

Allergy Series: Junior Member Affiliates Forum

Nasal involvement in allergic asthma

Even since the late 19th century, a relationship has been suspected between upper airway disease and the subsequent development or aggravation of asthma symptoms. To date, it has been generally accepted that pathologic conditions of the upper airways, e.g. allergic rhinitis, chronic sinusitis and nasal polyposis, may influence the lower airways. However, the mechanisms underlying this relationship were, for a long time, poorly understood. Recently, evidence has been accumulating which indicates a systemic connection as one of the responsible mechanisms in nasobronchial crosstalk. In this review, the pathophysiologic and immunologic aspects of the interaction between upper and lower airways will be discussed.

G.-J. Braunstahl¹, W. Fokkens²

¹Department of Pulmonary Medicine, Erasmus Medical Center Rotterdam, The Netherlands;

²Department of Otorhinolaryngology, Amsterdam Medical Center, The Netherlands

Key words: allergic rhinitis; asthma; clinical expression; link; mucosal inflammation; systemic interaction; treatment.

Dr G.-J. Braunstahl
Department of Pulmonary Medicine
Erasmus Medical Center Rotterdam
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands

Accepted for publication 29 July 2003

The key to the diagnosis lies in taking a good medical history. This rule especially applies to upper airway disease, e.g. allergic rhinitis, nasal polyposis and chronic sinusitis, and asthma. These conditions have in common that they are often underdiagnosed and are not given proper treatment (1, 2).

Allergic asthma is characterized by a history of episodes of cough, dyspnea, shortness of breath, chest tightness and wheezing, in combination with variable bronchoconstriction and/or bronchial hyperresponsiveness (BHR) (3, 4).

Allergic rhinitis is primarily based on a typical history of sneezing, rhinorrhoea, eye symptoms and nasal obstruction. As in allergic asthma, the atopic status needs to be confirmed (3, 5–7). In perennial rhinitis, chronic nasal obstruction can sometimes be the only symptom, which makes it difficult to confirm the diagnosis. The diagnosis of seasonal allergic rhinitis is less disputable, the symptomatology and seasonal occurrence are characteristic and have been well established for many years.

Sinusitis is an inflammatory process that involves mucous membranes of both nose and sinuses (2, 8). This explains why the term 'rhinosinusitis' is widely used. Sinusitis may be acute or chronic – the latter is frequently

associated with lower airway symptomatology (9, 10). Chronic sinusitis is clinically defined as symptoms (headache, discharge and nasal blockage) that last for more than 8 weeks or take place during more than four episodes a year (2).

Nasal polyposis is also regarded as a chronic inflammatory condition of the sinonasal mucous membrane. Polyps originate from a few square centimetres around the ostia of the ethmoidal sinuses and protrude into the nasal cavities leading to persistent nasal obstruction and loss of smell (2, 11).

The distinction between allergic asthma and upper airway disease may be difficult to make as symptom perception is widely variable; lung function can be normal in mild asthmatics and, although BHR is a constant feature of asthma, it is also frequently present in allergic rhinitis, nasal polyposis, and sinusitis (10–12).

Prevalence

In Europe, the prevalence of asthma has increased more than twofold in the last two decades and now affects between 10 and 15% of the adult population (13). The prevalence of rhinitis has also increased considerably being three times higher than that of asthma (14).

Allergic rhinitis and asthma frequently occur together. Almost 40% of the allergic rhinitis patients have lower airways involvement, whereas >80% of the allergic asthma patients have concomitant rhinitis symptoms

Abbreviations: BHR, bronchial hyperresponsiveness; CT, computer tomography; FEV₁, forced expiratory volume in 1 s; IL, interleukin; SBP, segmental bronchial provocation; VCAM-1, vascular cell adhesion molecule-1.

(15, 16). The latter percentage gets close to 95% when a careful nasal history is taken and physical examination is performed (1).

Sinusitis and nasal polyposis are conditions that need to be taken into account. In the general population, the prevalence of sinusitis is 15–18% (2) and of nasal polyposis 2–4% (8). Chronic sinusitis and nasal polyposis are associated with asthma. Recent reports have demonstrated that approximately 30% of patients with nasal polyposis have asthma (11), while nasal polyposis is present in almost 10% of the asthma patients. The association between chronic sinusitis and asthma is even stronger: over 50% of patients with sinus disease have asthma (17, 18) and up to 90% of patients with mild-to-moderate asthma have abnormal computer tomography (CT) findings of the paranasal sinuses (9). In patients with severe asthma, sinonasal involvement even approximates 100% (9).

Risk factors for asthma

Allergic rhinitis is regarded as a risk factor for the development of asthma, especially in the presence of BHR, (19, 20). Bronchial hyperresponsiveness and atopy are presumably co-inherited and associated with asthma (21). Patients with allergic rhinitis have a three times greater chance than normal subjects of developing asthma, regardless of the atopic status of the patient (22). Nasal polyposis (11) and chronic sinusitis (18) are also frequently accompanied by asymptomatic BHR. Although allergic rhinitis may exacerbate nasal polyposis and sinusitis, atopy, by itself, does not seem to play an important role in the pathogenesis of both conditions (8, 23). This stresses the importance of asymptomatic BHR as a risk factor for asthma, although other factors, such as atopy, may also contribute to this relationship (24).

Mucosal inflammation

It has been well-established that allergic rhinitis and asthma are characterized by a similar inflammatory process (25–29). Tissue eosinophilia and mast cell degranulation are characteristic findings in allergic inflammation, but are also present in nasal polyposis (8) and, to a lesser extent, in chronic sinusitis (2). The eosinophil is a source of leukotriens, prostaglandins, platelet activating factor, cytokines and cytotoxic proteins, which can be released upon stimulation and are toxic to the airway epithelium.

The primary response to an allergic (30) or irritating (31) stimulus takes place in the target organ and is generally more severe in patients with allergic rhinitis and asthma than in patients with only rhinitis (30). The primary response is initially local, but followed by a more

generalized airway reaction. The latter includes nasal and pulmonary symptoms, decreased airway patency and the development of an inflammatory infiltrate, dominated by eosinophils and T-lymphocytes (32–34).

Leukocyte migration is dependent on the expression of cytokines, chemokines, and adhesion molecules (35, 36). Several studies have stressed the importance of interleukin (IL)-5 and eotaxin for the chemotaxis of eosinophils in mucosal tissue (37–39) and blood (40, 41). Up-regulation of vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule with a certain eosinophil specificity, results in firm leukocyte-endothelial adherence and trans-endothelial migration of leukocytes along a chemotactic gradient (35). The role of the mast cell in asthma has also been subject to renewed interest. Mast cells are present in increased numbers in the smooth muscle of asthmatic patients and are related to BHR (42).

Although eosinophilia in bronchial mucosa is regarded as one of the hallmarks of allergic asthma (43), this may not be a very specific finding. Also, in allergic rhinitis patients without asthma, signs of allergic inflammation have been found in induced sputum (44, 45), broncho-alveolar lavage fluid (46, 47) and bronchial biopsies (48). Likewise, eosinophilic infiltration was present in the upper airways of asthmatic patients without nasal complaints (49). Although it is clear that the condition of the upper airways influences the lower airways, the mechanisms underlying this relationship are far from being understood.

Mechanisms of interaction

It has been suggested that several mechanisms could play a role in lower airway dysfunction among patients with rhinitis: i.e. altered breathing pattern, pulmonary aspiration of nasal contents, the nasal-bronchial reflex and uptake of inflammatory mediators in the systemic circulation (50).

Impaired nasal function

The nose and lungs are anatomically and physiologically closely-related organs. The nose acts as a filter and air-conditioner, therefore protecting the lower airways. Pathologic conditions of the nasal mucosa hamper these functions, which leads to increased exposure of the lower airways to allergens. In susceptible persons, this may lead to inflammatory changes and an increase in BHR. Several authors have demonstrated that surgical treatment of chronic rhino-sinusitis and nasal polyposis in asthmatic patients improved their asthmatic status (51, 52), suggesting that improvement of nasal function results in better asthma control. Inhalation of cold air was associated with a decreased forced expiratory volume in 1 s

(FEV₁) in asthmatic patients, while, as long as nasal breathing was maintained, this effect could be prevented (53). However, no difference was seen between patients with nasal polyposis, responsive or unresponsive to topical steroids, with regard to decrease in FEV₁ (54). Although nasal mucosal swelling in asthmatic patients leads to reduced ability to condition air, the decrease in nasal airway patency is not always related to airway symptoms (55, 56). In patients allergic to cats, no enhanced asthmatic response to cat allergen was demonstrated after blocking the nose with a nose-clip (57). Moreover, the degree of nasal blockage was not found to be related to changes in BHR (58). Therefore, the contribution of preferential mouth breathing to the development of asthma remains uncertain.

Postnasal drip

The 'mucociliary escalator' is another important mechanism in modulating airway condition through the removal of inhaled particles: all cilia in the nose, Eustachian tube, paranasal sinuses and the tracheobronchial tree, beat towards the pharynx. Particles trapped in the mucus layer are transported to the pharynx by the mucus escalator. In allergic rhinitis and sinusitis, nasal secretions, containing inflammatory cells and mediators, may be aspirated and could, therefore, be responsible for lower airways involvement (10, 50).

However, aspiration occurs only in patients with decreased consciousness and cough reflexes, and it is not likely to play a role in normally functioning human airways. Patients with chronic sinusitis showed no evidence of pulmonary aspiration after installation of radioactive tracer in the maxillary sinus (59). Nasal secretions are mainly swallowed and neutralized in the stomach. Moreover, inhalation studies with radiolabeled allergens have shown no deposition of allergen in the lungs after nasal allergen application (58). This mechanism definitely needs more extensive study.

The nasobronchial reflex

Afferent sensory innervation in the nose is carried by the trigeminal nerve and efferent parasympathetic fibers are part of the vidian nerve in the nose. The lower airways receive afferent and efferent innervation through the vagal nerve. In the bronchi, the parasympathetic nerves regulate smooth muscle tone (60). Mechanical or chemical stimulation of receptors in the nose, trachea, larynx or elsewhere in the respiratory tract may produce sneezing, coughing or bronchoconstriction to prevent deeper penetration of allergens or irritants into the airways.

Although exposure of the nasal mucosa to cold dry air can result in immediate bronchoconstriction and

BHR in asthmatic patients (61–64), no direct effect on FEV₁ could be detected after nasal allergen challenge (58, 65, 66). Corren et al. demonstrated increased BHR 30 min after nasal provocation, suggesting a role for a nasobronchial reflex mechanism (58). However, as increased BHR was still present after 4.30 h, other pathways, such as the systemic circulation, are more likely to contribute to the interaction. This is in line with findings that nasal allergen provocation may have a direct effect on bronchus symptoms, but that peak expiratory flow starts to decline only after 4–6 h in allergic rhinitis patients (34). Moreover, bronchial provocation in allergic rhinitis patients results in mast cell degranulation after 24 h, but not after 1 h (67). This suggests that neural reflex mechanisms have only a minor contribution to immunologic processes in nasobronchial interaction.

The systemic circulation

Blood eosinophilia is a frequent finding in allergic rhinitis (33, 45) and asthma (27, 42, 68). Nasal provocation with methacholine in asthmatic patients with rhinitis resulted in an increase in lower airway resistance that could be blocked by premedication of nasal mucosa with phenylephrine, suggesting a role for systemic mediators in the induction of lower airway resistance (69). Furthermore, studies in animals (40, 41, 70, 71) and patients with allergic rhinitis, asthma and other atopic diseases (35, 72, 73) have consequently shown a rise in circulating inflammatory cells and progenitors after allergen inhalation followed by recruitment to sites of allergic inflammation. CD34+ cells, capable of eosinophil differentiation, are also present in significant numbers in nasal polyposis, implying a role for hemopoietic mechanisms in nasal polyposis, as well (74). The association between sinusitis, blood eosinophils and lower airway inflammation, which has been demonstrated by ten Brinke et al., suggests that asthma is not just a local disorder but more a systemic disease (18).

The number of blood eosinophils and the concentration of serum-IL-5 (Fig. 1) increased in allergic subjects after natural (30) and experimental allergen exposure (33, 34). In contrast, levels of eosinophil cationic protein were elevated only locally and not systemically after allergen exposure, indicating that eosinophils become activated in the airway mucosa (30). After nasal provocation in allergic rhinitis patients without asthma, VCAM-1 and E-selectin were up-regulated on nasal and bronchial endothelium, coinciding with global airway eosinophilia (34).

Although other mechanisms i.e. neural reflexes, pulmonary aspiration and mouth breathing – may contribute to nasobronchial interaction, these recent data provide ample evidence for the existence of a systemic pathway (Fig. 2).

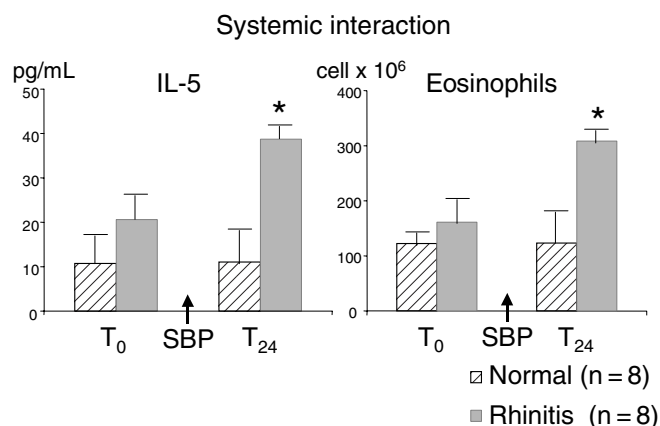


Figure 1. The concentration of human IL-5 and the number of eosinophils in the peripheral blood before (T₀) and 24 h (T₂₄) after segmental bronchial provocation (SBP) in allergic rhinitis patients and control subjects (redrawn from data in ref. 33).

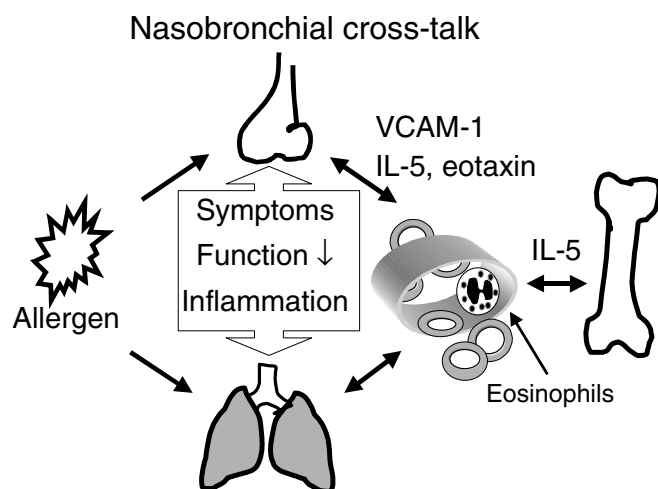


Figure 2. The systemic circulation as an important pathway in the interaction between upper and lower airways (Adapted from Braunstahl GJ, Curr Opin Pulm Med 2003;9:46–51).

Airway inflammation and clinical expression

Bronchial hyperresponsiveness and chronic mucosal inflammation are considered important features of allergic asthma. Although several studies have pointed towards a relationship between bronchial inflammation and BHR (44, 75), others have failed to detect a relationship (45, 76, 77). In fact, the presence of bronchial inflammation in nonasthmatic atopic patients, even in the absence of any airway symptoms at all (Fig. 3A), challenges the direct relationship between the presence of inflammatory cells, in particular eosinophils, and BHR (78). Therefore, the threshold above, which an allergic response is initiated in the bronchi in daily life is probably higher in patients with allergic rhinitis than in those with

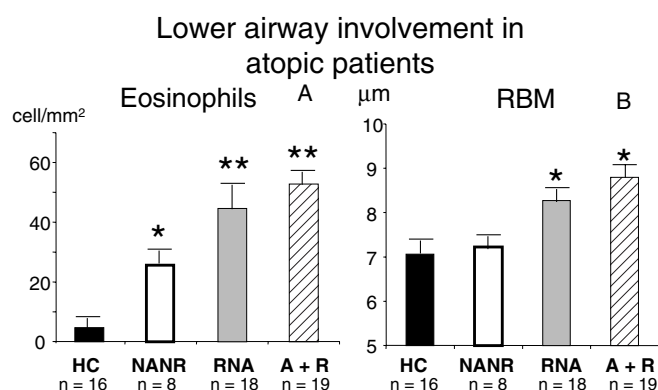


Figure 3. Numbers of eosinophils (major basic protein) (A) and thickness of reticular basement membrane (RBM) (B) in the bronchial mucosa. Abbreviations used: HC = healthy control subjects; NANR = atopic subjects, no asthma, no rhinitis; RNA = allergic rhinitis, no asthma; A + R = allergic asthma and rhinitis. * $P < 0.05$, ** $P < 0.01$ (compared with HC) (redrawn from data in ref. 78).

clinical asthma. Beckey Kelly et al. demonstrated in a bronchoprovocation model that the dose required to initiate comparable clinical responses was significantly lower in patients with asthma than in patients with allergic rhinitis without asthma (79). Moreover, the size of the inhaled allergen, as well as the duration and severity of the allergen exposure, could also affect the clinical manifestation (80). On the contrary, some patients with allergic rhinitis and asthma have such a poor perception of nasal (56) and bronchial symptoms (81) that this may also partly explain the discrepancy between mucosal inflammation and clinical expression.

Acute vs chronic inflammation

Eosinophil and mast cell degranulation may be relevant in the distinction between the chronic and the acute phase of the disease (82). Eosinophilic and basophilic infiltration in the lower airways have long been associated with the severity of asthma (27, 83, 84). Also, nasal allergic inflammation is generally related to clinical expression of seasonal allergic rhinitis (85, 86) and tends to be more severe in rhinitis patients with concomitant asthma (78). Few studies have investigated the allergic response in perennial allergic rhinitis patients. They show that mucosal eosinophilia is less marked in perennial than in seasonal disease and usually not related to symptom expression (87). Allergen provocation studies in nose and lung support these findings. These studies demonstrated persistent inflammation up to 2 weeks after allergen provocation, long after symptoms had disappeared (88, 89). We propose that acute inflammation is related to nasal and/or pulmonary symptoms and influences airway caliber through the release of a variety of mediators. The

relationship between chronic inflammation and clinical disease is, however, less straightforward. Generalized airway eosinophilia is a feature of both allergic rhinitis and asthma and not related to clinical severity in stable disease (78). The presence of inflammatory cells *per se* in mucosal tissue may, therefore, only be footprints of previous immunologic activity.

Mucosal inflammation and airway remodeling

In both asthmatic and nonasthmatic atopic subjects, structural changes are present in the lower airways (Fig. 3B), but usually not in the nose. Eosinophils have long been regarded as the cause of structural changes in the airway mucosa, as they are a source of degranulation products cytotoxic to the epithelial cells. Increased loss of bronchial epithelium has demonstrated to be present in asthmatic patients compared with nonasthmatic control subjects (90). However, epithelial desquamation is not frequently seen in the upper airways, despite a similar inflammatory pattern (28, 78, 91).

Thickening of the bronchial reticular basement membrane because of subepithelial collagen deposition is considered to be another important feature of allergic asthma. It has been demonstrated that the degree of basement membrane thickening was related to disease severity in asthmatics (92). However, increased basement membrane thickness has also been found in recently diagnosed mild asthmatic disease (93) and in nonasthmatic allergic subjects (94) as well as in nasal polyposis (95, 96). It seems unlikely that reticular basement membrane thickening is important in the pathophysiology of allergic rhinitis and chronic sinusitis. In nasal mucosa, no difference in reticular basement membrane thickening was seen between rhinitis patients and healthy controls (78). The role of subepithelial vascularity in the pathophysiology of asthma is also still controversial. Several reports have been published stating that vascularity in asthmatic airways is increased compared with normal controls and correlated with the severity of asthma (97–99), but other reports failed to detect such a relationship (78, 100).

In contrast to the poor relationship between local inflammatory and structural factors in nasal and bronchial mucosa, systemic factors, such as number of blood eosinophils and atopy severity, were associated with more extensive airway disease (Fig. 4) (78, 101, 102).

Clinical studies

Although accumulating evidence underlines the influence of nasal pathology on the control of asthma (103), both conditions are still treated as separate disorders. Few studies have investigated the effect of nasal treatment on asthma. Topical treatment with intranasal corticosteroids

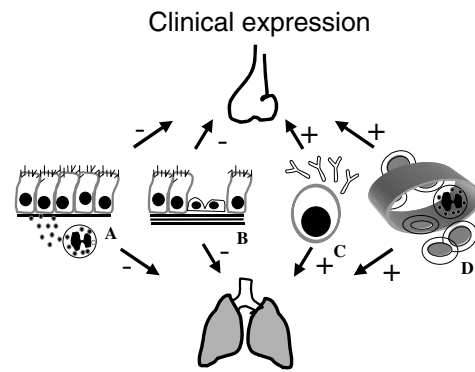


Figure 4. Local and systemic factors (A: mucosal inflammation, B: airway remodeling, C: severity of atopy, and D: blood eosinophilia) in perennial allergic patients and their (lack of) relationship (–/+) to clinical manifestations in nose and lungs (overview based on data from ref. 78).

reduces lower airway symptoms and decreases BHR in allergic rhinitis patients with seasonal asthma (104–107). In one study, delivery of beclomethasone to the nose had an even greater effect on BHR than delivery of the same dose via the oral route (108).

Chronic sinusitis and nasal polyposis are also considered to be inflammatory conditions, which make topical steroids a rational option for treatment. Corticosteroids can have an effect on signs and symptoms in both disorders and are an alternative for nasal surgery (2, 53, 74, 109).

The systemic link between allergic rhinitis and asthma provides a rationale for systemic treatment. Systemic agents, such as leukotriene receptor antagonists, proved to have an additional therapeutic effect on asthma (110, 111) and may be significant in inflammatory upper airway disease, as well (112). Also, anti-IgE antibodies are promising tools in asthma and rhinitis therapy. Anti-IgE treatment has proved to be effective in asthma, as it reduced symptoms, asthma exacerbations and the need for steroids (113, 114). Its usefulness in allergic rhinitis particularly as a steroid-sparing agent – has yet to be determined. Despite the benefit of antihistamines and cromoglycates in seasonal allergic rhinitis, the effect on lower airways is still doubtful (115). Avoidance of inhalant allergens (116) and immunotherapy (117) may be effective for both asthma and rhinitis on a long-term basis.

Future directions

It is clear that there is close interaction between upper and lower airways. Nasal therapy can influence lower airway symptoms in asthmatic patients with concomitant upper airway pathology. However, the effect of nasal therapy on bronchial inflammation and aspects of airway remodeling is still unexplored. The observation that

allergic rhinitis and sinusitis are ubiquitous in allergic asthma, and that both conditions are accompanied by bronchial inflammation, stresses the importance of such clinical trials.

Also, the question remains to be solved concerning the causes of the discrepancy between upper and lower airways with regard to airway remodeling. As the inflammatory pattern is very similar in nose and bronchi, it is still not clear, which inflammatory factors are responsible for the development of airway remodeling in the lower airways. We speculate that intrinsic factors in the bronchial airway epithelium or local repair mechanisms including myofibroblasts may contribute to the different responses of upper and lower airways to airway stimuli.

Conclusions

The relationship between nasal pathology and asthma has been well established in epidemiologic studies and clinical trials. The mechanisms of nasobronchial interaction have for a long time been subject to speculation. To date, most recently published data are in favor of a systemic pathway, involving bloodstream and bone marrow. What eventually determines the clinical phenotype in allergic airway disease is still not completely understood. Generalized airway inflammation is present in patients with allergic rhinitis, sinusitis and nasal polyposis, even in the absence of clinical asthma. Whether these subjects represent a group at risk for the development of asthma requires further study.

References

1. TOGIAS A. Mechanisms of nose-lung interaction. *Allergy* 1999;**54**:94–105.
2. BACHERT C, HORMANN K, MOSGES R, RASP G, RIECHELMANN H, MULLER R et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. *Allergy* 2003;**58**:176–191.
3. LUNDBACK B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;**28**:3–10.
4. PEARCE N, PEKKANEN J, BEASLEY R. How much asthma is really attributable to atopy? *Thorax* 1999;**54**:268–272.
5. International Consensus Report on the diagnosis and management of rhinitis. International Rhinitis Management Working Group. *Allergy* 1994;**49**:1–34.
6. PEDERSEN PA, WEEKE ER. Asthma and allergic rhinitis in the same patients. *Allergy* 1983;**38**:25–29.
7. MYGIND N, DAHL R, PEDERSEN S, Thstrup-Pedersen. atopic diseases. Essential allergy, 1st edn. Oxford: Blackwell Science Ltd, 1996:197–201.
8. MYGIND N, DAHL R, BACHERT C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax* 2000;**55**:S79–S83.
9. BRESCIANI M, PARADIS L, DES ROCHES A, VERNET H, VACHIER I, GODARD P et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;**107**:73–80.
10. TSAO CH, CHEN LC, YEH KW, HUANG JL. Concomitant chronic sinusitis treatment in children with mild asthma: the effect on bronchial hyperresponsiveness. *Chest* 2003;**123**:757–764.
11. LAMBLIN C, GOSSET P, SALEZ F, VANDEZANDE LM, PEREZ T, DARRAS J et al. Eosinophilic airway inflammation in nasal polyposis. *J Allergy Clin Immunol* 1999;**104**:85–92.
12. STEVENS WJ, VERMEIRE PA, VAN SCHIL LA. Bronchial hyperreactivity in rhinitis. *Eur J Respir Dis Suppl* 1983;**128**:72–80.
13. UPTON MN, MCCONNACHIE A, MCSHARRY C, HART CL, SMITH GD, GILLIS CR et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;**321**:88–92.
14. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225–1232.
15. DANIELSSON J, JESSEN M. The natural course of allergic rhinitis during 12 years of follow-up. *Allergy* 1997;**52**:331–334.
16. GREISNER WA, 3rd, SETTIPANE RJ, SETTIPANE GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 1998;**19**:185–188.
17. LEYNAERT B, NEUKIRCH F, DEMOLY P, BOUSQUET J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000;**106**:S201–S205.
18. TEN BRINKE A, GROOTENDORST DC, SCHMIDT JT, DE BRUINE FT, VAN BUCHEM MA, STERK PJ et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;**109**:621–626.
19. RAMSDALE EH, MORRIS MM, ROBERTS RS, HARGREAVE FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;**75**:573–577.
20. BRAMAN SS, BARROWS AA, DECOTIIS BA, SETTIPANE GA, CORRAO WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest* 1987;**91**:671–674.
21. POSTMA DS, BLEECKER ER, AMELUNG PJ, HOLROYD KJ, XU J, PANHUYSEN CI et al. Genetic susceptibility to asthma-bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995;**333**:894–900.
22. GUERRA S, SHERRILL DL, MARTINEZ FD, BARBEE RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;**109**:419–425.
23. SHAPIRO GG. Role of allergy in sinusitis. *Pediatr Infect Dis* 1985;**4**:S55–S59.
24. BOULET LP. Asymptomatic airway hyperresponsiveness: a curiosity or an opportunity to prevent asthma? *Am J Respir Crit Care Med* 2003;**167**:371–378.
25. GODTHELP T, FOKKENS WJ, KLEINJAN A, HOLM AF, MULDER PG, PRENS EP et al. Antigen presenting cells in the nasal mucosa of patients with allergic rhinitis during allergen provocation. *Clin Exp Allergy* 1996;**26**:677–688.
26. MOLLER GM, OVERBEEK SE, VAN HELDEN-MEEUWSEN CG, VAN HAARST JM, PRENS EP, MULDER PG et al. Increased numbers of dendritic cells in the bronchial mucosa of atopic asthmatic patients: downregulation by inhaled corticosteroids. *Clin Exp Allergy* 1996;**26**:517–524.

27. BOUSQUET J, CHANEZ P, LACOSTE JY, BARNEON G, GHAVANIAN N, ENANDER I et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;**323**:1033–1039.
28. CHANEZ P, VIGNOLA AM, VIC P, GUDDO F, BONSIGNORE G, GODARD P et al. Comparison between nasal and bronchial inflammation in asthmatic and control subjects. *Am J Respir Crit Care Med* 1999;**159**:588–595.
29. HOWARTH PH. The cellular basis for allergic rhinitis. *Allergy* 1995;**50**:6–10.
30. MARCUCCI F, SENSI LG, MIGALI E, CONIGLIO G. Eosinophil cationic protein and specific IgE in serum and nasal mucosa of patients with grass-pollen-allergic rhinitis and asthma. *Allergy* 2001;**56**:231–236.
31. PALCZYNSKI C, WALUSIAK J, RUTA U, GORSKI P. Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. *Allergy* 2001;**56**:1186–1191.
32. BENTLEY AM, JACOBSON MR, CUMBERWORTH V, BARKANS JR, MOQBEL R, Schwartz LB et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol* 1992;**89**:877–883.
33. BRAUNSTAHL GJ, KLEINJAN A, OVERBEEK SE, PRINS JB, HOOGSTEDEN HC, FOKKENS WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;**161**:2051–2057.
34. BRAUNSTAHL GJ, OVERBEEK SE, KLEINJAN A, PRINS JB, HOOGSTEDEN HC, FOKKENS WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;**107**:469–476.
35. WARDLAW AJ. Molecular basis for selective eosinophil trafficking in asthma: a multistep paradigm. *J Allergy Clin Immunol* 1999;**104**:917–926.
36. LEE BJ, NACLERIO RM, BOCHNER BS, TAYLOR RM, LIM MC, BAROODY FM. Nasal challenge with allergen upregulates the local expression of vascular endothelial adhesion molecules. *J Allergy Clin Immunol* 1994;**94**:1006–1016.
37. LUSTER AD, ROTHENBERG ME. Role of the monocyte chemoattractant protein and eotaxin subfamily of chemokines in allergic inflammation. *J Leukoc Biol* 1997;**62**:620–633.
38. MATTHEWS AN, FRIEND DS, ZIMMERMANN N, SARAFI MN, LUSTER AD, PEARLMAN E et al. Eotaxin is required for the baseline level of tissue eosinophils. *Proc Natl Acad Sci USA* 1998;**95**:6273–6278.
39. VAN DE RIJN M, MEHLHOP PD, JUDKINS A, ROTHENBERG ME, LUSTER AD, OETTGEN HC. A murine model of allergic rhinitis: studies on the role of IgE in pathogenesis and analysis of the eosinophil influx elicited by allergen and eotaxin. *J Allergy Clin Immunol* 1998;**102**:65–74.
40. INMAN MD, ELLIS R, WATTIE J, DENBURG JA, O'BYRNE PM. Allergen-induced increase in airway responsiveness, airway eosinophilia, and bone-marrow eosinophil progenitors in mice. *Am J Respir Cell Mol Biol* 1999;**21**:473–479.
41. PALFRAMAN RT, COLLINS PD, WILLIAMS TJ, RANKIN SM. Eotaxin induces a rapid release of eosinophils and their progenitors from the bone marrow. *Blood* 1998;**91**:2240–2248.
42. BRIGHTLING CE, BRADDDING P, SYMON FA, HOLGATE ST, WARDLAW AJ, PAVORD ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002;**346**:1699–1705.
43. DJUKANOVIC R, ROCHE WR, WILSON JW, BEASLEY CR, TWENTYMAN OP, HOWARTH RH et al. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990;**142**:434–457.
44. FORESI A, LEONE C, PELUCCHI A, MASTROPASQUA B, CHETTA A, D'IPPOLITO R et al. Eosinophils, mast cells, and basophils in induced sputum from patients with seasonal allergic rhinitis and perennial asthma: relationship to methacholine responsiveness. *J Allergy Clin Immunol* 1997;**100**:58–64.
45. ALVAREZ MJ, OLAGUIBEL JM, GARCIA BE, RODRIQUEZ A, TABAR AI, URBIOLA E. Airway inflammation in asthma and perennial allergic rhinitis. Relationship with nonspecific bronchial responsiveness and maximal airway narrowing. *Allergy* 2000;**55**:355–362.
46. SEDGWICK JB, CALHOUN WJ, GLEICH GJ, KITA H, ABRAMS JS, SCHWARTZ LB et al. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. *Am Rev Respir Dis* 1991;**144**:1274–1281.
47. SEDGWICK JB, CALHOUN WJ, VRTIS RF, BATES ME, McALLISTER PK, BUSSE WW. Comparison of airway and blood eosinophil function after *in vivo* antigen challenge. *J Immunol* 1992;**149**:3710–3718.
48. DJUKANOVIC R, LAI CK, WILSON JW, BRITTEN KM, WILSON SJ, ROCHE WR et al. Bronchial mucosal manifestations of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic nonasthmatics and healthy controls. *Eur Respir J* 1992;**5**:538–544.
49. GAGA M, LAMBROU P, PAPAGEORGIOU N, KOULOURIS NG, KOSMAS E, FRAGAKIS S et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000;**30**:663–669.
50. CORREN J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;**99**:S781–S786.
51. DUNLOP G, SCADDING GK, LUND VJ. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polypsis, and asthma. *Am J Rhinol* 1999;**13**:261–265.
52. IKEDA K, TANNO N, TAMURA G, SUZUKI H, OSHIMA T, SHIMOMURA A et al. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. *Ann Otol Rhinol Laryngol* 1999;**108**:355–359.
53. McLANE ML, NELSON JA, LENNER KA, HEJAL R, KOTARU C, SKOWRONSKI M et al. Integrated response of the upper and lower respiratory tract of asthmatic subjects to frigid air. *J Appl Physiol* 2000;**88**:1043–1050.
54. LAMBLIN C, BRICHET A, PEREZ T, DARRAS J, TONNEL AB, WALLAERT B. Long-term follow-up of pulmonary function in patients with nasal polypsis. *Am J Respir Crit Care Med* 2000;**161**:406–413.
55. ASSANASEN P, BAROODY FM, NAURECKAS E, SOLWAY J, NACLERIO RM. The nasal passage of subjects with asthma has a decreased ability to warm and humidify inspired air. *Am J Respir Crit Care Med* 2001;**164**:1640–1646.
56. HELLGREN J, TOREN K, BALDER B, PALMQVIST M, LOWHAGEN O, KARLSSON G. Increased nasal mucosal swelling in subjects with asthma. *Clin Exp Allergy* 2002;**32**:64–69.
57. WOOD RA, EGGLESTON PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. *Am J Respir Crit Care Med* 1995;**151**:315–320.

58. CORREN J, ADINOFF AD, IRVIN CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;**89**:611–618.
59. BARDIN PG, VAN HEERDEN BB, JOUBERT JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990;**86**:82–88.
60. UNDEM BJ, McALEXANDER M, HUNTER DD. Neurobiology of the upper and lower airways. *Allergy* 1999;**54**:81–93.
61. STRAUSS RH, McFADDEN ER JR, INGRAM RH JR, JAEGER JJ. Enhancement of exercise-induced asthma by cold air. *N Engl J Med* 1977;**297**:743–747.
62. STRAUSS RH, McFADDEN ER JR, INGRAM RH JR, DEAL EC JR, JAEGER JJ. Influence of heat and humidity on the airway obstruction induced by exercise in asthma. *J Clin Invest* 1978;**61**:433–440.
63. GRIFFIN MP, McFADDEN ER JR, INGRAM RH JR. Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. *J Allergy Clin Immunol* 1982;**69**:354–359.
64. NOLTE D, BERGER D. On vagal bronchoconstriction in asthmatic patients by nasal irritation. *Eur J Respir Dis Suppl* 1983;**128**:110–115.
65. ROSENBERG GL, ROSENTHAL RR, NORMAN PS. Inhalation challenge with ragweed pollen in ragweed-sensitive asthmatics. *J Allergy Clin Immunol* 1983;**71**:302–310.
66. SCHUMACHER MJ, COTA KA, TAUSSIG LM. Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma. *J Allergy Clin Immunol* 1986;**78**:30–35.
67. BRAUNSTAHL GJ, OVERBEEK SE, FOKKENS WJ, KLEINJAN A, McEUAN AR, WALLS AF et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001;**164**:858–865.
68. KROEGEL C, LIU MC, HUBBARD WC, LICHTENSTEIN LM, BOCHNER BS. Blood and bronchoalveolar eosinophils in allergic subjects after segmental antigen challenge: surface phenotype, density heterogeneity, and prostanoid production. *J Allergy Clin Immunol* 1994;**93**:725–734.
69. LITTELL NT, CARLISLE CC, MILLMAN RP, BRAMAN SS. Changes in airway resistance following nasal provocation. *Am Rev Respir Dis* 1990;**141**:580–583.
70. DENBURG JA, INMAN MD, WOOD L, ELLIS R, SEHMI R, DAHLBACK M et al. Bone marrow progenitors in allergic airways diseases: studies in canine and human models. *Int Arch Allergy Immunol* 1997;**113**:181–183.
71. SAITO H, HOWIE K, WATTIE J, DENBURG A, ELLIS R, INMAN MD et al. Allergen-induced murine upper airway inflammation: local and systemic changes in murine experimental allergic rhinitis. *Immunology* 2001;**104**:226–234.
72. DENBURG JA, INMAN MD, SEHMI R, UNO M, O'BYRNE PM. Hemopoietic mechanisms in allergic airway inflammation. *Int Arch Allergy Immunol* 1998;**117**:155–159.
73. WANG CH, HSIEH WY, SHIH LY, LIN HC, LIU CY, CHUNG KF et al. Increased progenitor cell proliferation in the peripheral blood of patients with bronchial asthma: the role of nitric oxide. *J Allergy Clin Immunol* 1999;**104**:803–810.
74. KIM YK, UNO M, HAMILOS DL, BECK L, BOCHNER B, SCHLEIMER R et al. Immunolocalization of CD34 in nasal polyposis. Effect of topical corticosteroids. *Am J Respir Cell Mol Biol* 1999;**20**:388–397.
75. BRADLEY BL, AZZAWI M, JACOBSON M, ASSOUEFI B, COLLINS JV, IRANI AM et al. Eosinophils, T-lymphocytes, mast cells, neutrophils, and macrophages in bronchial biopsy specimens from atopic subjects with asthma: comparison with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness. *J Allergy Clin Immunol* 1991;**88**:661–674.
76. POLOSA R, CIAMARRA I, MANGANO G, PROSPERINI G, PISTORIO MP, VANCHERI C et al. Bronchial hyperresponsiveness and airway inflammation markers in nonasthmatics with allergic rhinitis. *Eur Respir J* 2000;**15**:30–35.
77. CRIMI E, SPANEVELLO A, NERI M, IND PW, ROSSI GA, BRUSASCO V. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. *Am J Respir Crit Care Med* 1998;**157**:4–9.
78. BRAUNSTAHL G, FOKKENS W, OVERBEEK S, KLEINJAN A, HOOGSTEDEN H, PRINS J. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003;**33**:579–587.
79. BECKY KELLY EA, BUSSE WW, JARJOUR NN. A comparison of the airway response to segmental antigen bronchoprovocation in atopic asthma and allergic rhinitis. *J Allergy Clin Immunol* 2003;**111**:79–86.
80. WITTEMAN AM, SJAMSOEDIN DH, JANSEN HM, VAN DER ZEE JS. Differences in nonspecific bronchial responsiveness between patients with asthma and patients with rhinitis are not explained by type and degree of inhalant allergy. *Int Arch Allergy Immunol* 1997;**112**:65–72.
81. VAN DEN TOORN LM, OVERBEEK SE, DE JONGSTE JC, LEMAN K, HOOGSTEDEN HC, PRINS JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med* 2001;**164**:2107–2113.
82. GLEICH GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 2000;**105**:651–663.
83. LOUIS R, LAU LC, BRON AO, ROLDAAN AC, RADERMECKER M, DJUKANOVIC R. The relationship between airways inflammation and asthma severity. *Am J Respir Crit Care Med* 2000;**161**:9–16.
84. MARUYAMA N, TAMURA G, AIZAWA T, OHRUI T, SHIMURA S, SHIRATO K et al. Accumulation of basophils and their chemotactic activity in the airways during natural airway narrowing in asthmatic individuals. *Am J Respir Crit Care Med* 1994;**150**:1086–1093.
85. PIPKORN U, KARLSSON G, ENERBACK L. Nasal mucosal response to repeated challenges with pollen allergen. *Am Rev Respir Dis* 1989;**140**:729–736.
86. JULIUSSON S, PIPKORN U, KARLSSON G, ENERBACK L. Mast cells and eosinophils in the allergic mucosal response to allergen challenge: changes in distribution and signs of activation in relation to symptoms. *J Allergy Clin Immunol* 1992;**90**:898–909.
87. FEATHER I, WILSON S. Eosinophils in rhinitis. In: BUSSE W, HOLGATE S, eds. *Asthma and rhinitis*, 1st edn. Oxford: Blackwell Scientific Publications, 1995:347–363.
88. MIADONNA A, MILAZZO N, GIBELLI S, SALMASO C, LORINI M, TEDESCHI A. Nasal response to a single antigen challenge in patients with allergic rhinitis - inflammatory cell recruitment persists up to 48 hours. *Clin Exp Allergy* 1999;**29**:941–949.

89. KLEINJAN A, MCEUEN AR, DIJKSTRA MD, BUCKLEY MG, WALLS AF, FOKKENS WJ. Basophil and eosinophil accumulation and mast cell degranulation in the nasal mucosa of patients with hay fever after local allergen provocation. *J Allergy Clin Immunol* 2000;**106**:677–686.
90. JEFFERY PK, WARDLAW AJ, NELSON FC, COLLINS JV, KAY AB. Bronchial biopsies in asthma. an ultrastructural, quantitative study and correlation with hyperreactivity. *Am Rev Respir Dis* 1989;**140**:1745–1753.
91. KAWABORI S, NAKAMURA A, KANAI N. Tissue density and state of activation of eosinophils in the nasal mucosa of allergic and nonallergic rhinopathic patients. *Allergy* 1994;**49**:81–85.
92. CHETTA A, FORESI A, DONNO M, BERTORELLI G, PESCI A, OLIVIERI D. Airways remodeling is a distinctive feature of asthma and is related to severity of disease. *Chest* 1997;**111**:852–857.
93. BOULET LP, TURCOTTE H, LAVIOLETTE M, NAUD F, BERNIER MC, MARTEL S et al. Airway hyperresponsiveness, inflammation, and subepithelial collagen deposition in recently diagnosed versus long-standing mild asthma. Influence of inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;**162**:1308–1313.
94. CHAKIR J, LAVIOLETTE M, BOUTET M, LALIBERTE R, DUBE J, BOULET LP. Lower airways remodeling in nonasthmatic subjects with allergic rhinitis. *Lab Invest* 1996;**75**:735–744.
95. SILVESTRI M, SABATINI F, SCARSO L, CORDONE A, DASIC G, ROSSI GA. Fluticasone propionate downregulates nasal fibroblast functions involved in airway inflammation and remodeling. *Int Arch Allergy Immunol* 2002;**128**:51–58.
96. OHNO I, NITTA Y, YAMAUCHI K, HOSHI H, HONMA M, WOOLEY K et al. Eosinophils as a potential source of platelet-derived growth factor B-chain (PDGF-B) in nasal polyposis and bronchial asthma. *Am J Respir Cell Mol Biol* 1995;**13**:639–647.
97. LI X, WILSON JW. Increased vascularity of the bronchial mucosa in mild asthma. *Am J Respir Crit Care Med* 1997;**156**:229–233.
98. ORSIDA BE, LI X, HICKEY B, THIEN F, WILSON JW, WALTERS EH. Vascularity in asthmatic airways: relation to inhaled steroid dose. *Thorax* 1999;**54**:289–295.
99. SALVATO G. Quantitative and morphological analysis of the vascular bed in bronchial biopsy specimens from asthmatic and non-asthmatic subjects. *Thorax* 2001;**56**:902–906.
100. CARROLL NG, COOKE C, JAMES AL. Bronchial blood vessel dimensions in asthma. *Am J Respir Crit Care Med* 1997;**155**:689–695.
101. GERGEN PJ, TURKELTAUB PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second National Health and Nutrition Examination Survey, 1976–80 (NHANES II). *J Allergy Clin Immunol* 1992;**90**:579–588.
102. KERKHOF M, SCHOUTEN JP, DE MONCHY JG. The association of sensitization to inhalant allergens with allergy symptoms: the influence of bronchial hyperresponsiveness and blood eosinophil count. *Clin Exp Allergy* 2000;**30**:1387–1394.
103. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147–S334.
104. WELSH PW, STRICKER WE, CHU CP, NAESSENS JM, REESE ME, REED CE et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;**62**:125–134.
105. FORESI A, PELUCCI A, GHERSON G, MASTROPASQUA B, CHIAPPARINO A, TESTI R. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;**98**:274–282.
106. CORREN J, ADINOFF AD, BUCHMEIER AD, IRVIN CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;**90**:250–256.
107. LIPWORTH BJ, WHITE PS. Allergic inflammation in the unified airway: start with the nose. *Thorax* 2000;**55**:878–881.
108. AUBIER M, LEVY J, CLERICI C, NEUKIRCH F, HERMAN D. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. *Am Rev Respir Dis* 1992;**146**:122–126.
109. KANAI N, DENBURG J, JORDANA M, DOLOVICH J. Nasal polyp inflammation. Effect of topical nasal steroid. *Am J Respir Crit Care Med* 1994;**150**:1094–1100.
110. HORWITZ RJ, MCGILL KA, BUSSE WW. The role of leukotriene modifiers in the treatment of asthma. *Am J Respir Crit Care Med* 1997;**157**:1363–1371.
111. SAMPSON A, HOLGATE S. Leukotriene modifiers in the treatment of asthma. Look promising across the board of asthma severity. *BMJ* 1998;**316**:1257–1258.
112. BORISH L. The role of leukotrienes in upper and lower airway inflammation and the implications for treatment. *Ann Allergy Asthma Immunol* 2002;**88**:16–22.
113. BUSSE W, CORREN J, LANIER BQ, MCALARY M, FOWLER-TAYLOR A, CIOPPA GD et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;**108**:184–190.
114. HOLGATE S, BOUSQUET J, WENZEL S, FOX H, LIU J, CASTELLSAGUE J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin* 2001;**17**:233–240.
115. BOUSQUET J, GODARD P, MICHEL FB. Antihistamines in the treatment of asthma. *Eur Respir J* 1992;**5**:1137–1142.
116. WOODCOCK A, CUSTOVIC A. ABC of allergies. Avoiding exposure to indoor allergens. *BMJ* 1998;**316**:1075–1078.
117. DURHAM SR, WALKER SM, VARGA EM, JACOBSON MR, O'BRIEN F, NOBLE W et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–475.