New insights into the relationship between airway inflammation and asthma

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ABSTRACT

Asthma is a condition characterized by variable airflow obstruction, airway hyper-responsiveness (AHR) and airway inflammation which is usually, but not invariably, eosinophilic. Current thoughts on the pathogenesis of asthma are focused on the idea that it is caused by an inappropriate response of the specific immune system to harmless antigens, particularly allergens such as cat dander and house dust mite, that result in Th2-mediated chronic inflammation. However, the relationship between inflammation and asthma is complex, with no good correlation between the severity of inflammation, at least as measured by the number of eosinophils, and the severity of asthma. In addition, there are a number of conditions, such as eosinophilic bronchitis and allergic rhinitis, in which there is a Th2-mediated inflammatory response, but no asthma, as measured by variable airflow obstruction or AHR. Bronchoconstriction can also occur without obvious airway inflammation, and neutrophilic inflammation can in some cases be associated with asthma. When we compared the immunopathology of eosinophilic bronchitis and asthma, the only difference we observed was that, in asthma, the airway smooth muscle (ASM) was infiltrated by mast cells, suggesting that airway obstruction and AHR are due to an ASM mast cell myositis. This observation emphasizes that the features that characterize asthma, as opposed to bronchitis, are due to abnormalities in smooth muscle responsiveness, which could be intrinsic or acquired, and that inflammation is only relevant in that it leads to these abnormalities. It also emphasizes the importance of micro-localization as an organizing principle in physiological responses to airway inflammation. Thus, if inflammation is localized to the epithelium and lamina propria, then the symptoms of bronchitis (cough and mucus hypersecretion) result, and it is only if the ASM is involved – for reasons that remain to be established – that asthma occurs.

INTRODUCTION

Asthma is a condition that is characterized by variable airflow obstruction, airway hyper-responsiveness (AHR) and chronic airway inflammation that usually has an eosinophilic component. Pathophysiologically, as well as accumulation of eosinophils and CD4 lymphocytes, there is activation of the epithelium and smooth muscle, mucus hypersecretion, thickening of the sub-epithelial collagen layer, mast cell degranulation, and smooth muscle hypertrophy and hyperplasia [1]. A striking abnormality in patients that have died due to asthma is a

Key words: airway hyper-responsiveness, airway smooth muscle, asthma, eosinophils, inflammation.
Abbreviations: ASM, airway smooth muscle; AHR, airway hyper-responsiveness; BAL, bronchoalveolar lavage; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; EB, eosinophilic bronchitis; FEV1, forced expiratory volume in 1 s; GC, glucocorticoids; IL, interleukin; PC20, provocational concentration causing a 20% fall in FEV1; VLA, very-late antigen.
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A currently widely accepted model of asthma is of a disease caused by chronic inflammation of the airways, directed largely by Th2 lymphocytes reacting to inhaled allergens and antigens. In this model the major effector cell is the eosinophil (Eos), through the elaboration of specific granule proteins and leukotrienes. Th2 cytokines such as IL-4 and IL-13 are also thought to have a direct effect, particularly on mucus hypersecretion. Mast cells participate in acute bronchospasm, as modelled by the early response to antigen challenge, while structural cells amplify the inflammatory process by the production of cytokines and cell-recruiting chemokines. LT, leukotriene; PGD2, prostaglandin D2.

There has been a marked increase in the prevalence of asthma in the last quarter of the 20th century, and it is now thought to affect up to 20% of children and 5% of adults in industrialized countries, causing considerable morbidity and a significant degree of premature death [7]. Although airway inflammation had long been recognized from post-mortem studies of asthma deaths as being a feature of asthma, the bronchospastic elements of the disease had been given greater prominence, and it was not until the mid 1980s, when fibre-optic bronchoscopy studies demonstrated the presence of increased numbers of eosinophils, even in very mild disease, that asthma became viewed principally as a chronic inflammatory disease of the airways [8]. This paradigm was refined by the subsequent demonstration of increased numbers of cytokine-producing Th2 lymphocytes in the airways of atopic asthmatics, which has led to a widely supported model of asthma as a disease in which there is inappropriate activation of allergen-stimulated Th2 lymphocytes [9]. This is thought to cause eosinophilic inflammation of the airways, which in turn contributes to the abnormal physiology and pathology which characterizes the disease [10] (Figure 1). This model has been underpinned by the beneficial effects of glucocorticoids (GC) on both airway inflammation and clinical manifestations of the disease, which in turn has led to the early use of inhaled GC becoming the mainstay of current guidelines on asthma management [11].

The view of asthma as a disease of Th2-mediated inflammation has had a major impact on the direction of drug development, which has focused on anti-inflammatory strategies targeted at the Th2 pathway. This has included antagonists of interleukin-5 (IL-5) and very-late antigen-4 (VLA-4) to prevent airway eosinophilia, IL-4 antagonists to reduce eosinophil infiltration and IgE production, and therapies such as IL-12 that are directed at switching Th2 cells to Th1 cells [12–14]. The most
frequently used animal model of asthma involves allergen challenge of Th2-sensitized mice, where the key pathological feature is airway eosinophilia. However, Th2-mediated inflammation can explain at best only part of the pathophysiology of asthma. From the outset it was clear from bronchoscopic studies that there was no close relationship between the severity of airway inflammation and the severity of asthma, particularly as measured by AHR and FEV$_1$ (forced expiratory volume in 1 s). This dissociation has become even more obvious with the use of induced sputum to measure airway inflammation in larger groups of subjects with a broader range of disease severity and clinical phenotype than the mild extrinsic asthma that has been the staple of bronchoscopic studies [15]. In addition, there are a number of examples where eosinophilic airway inflammation is not accompanied by asthma, including patients with rhinitis without evidence of AHR or bronchoconstriction, and eosinophilic bronchitis (EB), a common cause of cough which is discussed in more detail below [16]. It seems clear, therefore, that while inflammation almost invariably accompanies asthma, it is not sufficient to explain all the features of the disease. Other factors, possibly intrinsic to the airway, must be involved. In this review we have re-examined the relationship between airway inflammation and asthma, and suggest that the intrinsic lung factor involves modulation of smooth muscle physiology.

**WHAT IS ASTHMA?**

There is general agreement that asthma is a disease characterized by symptoms of episodic cough, wheeze, breathlessness and chest tightness, which is usually relieved by bronchodilators and is associated with variable airflow obstruction [17]. Most definitions also include AHR and eosinophilic airway inflammation, although, remarkably in our opinion, these hallmarks of the disease are not routinely measured in making the diagnosis [18]. A significant smoking history (> 15 pack years) in the context of airflow obstruction makes a diagnosis of smoking-related airflow obstruction (COPD) more likely than asthma. There is, however, as discussed below, an overlap syndrome in which older adults with a significant smoking history have asthmatic features to their disease. In some, but far from all, cases these individuals will give a history of asthma in childhood or early adult life. There is an unresolved debate about whether this overlap syndrome simply represents co-existence of two common diseases or whether there are common pathogenic mechanisms. Our prejudice is the latter, but more information on this potentially informative group of patients is needed.

Unless serial measurements are undertaken, significant increases in FEV$_1$ after bronchodilators can only be demonstrated in a minority of patients with mild to moderate asthma [19]. In addition, home peak-flow readings are unreliable as a diagnostic tool because of poor technique and compliance [20,21]. The diagnosis of asthma, particularly in a primary-care setting, is often based largely on symptoms and home peak-flow readings, and is therefore likely to be inaccurate in many cases, although there are virtually no studies examining this important issue [22]. Indeed, there is a tendency to be nihilistic about establishing an accurate diagnosis of asthma, with some authorities viewing asthma as an ill-defined syndrome that is difficult to diagnose objectively [23]. We believe that this is incorrect. While there is currently no ‘gold standard’ for the diagnosis of asthma, our approach is to accept the diagnosis where a person has consistent symptoms, a less than 10-pack-year smoking history, and either directly demonstrable reversibility in FEV$_1$ or peak flow of greater than 20%, and/or a $P_{20}$ (provocational concentration causing a 20% fall in FEV$_1$) of less than 4 mg/mL. In borderline cases, for example where the $P_{20}$ is between 4 and 8 mg/mL without obvious reversibility, the presence of sputum eosinophilia (> 3%) is helpful in confirming the diagnosis. In a recent analysis of the sensitivity and specificity of $P_{20}$, sputum eosinophilia and measurement of variable airflow obstruction (either by home peak-flow monitoring or direct reversibility), $P_{20}$ is the most useful test, with a sensitivity and specificity greater than 90%, followed by the sputum eosinophilia [24]. AHR is perhaps the most distinctive physiological abnormality in asthma [25].

It is clear that, within this diagnostic framework, there are a number of phenotypes. These can be classified according to clinical features, presumed aetiology, or the pattern of inflammation (see Table 1). The extent to which these phenotypes represent different diseases with a similar physiological outcome, or a single disease with a variable aetiology and presentation, is uncertain. On current evidence their similarities in both patho-

Table 1  Asthma phenotypes

<table>
<thead>
<tr>
<th>Classification</th>
<th>Types</th>
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<tr>
<td>Symptom-based</td>
<td>Chronic (mild, moderate, severe)</td>
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<td>Pathological</td>
<td>Eosinophilic</td>
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<td></td>
<td>Neutrophilic</td>
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<td>Fixed airflow obstruction (airway remodelling)</td>
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Figure 2  Asthma is one of a number of overlapping obstructive airway diseases

While we envisage asthma as a single discrete disease, there are a number of other diseases and syndromes that overlap in terms of symptoms, pathology or physiology. A unifying hypothesis of asthma needs to explain the relationship with these other conditions. In this Figure the diseases that overlap with asthma include variable airflow obstruction as part of their pathophysiology, whereas the airway diseases that do not overlap, such as EB, are characterized by airway inflammation but without variable airflow obstruction. CF, cystic fibrosis.

physiology and clinical features outweigh their differences. In some cases the disease patterns represent easily understood differences in severity. For example, nocturnal asthma is usually simply a feature of poor disease control. In other cases, for example where neutrophils predominate over eosinophils (‘neutrophilic asthma’), or extrinsic compared with intrinsic asthma, the differences may be more fundamental. Our view is that asthma is a single disease with a number of aetiologies linked by AHR, variable airflow obstruction and chronic mucosal inflammation, in the same way that bronchiectasis is a single disease with different causes linked around defective lung defences, or hypertension has a number of aetiologies linked by abnormalities in vascular smooth muscle physiology.

As well as there being a number of different phenotypes within a diagnosis of asthma, there are several other airway diseases in which airway inflammation is associated with clinical and pathophysiological features that are seen in asthma, such as variable airflow obstruction, cough and wheeze (Figure 2). This is most obvious in COPD, where, as discussed above, reversible airflow obstruction is sometimes a prominent feature, particularly during exacerbations. Variable airflow obstruction is also a common feature of bronchiectasis [26]. In children, as well as some adults, virally induced wheeze overlaps with asthma in a still poorly understood manner [27]. In other conditions, airway inflammation occurs without AHR or variable airflow obstruction, for example EB and most cases of COPD. One can therefore conclude that bronchial inflammation can lead to two different outcomes: either episodic bronchoconstriction and AHR (asthma-like), or cough and sputum production (bronchitis) (Figure 3). While there is a bias for eosinophilic inflammation to be associated with asthma and neutrophilic inflammation with bronchitis, this is far from absolute. Both asthma and bronchitis can lead to fixed airflow obstruction (airway remodelling), although it is likely that this is due to a number of different pathological processes. The key question in asthma, therefore, is why do only some individuals develop AHR and bronchoconstriction in response to airway inflammation? Is this because of the nature of the inflammation, an intrinsic difference in the response of the airways to inflammation, or a combination of the two? It is also possible that AHR is entirely independent of inflammation, but the available evidence, in particular the almost invariable association of these two conditions, argues strongly against this.

ASTHMA AND AIRWAY INFLAMMATION

The relationship between airway inflammation and asthma is complex. In particular there is no close relationship between the severity of airway inflammation, measured either by cell counts or NO in exhaled air, and either the severity of AHR or abnormalities in FEV₁ [15,28]. A large number of studies have now examined this relationship in endobronchial biopsies, sputum and bronchoalveolar lavage (BAL) and bronchial wash, and the literature is generally very consistent in showing at best a weak correlation. For example, we have measured sputum eosinophilia in over 200 patients attending our...
outpatient clinics with a diagnosis of asthma [ranging in severity from step 1 to step 4 according to British Thoracic Society (BTS) guidelines], as defined by appropriate symptoms and either demonstrable variable airflow obstruction or AHR, and have found only a very weak correlation between sputum eosinophils or NO and AHR in atopic subjects, and no correlation at all in patients with non-atopic disease [29]. A caveat is that virtually all the studies that have investigated this relationship are cross-sectional, and what is lacking are longitudinal studies in clinical disease, relating changes in inflammation to changes in lung function and symptoms. Another caveat is that the level of activation of leucocytes such as T cells and eosinophils may be more important than cell numbers, although for eosinophils cell counts usually correlate well with concentrations of eosinophil-specific mediators in the BAL. There was a reasonable correlation between changes in sputum eosinophil numbers and AHR after allergen challenge, as well as in a study of treatment with inhaled steroids [30,31]. However, even if there was a better correlation between eosinophilic inflammation and severity of asthma within an individual, it would still mean that there was considerable variability in sensitivity to airway inflammation between individuals. Further support for the apparent dissociation between asthma and eosinophilic inflammation is provided by the study by Leckie et al. [32], in which an anti-IL-5 monoclonal antibody markedly reduced eosinophil numbers in the blood and sputum, but had no effect either on AHR in patients with mild asthma or on the late response to allergen challenge. It should be noted, however, that the interpretation of that study and others using the anti-IL-5 antibody is complicated by the observation that, in a group of mild asthmatics, there was still a significant tissue eosinophilia after 3 months of treatment with anti-IL-5, despite almost complete ablation of the BAL and blood eosinophilia [32a]. A dissociation between AHR and the eosinophilia has also been seen in animal models of allergen challenge. For example, an anti-VLA-4 monoclonal antibody was able to block ovalbumin-induced AHR, but not airway eosinophilia, when given by aerosol to mice [33]. Although the relevance of allergen challenge to clinical disease is debatable, these studies further illustrate the
complex relationship between inflammation and lung physiology.

Not all asthma is associated with eosinophilic inflammation. We have found that in 10–20% of asthmatics there is no increase in sputum eosinophils, even in those patients not taking inhaled steroids, and many of these patients have a sputum neutrophilia. A similar group has also been identified among patients with severe asthma by bronchial biopsy [34] and induced sputum [35]. The clinical features of ‘eosinophilic’ and ‘neutrophilic’ asthma are the same, so that obvious explanations, such as occult bronchiectasis and smoking, are unlikely. As eosinophilic inflammation is closely tied to a Th2 pattern of cytokine production, we speculate that in ‘neutrophilic’ asthma there is a Th1 pattern, suggesting a fundamentally different aetiological pathway. This would be important to demonstrate, because it would suggest that while Th2/eosinophilic inflammation commonly leads to asthma, other types of inflammation can equally well do so. Any unifying hypothesis of asthma therefore has to encompass all types of airflow inflammation. An important aspect of neutrophilic asthma is the possibility that these patients will be less responsive to treatment with GC, as response to steroids in both asthma and COPD correlates with the degree of airway eosinophilia [36]. Indeed, in a pilot study we found that our patients with neutrophilic asthma did less well on inhaled GC than eosinophilic asthmatics, and this has been confirmed by a 1-year longitudinal study, discussed below, in which the neutrophilic phenotype remained stable in terms of both cell counts and response to steroids [37]. This suggests that characterizing the type and pattern of airway inflammation in asthma should be an integral part of management.

**EB AND ASTHMA**

EB is a condition of unknown aetiology in which patients present with a chronic, minimally productive cough and are found to have an airway eosinophilia (> 3% in sputum), but without wheeze, shortness of breath, variable airflow obstruction or airway hyper-responsiveness [38]. It has been found in 13% of patients who present with cough (which is one of the commonest respiratory causes of presentation to both primary and secondary care), although it can only be diagnosed if measurement of airway eosinophils is undertaken [16]. The natural history of the disease is unclear, although in most cases it is steroid responsive. It is not obviously related to atopy. While EB is interesting in its own right, it has particular significance in offering clues as to why eosinophilic airway inflammation in some, but not all, individuals leads to asthma.

We have investigated the immunopathology of EB in comparison with that of mild (atopic and non-atopic) asthma, and have confirmed that EB is characterized by a submucosal eosinophilic inflammation which looks very similar to that in asthma, including the presence of subepithelial thickening of the collagen layer [39]. The expression of T-cell activation and of chemokine receptors and T-cell cytokines was also similar to those in asthma, with both showing a Th2 pattern of T-cell activation [40]. Indeed, the only difference we observed between the two conditions was infiltration of the airway smooth muscle (ASM) by mast cells in asthmatics, but not in patients with EB or in normal subjects [39]. There was also a significant correlation between the number of mast cells in the ASM and the PC_{20}. This was despite the observation that the overall numbers of mast cells in the airway lamina propria in the three groups was the same, and our previous demonstration that EB is characterized by increased amounts of histamine and prostaglandin D_{2} in the sputum, suggesting the presence of activated mast cells in the epithelium [41]. Strikingly, there was no infiltration of the ASM by eosinophils or T cells in asthma or EB.

On this evidence, it is therefore the localization of mast cells within the ASM that is implicated in causing bronchoconstriction and AHR. If this interpretation of the data is correct, then it has profound implications for our understanding of asthma, in that it implies that the key aspect of the inflammatory response is the way in which it alters ASM physiology. If the inflammatory response is restricted to the epithelium and submucosa, we would suggest that the patient will only suffer from symptoms of bronchitis (i.e. cough and sputum production). The idea that direct mast cell interactions with ASM cause asthma is plausible, as it is likely that cellular communication works across a distance of 1–2 μm rather than the thousands of μm involved in the depth of the lamina propria. Indeed micro-localization is likely to be a fundamental organizing principle of the inflammatory response, which has been relatively ignored because of the difficulty in co-localizing structures within the airway using endobronchial biopsies. Mast cell mediators are also of obvious relevance to ASM function [42,43].

Further support for our data is offered by a study of resected lung tissue in which those samples that contracted to allergen had increased numbers of mast cells within the ASM compared with samples where no contraction was observed. It was not possible to link this to the clinical status of the patients [44].

**ASTHMA AS A DISEASE OF ASM**

Stimulated by our study of EB, we propose that the asthmatic phenotype is caused fundamentally by an abnormality in disease ASM physiology, due, at least in part, to a mast cell myositis. Thus ASM hypertrophy...
A new model for asthma is presented in which an abnormality in ASM physiology is the fundamental cause of the disease. In mild asthma this abnormality is caused by a mast cell myositis (although T cells and eosinophils could be involved in more severe disease), but it may also occur as a result of respiratory viral and bacterial infections, or the toxic effects of low-molecular-mass chemicals in certain types of occupational asthma. These could be due to a direct effect on ASM or indirectly via a mast-cell-dependent pathway. Abnormal stretch responses could also lead to AHR. Localization of inflammation to the epithelium will lead to symptoms of bronchitis (cough and mucus production), but not asthma. HVS, hyperventilation syndrome; Eos, eosinophils; BHR, bronchial hyper-responsiveness.

could be caused by tryptase [45,46] and other mast cell-derived growth factors and AHR by a priming effect of mast cell mediators on ASM [47]. In a sense this is revisiting the ideas of the 1970s, when asthma was seen principally as a type 1 hypersensitivity reaction leading to smooth muscle bronchospasm. This hypothesis was undermined by the relative lack of efficacy of antihistamines and mast cell stabilizers, such as cromoglycate, in treating asthma. However, histamine is only one of a number of mast cell mediators, and both cromoglycate and nedocromil sodium have weak effects on mediator release from lung mast cells and exhibit tachyphylaxis [48,49]. In addition, chronic administration of $\beta_2$-adrenergceptor agonists, in contrast with attenuating mast cell secretion, can lead to enhanced release of mediators [50]. Furthermore, in asthma the predominant mechanism of mast cell degranulation appears to be piecemeal [51], which may well occur through a mechanism with distinct intracellular signalling pathways that are simply not susceptible to current therapies. Interest in the role of the ASM in asthma has continued, although relatively few investigators currently view asthma fundamentally as a disease of ASM, and in recent years attention has focused on the role of ASM as an amplifier of the inflammatory response through the generation of pro-inflammatory cytokines [52,53]. This function of ASM is consistent with our hypothesis, as mast cell recruitment to the ASM is likely to be due to a specific mast cell chemoattractant or growth factor, such as stem cell factor, which is known to be produced by the ASM [54].

Our model envisages AHR as being due to an exaggerated stimulus–response relationship between the ASM and bronchoconstrictor stimuli. This exaggerated response is likely to be partly acquired, for example as a result of mast cell infiltration, but on the background of a genetic predisposition. There is evidence for a genetic component to AHR in both animals and humans, although the picture is currently complex, with no single gene pattern emerging [55,56]. It is striking that many patients with atopic rhinitis have eosinophilic inflammation of the lower airways, but no AHR even after allergen challenge [57]. Is this because their ASM does not become infiltrated with mast cells or because they are genetically resistant to bronchoconstrictor stimuli? Does the failure of inhaled GC to return AHR to normal in many asthmatics reflect a failure to treat the underlying mast cell myositis or because an abnormality in the ASM remains even after the mast cells have gone [58]? Our model also explains the weak relationship between the various measures of airway inflammation and asthma, because, while it is probable that there is some connection between generalized airway inflammation and the development of an ASM mast cell myositis, this is likely to be complex, with eosinophil or neutrophil counts in
sputum and biopsies acting as a very indirect measure of the relevant abnormality.

Although a mast cell myositis may well be the final common pathway in all asthma phenotypes, it is possible that alternative mechanisms leading to abnormal ASM physiology are involved. While we have not observed eosinophil or T-cell infiltration of the ASM in our group of mild asthmatics, recruitment of these cells to the ASM may occur in more severe disease, especially as eosinophil infiltration of the ASM has been demonstrated in a guinea-pig model of asthma [59]. Indeed, the severity of asthma could be related to the intensity of the ASM myositis, in terms of both the number and range of inflammatory cells involved. Similarly, the T-cell-dependent, inflammation-independent, late-phase bronchoconstriction seen in some patients undergoing immunotherapy using Fel D1 peptides could be associated with migration of activated T cells into the ASM [60], especially as T-cell-derived cytokines have been shown to modulate ASM contraction [61]. One key message of our observation is the importance of leucocyte micro-localization in the physiological response to airway inflammation. As an estate agent might say, ‘location, location, location!’ This principle has also been emphasized by investigators proposing a primary neural mechanisms for asthma [62].

Non-inflammatory mechanisms could also lead to abnormal ASM physiology. For example, wheeze and AHR caused by respiratory viruses could be due to a direct effect on ASM [63]. Respiratory viruses have been shown in vitro to modulate ASM function, particularly when sensitized with atopic serum [64]. Wheeze associated with bacterial infections of the airways in COPD and bronchiectasis could be due to a direct effect of bacterial products on ASM. The interesting observations that inhibition of deep inspiration renders normal subjects hyper-responsive and that the bronchoprotective effect of deep inspiration is lost in asthma also implicate differential responses of the ASM as being central to AHR [65,66]. Stretch has a profound effect on smooth muscle cells [67], and one explanation for the high prevalence of asthma in hyperventilation syndrome and high-performance athletes could be the response of the ASM to exaggerated stretch associated with frequent periods of hyperventilation (Figure 4) [68].

**EOSINOPHILS AND SEVERE EXACERBATIONS OF ASThma**

Does this model imply that there is no role for eosinophils and Th2 cells in mediating the pathogenesis of asthma? It certainly implies that they are neither necessary nor sufficient for the development of AHR and variable airflow obstruction. However, there is increasing evidence that eosinophils are important in causing severe exacerbations of asthma. Severe exacerbations leading to acute severe asthma are the major cause of significant morbidity and mortality in asthma, and remain difficult to prevent and treat. The pathology of severe exacerbations can be assumed from that of asthma deaths, and encompasses marked eosinophilic inflammation and impaction of the airway with mucus and cell debris. It is this, as much as spasm of the ASM, that causes the airflow obstruction. In support of the idea that eosinophils are important in this aspect of asthma, we have undertaken a blinded, randomized study in which we have managed one group of moderately severe asthmatics according to standard BTS guidelines and the other group according to a protocol based on maintaining a normal sputum eosinophil count by appropriate use of corticosteroids. Over the course of 1 year we found that, whereas in the BTS group there were 108 severe exacerbations and six admissions for asthma, in the sputum group there were only 35 exacerbations and one admission. This was achieved without a difference in the amounts of treatment, including corticosteroids, used by the two groups. This strongly implies a close association between eosinophils and severe exacerbations, although whether it is causal remains to be seen [37].

Another key feature of asthma is the development of a degree of fixed airflow obstruction, suggesting the presence of permanent structural changes to the airway. This is often referred to as ‘airway remodelling’, although the terminology is somewhat confusing, as this phrase is also used to describe changes in the matrix composition of the airways, including the thickened sub-epithelial collagen layer, which is not related to severity of asthma, AHR or variable airflow obstruction. The pathophysiological basis for fixed airflow obstruction in asthma is largely unknown, although it is generally a feature of long-standing asthma and is presumed to be due to unopposed chronic inflammation.

**SUMMARY AND CONCLUSIONS**

Airway inflammation is closely associated with asthma, but the relationship is complex and indirect. The commonest pattern of inflammation in asthma is eosinophilic, mediated by Th2-derived cytokines, but neutrophilic asthma also occurs. Although the inflammatory response is usually caused by, or at least associated with, allergens, there are a number of other causes, including respiratory viruses and bacterial infections. Asthma is characterized by AHR and variable airflow obstruction which leads to wheeze and breathlessness, and bronchitis leading to cough. A minority of asthmatics develop severe exacerbations leading to acute severe asthma, and long-standing asthma can lead to a degree of fixed airflow obstruction. We hypothesize that AHR and variable airflow obstruction are caused principally by mast cell-mediated abnormalities in ASM responsiveness. On the
Figure 5  Relationship between patterns of airway inflammation and clinical and physiological outcomes in asthma

Asthma is a disease with a number of different clinical and physiological outcomes, which vary in prominence between different individuals and within the same individual over time. While some of these outcomes are likely to be influenced by the severity and longevity of the disease, we believe that they are underpinned by differences in the pattern of the inflammatory response, with bronchitic symptoms being due to inflammation localized to the epithelium, symptoms associated with variable airflow obstruction and AHR being due to a mast cell myositis, and severe exacerbations being due to eosinophil-mediated effects. The relationship between airway inflammation and the fixed airflow obstruction that occurs in some patients with asthma is not at all clear.

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How often is the diagnosis bronchial asthma correct?


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