

REVIEW

Local mucosal immunoglobulin E production: does allergy exist in non-allergic rhinitis?

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Summary

In this review, we critically evaluate the evidence for local IgE production in allergic rhinitis mucosa and the concept of local allergy in non-atopic idiopathic rhinitis. Significantly, fewer studies have focused on the disease pathways associated with non-allergic rhinitis compared with their allergic counterparts. Recently, there's been a revival of the hypothesis concerning the existence of local tissue-specific allergic disease confined to the nasal mucosa of some systemically non-atopic rhinitis subjects. Providing the evidence for local mucosal IgE production in allergic rhinitis is a pre-requisite to reviewing its existence in non-allergic rhinitis. In addition, practical and theoretical approaches useful in the detection of allergy in non-allergic rhinitis will be discussed. Furthermore, successful therapeutic regimens used in the treatment of non-allergic rhinitis will be examined as these could provide an insight into the underlying pathophysiology of this common but poorly understood disease.

Keywords allergic, atopy, entopy, IgE, inflammation, non-allergic, rhinitis, vasomotor

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Atopy and the definition of allergic and non-allergic rhinitis

Allergy is on the increase and a number of explanations for this have been proposed including the hygiene hypothesis and decreased air quality. While asthma and rhinitis may represent polarized forms of the same disease this should not underrate the heterogeneity seen in the collection of disease forms that constitute rhinitis.

Since the discovery of IgE [1], it has been recognized that an association exists between the expression of IgE and a predisposition to develop allergic-type disease, described by the term atopy. As allergic rhinitis is an IgE-mediated disease involving a T-helper type 2 (Th2) pathway [2] (Fig. 1), sufferers show affirmative tests for atopy. These include the presence of serum allergen specific IgE and a local inflammatory response when dermally inoculated with allergen, in sensitized individuals.

In non-allergic rhinitis there are no specific physiological responses which can be used to define this condition, despite reports of a diagnostic test for neurogenic type (vasomotor) rhinitis [3], diagnosis is usually made through a process of exclusion. The reliance on the absence of atopy as a selection criterion for the diagnosis of non-

allergic rhinitis is weakened by the existence of anomalies associated with atopy. For instance, it is known that the presence of atopy alone is not conclusive for the development of rhinitis because passive induction of dermal atopic responses does not result in rhinitis. Undoubtedly, some have found good association between atopy (IgE sensitization) tests and the development of allergic rhinitis symptoms [4], while others have not [5]. The presence of allergen-specific IgE is important in determining the relevance of atopy rather than total IgE levels which is unreliable.

What is the evidence for local immunoglobulin E production in allergic nasal mucosa?

The concept of local IgE production is not new. As long ago as 1970 ragweed-specific IgE antibodies were detected in nasal secretions of allergic rhinitis subjects [6] and while this is suggestive of local production, it is not confirmatory due to the confounding migratory behaviour of IgE-producing cells. Subsequently, several researchers attempted to demonstrate local mucosal IgE production. In 1979, Platts-Mills used a nasal provocation

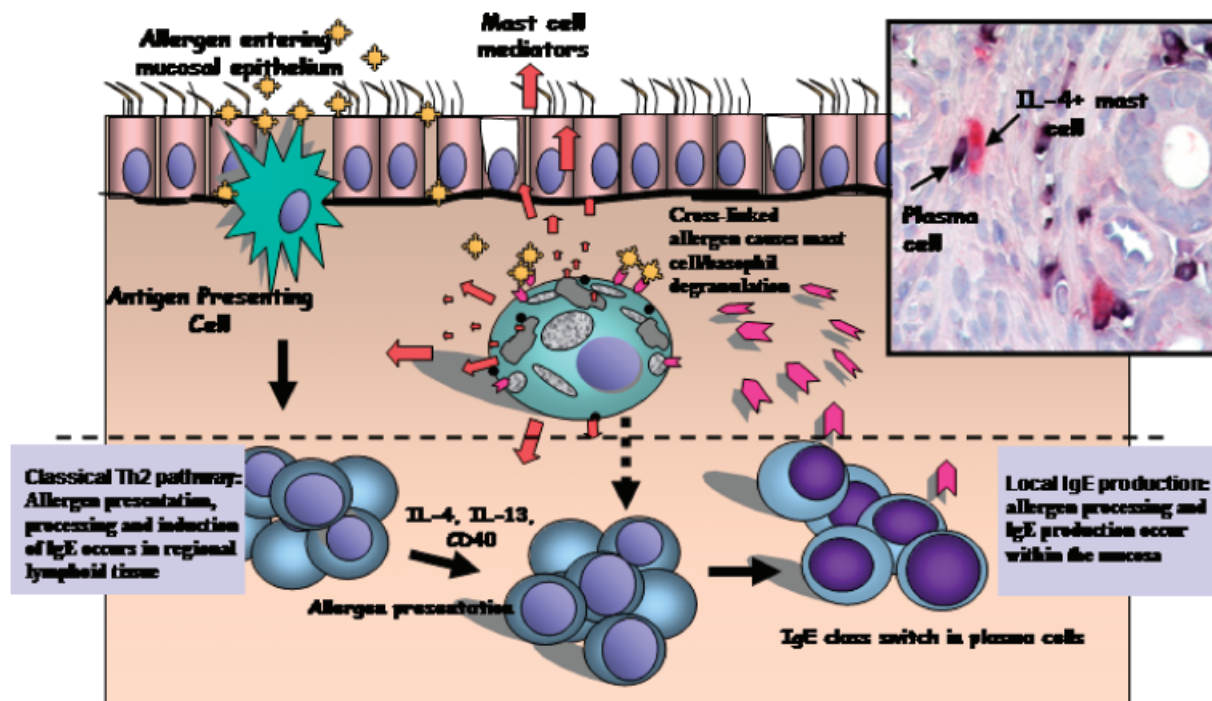


Fig. 1. The T-helper type 2 (Th2) IgE-mediated allergic disease pathway proposed for allergic rhinitis. Classically, IgE production occurs in regional lymphoid tissue (indicated by the broken line) but according to the concept of local mucosal IgE production, all events of the inflammatory cascade occur within the confines of nasal mucosa. IL-4 secreting CD40L(+) mast cells can directly activate B cells inducing IgE switch (central broken arrow); this process can be seen in sections of allergic mucosa (inset photo).

technique to investigate the production of rye-grass-specific IgE, IgG and IgA in nasal secretions, serum and saliva [7] of rye SPT-positive allergic rhinitis individuals, along with a mix of non-allergic control groups. Platts-Mills showed increased levels of specific IgE in nasal secretions from allergic subjects with an absence in saliva. Of note, subjects desensitized by subcutaneous pollen injections showed differences in their Ig levels compared with their untreated allergic counterparts prompting Platts-Mills to suggest that immune responses to allergens is tissue dependent.

Although multiple lymphoid tissue sites have been proposed for IgE production, mucosal-based local immune responses are attractive because they offer biological efficiencies in strategically dealing with allergen at its site of entry. Antigen-presenting cells are present in the epithelium of allergic and non-allergic rhinitis mucosa but are significantly increased in the former [8]. Previously, it has been shown that mucosal lymphoid cells show local organization with a prime example seen in gut-associated lymphoid tissue (GALT) [9] but more recently, this has been observed in nasal-associated lymphoid tissue too [10]. Activated lymphocytes are required for the functional production of IgE protein. T cells provide the mediators IL-4, IL-13 and CD40L needed to induce selective somatic recombination of the Ig heavy chain regions in B cells preceding their maturation into

plasma cells [11]. In allergic nasal mucosa, mast cells produce increased quantities of these mediators compared with their T cell counterparts, and have been shown to induce and possibly maintain local IgE production in B cells [12, 13]. Even though key inflammatory cells and mediators are in place, some have found IgE-positive cells to be elusive in nasal mucosa [14]. In contrast, a more recent study showed local IgE production confined to small numbers of B cells in allergic airways [15].

IgE production has been demonstrated in *in vitro* mucosal explants, and B cells derived from allergic nasal mucosa undergo increased IgE production and proliferation when allergen challenged *in vitro* [12, 16] and *in vivo* [17]. Critics might suggest that these findings are explained by pre-switched IgE B cells migrating into nasal mucosa from distant lymphoid tissues and so more recent studies have addressed this issue. In studies, performed by Durham et al. [18] and Cameron et al. [19], evidence of local IgE production in allergic nasal mucosa was provided using a similar approach in comparing the number of B cells expressing RNA transcripts for the epsilon initiator (I ϵ) and constant (C ϵ) exon regions in germline and mature switched (protein coding) RNA, before and after allergen challenge. The studies were extended using an isolated *in vitro* nasal mucosal explant model, where it was shown that the number of B cells undergoing direct and indirect immunoglobulin isotype

switch to IgE increased after allergen challenge [19, 20]. This process was associated with the simultaneous production of class-specific intermediate circular DNA released as a by-product from germline DNA recombination (Fig. 2). Furthermore, the RNA transcript coding for 'activation induced cytidine deaminase' (AID) enzyme involved in Ig gene switch has been identified in challenged nasal explant tissue [20].

Evidence for allergy in non-allergic rhinitis

The classification of rhinitis [21] is based on aetiology (Table 1) and by definition non-allergic rhinitis subjects are non-atopic because of an absence of an identifiable systemic IgE-mediated disease pathway. Up to 60% of non-allergic rhinitis subjects (representing 36% of all rhinitis sufferers) have idiopathic rhinitis (IR), with an unknown disease pathway. Previously, multiple names

have been used to synonymously describe this group including the term vasomotor rhinitis (VMR) but this should strictly be reserved for subjects where a neurogenic pathophysiology is implicated. Presently, subjects with Non-allergic Rhinitis with Eosinophilic Syndrome (NARES) are separately classified to IR but their exclusion from this category [22] is controversial because the cause and relevance of their characteristic mucosal eosinophil accumulation remains unknown.

In spite of negative systemic tests for atopy, several studies have sought the presence of an allergic disease pathway in the nasal mucosa of non-allergic rhinitis subjects. Broadly speaking, these studies can be categorized into

- The detection of allergen-specific IgE or inflammatory cell mediators in nasal secretions,
- The expression of allergic rhinitis symptoms or physiological changes in nasal airways after allergen provocation,
- Histological studies of inflammatory cells or their products localized in nasal mucosa,
- The ability of nasal mucosa of non-atopic subjects to bind specific allergens.

Detection of allergen-specific immunoglobulin E or inflammatory cell mediators in response to nasal provocation

In a study by Huggins and Brostoff (1975) the authors selected a group of house dust mite (HDM) SPT- and RAST-negative patients with a medical history suggesting sensitization to this allergen [23]. Following HDM nasal provocation, subjects experienced rhinitis symptoms and specific IgE antibodies were identified in nasal secretions, but not in their serum.

The expression of allergic rhinitis symptoms or physiological changes in the nasal airways

Exposure to allergens via the nasal route induces a change in nasal airway resistance in sensitized-allergic rhinitis subjects. Symptoms resulting from nasal allergen provocation can be regarded as the clinical gold standard for diagnosing suspected allergen sensitization and, coupled with rhinomanometry, affords an objective measure of response. In a study comparing subjects with perennial IR

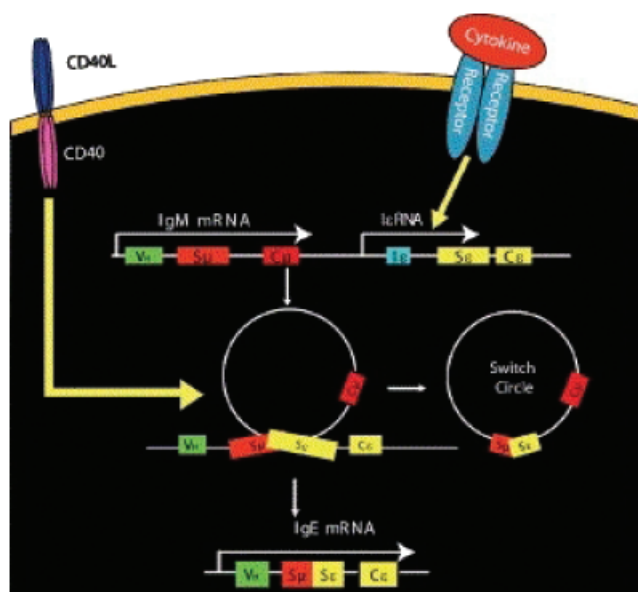


Fig. 2. Isotype switching involves two steps: germline transcription and DNA recombination. Cytokines cause the transcription of Iε RNA, which is essential for switching. CD40 ligand allows recombination to proceed. Products of isotype switching are a gene for an immunoglobulin isotype (here IgE) and a switch circle, which is composed of the intermediate region that was deleted from genomic DNA. (Reprinted from the *Journal of Allergy and Clinical Immunology*, Vol. 116, P Fiset, L Cameron, Q Hamid. Local isotype switching to IgE in airway mucosa, 2005, pp. 233–6, with permission from the American Academy of Allergy, Asthma, and Immunology.)

Table 1. This table shows how rhinitis is classified into two major forms according to the involvement of IgE giving rise to the concept of atopy

Allergic		Non-allergic			
Atopic SPT(+)/RAST (+)		Non-atopic SPT(–)/RAST (–)			
IgE-mediated pathophysiology	Idiopathic Including NARES	Occupational/Irritant	Hormonal	Infectious	Atrophic
		VMR	Emotional	Drug-induced	Structural

The idiopathic rhinitis group has members who have been shown to have mucosal similarities to the allergic group.

and perennial allergic rhinitis, it was shown that a significant proportion of non-atopic rhinitic subjects showed airway obstruction following allergen challenge, suggestive of a local allergic mucosal response [24]. Having demonstrated airway physiological changes in response to allergen provocation, additional evidence of an IgE-mediated disease pathway should be sought post-provocation, using RAST type tests on nasal secretions specific to the putative allergen. This is especially important for rhinitis subjects who previously produced negative SPT and serum allergen specificity tests.

More recently, Wedbäck et al. (2005) reported on a cohort of non-atopic patients with a syndrome they called 'Seasonal Non-Allergic Rhinitis' (SNAR) [25]. In spite of being SPT negative to birch pollen, 3/15 SNAR subjects showed a positive immediate response and 7/15 showed late phase symptoms after nasal provocation with birch pollen.

Histological studies of inflammatory cells or their products

Allergic rhinitis mucosa is characterized by increased numbers of Th2 cells (Fig. 1) including CD4 T-helper cells, eosinophils and mast cells. Similarly, a proportion of subjects with non-atopic rhinitis have been shown to have increased numbers of mucosal mast cells [15, 26] and eosinophils [15]. Importantly, the presence of IgE-expressing cells in the nasal mucosa of some idiopathic subjects support an underlying allergic disease pathway [15]. Support for the concept of locally produced mucosal IgE is also provided by striking similarities seen in the pathophysiology between atopic (extrinsic) and non-atopic (intrinsic) asthma. Both forms of asthma show increased levels of the cytokines (IL-4 and IL-13) needed for IgE class switch induction [27, 28] and of the ϵ heavy chain Ig [29] compared with healthy lung.

In contrast, a study on VMR [30] and IR [31] failed to detect a significant difference in mucosal Th2 cells but both studies identified a couple of non-allergic subjects with increased numbers of mast cells, eosinophils and IgE+ cells. Van Rijswijk et al. suggested the apparent conflict between the different studies for Th2-associated mucosal cell distribution in IR can be explained by sampling error (due to the size of tissue analysed), and differences in patient selection.

The ability of nasal mucosa of non-atopic subjects to bind specific allergens

Binding of labelled grass pollen allergen by mast cells has been shown in thin sections of nasal mucosa obtained from serum and SPT pollen-negative non-atopic subjects with IR [32]. Powe et al. proposed the term *entropy* to describe localized allergen sensitization confined to the nasal mucosa of subjects who are systemically non-atopic for the same allergen.

Explanation for the existence of localized allergy in non-allergic rhinitis subjects

Inadequate atopic tests and low immunoglobulin E detection sensitivity

Whereas SPT test for the functionality of the allergic inflammatory cell cascade, RAST tests assess the presence of serum-specific IgE. Excluding poor SPT technique, the absence of atopy in 'non-atopic' subjects might be explained by the quality of allergen used. Highly pure allergens give good specificity but compared with cruder preparations, may offer a reduced evocation potential upon allergen challenge. Some allergens share common determinant regions giving rise to the concept of pan-allergy [33]. Furthermore, chemical contaminants present in allergen extracts might have an adjuvant affect, for instance diesel fuel particulates boost-allergic responses.

An additional explanation for non-detection of IgE in non-allergic rhinitis could be due to its low abundance in tissues away from its site of synthesis. In other words, if localized nasal mucosal production occurs, levels of systemic IgE might fall outside the range of detection sensitivity. Furthermore, low numbers of IgE-producing plasma cells are seen in nasal mucosa and unless bound, IgE might be actively transported from the submucosal region as a component of nasal secretions. For these reasons, detection of locally produced allergen-specific IgE in nasal secretions after a specific nasal provocation test is likely to be more sensitive than SPT and RAST.

Covert allergy

Covert allergy is defined as sensitivity to an allergen not tested for. There are a number of underestimated suspect allergens not routinely screened for, with arthropods (insects, arachnids, crustaceans, molluscs) coming under suspicion as a major source of allergenicity in the home [33].

Site-specific immune responses – tissue compartment concept

Host immune responses need to be directed and appropriate to the level of assault, warranting local immune defence mechanisms. The migratory mechanisms of mature granulocyte inflammatory cells in circulating blood, including mast cells, support the concept of *in situ* maturation of precursor cells at sites of inflammation. Just as an *in vitro* explant model of allergic nasal mucosa has been used to demonstrate local IgE production [19, 20], Cameron et al. used the same approach to show '*in situ* haemopoiesis' (local maturation) for eosinophils [34]. Combined with this, tissue-specific immune responses to allergen appear possible, with the nature of

the response being dependent on the route and dose of antigen given [35].

Non-immunoglobulin E-mediated allergy

The confounding absence of atopy in subjects with a medical history suggestive of allergic rhinitis could be explained by non-IgE-mediated allergic type hypersensitivity. Using an IgE knock-out model, it is still possible to obtain an anaphylactic response in sensitized mice [36], mediated by IgG antibodies. New evidence also supports a role for free light chain Igs in sensitizing mast cells and causing allergic type hypersensitivity [37].

Detection of allergy in non-allergic rhinitis. Does the treatment of non-allergic rhinitis give an indication to the underlying disease pathophysiology?

Although the diagnosis of non-allergic rhinitis is arrived at through a process of exclusion, some advocate the use of cold dry air (CDA) provocation for the detection of neurogenic-type rhinitis (VMR)(3). Mast cell inflammatory mediators have been identified after CDA but their relevance remains obscure. The gold standard for confirmation of suspected allergy is NPT but this can only be performed when a candidate allergen has been identified from a good medical history. The detection of exhaled nitric oxide (eNO) although indicative of generalized airway inflammation could theoretically be capable of detecting the local allergic form (entopic) of non-allergic rhinitis because eNO levels are increased in atopic inflammation [38], independently of the presence of neutrophils or underlying infections.

The underlying disease pathway in non-allergic rhinitis can be inferred from the pharmacology employed in successful treatment. For many non-allergic rhinitis patients, treatment with topical anti-inflammatories remains the first choice adding support to the presence of a mucosal immune inflammatory cell component. Because of the reported presence of mucosal mast cells in some IR [15] and some VMR subjects, the use of anti-histamines is advocated. 'Double antagonist' topical antihistamines alleviate symptoms generated by nascent mucosal histamine as they block the histamine ligand and its H₁ receptor. In particular, the topical antihistamine azelastine has been shown to be effective in treating non-allergic rhinitis including VMR [39]. In addition, the use of capsaicin [40] and ipratropium bromide [41] is reported to be beneficial in alleviating symptoms of nasal blockage and rhinorrhea, respectively, in VMR. Non-allergic rhinitis with eosinophilia syndrome (NARES) should respond favourably to topical steroid treatment as these anti-inflammatories are reported to selectively induce eosinophil clearance and to inhibit the chemokine responsible for their recruitment. For similar pharmacological reasons, blocking of the chemo-

kine eotaxin pathway via monoclonal antibodies against the TNF- α receptor and TNF- α converting enzyme inhibitor could theoretically offer therapeutic benefits. The use of humanized anti-IgE monoclonal antibodies while reducing systemic levels of free IgE do not reduce nasal mucosal-generated IgE [42], negating their use for localized allergy in non-allergic rhinitis.

Summary

There is strong evidence that local IgE production occurs in sensitized allergen challenged nasal mucosa. Meanwhile, no consensus exists for the concept of local IgE-mediated-allergic disease present in some non-atopic rhinitis subjects. In spite of this, the similarity between allergic and non-allergic rhinitis in terms of symptoms, mucosal inflammatory cells and mediators, is most easily explained by a proportion of the non-allergic group sharing the same disease pathway as their allergic counterparts. More studies are needed to resolve the intricacies of local mucosal allergy in the absence of systemic atopy-entopy. Further studies are required in developing techniques for the detection of local allergy, including pan-IgE screening techniques as a prelude to allergen specific tests following allergen challenge, for use in allergic and non-allergic rhinitis sufferers. Once in place, the epidemiology of allergy in non-allergic rhinitis subjects can be more accurately assessed and targeted treatment strategies employed.

References

- 1 Ishizaka K, Ishizaka T, Hornbrook M. Physicochemical properties of human reagenic antibody. V. Presence of a unique immunoglobulin as a carrier of reagenic activity. *J Immunol* 1966; **97**:75.
- 2 Durham S, Ying S, Varney V *et al*. Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/macrophage-colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship to eosinophilia. *J Immunol* 1992; **148**:2390-4.
- 3 Braat J, Mulder P, Fokkens W *et al*. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyperreactivity in nonallergic noninfectious perennial rhinitis. *Am J Respir Crit Care Med* 1998; **157**: 1748-55.
- 4 Hagy GW, Settupane GA. Risk-factors for developing asthma and allergic rhinitis - 7 year follow-up-study of college students. *J Allergy Clin Immunol* 1976; **58**:330-6.
- 5 Ng M, Warlow R, Chrishanthan N, Ellis C, Walls R. Preliminary criteria for the definition of allergic rhinitis: a systemic evaluation of clinical parameters in a disease cohort (II). *Clin Exp Allergy* 2000; **30**:1417-22.
- 6 Tse KS, Wicher K, Arbesman CE. IgE antibodies in nasal secretions of ragweed-allergic subjects. *J Allergy* 1970; **46**:352.
- 7 Platts-Mills T. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol* 1979; **122**:2218-25.

- 8 Powe DG, Huskisson RS, Carney AS *et al.* Mucosal T-cell phenotypes in persistent atopic and nonatopic rhinitis show an association with mast cells. *Allergy* 2004; **59**:204–12.
- 9 Moghaddami M, Cummins A, Mayrhofer G. Lymphocyte-filled villi: comparison with other lymphoid aggregations in the mucosa of the human small intestine. *Gastroenterology* 1998; **115**:1414–25.
- 10 Harmsen A, Kusser K, Hartson L *et al.* Cutting edge: organogenesis of nasal-associated lymphoid tissue (NALT) occurs independently of lymphotoxin- α (LT- α) and retinoic acid receptor-related organ receptor- γ , but the organization of NALT is LT- α dependent. *J Immunol* 2002; **168**:986–90.
- 11 Gauchat J, Lebman D, Coffman R *et al.* Structure and expression of germline ϵ transcripts in human B cells induced by interleukin-4 to switch to IgE production. *J Exp Med* 1990; **172**:463–73.
- 12 Pawankar R, Okuda M, Yssel H *et al.* Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc ϵ R1, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997; **99**:1492–9.
- 13 Pawankar R, Yamagishi S, Yagi T. Revisiting the roles of mast cells and its relation to local IgE synthesis. *Am J Rhinol* 2000; **14**:309–17.
- 14 Ganzer U, Bachert C. Localization of IgE synthesis in immediate-type allergy of the upper respiratory tract. *J Otorhinol Relat Spec* 1988; **50**:257–64.
- 15 Powe DG, Huskisson R, Carney A *et al.* Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy* 2001; **31**:864–72.
- 16 Zurcher AW, Derer T, Lang AB, Stadler BM. Culture and IgE synthesis of nasal B cells. *Int Arch Allergy Immunol* 1996; **111**:77–82.
- 17 Kleinjan A, Godthelp T, van Toornenbergen AW, Fokkens WJ. Allergen binding to specific IgE in the nasal mucosa of allergic patients. *J Allergy Clin Immunol* 1997; **99**:515–21.
- 18 Durham SR, Gould H, Thienes CP *et al.* Expression of the epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. *Eur J Immunol* 1997; **27**:2899–906.
- 19 Cameron L, Gounni A, Frenkiel S *et al.* SeeSm and SeSy switch circles in human nasal mucosa following *ex vivo* allergen challenge: evidence for direct as well as sequential class switch recombination. *J Immunol* 2003; **171**:3816–22.
- 20 Takhar P, Smurthwaite L, Coker HA *et al.* Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol* 2005; **174**:5024–32.
- 21 Lund V. Report of the International Rhinitis Management Working Group. *Allergy* 1994; **91**:1–34.
- 22 Fokkens W. Thoughts on the pathophysiology of nonallergic rhinitis. *Curr Allergy Asthma Rep* 2002; **2**:203–9.
- 23 Huggins K, Brostoff J. Local production of specific IgE antibodies in allergic rhinitis patients with negative skin tests. *Lancet* 1975; **2**:148.
- 24 Carney A, Powe D, Huskisson R, Jones N. Atypical nasal challenges results in patients with idiopathic rhinitis: more evidence for the existence of 'local allergy'. *Clin Exp Allergy* 2002; **32**:1436–40.
- 25 Wedback A, Enbom H, Eriksson N *et al.* Seasonal non-allergic rhinitis (SNAR) – a new disease entity? A clinical and immunological comparison between SNAR, seasonal allergic rhinitis and persistent non-allergic rhinitis. *Rhinology* 2005; **43**:86–92.
- 26 Berger G, Goldberg A, Ophir D. The inferior turbinate mast cell population of patients with perennial allergic and nonallergic rhinitis. *Am J Rhinol* 1997; **11**:63–6.
- 27 Humbert M, Durham SR, Ying S *et al.* IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against 'intrinsic' asthma being a distinct immunopathologic entity. *Am J Resp Crit Care Med* 1996; **154**:1497–504.
- 28 Humbert M, Durham SR, Kimmitt P *et al.* Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and nonatopic subjects with asthma. *J Allergy Clin Immunol* 1997; **99**:657–65.
- 29 Ying S, Humbert M, Meng Q *et al.* Local expression of epsilon germline gene transcripts and RNA for the epsilon heavy chain of IgE in the bronchial mucosa in atonic and nonatopic asthma. *J Allergy Clin Immunol* 2001; **107**:686–92.
- 30 Blom H, Godthelp T, Fokkens W *et al.* Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. *Eur Arch Otorhinolaryngol* 1995; **1** (Suppl.):S33–S9.
- 31 Van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy* 2005; **60**:1471–81.
- 32 Powe DG, Mason M, Jagger C *et al.* 'Entropy': localised mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy* 2003; **33**:1374–9.
- 33 Panzani R, Ariano R. Arthropods and invertebrates allergy (with the exclusion of mites): the concept of panallergy. *Allergy* 2001; **56**:1–22.
- 34 Cameron L, Christodouloupoulos P, Lavigne F *et al.* Evidence for local eosinophil differentiation within allergic nasal mucosa: inhibition with soluble IL-5 receptor. *J Immunol* 2000; **164**:1538–45.
- 35 Till S, Francis J, Nouri-Aria K, Durham S. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004; **113**:1025–34.
- 36 Oettgen HC, Martin TR, Wynshawboris A *et al.* Active anaphylaxis in IgE-deficient mice. *Nature* 1994; **370**:367–70.
- 37 Redegeld FA, Nijkamp FP. Immunoglobulin free light chains and mast cell: pivotal role in T-cell-mediated immune reactions? *Trends Immunol* 2003; **24**:181–5.
- 38 Jouaville LF, Annesi-Maesano I, Nguyen LT *et al.* Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. *Clin Exp Allergy* 2003; **33**:1506–11.
- 39 Lieberman P, Kaliner M, Wheeler W. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opinion* 2005; **21**:611–8.
- 40 Van Rijswijk JB, Boeke EL, Keizer JM *et al.* Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. *Allergy* 2003; **58**:754–61.
- 41 Bronsky EA, Druce H, Findlay SR *et al.* A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. *J Allergy Clin Immunol* 1995; **95**:1117–22.
- 42 Corren J, Diaz-Sanchez D, Saxon A *et al.* Effects of omalizumab, a humanized monoclonal anti-IgE antibody, on nasal reactivity to allergen and local IgE synthesis. *Ann Allergy Asthma Immunol* 2004; **93**:243–8.