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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 $mg \cdot ml^{-1}$ 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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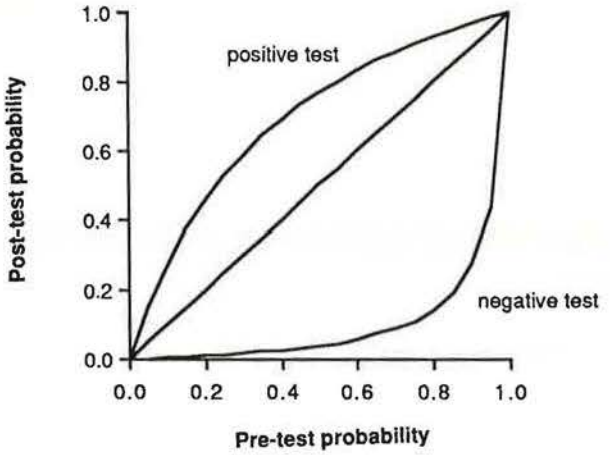

Fig. 1. – Pre- and post-test probability (prevalence or prior probability and posterior probability) of asthma in relation to measurement of PC_{20} histamine, based on the data of COCKCROFT and co-workers [1].

study of COCKROFT and co-workers [1] were approximately 97 and 71% respectively, and the predictive value of a positive and negative test 77 and 95%. Thus, in the context of their study, a negative test was useful, since it excluded asthma in all but 5% of individuals with a negative test result, whilst a positive test was of some help in confirming the diagnosis. However, these predictive values do not necessarily apply in other contexts, partly because it is not clear whether the 8 $mg \cdot ml^{-1}$ limit was determined prospectively or retrospectively in this study, but more importantly because of the dependence of the predictive value on the prior probability or prevalence of disease. The prevalence of asthma in the study of COCKCROFT and co-workers was 51% [1], a level at which the effect of a test result on the probability of disease in an individual is near maximum. The predictive value changes as prevalence increases or decreases, as shown in figure 1, which illustrates the effect of positive and negative test results with 97% sensitivity and 71% specificity on the probability of disease over a full range of prevalence values. The figure demonstrates that a negative test provides reasonable grounds to exclude asthma over a wide range of prevalence, whilst a positive test leaves considerable doubt over the diagnosis at all but the highest prevalence values. It is, therefore, hardly suprising that in one prospective assessment of a similar test, the results did not fulfill the authors expectations [9].

Thus, it is argued that although hyperreactivity is undoubtedly associated with asthma, there is considerable disparity between the two conditions both in populations and in individuals. The poor performance of measurement of PD_{20} as a diagnostic test for asthma may be due in part to shortcomings in the repeatability and validity of measurements of PD_{20}, and in part to a loss of information resulting from dichotomization of continuously distributed test results into normal and abnormal. On present evidence, however, it appears to be inappropriate to consider hyperreactivity and asthma to be the same.

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