Does non-specific bronchial responsiveness indicate the severity of asthma?

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ABSTRACT: It is difficult to analyse the relationship between bronchial responsiveness and the severity of asthma since each alone is difficult to assess. Asthma is a heterogeneous condition with many patterns of expression, and clinical methods used to assess its severity have their limitations. Problems also arise in interpreting the results of bronchial provocation tests and methodological differences make comparisons between studies difficult. The findings of both cross-sectional and longitudinal studies have shown a general relationship between the degree of responsiveness and the severity of asthma, but within subjects the relationship is weaker. A greater understanding must await increased knowledge of the mechanisms underlying asthma and the contribution which hyperresponsiveness makes to each of these.
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A characteristic feature of asthma is the tendency of the bronchi to respond to a variety of stimuli both more readily and with a greater degree of narrowing than do the bronchi of normal subjects. In most patients with asthma this phenomenon can be reproduced artificially by bronchial provocation with certain "non-specific" pharmacological or physical stimuli, such as histamine, methacholine or exercise. It is widely believed that the response to artificial challenge reflects the underlying lability of the airways in asthma, and that measured levels of "bronchial responsiveness" reflect the severity of the disease. Given the limitations of clinical methods of assessment, such an objective index of severity would be of potential value in the management of asthma, particularly for evaluating the effects of therapy and for identifying patients at risk of sudden life-threatening attacks.

The aim of this paper is to review current knowledge concerning the relationship between responsiveness and asthma severity; however, before considering the findings of studies which have investigated this, it is necessary to examine various problems relating, on the one hand, to the concept of what constitutes severity of asthma and, on the other hand, to methodological aspects and the interpretation of provocation tests.

Asthma severity

Asthma, as defined by SCADDING [1], does not imply a single disease, though common use of the term has tended to lead to this assumption. The term encompasses many patterns of response to a variety of stimuli, which find common expression in variable airflow obstruction. Within this heterogeneous condition, there is no single criterion by which severity may be adequately described; in some patients frequent acute attacks, even if not dangerous in themselves, may impose considerable restriction of normal activities. In others occasional but very severe attacks constitute severity of a different kind, often involving danger of death. In yet others airflow obstruction may be persistent, resulting in chronic disability. Furthermore, in any patients who are taking anti-asthma therapy, clinical severity is the result of the inherent intensity of their asthma and the modifying effects of treatment upon it.

Assessment of severity usually relies on history, examination and simple tests of ventilatory function, though each of these has its limitations. Symptoms may be absent despite considerable airflow obstruction: some patients perceive airflow obstruction poorly [2], while others adapt to severe airflow obstruction and no longer appreciate their disability. Physical examination, especially auscultation, can be equally misleading. While measurements of forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) are invaluable in the assessment of the degree and variability of airflow obstruction, reduction in airway calibre may occur over short periods of time and not be revealed by only occasional measurements. Treatment requirements are often considered to reflect asthma severity, but will be affected by differences in a subject's ability to detect airflow obstruction, to tolerate symptoms, and differences in lifestyle (especially physical activity) which would affect a subject's individual need for treatment.

Bronchial responsiveness

Difficulties arise in interpreting the results of bronchial provocation tests. Methodological factors, including subject selection, the provoking stimulus employed, measurement of the response and analysis of the dose-response relationship, may all influence the results obtained and make it difficult to compare the findings from different studies. Problems of terminology have led to further confusion, with a wide variety of terms such as "reactivity", "responsiveness" and "sensitivity" being used in different senses by different authors.

"Non-specific" responsiveness is most commonly measured using histamine or methacholine, though a variety of other chemical or physical stimuli have been used. Hyperresponsiveness to these stimuli is termed "non-specific" to distinguish it from the specific sensitization of some asthmatic subjects to allergens or certain occupational agents. While in a group of subjects there is generally a good correlation between responsiveness to histamine and methacholine [3], this is not necessarily so for an individual [4]. In addition, responsiveness to pharmacological stimuli is less well correlated with responsiveness to exercise [5, 6] and poorly correlated with the response to hypo- and hyper-osmolar stimuli [7, 8]. Since it is probable that different mechanisms underlie the response to different agents used for provocation, the concept of "non-specific" responsiveness may be an oversimplification and the observed relationship between responsiveness and clinical asthma may be affected by the nature of the stimulus used to investigate it [9].

There is no one standard technique of delivering aerosols of histamine or methacholine, though three principal methods are currently in widespread use. In the method described by COCKCROFT *et al.* [10], aerosols are generated by a continuous output nebulizer and inhaled during timed periods of tidal breathing. In the method of CHAI *et al.* [11], a pre-determined number of breaths are taken from an intermittent dosing device powering a nebulizer and the aerosol is inhaled by inspiration to total lung capacity. In the most recently described method of YAN *et al.* [12], hand-held nebulizers are used to deliver increasing doses of agonist, synchronizing full inspiration with actuation of the nebulizer. Studies which have compared these methods have shown a good correlation between them [13, 14].

There are no direct methods for measuring airway calibre. The tests most widely used involve maximal inspiratory and expiratory manoeuvres, and these may exert their own unpredictable effects on the results of the challenge [15]. In the situation of induced bronchoconstriction, a deep inspiration generally reduces [15, 16] though sometimes increases [17] bronchial tone in subjects with asthma, resulting in a variable effect on the results of bronchial challenge even though the degree of pharmacologically-induced airway narrowing may be similar. Notwithstanding the problems associated with maximal respiratory manoeuvres, FEV_1 is the most commonly used measure of airflow obstruction; other indices, such as airways resistance or specific airways conductance, though more sensitive to changes in airway

calibre than measurements of FEV_1, are less repeatable [18].

A variety of indices of the dose-response relationship have been used to express responsiveness. The most widely used is the provoking dose or concentration which causes a given percentage change in lung function *e.g.* a fall of 20% in FEV_1 (the PD_{20} or PC_{20}). Responsiveness can also be described in terms of the threshold dose or concentration, which is the point at which a significant reduction in airway calibre first occurs. Both the threshold and the PC_{20} or PD_{20} indicate the position of the dose-response curve rather than its shape, and reflect the sensitivity to airway narrowing stimuli. However, these measures alone may not adequately characterize the response to bronchial provocation and other indices derived from the curve, such as its slope or maximal response, might be important [19]. In particular, the maximal response reflects the extent to which the airways can narrow when exposed to high doses of inhaled stimuli and may be an important aspect of the relationship in subjects with asthma.

Literature review

The findings of studies which have investigated the prevalence of non-specific hyperresponsiveness in different populations suggest that there is no simple relationship between asthma and levels of responsiveness. Hyperresponsiveness has been demonstrated in 3% of normal adults [10], and more frequently in relatives of atopic or asthmatic subjects [20], and in 15–22% of subjects who have rhinitis [10, 21]. In children, hyperresponsiveness has been reported in 6–8% of those without symptoms [22, 23] but was absent in about a third of those with recurrent wheezing [23, 24].

In subjects with a past history of asthma, bronchial hyperresponsiveness frequently persists, though usually at lower levels than in subjects with current disease [25–27]. In patients who had been free of asthma for 1–20 yrs, TOWNLEY *et al.* [21] found a relationship between the degree of bronchial hyperresponsiveness and the severity of previous asthma.

In subjects with current asthma, the relationship between responsiveness and severity of asthma has been investigated by both cross-sectional and longitudinal studies. Severity of asthma has been assessed in terms of symptoms and other features in the history, the degree of airflow obstruction and the level of of treatment needed to control symptoms.

Cross-sectional studies (table 1)

MAKINO [28] investigated the relationship between symptoms of asthma and the threshold dose of acetylcholine or histamine in 89 adults who were asymptomatic at the time of challenge. A modest correlation was found between levels of responsiveness and several features in the history (r=-0.37 to -0.46) though levels were not related to symptom scores during the preceding two weeks.

Table 1. – Cross-sectional studies examining the relationship between bronchial responsiveness and the severity of asthma

Reference	Population (n)	Age range (yrs)	Challenge test Agent/dose/index BR	Criteria Asthma severity	Results
MAKINO [28] 1966	Asthma (54)	14–64	Ach 39.7–20,000 µg	Symptoms 2 wk before test Symptoms 1 yr before test	No corr. Ach or H Corr. Ach and H
	Asthma (35)	14–63	H 4.0–2,000 µg TD producing >10% fall FEV_1	Symptoms since onset asthma	Corr. Ach and H
MURRAY [29] 1981	Asthma (78)	6–18	H 0.03–8 mg·ml^{-1} PC_{20} (FEV_1)	History score 1 yr before test: estimate severity; no. days symptoms; no. days on Rx; need for CSd; wheeze on exertion	Corr. each index
RYAN [30] 1982	Current (27) Asthma Past (5) Asthma	21–67 35–52	H 0.03–64 mg·ml^{-1} PC_{20} (FEV_1)	PEF am and pm for 7 days after test: mean am PEF% max; mean pm PEF% max; mean increase am/pm PEF after salbutamol; diurnal variation PEF	Corr. each index
BAHOUS [31] 1985	Subjects (27) with episodic cough, dyspnoea or wheezing and mild to moderate BHR (PC_{20} 0.3–16 mg·ml^{-1}) on no regular treatment	15–48	H 0.03–16 mg·ml^{-1} PC_{20} (FEV_1)	PEF 4 times daily for >7 days after test: mean daily % change PEF	Corr.
SPECTOR [4] 1975	Asthma (185)	14–70	M 0.25–10 mg·ml^{-1} (increasing breath method) and 0.075–25 mg·ml^{-1} (constant breath method) H 0.02–1 mg·ml^{-1} (increasing breath method) and 0.03–10 mg·ml^{-1} (constant breath method) TD producing >20% fall in FEV_1: low, medium, high categories BR	Discharge dose CSd; prednisone (5 mg) or methylprednisone (4 mg) 3 categories: low (≤3 tabs alt. days) med (>3 tabs alt. days) high (daily tabs)	All subjects with low BR M discharged on low dose CSd; Corr. dose CSd with BR M but not with BR H
COCKCROFT [10] 1977	Asthma (156)	Adults	H 0.03–8 mg·ml^{-1} PC_{20} (FEV_1)	Minimum Rx 1. none 2. bronchodilator as required 3. regular bronchodilator 4. CSd	Mean BR different each group; 4>3>2>1
JUNIPER [32] 1981	Asthma (51)	15–70	H and M 0.03–16 mg·ml^{-1} PC_{20} (FEV_1) mean H and M	Minimum Rx 4 categories as above [10]	Mean BR different each group; 4>3>2>1

BR: bronchial responsiveness; BHR: bronchial hyperresponsiveness; Ach: acetylcholine; H: histamine; TD: threshold dose; Corr: correlation; PC_{20} (FEV_1): concentration resulting in a 20% fall in forced expiratory volume in one second: no.: number; Rx: treatment; CSd: corticosteroid; am: morning; pm: evening; M: methacholine; med: medium.

Broadly similar findings were reported by MURRAY et al. [29] in 78 children with asthma who were studied on a day when they were asymptomatic. A significant relationship was found between responsiveness (PC_{20} histamine) and individual features in the history considered to reflect the severity of asthma over the previous year (r=-0.22 to -0.43), with a strengthening of the correlation when these features were combined (r=-0.61).

Serial measurements of airflow obstruction were used as an index of asthma severity by RYAN et al. [30] who studied the relationship between variability in peak expiratory flow (PEF) and PC_{20} histamine in subjects with current asthma, a past history of asthma and in normal subjects. A single measurement of responsiveness was made and, for the following seven days, PEF was measured each morning and evening, before and after inhaling salbutamol. A strong association was found between the level of responsiveness and the degree of reduction in morning PEF (r=0.79), the amount by which this improved after salbutamol (morning r=-0.75,

evening r=-0.80) and the diurnal variation in PEF, as measured by the difference between the lowest pre-salbutamol level and the highest post-salbutamol level (r=-0.81). However, when they examined the relationship between responsiveness and the degree of naturally occurring diurnal variation in PEF (without salbutamol), a weaker correlation was observed (r=0.41). Similar findings were reported by BAHOUS et al. [31] who studied 27 adults with mild symptoms of bronchial irritability and low or moderate levels of hyperresponsiveness (PC$_{20}$ 0.3–16 mg·ml^{-1} histamine), most of whom had no clinically significant airflow obstruction. A modest relationship was found between diurnal changes in PEF without bronchodilator and PC$_{20}$ (r=-0.51).

Treatment requirements have been used by other investigators as an index of asthma severity. SPECTOR and FARR [4] reported that levels of responsiveness were related to corticosteroid requirements in 200 subjects referred because of difficulty in controlling their asthma. Applying the principle that corticosteroids were the last medication to be added to an individual's treatment regime and the first to be discontinued, they proposed that the dose of corticosteroid at the time of hospital discharge was a reflection of the severity of a subject's asthma; they related an individual's responsiveness to both histamine and methacholine on admission to that subject's dose of corticosteroid on discharge. Arbitrarily dividing responsiveness into low, medium and high categories, according to the concentrations of histamine or methacholine tolerated, they found that all subjects with low levels of responsiveness to methacholine were discharged on no more than 15 mg prednisone or 12 mg methylprednisolone on alternate days. However, the converse was not true in that not all subjects with the highest levels of responsiveness required high doses of corticosteroids. These findings were not confirmed with respect to histamine, in that no significant correlation was observed between responsiveness to histamine and the discharge dose of corticosteroids, although none of the subjects discharged without corticosteroids were in the highly reactive group.

COCKCROFT et al. [10] observed that, in 156 well-controlled asthmatic subjects, mean levels of responsiveness increased with increasing treatment requirements. This was a retrospective study of subjects in whom the general principle of minimum medication for control of asthma was applied. There was a difference in PC$_{20}$ histamine between groups of subjects who were asymptomatic and on no treatment, those who required bronchodilators occasionally, those who required them regularly, and those who were steroid dependent. However, while the mean PC$_{20}$ in each subgroup was significantly lower than for the preceding category, there was considerable overlap between the ranges of responsiveness observed in each group. A prospective study by JUNIPER et al. [32] confirmed these results: using similar categories of treatment as in the study by COCKCROFT et al. [10], a significant difference was found between the mean PC$_{20}$ values in each treatment group, but again there was a considerable range of PC$_{20}$ values within each group and overlap between groups. The authors

suggested that this implied factors other than enhanced responsiveness were important in contributing to the severity of asthma.

One problem in interpreting the findings of cross-sectional studies is that subjects have generally been investigated when in a stable state and when such factors as respiratory viral infection, allergen exposure or recent exacerbations, which are believed to influence responsiveness, have been avoided in the weeks directly preceding the test. Since asthma is a condition whose hallmark is its variability, the conclusions from such studies may clearly not be applicable to the disease as it is encountered in clinical practice.

Longitudinal studies

In longitudinal studies, measurements of responsiveness are made on multiple occasions, in order to relate any observed changes in responsiveness to changes in the severity of asthma. In these studies the relationship between responsiveness and indices of asthma severity has been less clear-cut. BEAUPRÉ et al. [33] measured responsiveness to histamine in 15 adult asthmatics on two occasions, one year apart. They concluded that changes in responsiveness (PD$_{20}$) were related to changes in the state of asthma. The initial test was performed when each subject's asthma had been stable for 2 months; at the time of the second test, a change in at least 2 of the 3 variables, *i.e.* symptoms, treatment or a greater than 10% change in baseline FEV$_1$, constituted a "changed state". On this basis, changes in PC$_{20}$ of more than a single doubling dilution were shown by 5 out of 6 subjects not in a stable state, but by none of 9 subjects who were stable. This relationship was only confirmed for PC$_{20}$, the changes in slope of the dose-response curve failing to differentiate stable from non-stable subjects.

In a community survey of 78 subjects with respiratory symptoms by BRITTON et al. [34], PD$_{20}$ histamine was measured in September and March to assess the seasonal variation in responsiveness and its clinical correlates. Cross-sectional analysis of this data showed that, at both times of the year, there was a significant negative correlation between PD$_{20}$ and the current frequency of wheezing in the previous week and month, and with the amount of treatment needed. In 45 of these subjects, the majority of whom had diagnosed asthma, PD$_{20}$ was measurable on one or both occasions (<8 μmol histamine). In these subjects, responsiveness fell between September and March and, within subjects, the change in PD$_{20}$ was inversely related to the change in frequency of wheeze within the previous month (but not significantly to changes within the previous week) and to changes in treatment.

Measuring responsiveness on multiple occasions in 120 children with asthma, and defining the threshold dose of histamine as that which increased the total lung resistance by 100% of baseline values, GEUBELLE et al. [35] found the threshold to be reproducible in asymptomatic children whose baseline lung function remained stable between tests. They observed a within-group relationship

between responsiveness and asthma severity, in that the number of attacks of asthma since the onset of the disease was inversely related to the threshold dose. In addition, within individuals, the level of responsiveness increased in the few days following an exacerbation.

Other studies have cast doubt on the relationship between responsiveness and the clinical severity of asthma. In 25 children with severe perennial asthma given intensive treatment for 2 months, minimal changes in levels of exercise-induced asthma, or in responsiveness to histamine, occurred despite marked clinical improvement reflected by a mean increase in PEF from 54 to 72% predicted [36]. Similarly, in 9 adults with a history of asthma related to ragweed exposure, five developed a significant exacerbation after exposure to ragweed, though no change in PD_{20} methacholine was observed in either these subjects or in those four who did not develop symptoms or signs of airflow obstruction [37].

RUBINFELD and PAIN [38] studied 11 adult asthmatics, measuring responsiveness to methacholine on 1–4 occasions over an 18 month period. They measured changes in airway conductance (sGaw), continuing the test until a 50% fall had been observed. Using changes in sGaw with respect to time as the index of responsiveness, they analysed the slopes of the dose-response curves. For the group, no correlation was found between responsiveness and the severity of asthma as defined by the frequency or severity of wheeze, sleep disturbance, impairment of activities, absence from work or treatment needs. Within subjects, five had multiple tests and stable asthma scores while four had multiple tests and variable asthma scores. In all cases, the slopes of the dose-response curves were essentially unchanged.

STANESCU and FRANS [39] observed 9 adults with asthma during an 8 month period and found bronchial hyperresponsiveness was not a constant feature. In these subjects, a less than 10% fall in FEV_1 was observed after acetylcholine or histamine was given in doses which produced a 40% change in FEV_1 in most of their asthmatic subjects. In 4 subjects with intrinsic asthma who were studied at times of naturally occurring exacerbations, bronchial hyperresponsiveness could not be demonstrated before or after a spontaneously occurring obstructive episode. In one subject, there was no change *during* the episode, despite the occurrence of significant airflow obstruction. That the airflow obstruction was probably due to bronchial muscle constriction was suggested by the fact that, in 3 of the 4 subjects, significant bronchodilator reversibility was demonstrated.

In order to examine the variability and significance of responsiveness in a clinical context, we undertook a longitudinal study of 20 subjects (12 adults and 8 children) with current asthma [40]. Over a period of 12–18 months subjects attended 2–3 times weekly for methacholine bronchial challenge, and throughout the study recorded their symptoms each day and measured their PEF twice daily. In each subject, between 15–34 measurements of PD_{20} (mean 25) were made. In support of the observations made by STANESCU and FRANS [39], we also found bronchial hyperresponsiveness was not a constant finding, being absent on at least one occasion in

9 of our 20 subjects and on multiple occasions in seven, including in several patients at times of exacerbations. Nevertheless, in support of the majority of cross-sectional studies which have examined the relationship between responsiveness and asthma severity, subjects whose overall levels of responsiveness were highest within the group had asthma which was considered, on clinical grounds, to be severe; while treatment requirements were high in these subjects, several of those with the lowest demonstrable levels of responsiveness were able to discontinue regular treatment for several months. For the group as a whole, we demonstrated a significant relationship between subjects' overall levels of responsiveness (median PD_{20}) and both their average day-to-day variation in morning PEF (Spearman's rho =-0.53) and diurnal variation in PEF (Spearman's rho=-0.60). However, *within subjects*, no consistent relationship was observed between levels of responsiveness and the state of their asthma: in particular, individual measurements of PD_{20} were not consistently related to concurrent asthma severity. Indeed, in only 6 subjects did changes in PD_{20} appear to reflect simultaneous trends in symptoms or PEF. These observations were supported by statistical analysis, which was designed to quantify the relationship in each subject between individual PD_{20} measurements and the state of asthma around the time of each test (fig. 1). Three of the 20 subjects rarely had measurable levels of responsiveness (PD_{20} >12.8 μmol on more than 75% of occasions) and were excluded from this analysis. In the remaining 17 subjects, Spearman's rank correlation was used to assess the strength of the relationship between PD_{20} and mean morning PEF, diurnal variation in PEF and mean symptom score for the 3 days surrounding each bronchial challenge. The correlation coefficients for those six subjects in whom we could identify a relationship between levels of responsiveness and the clinical state of asthma were generally the highest among the group, and in most of them the relationships were statistically significant. In the rest of the group, an association between responsiveness and asthma was suggested by the predominantly positive correlation between PD_{20} and morning PEF and the generally negative correlation between PD_{20} and both diurnal variation in PEF and symptoms. However, the low values of Spearman's rho in the majority of these subjects (fig. 1) indicated that any such relationship was weak. In addition, many of our subjects demonstrated marked changes in levels of responsiveness over the course of 12–18 months, indicating the limitations of a single measurement in adequately describing the severity of the disease.

The effect of initial airway calibre

The way in which the response to bronchial provocation is affected by the degree of obstruction present at the beginning of the test is still unclear. There are a number of theoretical reasons, consequent on airway geometry, why the *in vivo* measurement of responsiveness might be influenced by pre-challenge airway calibre [41]. Alternatively, airflow obstruction

might itself be a consequence of the bronchial hyperresponsiveness or both may be separate expressions of the underlying disease process, each reflecting the severity of asthma. Several studies have observed a modest correlation between levels of responsiveness and baseline measurements of lung function [10, 28, 29, 33]. Other studies have failed to find any significant relationship, particularly when pulmonary function is only mildly abnormal [32, 38, 42–45]. RYAN *et al.* [30] have shown that a moderate or severe increase in responsiveness (PC_{20}<2.0 mg·ml^{-1} histamine) can be present at a time when FEV_1 is "normal" and within 10% of a subject's maximum value after salbutamol. Other workers have observed changes in airway calibre occurring in the absence of changes in responsiveness [37, 38] and changes in responsiveness have been observed without changes in airway calibre [46–49] suggesting that other factors are involved in the pathogenesis of hyperresponsiveness.
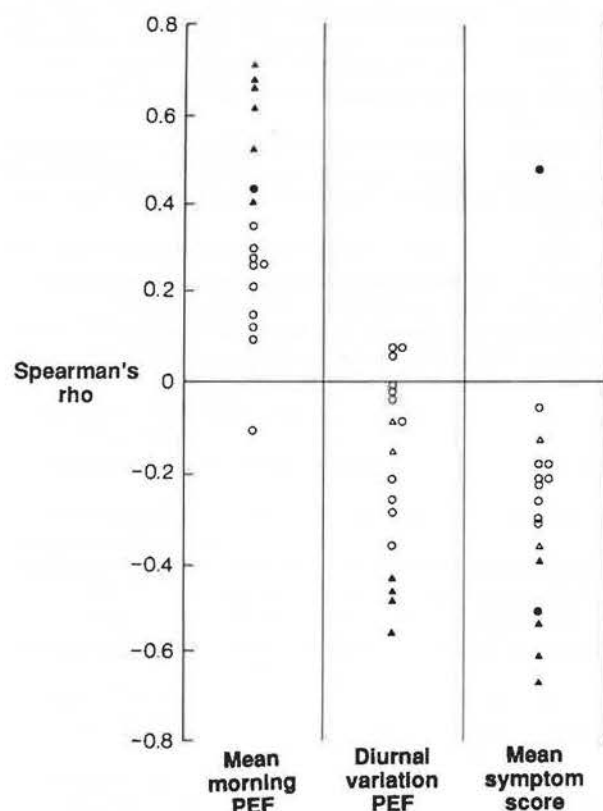

Fig. 1. – Strength of the relationship between provoking dose causing a 20% fall in forced expiratory volume in one second (PD_{20}) and mean morning peak expiratory flow (PEF), diurnal variation in PEF and mean asthma symptom score for the three days surrounding each bronchial challenge *i.e.* the test day, the day before and the day after. Spearman's rank correlation coefficient, rho, denotes the strength of the relationship between PD_{20} and each of these indices, the number of challenges to which rho relates ranging between subjects from 15–25 (mean 25). Diurnal variation in PEF refers to the difference between the highest and the lowest daily PE expressed as a percentage of the mean daily PEF, averaged for each three day period. Those subjects in whom we observed a relationship between PD_{20} and the state of asthma are represented by triangles, while circles denote the remaining subjects. Symbols are closed in those subjects in whom the relationships have reached statistical significance (p<0.05). (Reprinted with permission. From: JOSEPHS *et al.* [40]).

Discussion

Most of the available evidence suggests that, within a group of subjects, levels of non-specific bronchial responsiveness are related to the severity of asthma. However, within subjects the situation is less clear, in part due to the limitations of assessing both responsiveness and asthma severity.

It is important to consider the ways in which bronchial responsiveness might relate to the severity of asthma, and the reasons why any relationship between them might be inconstant. Hyperresponsiveness is a functional abnormality which might reflect underlying pathological processes in the airways rather than relating directly to current levels of airflow obstruction, as do those clinical indices used to assess the severity of asthma. Thus, symptoms and measurements of airway calibre reflect the degree of airflow obstruction present at any one time, while measures of responsiveness might indicate the likelihood of airflow obstruction developing if an appropriate stimulus is encountered. The resultant airflow obstruction would therefore depend on both the level of responsiveness and the strength of the stimulus to which the airways are exposed [19]. A clear relationship between responsiveness and clinical indices of severity would not be expected unless account is taken of the strength of any such stimulus, and this might explain the weak relationship reported by various investigators concerning some of their within-subject analyses [37, 39, 40].

Another possibility which must be considered is that, given the heterogeneous nature of asthma, airflow obstruction is likely to be the final common pathway of a variety of pathological processes, to which hyperresponsiveness contributes to a differing extent. Thus, hyper responsiveness might play a variable role in different individuals and, within the same individual, at different times.

The potential usefulness of measurements of responsiveness in clinical practice lies in the fact that they might give additional information about the state of the airways than that provided by clinical indices of asthma severity. They would be of value in identifying those patients at risk of a life-threatening attack who might not have current symptoms or signs of airflow obstruction. Another possible use might be in decisions regarding the safety of stopping maintenance treatment in patients whose asthma appears well controlled: the persistence of hyperresponsiveness when clinical indices seem to denote satisfactory control, would indicate the need to continue therapy on the assumption that the underlying instability of the airways remained.

In the present state of knowledge, the lack of a clear relationship between responsiveness and asthma severity is unlikely to be improved so long as there are still deficiencies in our understanding of the pathological features underlying asthma and of the interaction of different agents with them. Inflammation of the airways appears to be the common factor in both asthma and hyperresponsiveness [50, 51]. Events which are known to cause inflammatory changes in the airways and

exacerbations of asthma, such as viral respiratory infection [52, 53] and allergen exposure [42, 54, 55], have also been shown to be capable of inducing increased bronchial responsiveness. In addition, the degree of inflammation, as indicated by the presence and activity of various inflammatory cells in the bronchi, has been shown to relate to levels of responsiveness [56–59]. Little is known, however, about the relationship between these inflammatory changes and the clinical manifestations of asthma. If those features which constitute severity were better understood and the various aspects identified, the value of provocation tests could be put into context and their particular areas of usefulness delineated.

Carefully standardized and controlled longitudinal studies will be required to resolve these problems and to define a role for the measurement of responsiveness in the management of asthma. At present, given the presence of many uncontrolled variables in the clinical setting whose influence on bronchial responsiveness is unpredictable, the limitations of a single measurement of responsiveness in adequately reflecting a variable disease, and the inconstant relationship between responsiveness and asthma in an individual subject, it would seem that the clinical usefulness of measuring responsiveness to assess the severity of asthma must be limited.

References

1. Scadding JG. – Definition and clinical categorisation. *In:* Bronchial asthma: mechanisms and therapeutics. eds,. E.B. Weiss, M.S. Segal. Little, Brown and Co, Boston, 1976, pp. 19–30.
2. Rubinfeld AR, Pain MCF. – Perception of asthma. *Lancet*, 1976, i, 882–884.
3. Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. – Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax*, 1978, 33, 705–710.
4. Spector SL, Farr RS. – A comparison of methacholine and histamine inhalations in asthmatics. *J Allergy Clin Immunol*, 1975, 56, 308–316.
5. Eggleston PA. – A comparison of the asthmatic response to methacholine and exercise. *J Allergy Clin Immunol*, 1979, 63, 104–110.
6. Anderton RC, Cuff MT, Frith PA, Cockcroft DW, Morse JLC, Jones NL, Hargreave FE. – Bronchial responsiveness to inhaled histamine and exercise. *J Allergy Clin Immunol*, 1979, 63, 315–320.
7. Anderson SD, Schoeffel RE. – The inhalation of ultrasonically nebulised aerosols as a provocation test for asthma. *In:* Airway responsiveness, measurement and interpretation. eds,. F.E. Hargreave, A.J. Woolcock Astra Pharmaceuticals, Mississauga, Canada, 1985, pp. 39–48.
8. Boulet LP, Legris C, Thibault L, Turcotte H. – Comparative bronchial responses to hyperosmolar saline and methacholine in asthma. *Thorax*, 1987, 42, 953–958.
9. Pauwels R, Joos G, Van der Straeten M. – Bronchial hyperresponsiveness is not bronchial hyperresponsiveness is not bronchial asthma. *Clin Allergy*, 1988, 18, 317–321.
10. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. –

11. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy*, 1977, 7, 235–243.
11. Chai H, Farr RS, Froelich LA, Mathison DA, Mclean JA, Rosenthal RR, Sheffer AL, Spector SL, Townley RG. – Standardisation of bronchial inhalation challenge procedures. *J Allergy Clin Immunol*, 1975, 56, 323–327.
12. Yan K, Salome C, Woolcock AJ. – Rapid method for measuring bronchial responsiveness. *Thorax*, 1983, 38, 760–765.
13. Ryan G, Dolovich MB, Roberts RS *et al.* – Standardisation of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis*, 1981, 123, 195–199.
14. Britton J, Mortagy A, Tattersfield A. – Histamine challenge testing: comparison of three methods. *Thorax*, 1986, 41, 128–132.
15. Orehek J, Nicoli MM, Delpierre S, Beaupré A. – Influence of the previous deep inspiration on the spirometric measurement of provoked bronchoconstriction in asthma. *Am Rev Respir Dis*, 1981, 123, 269–272.
16. Beaupré A, Orehek J. – Factors influencing the bronchodilator effect of a deep inspiration in asthmatic patients with provoked bronchoconstriction. *Thorax*, 1982, 37, 124–128.
17. Orehek J, Gayrard P, Grimaud C, Charpin J. – Effect of maximal respiratory manouevres on bronchial sensitivity of asthmatic patients as compared to normal people. *Br Med J*, 1975, 1, 123–125.
18. Dehaut P, Rachiele A, Martin RR, Malo JL. – Histamine dose-response curves in asthma: reproducibility and sensitivity of different indices to assess response. *Thorax*, 1983, 38, 516–522.
19. Sterk PJ, Bel EH. – Bronchial hyperresponsiveness: the need for a distinction between hypersensitivity and excessive airway narrowing. *Eur Respir J*, 1989, 2, 267–274.
20. Townley RG, Bewtra AK, Nair NM, Brodkey FD, Watt GD, Burke KM. – Methacholine inhalation challenge studies. *J Allergy Clin Immunol*, 1979, 64, 569–574.
21. Townley RG, Ryo UY, Kolotkin BM, Kang B. – Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. *J Allergy Clin Immunol*, 1985, 56, 429–442.
22. 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, 271–281.
23. Sears MR, Jones DT, Holdaway MD, *et al.* – Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax*, 1986, 41, 283–289.
24. Lee DA, Winslow NR, Speight ANP, Hey EN. – Prevalence and spectrum of asthma in childhood. *Br Med J*, 1983, 286, 1256–1258.
25. Muranaka M, Suzuki S, Miyamoto T, Takeda K, Okumura H, Makino S. – Bronchial reactivities to acetyl choline and IgE levels in asthmatic subjects after long-term remissions. *J Allergy Clin Immunol*, 1974, 54, 32–40.
26. Townley RG, Ryo UY, Kang B. – Bronchial sensitivity to methacholine in asthmatic subjects free of symptoms for one to twenty-one years. *J Allergy*, 1971, 47, 91–92.
27. Parker CD, Bilbo RE, Reed CE. – Methacholine aerosol as a test for bronchial asthma. *Arch Int Med*, 1965, 115, 452–458.
28. Makino S. – Clinical significance of bronchial sensitivity to acetyl choline and histamine in bronchial asthma. *J Allergy*, 1966, 38, 127–142.
29. Murray AB, Ferguson AC, Morrison B. – Airway responsiveness to histamine as a test for overall severity of asthma in children. *J Allergy Clin Immunol*, 1981, 68, 119–124.
30. Ryan G, Latimer KM, Dolovich J, Hargreave FE. – Bronchial responsiveness to histamine: relationship to diurnal

variation in peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax*, 1982, 37, 423–429.

31. Bahous J, Cartier A, Malo JL. – Monitoring of peak expiratory flow rates in subjects with mild airway hyperexcitability. *Bull Eur Physiopathol Respir*, 1985, 21, 25–30.

32. Juniper EF, Frith PA, Hargreave FE. – Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax*, 1981, 36, 575–579.

33. Beaupré A, Malo JL. – Histamine dose-response curves in asthma: relevance of the distinction between PC_{20} and reactivity in characterising clinical state. *Thorax*, 1981, 36, 731–736.

34. Britton JR, Burney PGJ, Chinn S, Papacosta AO, Tattersfield AE. – The relation between airway reactivity and change in respiratory symptoms and medication in a community study. *Am Rev Respir Dis*, 1988, 138, 530–534.

35. Geubelle F, Borlee-Hermans G, Leclercq-Foucart J. – Hyperreactivity of the bronchial tree to histamine in asthmatic children and its variations. *Bull Eur Physiopathol Respir*, 1971, 7, 839–840.

36. Silverman M, Connolly N, Balfour-Lynn L, Godfrey S. – Long-term trial of disodium cromoglycate and isoprenaline in children with asthma. *Br Med J*, 1972, iii, 378–381.

37. Bleecker ER, Rosenthal RR, Zilber P, Norman PS, Menkes H, Permutt S. – Prolonged bronchospasm after inhaled antigen in ragweed asthmatics. *Am Rev Respir Dis*, 1979, 119, 60A.

38. Rubinfeld AR, Pain MCF. – Relationship between bronchial reactivity, airway calibre and severity of asthma. *Am Rev Respir Dis*, 1977, 381–387.

39. Stanescu DC, Frans A. – Bronchial asthma without increased airway reactivity. *Eur J Respir Dis*, 1982, 63, 5–12.

40. Josephs LK, Gregg I, Mullee MA, Holgate ST. – Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma: a longitudinal study. *Am Rev Respir Dis*, 1989, 140, 350–357.

41. Tattersfield AE. – Relationship of resting airway calibre to measurements of airway responsiveness in man. *In:* Airway responsiveness: measurement and interpretation. eds. F.E. Hargreave, A.J. Woolcock Astra Pharmaceuticals, Mississauga, Canada, 1985, pp. 94–103.

42. Cockroft DW, Ruffin RE, Dolovich J, Hargreave FE. – Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy*, 1977, 7, 503–513.

43. Cade JF, Pain MCF. – Role of bronchial reactivity in aetiology of asthma. *Lancet*, 1971, ii, 186–188.

44. Fish JE, Kelly JF, Peterman VI. – Bronchoconstrictor responses in asymptomatic asthma: effect of prechallenge pulmonary function. *J Allergy Clin Immunol*, 1978, 61, 140.

45. Silverman M, Anderson SD. – Standardisation of exercise tests in asthmatic children. *Arch Dis Child*, 1972, 47, 882–889.

46. Cockroft DW, Cotton DJ, Mink JT. – Nonspecific bronchial hyperreactivity after exposure to western red cedar. *Am Rev Respir Dis*, 1979, 119, 505–510.

47. Cartier A, Thomson NC, Frith PA, Roberts R, Hargreave FE. – Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol*, 1982, 70, 170–177.

48. De Vries K, Goei JT, Booy-Noord H, Orie NGM. – Changes during 24 hours in the lung function and histamine

hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy*, 1962, 20, 93–101.

49. Durham SR, Craddock CF, Cookson WO, Benson MK. – Increases in airway responsiveness to histamine precede allergen-induced late asthmatic responses. *J Allergy Clin Immunol*, 1988, 82, 764–770.

50. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. – Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis*, 1985, 131, 599–606.

51. Chung KF. – Role of inflammation in the hyperreactivity of the airways in asthma. *Thorax*, 1986, 41, 657–662.

52. Jenkins CR, Breslin ABX. – Upper respiratory tract infections and airway reactivity in normal and asthmatic subjects. *Am Rev Respir Dis*, 1984, 130, 879–883.

53. Halperin SA, Eggleston PA, Beasley P, Suratt P, Hendley JO, Groschel DHM, Gwaltney JM Jr. – Exacerbations of asthma in adults during experimental rhinovirus infection. *Am Rev Respir Dis*, 1985, 132, 976–980.

54. Altounyan REC. – Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. *In:* Sodium cromoglycate in allergic airways disease. eds. J. Pepys, A.W. Frankland Butterworths, London, 1970, pp. 47–53.

55. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. – Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol*, 1983, 71, 399–406.

56. Kelly C, Ward C, Stenton CS, Bird G, Hendrick DJ, Walters EH. – Number and activity of inflammatory cells in bronchoalveolar lavage fluid in asthma and their relation to airway responsiveness. *Thorax*, 1988, 43, 684–692.

57. Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM. – Bronchoalveolar cell profiles of asthmatic and non-asthmatic subjects. *Am Rev Respir Dis*, 1987, 136, 379–383.

58. Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. – Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma: relationship to bronchial hyperreactivity. *Am Rev Respir Dis*, 1988, 137, 62–69.

59. Neijens HJ, Degenhart HJ, Raatgeep R, Kerrebijn KF. – The correlation between increased reactivity of the bronchi and of mediator releasing cells in asthma. *Clin Allergy*, 1980, 10, 535–539.

Revue générale. La réactivité bronchique non spécifique est-elle une indication de la sévérité de l'asthme? L.K. Josephs, I. Gregg, S.T. Holgate.

RÉSUMÉ: Il est difficile d'analyser les relations entre la réactivité bronchique et la sévérité de l'asthme, car chacun de ces deux paramètres est difficile à évaluer. L'asthme est une affection polymorphe, à modes d'expression multiples, et les méthodes cliniques utilisées pour en évaluer la sévérité ont des limites. Des tests de provocation bronchique sont également difficiles à interpréter, au point que la comparaison entre les diverses études est rendue difficile par suite des différences méthodologiques. Les études épidémiologiques, longitudinales ou transversales, révèlent une relation globale entre le degré de réactivité et la sévérité de l'asthme. La relation est toutefois beacoup moins nette quand il s'agit de cas individuels. Pour arriver à mieux comprendre le phénomène, l'on devrait connaître mieux les mécanismes à l'origine de l'asthme et la contribution de l'hyperréactivité bronchique à sa pathogénie. *Eur Respir J., 1990, 3, 220–227.*