in parentheses

Therapeutic group	Medication				
	None	β_2 -agonists only	All bronchodilators	Local	Steroids Systemic
n	44	33	15	34	7
M/F	20/24	14/19	9/6	12/22	3/4
Age	35 (17–66)	35 (16–75)	28 (18–77)	34 (16–57)	33 (17–50)
Height	175 (155–212)	171 (141–188)	172 (156–193)	168 (155–183)	171 (166–185)
FEV ₁ % pred.	99 (61–135)	92 (61–129)	87 (63–134)	92 (60–130)	88 (75–105)
R_t baseline	0.31 (0.16–0.58)	0.39 (0.18–0.67)	0.33 (0.16–0.65)	0.40 (0.20–0.89)	0.28 (0.16–0.68)
PC ₄₀ - R_t	2.162 (0.03–16.00)	0.238 (0.03–16.00)	0.057 (0.03–2.282)	0.154 (0.03–6.189)	0.564 (0.03–3.335)
Δ PEF % pred.	8 (0–60)	25 (3–65)	14 (4–40)	22 (3–49)	28 (10–51)

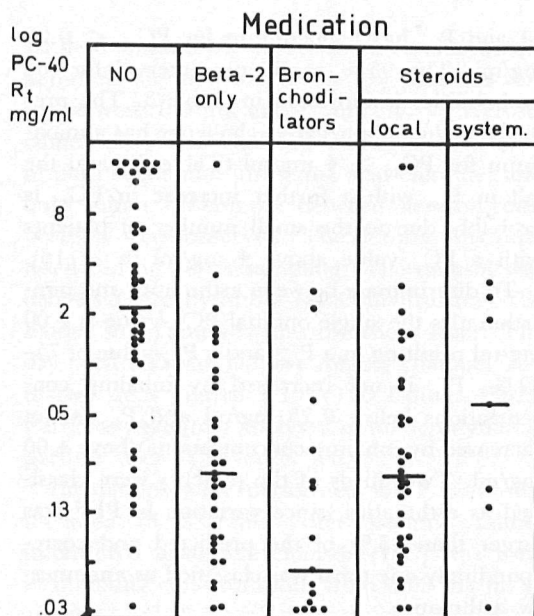


Fig. 2. Distribution of $PC_{40}-R_t$ in five therapeutic groups.

function. If concurrent causes of bronchial obstruction such as bronchiolitis and oedema could be excluded, changes of a certain magnitude in R_t or FEV_1 are pathognomonic for asthma. A rapid diagnosis of bronchial asthma can in some patients be obtained through a bronchodilator reversibility test or, if the patient has allergic asthma, exposure to the specific allergen. Exclusion of asthma demands, if attacks are rare, careful monitoring of lung function, maybe for years.

It was necessary to classify a group of patients without documented changes in PEF as anamnestic asthmatics. Some patients only have few spontaneous attacks of asthma, and in some patients variation in PEF is only seen during specific allergen exposure which may seldomly occur. In this study all patients classified as anamnestic asthmatics showing normal spirometry at each visit to the clinic were included, and BC, especially in these patients, seems to be a valuable diagnostic test. If hyper-reactive patients without bronchial asthma were classified as asthmatics, the result would have been a false high predictive value of a positive test. Non-specific bronchial hyperreactivity has been found to increase in several other condi-

tions besides bronchial asthma, and some of these may give rise to episodic breathlessness and thus simulate bronchial asthma. Increased bronchial reactivity can be a manifestation of pulmonary tuberculosis (14), pulmonary sarcoidosis (15), bronchiectasis or cystic fibrosis (33). On account of normal roentgenograms and evaluation of medical records (without knowledge of PC -values), the risk of including patients with the above-mentioned disorders was only minor in this study. Farmers lung, other types of extrinsic allergic alveolitis, and hypersensitive pneumonitis may result in episodic breathlessness, variation in PEF and recurrent pulmonary infiltrates. Patients suffering from farmers lung have increased bronchial hyperreactivity (20) which initially can simulate bronchial asthma. However, the occurrence of these disorders is low in our clinic (one to two cases per year), and usually they are identified by the questionnaire (9, 25) at the first visit. Simple chronic bronchitis (10) (cough and mucopurulent expectoration without airway obstruction) and chronic obstructive bronchiolitis are different disorders, and airway reactivity has been found increased in both (29). The hyperreactivity found in patients with obstructive bronchiolitis (29) may be due to low prechallenge FEV_1 . In this study, however, patients with prechallenge FEV_1 predicted $< 60\%$ were excluded. Bronchial hyperreactivity in simple bronchitis, allergic rhinitis (19)

Table 3

$PC_{40}-R_t$	Predictive value of a positive test $PC_{40} < x$ mg/ml %	$PC_{40}-R_t$	Predictive value of a negative test $PC_{40} \geq x$ mg/ml %
0.03	85 (60-98)	0.03	39 (30-48)
0.06	88 (70-98)	0.06	43 (33-53)
0.12	89 (73-96)	0.12	47 (40-62)
0.25	91 (81-97)	0.25	58 (45-69)
0.50	87 (77-94)	0.50	63 (49-74)
1.00	83 (72-90)	1.00	66 (51-78)
2.00	75 (65-82)	2.00	72 (53-86)
4.00	69 (63-80)	4.00	81 (55-96)
8.00	67 (57-75)	8.00	80 (45-98)
16.00	66 (57-74)	16.00	75 (35-97)

Asthma $n = 83$.

Non-asthma $n = 50$.

or chronic coughing (7) has not biased this study, since variations in PEF or episodic dyspnoea are not found in these disorders.

In the present study we have found R_t determined by the interrupter method able to discriminate between asthmatics and non-asthmatics. If only one PC value was used to define the BC as positive or negative the maximal diagnostic specificity and sensitivity of R_t was 0.75 and 0.72, respectively at 2 mg/ml. Previously, we have found the corresponding maximal diagnostic specificity and sensitivity of PC_{20} - FEV_1 to be 0.76 and 0.81, respectively, for a concentration of 4 mg/ml (17). By lowering the limit for a positive test to 0.25 mg/ml a maximal diagnostic specificity of 0.91 is obtained, which is slightly, but statistically not significantly lower than the corresponding value obtained by the PC_{20} - FEV_1 which was 1.00. When comparing the diagnostic sensitivity and specificity obtained in the present study with others, the definition of asthma and the actual prevalence of asthma in the population should be taken into consideration, since a high prevalence will increase the diagnostic specificity and decrease the diagnostic sensitivity and a low prevalence will have the opposite effect. If Cockcroft's material (4), in which the prevalence of asthma was 0.51, is recalculated and the limit for a positive challenge is placed at 8 mg/ml, the diagnostic specificity is 0.83 and the sensitivity 1.00. If patients with rhinitis and cough are excluded from Cockcroft's material the diagnostic specificity increases to 1.00.

Based on theoretical considerations (28) the SEPCR Working group on "Bronchial hyper-reactivity" has stated that "the airway interrupter technique is unsuitable for recording responses to bronchial challenge since, as the lungs' mechanical properties are not homogeneous, its validity in severely obstructed patients is controversial".

Nevertheless, we found R_t useful as a measurement of response to diagnostic challenge. The value of the interrupter technique in the assessment of hyperreactivity has only been reported in one study. Plas & Vooren (24) found that histamine affects the entire airway, and for practical purposes such effects can be

well assessed by either spirometry or the opening interrupter (24).

The airway interruption technique is old. It has the obvious advantage of being easily performed during normal, quiet breathing. It has not been widely used for BC. The working group of the European Society for Respiratory Physiology (28) finds the method unsuitable for BC. It is argued that the inhomogeneity of the lungs' mechanical properties invalidates the method for BC.

The aim of the present study was to test this statement and to report the predictive values of R_t in the diagnosis of asthma. The repeatability of PC_{40} - R_t is sufficient for diagnostic and research purposes (22), whereas the PC_{30} - R_t is unsuitable for clinical and research purposes because of its low repeatability (16). In the present study we have shown that the interrupter method determined R_t can be used for diagnostic BC when patients are without severe bronchial obstruction ($FEV_1 > 60\%$ of predicted). The mechanical inhomogeneity of the lungs increases with increase in bronchial obstruction, and until the method has been tested in patients with obstruction it should be restricted to the relatively non-obstructive patients.

By means of the interrupter method the R_t can be determined without a previous deep inspiration, which could reduce the response to bronchoconstrictor agents (21), and R_t can be measured simultaneously with the inhalation of aerosols making cumulative studies easy to perform.

Compared to the body plethysmograph the interrupter is mobile, but unable to correct for changes in lung volume during challenge. Compared to spirometry the patient should be accustomed to both the body box and the interrupter for a longer period of time.

At present the FEV_1 and R_t seem almost equally suited for diagnostic bronchial histamine challenge (17). If a higher diagnostic sensitivity and specificity are needed it would be possible to combine the measurement of R_t or sGaw with the determination of flows at 25 or 50 % of total lung capacity on a partial expiratory flow curve.

ACKNOWLEDGEMENTS

The technical help and care of the patients by Mrs Jytte Bjørnsten and Mrs Ruth Møller are gratefully acknowledged. Particle size: Draco AB made determination of the aerosol composition possible by giving us access to the TCI analyser. The study was supported by grants from the Augustinus Foundation and A. P. Møller og Hustru Christine McKinney Møllers Fond til almene Formaal.

REFERENCES

- Berger, D. & Nolte, D.: Erlebt die Atemwiderstandsmessung mit der Unterbrechermethode eine Renaissance? *Prax. Pneumol.* 33, 726-730, 1979.
- Berglund, E., Birath, G., Bjure, J., et al.: Spirometric studies in normal subjects. *Acta Med. Scand.* 173, 185-192, 1963.
- Cockcroft, D. W. & Borscheid, B. A.: Measurement of responsiveness to inhaled histamine: Comparison of FEV₁ and sGaw. *Ann. Allergy* 51, 374-377, 1983.
- Cockcroft, D. W., Killian, D. N., Mellon, J. J. A. & Hargreave, F. E.: Bronchial reactivity to inhaled histamine. A method and clinical survey. *Clin. Allergy* 7, 235-243, 1977.
- Conover, W. J.: Practical non-parametric statistics. 2nd ed. Wiley, New York, 1980.
- Cartier, A., Pineau, L. & Malo, J. L.: Monitoring of maximum expiratory flow rates and histamine inhalation tests in the investigation of occupational asthma. *Clin. Allergy* 14, 193-196, 1984.
- Carrao, W. M., Braman, S. S. & Irwin, R. S.: Chronic cough as the sole presenting manifestation of bronchial asthma. *N. Engl. J. Med.* 300, 633-637, 1979.
- Dehaut, P., Rachiele, A., Martin, R. R. & Malo, J. L.: Histamine dose-response curves in asthma: reproducibility and sensitivity of different indices to assess response. *Thorax* 38, 516-522, 1983.
- Dirksen, A.: Clinical vs. paraclinical data in allergy. *Danish Med. Bull.* 29, Suppl. 2, 1982.
- Fletcher, C., Peto, R., Tinger, C. & Speizer, F. E.: The natural history of chronic bronchitis and emphysema. Oxford University Press, New York, 1977.
- Gregg, I. & Nunn, A. J.: Peak expiratory flow in normal subjects. *Br. Med. J.* 3, 282-284, 1973.
- Hargreave, F. E., Ryan, G., Thompson, N. C., et al.: Bronchial responsiveness to histamine or metacholine in asthma: measurement and clinical significance. *J. Allergy Clin. Immunol.* 68, 347-355, 1981.
- Juniper, E. F., Frith, P. A., Dunnet, C., Cockcroft, D. W. & Hargreave, F. E.: Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 33, 705-710, 1978.
- Laitinen, L. A. I.: Histamine and metacholine challenge in the testing of bronchial reactivity. *Scand. J. Respir. Dis. Suppl.* 86, 1974.
- Laitinen, L. A., Haahtela, T., Kava, T. & Laitinen, A.: Non-specific bronchial reactivity and ultrastructure of the airway epithelium in patients with sarcoidosis and allergic alveolitis. *Eur. J. Respir. Dis.* 64, Suppl. 131, 267-284, 1983.
- Madsen, F., Holstein-Rathlou, N.-H., Frølund, L., Svendsen, U. G. & Weeke, B.: Short and long-term reproducibility of responsiveness to histamine. R₁ compared to FEV₁ as measurement of response to challenge. *Eur. J. Respir. Dis.* 1985 67:193-203.
- Madsen, F., Holstein-Rathlou, N.-H., Mosbech, H., Svendsen, U. G. & Weeke, B.: The predictive value of bronchial histamine challenge in the diagnosis of bronchial asthma. *Scand. J. Clin. Lab. Invest.* 1985 45, 453-460.
- Michoud, M. C., Ghezzi, H. & Amyot, R.: A comparison of pulmonary function tests used for bronchial challenges. *Bull. Eur. Physiopathol. Respir.* 18, 609-621, 1982.
- Mygind, N.: Nasal allergy. Blackwell, Oxford, 1978.
- Mönkare, S.: Clinical aspects of farmer's lung: airway reactivity, treatment and prognosis. *Eur. J. Respir. Dis.* 65, Suppl. 65, 1984.
- Orchek, J., Gayraud, P., Grimaud, C. & Charpin, J.: Effects of a maximal expiratory manoeuvres on bronchial sensitivity of asthmatic patients as compared to normal people. *Br. Med. J.* 1, 123-125, 1975.
- Pavlovic, M., Holstein-Rathlou, N.-H., Madsen, F., Svendsen, U. G. & Weeke, B.: Bronchial histamine challenge. A combined interrupter-dosimeter method compared with a standard method. *Allergy* 40, 574-579, 1985.
- Phillips, M. J., Ollier, S., Gould, C. A. L. & Davies, R. J.: Effect of antihistamines and antiallergic drugs on responses to allergen and histamine provocation tests in asthma. *Thorax* 39, 345-351, 1984.
- Plas, K. & Vooren, P.: The "opening" interrupter. *Eur. J. Respir. Dis.* 63, 449-458, 1982.
- Questionnaire on Respiratory Symptoms. Medical Research Council, London, 1976.
- Ryan, G., Dolovich, M. B., Roberts, R. S., et al.: Standardization of inhalation provocation tests: Two techniques of aerosol generation and inhalation compared. *Am. Rev. Respir. Dis.* 123, 195-199, 1981.
- Scadding, J. G.: Definition and clinical categories of asthma. In Clark, T. J. H. & Godfrey, S. (eds.): *Asthma*, pp. 1-10. Chapman & Hall, London, 1977.
- SEPCR Working Group: Bronchial hyperreactivity. In Eiser, N. M., Kerrebijn, K. F. & Quanjer, P. H. (eds.): *Guidelines for standardization of bronchial challenges with (nonspecific) bronchoconstrictor agents*. *Bull. Eur. Physiopathol. Respir.* 19, 495-514, 1983.
- Simonsson, B.: Studies on chronic bronchitis. (Thesis), Gothenburg, 1965.
- Sobol, B. J. & Emergil, C.: Pulmonary function tests and the diagnosis of bronchial asthma. *Ann. Allergy* 37, 340-345, 1976.
- Sterk, P. J., Plomp, A., van de Vate, J. F. & Quanjer, P. H.: Physical properties of aerosols produced by several jet- and ultrasonic nebulizers. *Bull. Eur. Physiopathol. Respir.* 20, 65-72, 1984.
- Vecchio, T. J.: Predictive value of a single diagnostic

- test in unselected populations. *N. Engl. J. Med.* 274, 1171-1173, 1966.
33. Varpela, E., Laitinen, L. A., Keskinen, H. & Korhola, O.: Asthma, allergy and bronchial hyperreactivity in patients with bronchiectasis. *Clin. Allergy* 8, 273-280, 1978.
34. Wulff, H. R.: Rational diagnosis and treatment. Blackwell, Oxford, 1981.
- Address:
Flemming Madsen, M.D.
Medical Dept. TA
Allergy Unit 7511
Rigshospitalet
Tagensvej 20
DK-2200 Copenhagen N
Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.