

Review article

Bronchial hyperresponsiveness, atopy, airway inflammation, and asthma

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Airway inflammation particularly with eosinophil infiltration is an almost invariant feature of asthma, though it may not be exclusive to asthma. BHR and atopy are common phenomena in asthmatics but not invariably so. Allergen-induced late asthmatic responses can increase non-specific hyperresponsiveness and bronchial responsiveness in turn is, at least from some studies, correlated with the degree of airway inflammation. Atopy is a major risk factor for the development of asthma and its persistence from childhood into adulthood. Airway inflammation occurs very early in the natural history of asthma. No therapeutic intervention in established asthma has been shown to achieve a cure or even modify the natural history of the disease. Therefore, further studies are urgently required to identify whether strategies of early intervention to prevent the development of airway inflammation will modify the natural history of the disease.

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The *sine qua non* of asthma in the 1950s, '60s and '70s was bronchial hyperresponsiveness (BHR) and this concept was encompassed in the definition, which stated that asthma was a condition of variable airflow limitation which altered over short periods of time, either spontaneously or under the influence of treatment (1). As such, bronchospasm was seen as the key element of the disease which could be highlighted by a range of provocation tests which demonstrated BHR. This, in turn, meant that the key therapeutic intervention was with bronchodilators. Airway inflammation was only considered relevant to acute severe disease and the contribution of atopy to the asthma phenotype was not rated particularly high (2). It became increasingly apparent during the 1970s that BHR and diagnosed asthma were not synonymous. Hyperresponsiveness could be demonstrated to occur in individuals who neither had asthma nor ever developed asthma. Indeed, it occurred transiently in many normal individuals in association with intercurrent viral infection (3) and occurred commonly in patients with chronic suppurative lung diseases such as cystic fibrosis (4). Furthermore, it was sometimes difficult to demonstrate BHR, at least during bronchial challenge, in individuals with obvious asthma (5). Moreover, the effect of drugs on BHR did not necessarily predict their efficacy in the management of asthma. Thus, cromolyn sodium and corticosteroids have no immediate

impact on BHR, while calcium antagonists have a clear inhibitory effect (6). Nevertheless, there is an association between degree of BHR and severity of disease (7), and remission of asthma, as sometimes occurs in adolescence, is associated with loss of BHR (8).

Much confusion about BHR has arisen because it has been assumed that the host of different non-specific provocation methods and indices of response give much the same information. This is clearly not the case. There are different receptor and cell targets for histamine, metacholine, cold air, etc., and each is blocked to a greater or lesser extent by different antagonists. Exercise responses are partly mediated by mast cell activation and may be followed by a late response (9), though this is disputed by some (10). The challenges now considered to be more discerning are rather different from the standard histamine and metacholine inhalations which held sway in previous decades. Thus exercise (11), cold dry air (12), hypertonic saline or ultrasonic nebulised water (13) and adenosine challenges (11) are now seen to be more discriminatory in relation to asthma and its treatment.

The index of BHR for pharmacological challenges is usually either the provocation concentration (PC) or provocation dose (PD) to produce a 15 or 20% fall in lung function. This threshold is estimated by extrapolation either linearly, between points on either side of the critical lung function fall, or

logarithmically, taking the whole dose/response curve into account (14). While there is a weak association between severity of asthma and PD or PC 15–20 (7), some have suggested that bronchial reactivity may be more important. This latter index represents the slope of the dose/response curve which becomes ever steeper with increased severity of disease. Indeed, high degrees of reactivity have been associated with increased risk of death from asthma (15, 16).

Thus, BHR and bronchial reactivity do provide some information about asthma severity but rarely have any utility in monitoring disease. They do not reliably support or refute the diagnosis of asthma, though they do have some value in population studies investigating the prevalence of disease.

Atopy

Over 90% of asthmatic children are atopic with both a high frequency of positive family history of atopic disease and associated positive skin prick tests to common inhalant and/or ingestant allergens (17). Furthermore, asthma is commonly associated with other atopic diseases such as eczema and allergic rhinitis. The presence of atopy in infants, particularly in relation to egg and house mite allergy, predicts the later development of asthma (18, 19), and early onset allergy is associated with prolonged BHR and asthma symptoms through childhood into adolescence (20). Although increased BHR is associated with a higher probability for the development and persistence of asthma (21), it is not a significant factor in the absence of allergy (22).

The immediate allergen-induced bronchial response is little different in characteristics to that of a pharmacologically-induced bronchospasm. It is completely prevented by predosing with a beta-agonist and is uninfluenced by predosing with steroids. The magnitude of the immediate response to allergen can, to a certain extent, be predicted by the degree of non-specific BHR (23). Furthermore, the presence of allergy is not synonymous with asthma. Thus, atopic eczema and allergic rhinitis can occur in the absence of asthma, and asthma can occur in the absence of allergy (24) or can be driven by non-IgE dependent mechanisms in association with occupational chemical sensitivities (25).

Many patients when challenged with allergen have not only an immediate response but also a late reaction that evolves three to six hours after challenge. This late reaction is more prolonged, often more severe and has many of the characteristics of more severe asthma (26). There is evidence of more diffuse, smaller airway involvement which is less bronchodilator responsive but appreciably prevented by steroids and also, indeed, sodium cromogly-

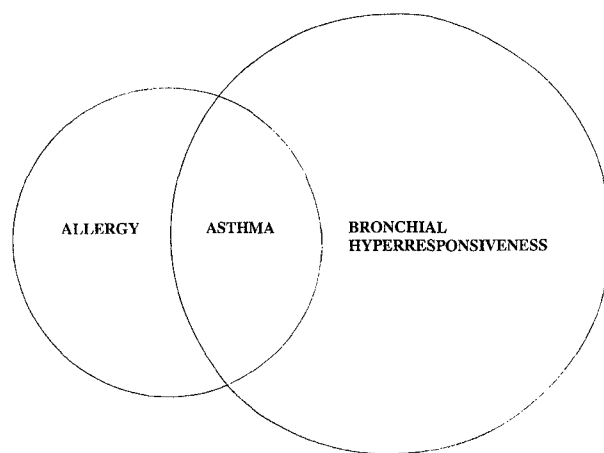


Fig. 1. Diagram indicating a hypothetical way in which allergy and bronchial hyperresponsiveness might together provide the prerequisite for the development of asthma.

cate and, more recently, leukotriene receptor antagonists (27). Furthermore, late allergen-induced reactions increase non-specific BHR for days or even weeks after a challenge (28). It tends to occur in individuals with more severe asthma (26). The immunopathology of the late reaction is very much more like that of chronic asthma with neutrophil and eosinophil recruitment to the airways during the evolution of the reaction (29).

Effective allergen avoidance can be shown to reduce symptoms of asthma, drug requirements and BHR (30). This intervention can even influence the effect of the allergen-induced late reaction on non-specific BHR (31). Conversely, higher allergen exposure of allergic asthmatics increases symptoms, BHR (32) and risk of hospital admission with acute exacerbation (33). Specific allergen immunotherapy can reduce both immediate and late allergen-induced bronchial responses, but it is the effect on the late reaction that is associated with the best clinical responses (34, 35).

Thus, atopy is very commonly associated with asthma and indeed BHR, but there is a dissociation between them. A component additional to atopy must dictate whether allergy will influence the course of asthma. Perhaps a predisposition to both allergy and BHR is necessary for asthma to manifest itself (Fig. 1). Once atopic asthma occurs, it is clear that the late allergen-induced response is much more relevant to the disease than the classical immediate response, the latter being as much a manifestation of BHR as allergy.

Airway inflammation

The 1980s and '90s have heralded a new approach to asthma based on observations of the histopathol-

ogy in the airway. The very first observation that even mild asthmatics have airway inflammation was made on two children undergoing open lung biopsies for other reasons (36). They had identical ultrastructural changes within their airways to children who had died of asthma. Subsequent adult studies using fiberoptic bronchoscopy and bronchial biopsy established that airway inflammation, characterised particularly by infiltration of eosinophils and mast cells, was an almost inevitable finding amongst asthmatics of all severities (37). The degree to which this may be found in non-asthmatic individuals has yet to be established. The consequence of new insights into the immunopathology of asthma have informed the current guidelines on treatment which emphasise the use of disease modifying agents which have the capacity to reduce airway inflammation (38). In general, this has led to ever-increasing recommendations for the use of inhaled corticosteroid, as evidence for any other compounds having much effect is relatively limited (39). There are few studies in relation to the use of sodium cromoglycate (40), though there are now studies suggesting that the leukotriene receptor antagonists also have anti-inflammatory properties (41).

Adult studies have been rather conflicting in their attempts to associate the degree of inflammation in the airways with either severity of disease or lung function. Some studies suggest there is a correlation with BHR (42) and others fail to demonstrate this (43). However, improvement in airway inflammation by the use of inhaled corticosteroid can to some extent be associated with improvement in the disease. Thus inhaled corticosteroids clearly reduce eosinophil numbers and even the levels of circulating eosinophil activation proteins (44). This, in turn, correlates weakly with improved lung function (45).

Information from children has been relatively slow to accumulate because of ethical issues in relation to performing bronchoscopies on mild asthmatics for research purposes. Non-bronchoscopic lavage has been done opportunely during routine surgery. This has highlighted that there is indeed an increase in eosinophils and mast cells amongst atopic asthmatics by comparison with atopic non-asthmatics and non-atopic, virus-induced wheezers (46). We now have some data which confirm that eosinophils are indeed increased in broncho-alveolar lavage from asthmatics. There are also increased numbers of shed epithelial cells (47). Stimulated alveolar macrophages from asthmatic children produce larger amounts of thromboxane and cysteinile leukotrienes than controls. Interestingly, while the excess production of thromboxane can be inhibited by steroids, this is not the case for leukotriene release (48).

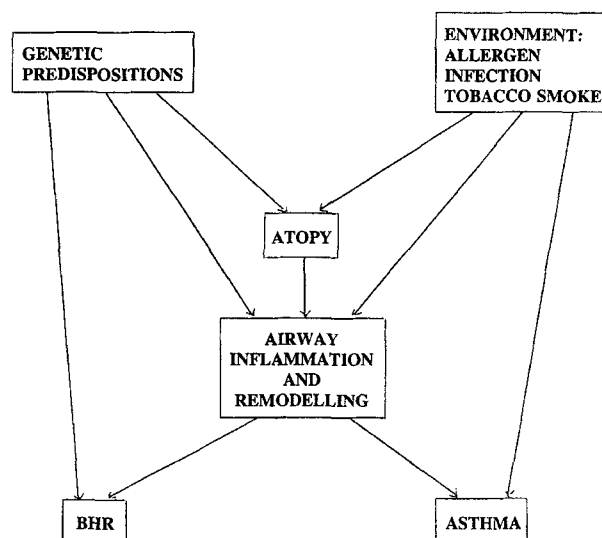


Fig. 2. A unifying hypothesis linking atopy, bronchial hyperresponsiveness (BHR) and airway inflammation, in which perhaps closely linked genetic predispositions together with environmental influences produce asthma.

Airway remodelling

Another concept that has arisen as a consequence of studying bronchial biopsies is that of remodelling. In addition to there being evidence of inflammatory cell infiltration with a predominance of eosinophils, there is also increased deposition of collagen in the lamina reticularis below the basement membrane and also in the lamina propria, besides an increase in the smooth muscle bulk (49). It has been felt that this is a slowly evolving process consequent upon the inflammation damaging respiratory epithelium and thereby inducing an attempt at repair. The remodelling process is felt to confer some degree of irreversibility to the airflow limitation, and to be a consequence of delaying the introduction of the effective anti-airway inflammation therapy (50, 51).

We also have data on bronchial biopsies from a small number of young children who were bronchoscoped at a time when their respiratory diagnosis was uncertain. Subsequent follow-up has been able to characterise two groups of children—those with definite asthma and those definitely without asthma. Irrespective of atopic status, the subsequent asthmatics had increased eosinophil numbers in their lamina propria and also significantly thicker lamina reticularis. There was no correlation between either the degree of eosinophil infiltration or the thickness of the lamina reticularis and duration of symptoms up to the point of biopsy (52). This raises a number of issues. It suggests that at least some of the remodelling process is not a phenomenon of chronic long-

standing inflammation but occurs early, if not simultaneously, with the inflammation. It also suggests that airway inflammation may be established very early, if not before the onset of first symptoms. This would seem to be very likely.

It has been proposed that the airway epithelium is the key orchestrator of the remodelling process in asthma (53). Indeed, it is possible there is a fundamental defect at this level which might explain how atopy sometimes produces airway inflammation and thereby BHR and asthma (Fig. 2).

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