Allergens, germs and asthma

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Abstract

Objective: To explore asthma pathogenesis using data from upper and lower airways.

Data Source: English-language papers on human asthma and nasal polyp subjects from 1990 onwards.

Study Selection: High-quality studies in established journals.

Results: The recognition of its inflammatory nature led to a quantum leap in the understanding and treatment of asthma, with lives saved by inhaled corticosteroids. Further work at genetic, molecular, histological and clinical levels has shown that asthma is polymorphic and rarely involves isolated Th2 bronchial inflammation.

Viral infections may act as an initiating event in children and adults, showing synergy with atopy. Chronic staphylococcal colonization of the mucosa may act as a promoter, as in atopic dermatitis. These two observations may be linked, with viruses providing an entry for bacteria into the mucosal epithelium.

Conclusions: Most asthma begins in the nose and involves allergy and infection: both viral and bacterial. The combination of atopy and infection suggests new possibilities for therapy.

Please cite this paper as: Scadding GK. Allergens, germs and asthma. Clin Respir J 2015; 9: 153–156.

Key words
airway epithelium – asthma – asthma mechanisms – bacterial infection – viral infection

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Received: 17 September 2013
Revision requested: 03 February 2014
Accepted: 02 March 2014
DOI:10.1111/crj.12128

Authorship and contributorship
Glenis K. Scadding is the sole author.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

The relationship between allergy and asthma has long been the subject of debate. It is obvious that allergen exposure in Immunoglobulin E (IgE)-sensitized asthmatic subjects can provoke wheezing, shortness of breath and falls in forced expiratory volume in 1 second (1). However, allergen avoidance and allergen-specific immunotherapy have not proven consistently effective in asthma (2, 3), which involves mechanisms other than Th2 inflammation, such as Th1 inflammation and remodeling (4, 5). Anti-IgE therapy has reopened the issue: it is undoubtedly effective in severe asthma (6), but it appears that eosinophils, rather than IgE, may be a better biomarker for those likely to benefit, since non-atopic severe asthmatics also respond (7), as do nasal polyps (8). Local IgE formation, without evidence of sensitization at systemic level, i.e. negative skin prick and blood IgE tests, may provide an answer (9–12), since the immunopathology of allergic and intrinsic asthma is similar (13).

An interaction between infection and allergy has been noted: children with allergic rhinitis suffer more and for longer with viral colds (14). Most acute asthma exacerbations start in the nose with a viral cold (15, 16). In allergic asthmatic children who are exposed to the relevant allergen and who then catch a cold, the odds ratio for hospital admission for asthma is 19 (17).

In fact, asthma itself usually begins with nasal disease. The European Community Respiratory Health Survey data show that both allergic and non-allergic rhinitis are risk factors for subsequent asthma development (18). The combination of recurrent viral colds and allergic rhinitis in children carries a high odds
ratio for progression to asthma (19). The systemic link demonstrated between nose and chest by Braunstahl et al. – showing that nasal allergen challenge provokes inflammation in both the upper airway and the bronchi, and vice versa – provides one possible mechanism for the spread of inflammation from nose to bronchi (20).

The pathogenesis of one asthma phenotype – non-atopic (intrinsic) asthma associated with aspirin sensitivity and nasal polypsis, known as aspirin exacerbated respiratory disease (AERD) – is becoming unraveled. The European Network on Aspirin-Induced Asthma provided information from over 500 sufferers that the problem starts at age 29 ± 12 years with persistent rhinitis, and with subsequent development of nasal polyps, asthma and aspirin intolerance, in variable order. The disease tends to occur earlier in females and atopics (21).

The late Andrew Szczeklik suggested an initiating viral upper respiratory tract infection, based on the history given by many sufferers of being well until the sudden onset of a severe cold, which never went away, and upon the demonstration of virus-like particles in the bronchial mucosa (22). Interferon gamma hyperproduction, which differentiates AERD from other forms of eosinophilic asthma (23), is in accord with a chronic viral presence. Microorganisms other than viruses may also be involved: Bachert and his group have noted that nasal colonization with Staphylococcus aureus is particularly high in AERD patients at 88%, compared with around 30% in control subjects, and that most have formed IgE to staphylococcal enterotoxins (24). These appear to be disease drivers since they act as superantigens: activating over 20% of T lymphocytes to elaborate cytokines such as IL5 and IL4, which cause local polyclonal IgE production and predominantly eosinophilic inflammation (12). The systemic link is again apparent with elevated blood eosinophils which migrate out of the bone marrow and localize in both the upper and lower airways (25). Staphylococci are located within the mucosa and even within cells in biopsy studies (26).

The presence of IgE to staphylococcal enterotoxins in blood confers a risk factor of 7.25 (2.7–19.1) for asthma and 11.09 (4.1–29.6) for severe asthma, where 59.6% of sufferers were positive compared with 13% of controls (27).

These observations: – origin in the nose with atopy, systemic or local, as a factor; possible viral co-initiation and staphylococcal promotion – have been linked by recent observations that herpes simplex virus can penetrate the nasal epithelium and allow Staphylococci to enter the mucosa (28, 29). Rhinoviruses, the most frequent cause of the common cold, probably behave similarly. There is, thus, a multi-hit initiation of disease (Fig. 1), with epithelial genes and those for bacterial and viral resistance probably relevant, as well as those involved in atopy and remodeling (30, 31). Repeated observations of sphingolipid abnormalities in asthma may be relevant: sphingolipids are thought to protect the cell surface against harmful environmental factors by forming a mechanically stable and chemically resistant outer leaflet of the plasma membrane lipid bilayer. Polymorphisms controlling orosomucoid-like 3 (ORMDL3) expression in the asthma susceptibility locus 17q21 are associated with childhood asthma, but not with atopy (32, 33), suggesting that ORMDL3 affects asthma susceptibility independent of atopic or immunoglobulin E-mediated pathways (33).

Figure 1. Allergic-type asthma could result from a multi-hit phenomenon: the primary event in the allergic airway is TH2 inflammation, usually arising in the upper airway (as rhinitis) before progressing to the lower, where it is initially intermittent. At this stage, the disease is amenable to treatments such as allergen avoidance and immunotherapy. However, infections such as rhinoviruses are handled less effectively by the inflamed mucosa, possibly because of defects in interferons and/or sphingolipids. Epithelial permeability is compromised, and persistence of microorganisms such as Staphylococci is permitted. This further perturbs local immunity with nonspecific activation of T lymphocytes via V beta receptors and chronic local Th1, Th17 and Th2 inflammation which is no longer as responsive to anti-allergic treatment. Since the bacteria are intra-epithelial, antibiotics cannot eliminate them. Topical corticosteroids are useful as anti-inflammatorieties at all stages, but doses needed rise as inflammation becomes more complex and persistent. There is a continued attempt at tissue repair, evident as airways remodeling. Non-allergic asthma could begin at stage 2.
There may be further microorganisms, including other bacteria, mycoplasma and fungi, that can initiate or maintain asthma in a similar fashion in other phenotypes: allergic bronchopulmonary aspergillosis is one example. The microbiome of induced sputum is different in asthma compared with controls: patients with mild asthma have an altered microbial composition in the respiratory tract that is similar to that observed in patients with more severe asthma (34). An IgE response to staphylococcal enterotoxins has also been demonstrated in adenoid tissues from atopic children (35). Interestingly in teenagers, although Staphylococci are implicated, some other microorganisms appear protective (36).

This has important implications. The first is that there is possibly a window of opportunity for prevention of asthma in allergic rhinitis. Grass pollen-specific immunotherapy by the subcutaneous route probably reduces asthma development (37); the sublingual route is under investigation (38). If proven effective, the threshold for its use should be reconsidered and the preventative effects of immunotherapy for other allergens, such as house dust mite, evaluated. Furthermore, pharmacotherapy for rhinitis used regularly with good control of minimal persistent upper respiratory tract inflammation (39) might also reduce progression to asthma, or reduce exacerbations in those already suffering from associated asthma. This needs exploration.

The second is that prevention of colds is vitally important and the search for a cure needs to continue. Whether amelioration of symptoms and inflammation during a viral upper respiratory tract infection (URTI) is helpful is unknown. Meanwhile, simple public health measures, such as hand washing, use of disposable tissues, etc., should be taught. Vitamin D may be relevant in protection against URTI, with low levels predisposing to infection frequency and/or severity (40).

Finally, if the pro-inflammatory stimulus is infective but intra-mucosal, then perhaps asthma therapy might benefit from a rethink. Inhaled corticosteroids are obviously needed, but instead of additional chronic anti-inflammatory therapy with increasingly expensive or toxic molecules the idea of stimulus removal could be mooted. Systemic antibiotics have shown some effectiveness in asthma and in nasal polyposis associated with asthma (41, 42), but intra-mucosal or surface biofilms are resistant to them and planktonic form reemerge once the course is completed. Local use of anti-microbials needs exploration. Bronchial thermoplasty, which destroys the respiratory epithelium, might act via bacterial killing, in a fashion analogous to the treatment of syphilis by heat (43).

The pathogenesis of asthma is unraveling further and provides us with an opportunity by careful research not only to improve the way in which patients are treated, but possibly also to prevent some of them from developing this lifelong, troubling and expensive disease in the first place.

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