

## The clinical significance of bronchial hyperreactivity\*

Editor D. Hughes

### Bronchial reactivity in the community

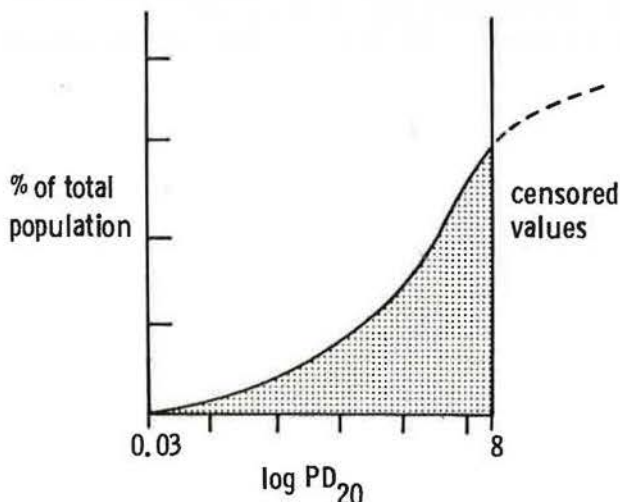
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Bronchial reactivity testing is widely used in epidemiological and clinical studies, usually in selected populations of subjects. Some of these findings can only be placed in perspective if the distribution of bronchial reactivity in the community is known. Comparison of bronchial reactivity measurements in different countries may shed light on differences in asthma prevalence and mortality and the relationship between the two. The measurement of bronchial reactivity is objective and, unlike symptom questionnaires, is not subject to problems with language and interpretation between different communities and cultures.

#### Prevalence of bronchial hyperreactivity in community populations

Most studies of bronchial reactivity in the community have used an inhalation challenge with histamine or methacholine, measuring the provocative dose ( $PD_{20}$ ), or concentration ( $PC_{20}$ ), of agonist causing a 20% fall in forced expiratory volume in one second ( $FEV_1$ ). Two caveats about methodology need to be emphasized. The first is the question of defining 'hyperreactivity'. In all studies of randomly selected community populations, whether adult or children, the measurement of bronchial reactivity has shown a log-normal distribution in the proportion of the population in whom it can be measured (fig. 1). The point at which hyperreactivity is separated from normal reactivity is therefore highly arbitrary and, as can be seen in the results reported below, has varied from study to study. The second caveat is that different methods of administration of histamine and methacholine have been used, though fortunately several studies have used the method of YAN *et al.* [1] and the results of these can therefore be compared with more confidence.

School children provide an easily accessible group to study and bronchial reactivity has been measured in fairly large numbers of 8-10 year olds in Australia and New Zealand. Studies using the Yan method [1], and defining hyperreactivity as a  $PD_{20}$  of less than  $8 \mu\text{mol}$ , have found a similar prevalence of bronchial hyperreactivity (BHR) in inland New South Wales and



Auckland, 19 and 20% [2, 3], respectively, and a lower value of 15% in coastal New South Wales [2]. The prevalence of BHR in 9 year olds in Dunedin, using a slightly different method, was 22% [4]. To date, therefore, the higher mortality from asthma in New Zealand is not obviously related to a higher prevalence of BHR in this age group, although more information is required.

The study by VAN NIEKERK *et al.* [5] in children of the Xhosa tribe suggests that environment can have an important effect on BHR. Of 694 children living in Cape Town, 22 had a 15% fall in  $FEV_1$  and peak expiratory flow (PEF) following an exercise challenge, compared to only 1 of 671 children still living in rural Transkei.

Studying a random population of adults is much more difficult and most studies have looked at relatively selected populations, such as college students or the parents of schoolchildren. Two recent studies have attempted to measure bronchial reactivity in a large community population. Both studies had a considerably lower compliance rate than the studies in school children and to some extent this is inevitable. WOOLCOCK *et al.* [6], studying a random sample of 916 adults aged 18-88 yr in Busselton, Western Australia, found that 10.5% had a  $PD_{20}$  of  $4 \mu\text{mol}$  or less and another 10% had a fall in  $FEV_1$  of between 10 and 20% after the  $4 \mu\text{mol}$  dose. Bronchial hyperresponsiveness was associated with

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respiratory symptoms, atopy, cigarette smoking and abnormal lung function.

In a study in the South of England we looked at the distribution of bronchial reactivity in 511 subjects aged 18–65 yr obtained at random from the electoral role [7]. Overall 14% of subjects had a  $PD_{20} < 8 \mu\text{mol}$ . Bronchial reactivity varied with age, being lowest in the 30–40 year old age group. In young people atopy was the main determinant of bronchial reactivity, whereas in older subjects cigarette smoking was most important. Unfortunately, because our analysis differs slightly from that of WOOLCOCK *et al.* [6], we are unable to compare prevalence rates directly.

#### Temporal changes in bronchial reactivity

Little information is available of long-term changes in bronchial reactivity in the community, although short-term changes have been demonstrated in grass pollen sensitive patients, with an average increase in airway responsiveness during the pollen season of one doubling-dose of carbachol.

Changes of a similar magnitude were found in a cohort of subjects from our community study who had repeat histamine challenge tests over 12 months, in March 1984, in June (during the pollen season), in September (when asthma mortality is highest in Britain), and again the following March (BRITTON *et al.*, *J Allergy Clin Immunol*, in press). Of the forty subjects who had a histamine inhalation on all four occasions there was a fall in  $PD_{20}$  in both June (0.82  $\mu\text{mol}$ ) and September (0.92  $\mu\text{mol}$ ) relative to the values in March 1984 (1.38  $\mu\text{mol}$ ) and March 1985 (1.2  $\mu\text{mol}$ ). Although the majority of subjects studied were atopic, we were unable to show any relationship between the fall in  $PD_{20}$  in June and skin test response to grass pollen or other common antigens, although surprisingly, the fall in  $PD_{20}$  in September was related to grass pollen response. Symptoms of respiratory tract infection were not associated with significant changes in bronchial reactivity. We were also able to show a relationship between change in  $PD_{20}$  between September and March and change in frequency of wheezing and drug use in the last month, an increase in  $PD_{20}$  being associated with less frequent wheezing and less medication. Thus, within a community population, change in bronchial reactivity is associated with a change in respiratory symptoms and drug use.

#### Methods of measurement

Measurement of bronchial reactivity in the community is hampered by the fact that a measurement of  $PD_{20}$  or  $PC_{20}$  can only be obtained in a small proportion of the population and by the fact that the measurement is inevitably less repeatable in this situation than when carried out in trained subjects in the laboratory. Exercise and cold air have been used for community studies but they have certain disadvantages relative to histamine and methacholine challenge. Both tests normally involve the administration of a single stimulus to which the response is measured and they are consequently less sensitive. The

tests are more cumbersome, less acceptable to older subjects in particular and logistically more difficult to carry out in a community setting.

Since histamine and methacholine are the agents which have been most widely used, we set out to compare the two tests in the community to try to answer three questions (HIGGINS *et al.*, submitted for publication): 1) Does methacholine allow more  $PD_{20}$  measurements to be made with fewer side effects? 2) How does the repeatability of histamine and methacholine compare? 3) Do histamine and methacholine  $PD_{20}$  values give the same information?

We studied 108 subjects from a random population and 191 subjects selected because of wheeze in the last year to increase the number of subjects with a  $PD_{20}$  value. Using the method of YAN *et al.* [1], histamine was given up to a dose of 4  $\mu\text{mol}$  and methacholine up to 12  $\mu\text{mol}$  and the results extrapolated in each case to one further doubling-dose (8 and 24  $\mu\text{mol}$ ). We found that with methacholine subjects had more measurable  $PD_{20}$  values in both the random group and the wheezers (25 and 67%) than with histamine (11 and 48%), yet methacholine caused fewer side effects and repeatability was marginally better. Histamine and methacholine were virtually equipotent in this community population when expressed in  $\mu\text{mol}$ . We looked at the relationship between histamine and methacholine, to see whether we could find evidence to support the suggestion that the two agonists are measuring different pathophysiological processes. We found no evidence for this; the agreement between  $PD_{20}$  histamine and  $PD_{20}$  methacholine was as close as the agreement between repeat measurements of the same agent. Furthermore the relationship between  $PD_{20}$  histamine and  $PD_{20}$  methacholine was similar for different groups, *e.g.* smokers and nonsmokers and atopic and non-atopic subjects.

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## Is hyperreactivity the same as asthma?

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Bronchial reactivity is a conceptual term which describes the responsiveness of the airways to a bronchoconstricting stimulus. Relative to normal subjects, patients with asthma show increased bronchial reactivity, referred to as hyperreactivity or hyperresponsiveness. Bronchial reactivity is measured in terms of the provocative dose (PD) of an agent such as inhaled histamine, methacholine or cold air which provokes a specified fall in airflow, commonly a 20% fall in forced expiratory volume in one second ( $PD_{20}$ ). Bronchial reactivity and  $PD_{20}$  are often used interchangeably, although strictly this practice is inappropriate, since the former term refers to a biological process, whilst the latter is its empirical estimate.

If asthma and hyperreactivity were the same, and there was no difficulty in distinguishing asthma from normality, then the distribution of reactivity in the population would be bimodal. Any blurring of the distinction between hyperreactivity and normality in this distribution would be attributable to measurement error. An impression of bimodality is easily inferred from studies which compare clinically discrete groups of asthmatic and normal subjects, and an uncritical assessment of such comparisons has led some investigators to the conclusion that hyperreactivity and asthma are indeed the same. However, surveys which include other clinical groups [1] or more general population samples [2] suggest that bronchial reactivity is unimodally and probably log-normally distributed, and demonstrate that although asthmatic subjects tend to lie in the more reactive tail of this distribution, extensive overlap between  $PD_{20}$  values in asthmatic and non-asthmatic subjects occurs.

The extent of the overlap between asthma and other clinically defined groups has been reviewed previously [3]. In summary,  $PD_{20}$  values comparable with those measured in asthmatic subjects are found in some subjects with atopy [2] or rhinitis [1], and in subjects with chronic bronchitis or chronic airflow obstruction [4].  $PD_{20}$  values are the same or may be increased [5] in younger asymptomatic smokers, relative to non-smokers, but are decreased in older smokers [6]. The mechanisms underlying hyperreactivity in some of these groups may differ, since amongst subjects with atopy or rhinitis a low  $PD_{20}$  occurs with relatively

normal airflow, whilst in hyperreactive smokers and patients with chronic bronchitis  $PD_{20}$  is decreased more obviously in relation to the degree of airflow obstruction [4].

This evidence suggests that, amongst other factors, atopy and smoking (or perhaps smoking-related disease) may be important correlates of hyperreactivity, and two recent epidemiological studies of bronchial reactivity support this suggestion [7, 8]. Our own study also demonstrated the age-dependency of the relationships [8], atopy being the stronger predictor of a low  $PD_{20}$  in young adults, and smoking the stronger predictor of a low  $PD_{20}$  in older subjects. Low  $PD_{20}$  values have been shown to be associated with a diagnosis of asthma in young adults [2], and also in a broader community cross-section [7], indicating that for epidemiological studies of asthma prevalence, in which the diagnosis of asthma by more conventional means presents serious logistic difficulties, measurement of  $PD_{20}$  may be an alternative means of diagnosing the disease. However, an association between hyperreactivity and asthma in populations does not necessarily imply a close association in individuals. The relationship between hyperreactivity and asthma in individuals is assessed more appropriately by examining the diagnostic value of measurements of  $PD_{20}$ .

The diagnostic value of a test is determined by its sensitivity and specificity in relation to a reference standard for the disease, and by the prior probability of disease in an individual. In the case of asthma, no reference standard exists and  $PD_{20}$  measurements are compared with clinical criteria. Although clinical diagnostic criteria are also far from standardized, it is still instructive to examine the predictive value of reactivity measurements based on the best available data. The study by COCKCROFT and colleagues [1] is a suitable example, since this paper described a standardized method of measuring reactivity to histamine, expressing results in terms of histamine concentration ( $PC_{20}$ ), and gave data from challenges in 307 subjects from several clinical groups. The paper defined increased reactivity arbitrarily as a  $PC_{20}$  of 8 mg·ml<sup>-1</sup> or less, and found that this value distinguished current asthmatics from normal controls. If we take this value and apply it prospectively, how useful is it likely to be in the diagnosis of asthma?

The sensitivity and specificity of the test in the

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