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Nasal hyperreactivity and inflammation in allergic rhinitis

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THE history of allergic disease goes back to 1819, when Bostock described his own 'periodical affection of the eyes and chest', which he called 'summer catarrh'. Since they thought it was produced by the effluvium of new hay, this condition was also called hay fever. Later, in 1873, Blackley established that pollen played an important role in the causation of hay fever. Nowadays, the definition of allergy is 'An untoward physiologic event mediated by a variety of different immunologic reactions'. In this review, the term allergy will be restricted to the IgE-dependent reactions. The most important clinical manifestations of IgE-dependent reactions are allergic conjunctivitis, allergic rhinitis, allergic asthma and atopic dermatitis. However, this review will be restricted to allergic rhinitis. The histopathological features of allergic inflammation involve an increase in blood flow and vascular permeability, leading to plasma exudation and the formation of oedema. In addition, a cascade of events occurs which involves a variety of inflammatory cells. These inflammatory cells migrate under the influence of chemotactic agents to the site of injury and induce the process of repair. Several types of inflammatory cells have been implicated in the pathogenesis of allergic rhinitis. After specific or nonspecific stimuli, inflammatory mediators are generated from cells normally found in the nose, such as mast cells, antigen-presenting cells and epithelial cells (primary effector cells) and from cells recruited into the nose, such as basophils, eosinophils, lymphocytes, platelets and neutrophils (secondary effector cells). This review describes the identification of each of the inflammatory cells and their mediators which play a role in the perennial allergic processes in the nose of rhinitis patients.

Key words: Allergy, nasal hyperreactivity, nasal inflammation, rhinitis

History of Allergy

The history of allergic diseases goes back to 1819, when Bostock described his own 'periodical affection of the eyes and chest', which he called 'summer catarrh'. Since they thought it was produced by the effluvium of new hay, this condition was also called hay fever. Later, in 1873, Blackley[1] established that pollen played an important role in the causation of hay fever.

In 1902 Portier and Richet described the development of anaphylaxis in dogs a few minutes after reinjection with anemone toxine. By this experiment they demonstrated that, in this case, immunity was not protective but damaging to the individual. Arthus observed in 1903 that after repeated injections with substances which had not caused any reaction the first time, the injected tissues became inflamed. Von Pirquet[2] noted that under some conditions, patients, instead of developing immunity, had an increased reactivity to repeated exposure with foreign substances. By putting together the Greek words 'allos' meaning different or changed, and 'ergos' meaning work or action, he introduced in 1906 the term allergy. Both immunity and hypersensitivity were thought to have similar underlying immunologic mechanisms. Later, in 1923, Coca and Cooke[3] proposed the term atopy for the clinical forms of allergy, manifested by hay fever and asthma, in which 'the individuals as a group possess a peculiar capacity to become sensitive to certain proteins to which their environment and habits of life frequently expose them'. Thus,

an inherited predisposition to become sensitized is a characteristic feature of atopy. Prausnitz and Küstner[4] demonstrated in 1921 that the serum of allergic individuals contained a humoral factor that caused specific allergen sensitiveness in a non-allergic individual. The factor responsible for the Prausnitz–Küstner reaction was named reagin by Coca and Cooke. These reagins were characterized by Ishizaka *et al.*[5] and independently at the same time also by Johansson and Bennich[6] as a new immunoglobulin class which they named immunoglobulin E (IgE). Gell and Coombs[7] subdivided allergy into four types: immediate IgE-dependent reaction (I), cytotoxic reaction (II), immune complex reaction (III), delayed cellular immune reaction (IV).

From a clinical view, Voorhorst[8] defined allergy in 1962 as an altered sensitivity, deviating from the norm (i.e. normergy) in a quantitative sense.

Nowadays, the definition of allergy as an 'untoward physiologic event mediated by a variety of different immunologic reactions', described by Middleton, Reed and Ellis,[9] is used. Accepting this definition, one should also keep in mind the following three criteria: (1) identification of the allergen, (2) establishment of a causal relationship between exposure to the antigen and occurrence of the lesion, and (3) identification of the immunologic mechanism involved in the illness.

In this review, the term allergy will be restricted to the IgE-dependent reactions. The most important clinical manifestations of IgE-dependent reactions are allergic conjunctivitis, allergic rhinitis, allergic asthma and atopic dermatitis. However, this review will be restricted to allergic rhinitis.

Allergic Rhinitis

Epidemiology: Allergic rhinitis is the most common manifestation of the IgE-mediated disorders, with a prevalence ranging from 2 to 20%.[10] The prevalence of allergic rhinitis seems to be increasing. In a study performed in Swedish army recruits, the prevalence of hay fever increased from 4.4% in 1971 to 8.4% in 1981.[11] The prevalence of allergic skin test reactivity, i.e. atopy, increased from 39% to 50% in a community sample in the USA of individuals of all ages for a mean of 8 years.[12] Since skin reactivity and allergic disease are associated; this suggests that the prevalence of allergic rhinitis is also increasing.

Clinical aspects of allergic rhinitis: According to the international consensus rhinitis is defined as an inflammation of the nasal mucosa characterized by one of the following symptoms: nasal itchiness, sneezing, rhinorrhoea and nasal congestion.[13] Other symptoms, such as 'popping' of the ears, headache, throat clearing and coughing, are less common. Allergic rhinitis can be subdivided in seasonal and perennial rhinitis. In seasonal rhinitis symptoms are triggered by exposure to tree, grass, and/or weed pollen. In non-tropical parts of the world, seasonal allergic rhinitis occurs during a defined period of the year, which implies that patients also have a symptom free period. In contrast, patients with perennial rhinitis suffer from almost continuous nasal symptoms throughout the year. The most common perennial allergens are indoor allergens such as the house dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) and animal danders, and in some areas certain mould species and cockroaches, as well.

However, patients with rhinitis are not only troubled by nasal symptoms that interfere with their day-to-day lives and their quality of life. Patients are limited in their daily activities; concentration and sleep are impaired. Associated symptoms, such as headache, are troublesome, and practical aspects, such as the availability of a handkerchief and blowing the nose, are a nuisance. Social interaction is limited and there is an impact on emotional well-being.[14] In addition to the costs of medication, health services and sick absence, the loss in personal income contributes to the economic impact of rhinitis. To measure the influence of nasal symptoms on day-to-day life, rhinitis quality of life (QOL) questionnaires have been developed.[14] Juniper *et al.*[14] demonstrated that QOL deteriorated after allergen exposure (pollen season) and increased after symptomatic treatment.

Reactions of Nasal Mucosa on Allergen Exposure

Most studies concerning the pathophysiology of allergic rhinitis have been performed in patients with seasonal rhinitis. The effect of pollen exposure on the nasal mucosa can be determined during the natural pollen season or by nasal challenge models performed outside the pollen season. In nasal allergen challenge studies, well-known amounts of standardized allergen are administered into the nose. In most studies, nasal challenges are used to investigate the pathophysiology of allergic rhinitis. However, one should keep in mind that the mode of exposure is not natural and that in a short time high concentrations of allergens are administered to elicit a clear nasal response instead of continuous exposure to lower and variable amounts of aller-

gens. The problem of monitoring nasal response during natural exposure is the variable and unknown level and spectrum of allergen content.

Several methods have been used to perform nasal allergen challenges. Connell[15] developed a quantitated challenge with ragweed pollen. Later, standardized liquid allergen extracts were developed, which can be insufflated into the nose or can be administered by filter paper discs or by special equipment like the 'nasal pool device'.[16,17]

Nasal response to allergen challenge can be determined by different methods. Usually, the symptomatic response is monitored by the number of sneezes, the amount of secretion, and nasal blockage. Sneezing and itchiness are the results of a central reflect elicited in the sensory nerve endings in the nasal mucosa. Sneezing and itchiness can also be subjectively measured by symptom scoring. Nasal blockage is the result of pooling of blood in the capacitance vessels of the mucosa, and to some degree the result of tissue oedema. It can be assessed subjectively by means of symptom scoring. An objective estimation of nasal blockage can be made by methods such as rhinomanometry,[18] nasal peak flow determination,[19] acoustic rhinometry[20] and rhinostereometry.[21] Nasal secretion can be assessed by weighing the blown secretion or by measuring the volume of secretion collected in a funnel equipped tube or syringe while the subject is bending her/his head forwards. Several scoring methods have been developed: visual analogue scales, combined symptom scores taking nasal blockage, secretion and sneezes[22] and a combination of all signs and symptoms.[23] Nasal response can also be monitored by analysis of nasal biopsies,[24] brushes,[25] smears,[26] or lavages.[27]

Immediate allergic reaction: When the nasal mucosa of patients with allergic rhinitis is exposed to allergen, allergen activates mast cells and basophils by bridging two or more IgE molecules on their surfaces. After being activated these cells produce and release biochemical mediators.[17] Gomez *et al.*[27] and Fokkens *et al.*[28] demonstrated in biopsy studies an increased percentage of degranulated mast cells at the surface of the nasal mucosa after nasal pollen challenge. The released substances act on the local cells, vessels and sensory nerve endings, leading to nasal itching, sneezing, rhinorrhoea and nasal blockage in this immediate allergic reaction.

Late allergic reaction: Blackley[1] in 1873 was the first to describe the recurrence of symptoms several hours after the introduction of grass pollen in his nose. This recurrence of symptoms has been termed the late phase reaction.[29] To define the late phase reaction in the nose is difficult. Mygind *et al.*[30] could not detect late phase reactions by means of symptom scores. Since it is hard for patients to estimate their nasal patency, and late phase responses are mainly characterized by nasal blockage and to a lesser extent by mild rhinorrhoea, this might show the problems detecting clinical late phase responses. When estimating nasal obstruction by rhinomanometry, a recurrence of nasal blockage could be demonstrated.[31] In other studies late phase reactions were determined by measurement of nasal obstruction and analysis of nasal lavage fluid.

We demonstrated both an immediate and a late phase reaction by symptom scores when the nasal mucosa of perennial allergic rhinitis patients were challenged with a house dust mite extract.[32]

Nasal priming: In the 1960s Connell[33] described a phenomenon known as nasal priming—repetitive exposure to allergen causes an increased sensitivity to allergens. This has been demonstrated with repetitive exposures to a pollen-rich natural environment as well as by repetitive nasal provocation with allergen. This effect was confirmed by others by nasal challenge studies.[34] However, the exact processes resulting in nasal priming remain unclear. In perennial rhinitis the priming phenomenon has only been examined in one study.[35] This Dutch study demonstrated an increased threshold sensitivity to house dust mite challenge in autumn, compared to spring months, corresponding with the peak of house dust mite levels between August and October.

Allergen-induced Nasal Hyperreactivity

Hyperreactivity can be described as a clinical feature characterized by an exaggerated response of the nasal mucosa to everyday stimuli (perfume, tobacco smoke, change of temperature) as estimated by history (clinical hyperreactivity). In comparison to allergens, these stimuli are nonspecific, that is, they can affect the nasal mucosa of any individual, albeit to a different extent. By analogy to challenge studies in bronchial asthma, rhinitis patients were challenged with histamine and methacholine to measure nonspecific nasal hyperreactivity.[36] Gerth van Wijk *et al.*[37] demonstrated that the amount of secretion and the number of sneezes in response to histamine challenge were associated with the clinical hyperreactivity assessed by a hyperreactivity score. It was also demonstrated that assess-

ment of the number of sneezes and the amount of secretion is more appropriate in distinguishing patients from healthy subjects in terms of reproducibility and estimation of clinical hyperreactivity compared with assessment of nasal airway resistance after histamine challenge.[38]

In patients with allergic rhinitis, part of the symptoms is due to exposure to nonspecific stimuli. Repetitive exposure to allergen not only increases sensitivity allergens, but also to nonspecific stimuli. Borum *et al.*[39] demonstrated that in patients with seasonal allergic rhinitis the nasal response to histamine and methacholine increased during the pollen season. Allergen challenge also increased nasal response to histamine and methacholine.[40] In contrast, repeated challenges with histamine or methacholine do not increase nasal responsiveness to histamine.

In a few studies evaluating the effect of topical corticosteroids, effective anti-inflammatory drugs, nasal hyperreactivity was reduced,[41] which might indirectly give evidence of the involvement of inflammation in this process. This is confirmed by our recent work on perennial allergic rhinitis.[42] Gerth van Wijk *et al.*[37] found that in perennial allergic rhinitis patients nasal reactivity to histamine was associated with clinical symptoms and the sensitivity to everyday stimuli.

The exact mechanism of nasal hyperactivity is unknown. Several hypotheses with respect to the mechanisms underlying hyperreactivity have been advanced. (1) Increased epithelial permeability, which would lead to an increased accessibility for stimuli to sensory nerve endings, vessels and nasal glands. An indirect support to this hypothesis has been delivered by Buckle and Cohen,[43] who demonstrated that topically applied ^{125}I-albumin penetrates better into the nasal mucosa of allergic rhinitis patients compared with healthy subjects. However, in more recent studies there is little evidence that the nasal epithelium suffers much damage in acute or chronic allergic rhinitis.[24] (2) Increase sensitivity of sensory nerve endings would induce an exaggerated response to normal stimuli. No firm data are available to confirm this theory. (3) Imbalance of the autonomic nerve regulation caused by changes of the neuroreceptors in the nasal mucosa. Megen *et al.*[44] demonstrated an increased sensitivity and a decreased number of muscarinic receptors in the nasal mucosa of allergic subjects. Increased presence of the neuropeptide substance P or diminished levels of vasoactive intestinal peptide (VIP) might contribute to hyperreactivity. Until now, evidence for this hypothesis has only been demonstrated in the lower airways.[45]

Allergic Rhinitis: A Model to Study Airway Inflammation?

Asthma and allergic rhinitis are common disorders, with a high socio-economic impact and the cause of much morbidity. Many studies have been performed concerning the pathophysiological mechanisms. Such studies are easier to perform in the nose, as this is readily accessible, and biopsies and lavages accompanied by less risk and discomfort to the patient. It would therefore be easy if studies evaluating the pathophysiology and therapeutic intervention of asthma were to be replaced by a study of the nasal mucosa. However, the upper and lower airways are not entirely similar since some of the symptoms in asthma are caused by contraction of smooth muscle tissue, resulting in bronchoconstriction.

Repetitive allergen challenge causes an increased sensitivity to allergen and nonspecific stimuli. This phenomenon was first described for the lower airways[46] and could also be explored in the nose.[40] In the lower airways, the late phase response to allergen challenge was found to be associated with inflammation and bronchial hyperreactivity,[47] suggesting that inflammation is involved in the pathogenesis of hyperreactivity. Several studies have been performed to determine whether similar associations could also be shown in patients with allergic rhinitis. However, in studies performed in pollinosis patients tested outside the pollen season, no relation was found between nasal hyperreactivity and late nasal response,[48] between nasal hyperreactivity and activation of eosinophils,[40] or between nasal priming and late nasal response.[49]

In contrast, in a study with rhinitis patients allergic to house dust mite, an association between nasal responsiveness to allergen and pre-existent nasal hyperreactivity was found,[42,50] a finding more in agreement with data from the lower airways. So this subpopulation might be more suitable to study the association between nasal hyperreactivity, nasal inflammation and the late phase response and might serve as a better model to study airway inflammation.

Histopathology

The histopathological features of allergic inflammation involve an increase in blood flow and in vascular permeability leading to plasma exudation and the formation of oedema. In addition, a cascade of events occurs which involves a variety of inflammatory cells. These inflammatory cells migrate under the influence of chemotactic agents to the site of injury and induce the

Table 1. Cells and products in allergic rhinitis

Cells	Arachidonic acid metabolites	Cytokines	Others
Mast cells	PGD_2,[52] TB_4[53] $LTC_4/D_4/E_4$,[52] PAF[54]	IL-4,5,6, TNF-α,[55] IL-3, GM-CSF[56]	Histamine,[52] Adenosine,[57] Tryptase,[58] Chymase,[59] NOS[60]
Macrophages, Monocytes	PGD_2, $PGF_{2\alpha}$,[70] LTB_4,[70,71] PGE_2, LTC_4,[70] TxA_2,[72] PAF[54]	IL-6, TNF-α,[73] IL-1β,[74] GM-SCF,[75] IL-10[76]	β-Glucuronidase, Neutral proteases, Lysosomal enzymes, Superanion,[77] NOS[78]
Epithelial cells	8-HETE, 12-HETE, 15-HETE,[80] PGE_2,[81] $PGF_{2\alpha}$, PAF[83]	IL-6, IL-8, TNF-α,[84] GM-CSF[85]	iNOS, cNOS[86]
Basophils	LTC_4,[98] PAF,[54], 1-acyl-PAF[99]	IL-4, TNF-α[100]	Tryptase,[101] histamine[98]
Eosinophils	$LTC_4/D_4/E_4$,[105] PGE_2, TxB_2,[106] 15-HETE,[106a] PAF[54]	IL-3, GM-CSF,[107] IL-5,[108] IL-6,[109] IL-8, TNF-α[110]	EPO, MBP, ECP, EDN,[111] Superoxide, H_2O_2, hydroxyl radical[112]
Neutrophils	LTB_4, LTC_4, 5-HETE, PGE_2, TxA_2,[122] PAF[54]	IL-1, TNF-α,[120] IL-3, GM-CSF,[107] IL-8[123]	O_2^--radicals, Myeloperoxidase,[124] NOS[78]
Lymphocytes			
T_{H1}		IFN-γ, IL-2,5,6, TNF-α, GM-CSS[131]	
T_{H2}		IL-4,5,6, TNF-α, GM-CSF[131]	
Platelets	TxA_2,[139] 12-HETE, PAF,[139,140] PGD_2[141]		Adenosine diphosphate, Serotonin, Platelet factor 4, β-Glucuronidase,[139] H_2O_2,[142] NO[143]

process of repair. Several types of inflammatory cells have been implicated in the pathogenesis of allergic rhinitis. What remains unclear is how the different cellular components interact with each other to induce the pathological symptoms of allergic rhinitis, and the relationship between the inflammatory infiltration, cellular activation and hyperreactivity still need to be established. After specific or nonspecific stimuli, inflammatory mediators are generated from cells normally found in the nose, such as mast cells, antigen-presenting cells and epithelial cells (primary effector cells) and from cells recruited into the nose, such as basophils, eosinophils, lymphocytes, platelets and neutrophils (secondary effector cells). This review describes the identification of each of the inflammatory cells and their mediators which play a role in the perennial allergic processes in the nose of rhinitis patients.

Cells in Allergic Rhinitis

The cells involved in allergic rhinitis, together with their products (arachidonic acid metabolites, cytokines, and others) are given in Table 1.

Primary effector cells:

Mast cells. Human mast cells can be characterized by the presence of tryptase on the one hand (MC_T) or tryptase and chymase (MC_{TC}) on the other. More than 95% of the epithelial mast cells and 75% of the subepithelial mast cells in human airways are of the MC_T-subtype.[51]

Binding of allergen to specific IgE molecules on mast cells leads to secretion of mediators.[42] Mast cell-derived mediators can be divided into two main categories: pre-formed or granule-associated mediators and the newly formed or membrane-derived mediators.

Mast cells have been implicated in the pathogenesis of allergic diseases ever since histamine was localized to these cells.[61] The number of mast cells in the nasal mucosa is increased in allergic rhinitis.[28] Elevated levels of mast cell mediators are present in the nasal lavage fluid after experimental allergen challenge[17] and challenge with cold dry air,[62] and experimental application of mast cell mediators to the nasal mucosa produces symptoms of rhinitis. Several studies have demonstrated that the amount of mast cells in the epithelial layer is increased after

allergen exposure, which can be interpreted as shift of cells from the lamina propria to the epithelium or proliferation of precursor cells in the epithelium.[63,64] Borres demonstrated that metachromatic cells can be found superficially in the nasal mucosa 5–24 h after allergen challenge, with a correlation between the amount of cells and symptom score.[65]

Mast cells are multifunctional cells which can play more than one role and can contribute to the chronic inflammation underlying allergic diseases by producing a number of immunomodulatory and proinflammatory cytokines and mediators.[66]

Antigen-presenting cells. Responses to most antigens require processing of the antigen by antigen-presenting cells (APC), because T-cells ordinarily recognize antigens only together with major histocompatibility complex (HMC; human leukocyte antigen HLA-DR,-DQ,-DP) antigens on the surface of other cells. These MHC proteins are expressed on the surface cell membrane of macrophages, dendritic cells in lymphoid tissue, Langerhans cells in the skin and the nose, Kupffer cells in the liver, microglial cells in the central nervous system tissue, epithelial cells and B-cells. B-cells are relatively poor activators of T-cells when presenting antigens, possible because such T-cells require activating factors such as interleukins which B-cells fail to provide. Therefore, it is believed that macrophages or Langerhans cells probably play the dominant role as APCs in the initial or primary immune response whereas B-cells may dominate in the memory or secondary response.[67,68]

Macrophages play a central role in host defence, which includes ingesting and killing invading organisms/antigens and releasing a number of factors involved in host defence and inflammation. Macrophages possess low affinity IgE receptors and after binding of IgE they will release mediators.[69]

Although macrophages are the most common cell type residing in the lumen of the lower airways, little is known about the presence and pathogenic implications of macrophages in the upper airways. Both local allergen challenge and natural exposure increase the number of macrophages on the mucosal surface during the immediate as well as late phase reactions, indicating that macrophages are involved in the inflammatory processes of allergic rhinitis.[68]

It is important to note that the undoubtedly effective antigen-presenting ability of pulmonary interstitial dendritic cells may be limited to the interstitial lung-compartment.[79] This is in contrast with other investigators, who found that Langerhans cells were found in the epithelium and lamina propria of the nasal mucosa and higher amounts of Langerhans cells were detected in nasal biopsies of allergic patients compared with controls.[28] During the grass-pollen season, the nasal epithelium of patients with an isolated grass-pollen allergy demonstrated more Langerhans cells than before or after the season.[67]

Epithelial cells. Epithelial cells play an important role in the defence of the airways and in inflammatory processes, but it seems to be more than a protective barrier. Immunohistochemical studies of human lung tissue have reported that epithelial cells have the ability to express the HLA-DR antigens, suggesting that these cells play an important role in the antigen presentation and immunoregulation.

The epithelial layer in the airways is enriched with nerve endings which contain tachykinins, such as substance P, which is chemotactic for neutrophils[86a] and monocytes,[87] and potentiates phagocytosis and lysosomal enzyme release by neutrophils and macrophages.[88] Substance P is mitogenic for T-lymphocytes[89] and stimulates histamine release by mast cells.[90] It also stimulates airway epithelial ion transport,[91] causes airway smooth muscle contraction[92] and stimulates submucosal-gland secretion.[91]

Although damage of the epithelial layer causes an increased permeability to antigens, exposure of sensory nerve fibres and actuation of local reflex mechanisms, changes in osmolarity of the bronchial surface lining fluid and a decreased production of epithelial relaxant factors,[45] this has not been demonstrated in the nose. Epithelial cells may play an important role in the local recruitment, differentiation, and survival of inflammatory migrating cells,[94] and contribute to the pathologic and clinical events which occur in allergic rhinitis.

Secondary effector cells:

Basophils. The blood basophil count increases during the pollen season, suggesting that basophilopoiesis may be influenced by environmental factors, such as allergens,[95] but this has not been confirmed by others.[63] Several studies have demonstrated that the amount of basophils in the mucus and in the nasal lavage fluid is increased 4–11 h after allergen exposure, which can be interpreted as a shift of cells to the superficial layers of the mucosa.[96]

It has been suggested that basophils play an important role in the late phase of the allergic process, based on their release of lipid media-

tors.[92] However, whether basophils are associated with hyperresponsiveness is not known.

Eosinophils. In vitro experiments have shown that eosinophil-derived enzymes are capable of degrading mast cell products, such as histamine and leukotrienes.[102,103] Eosinophils have cytoplasmic granules which contain cytotoxic proteins, which can stimulate upregulation of intercellular adhesion molecule-1 (ICAM-1) on human nasal epithelial cells, which suggests a positive feedback mechanism in which the products released from migrating eosinophils might promote additional human nasal epithelial cell-leukocyte adherence.[104]

The role of eosinophilic inflammation in allergy has been studied most thoroughly in the pathogenesis of the airway inflammatory response in asthma. Cytotoxic proteins which are cytotoxic towards respiratory epithelium and cause histamine release,[113] are elevated in sputum and bronchoalveolar lavage fluid of asthmatics. There is evidence for eosinophil participation in the induction of airway hyperreactivity in asthma.[114]

A relationship between the influx of eosinophils into the nasal mucosa and allergic rhinitis was noted[115] and during asymptomatic periods, the eosinophils were absent from the nasal secretions.[116] There are numerous factors, like GM-CSF, PAF and lymphocyte chemotactic factor (LCF), which have been shown to be chemotactic for eosinophils, to prolong eosinophil progenitor multiplication, maturation and differentiation.[117] The eosinophils are probably derived, in part, from progenitors at the site of inflammation, which, in turn, are derived from the bone marrow via the circulation. The role of the eosinophil in perennial rhinitis has been rather less intensively studied than in seasonal rhinitis. It has been shown that the number of eosinophils is increased in the biopsies and secretions compared with controls. An eosinophil infiltration has been identified in nasal secretions as early as 30 min after nasal antigen challenge and has been shown to persist for as long as 48 h.[118,119]

Neutrophils. One of the earliest events in acute inflammation is increased adherence of circulating neutrophils to vascular endothelium.[120] In response to bacterial lipopolysaccharides and cytokines, such as IL-1, TNF and IFN-γ, endothelial cells become adhesive for neutrophils.[121] A large number of chemotactic factors can recruit neutrophils to sites of tissue inflammation. Cellular sources of factors chemotactic for neutrophils include bacteria, macrophages, lymphocytes, platelets and mast cells.

Due to their ability to produce these inflammatory mediators, neutrophils could play an important role in allergic rhinitis, although the role of neutrophils is still unclear.[125] An increased influx of neutrophils is measured in nasal lavages of rhinitis patients after exposure to ozone.[126]

Monocytes/macrophages. The tissue macrophages arise either by immigration of monocytes from the blood (probably the predominant mechanism) or by proliferation of precursors in local sites. During differentiation of monocytes to macrophages, the azurophilic peroxidase-containing cytoplasmic granules are lost and lysosymes containing hydrolytic enzymes become prominent. Although monocytes produce myeloperoxidase, macrophages do not.[127] Their role in rhinitis has already been outlined on page 84.

Lymphocytes. On the basis of expression of cell surface markers called clusters of differentiation (CD) and by their antigen receptors, three distinct lineages of lymphocytes have been identified: thymus-derived lymphocytes (T-cells), bone-marrow-derived lymphocytes (B-cells) and natural-killer (NK)-cells. Moreover, the presence or absence of certain cell surface markers has been used to delineate stages of differentiation, states of cellular activation and functionally distinct subsets of lymphocytes. After direct interaction with antigen, B-cells can differentiate into plasma cells, which can secrete large amounts of all immunoglobulin subclasses, including IgE. After the same exposure to antigen, some B-cells can differentiate to memory B-cells which are responsible for the rapid recall response observed after re-exposure to antigens previously recognized by the immune system. In addition to producing immunoglobulin, B-cells can secrete certain mediators, so-called lymphokines, such as IL-6 that affect the growth and differentiation of B-cells and other lymphocytes.

APCs present the processed antigen to the helper/inducer T-cells (T_H), expressing the surface protein CD4. The T-cell receptor complex on the cell surface of the T_H-cell binds to the peptide/MHC (class II) on the APC. This interaction generates an activation signal for the T-cells, leading to differentiation and proliferation with the formation of T-lymphoblasts and the secretion of soluble mediators, such as IL-4 and IL-5 which augment to help B-cells to respond and regulate the IgE production.[128]

Two functional subclasses of murine T-helper clones have been described and are commonly designated T_{H1} and T_{H2}.[129] The murine T_{H1}-lymphocytes produce dominantly IL-2, IFN-γ and TNF-α, and they are thought to be involved in

delayed-type hypersensitivity reactions and in the synthesis of IgM and some IgG subclasses. The murine T_{H2}- lymphocytes, on the other hand, have been shown to synthesize IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, and also TNF-α and are thought to be important in allergic-type inflammatory reactions and defence against parasites.[130] In humans, atopic allergic disorders seem to be related with the activation of T-helper lymphocytes with a type 2 cytokine secretion profile.[131] Non-atopic T lymphocytes resembled murine T_{H1}-cells. The atopics' T_{H2}-cells were excellent helper cells for IgE induction and the non-atopic T_{H1}-cells were cytolytic, with activity towards autologous antigen presenting cells.

Cytotoxic/suppressor T-cells ($T_{c/s}$), expressing the surface protein CD8, have the ability to kill other cells that are perceived as foreign, for example virus-infected cells. These $T_{c/s}$ cells recognize peptide antigens bound to class I MHC molecules on the cell surface of the target cell, whereafter the target cell is destroyed by the $T_{c/s}$-cell.

A few studies have shown that T-cell subsets change in bronchoalveolar fluid and peripheral blood from asthmatic patients.[132] The production of IFN-γ, IL-4 and IL-5 is enhanced in asthmatics, showing an increased activity of T_H-cells.[133]

It was recently demonstrated in biopsies from allergic patients and nonallergic controls that there were no differences between the number of T-helper cells and cytotoxic T-cells in the epithelium, but a higher number of activated T-cells expressing CD4 was found in the allergic group in the lamina propria. Following a local allergen challenge of the nose, an increased number of CD4+ T-helper cells were found in the nasal submucosa.[134]

Platelets. The role of platelets in inflammatory reactions is not as well defined as that of neutrophils, eosinophils, macrophages or mast cells. An increased number of platelets have been observed at the sites of the reaction in asthma after allergen challenge.[135] Cooperation of platelets with basophils and/or mast cells was reported in the release of histamine during antigen challenge of asthmatics, which resulted in a potentiated six-fold increase of histamine release.[136]

A significant increase in platelet volume and a shorter life-span (2–3 days) of platelets was noticed in patients with allergic rhinitis compared with controls.[137] A potential role of platelet release compounds in the development of delayed responses in allergic patients has been proposed.[138] These findings suggest that platelets participate in the pathogenesis in the allergic disease.

Products of Allergic Inflammation

The role of each product itself is complex and their interactions are even more complex. The most important features of the products relevant for rhinitis are reviewed in the following paragraphs.

Inflammatory products may have a large spectrum of effects on a variety of target cells in the airways, which are relevant in rhinitis. Some of them lead directly and indirectly to contraction of smooth muscle or enhance muscle tone, via secondary mediators or neuronal substances. They may also lead to oedema of the airways and exudation of plasma into the lumen. These inflammatory products can attract and activate inflammatory cells which thereafter can release mediators themselves, consequently leading to on-going inflammation.

Histamine: Histamine may be released by a number of immunologic substances, such as IgE, antigen and cytokines, and non-immunologic substances, such as anaphylatoxins, peptides (e.g. substance P), drugs (e.g. opiates), and physical stimuli. After release from the storage granules, histamine rapidly diffuses into the surrounding tissues, and changes in blood concentration may be detected within minutes.[144]

Released histamine interacts with specific receptors on target cells. To date, three subtypes of histamine receptors have been characterized: H_1, H_2 and H_3 receptors. The first physiologic action of histamine to be described was smooth muscle contraction.[145] *In vitro* blockade of smooth muscle contraction by histamine H_1 receptor antagonists has clearly demonstrated that this effect is mediated predominantly via the H_1 receptor subtype.[146] In human airways smooth muscle contraction in response to histamine causes bronchoconstriction.[147] Histamine increases vascular permeability to macromolecules by the formation of intercellular gaps in the postcapillary venules.[148] Histamine affects both the quantity and viscosity of mucus secretion, mediated via H_2[149] and H_1[150] receptors, respectively. The chemotactic activity of eosinophils[151] and neutrophils[152] may be increased by histamine and the antigen-induced histamine release from basophils is controlled.[153] Histamine also modulates immunoglobulin synthesis, which includes interference with the maturation of antigen-stimulated B-cells,[154] suppressing antibody secretion from plasma cells,[155] and modu-

lating immunoglobulin production of mature mononuclear cells.[156]

Nasal challenge of rhinitis patients with histamine induces nasal blockage, measured by nasal airway resistance (NAR), and is accompanied by dose-dependent sneezing and rhinorrhoea.[36] A greater change in NAR is found in rhinitis patients compared with controls, suggesting non-specific hyperreactivity of the upper airways,[157] which is in contrast with other investigations, in which an equal effect of histamine provocation on NAR in patients and controls was found.[38]

Thus, histamine derived from mast cells and acting via H_1 and H_2 receptors is responsible for much of the sneezing, nasal blockage and rhinorrhoea during the early response to nasal allergen challenge. Increased concentrations of histamine are found in nasal washings of rhinitis patients immediately after allergen provocation.[48] Also during the late phase response histamine, released from basophils, is found in increased concentrations in nasal washings.[96]

Tryptase: Dog mast cell tryptase has been reported to increase the contractile response of canine bronchial smooth muscle strips to histamine and other agonists. This effect appeared to be dependent on the enzymatic activity and was prevented by H_1 receptor antagonists and voltage dependent Ca^{2+} channel blockers. This observation has not been confirmed with human tissues, but raises the possibility that tryptase could contribute to bronchial hyperreactivity. Tryptase has been found to increase vascular permeability, when injected into guinea-pig skin and stimulate neutrophil accumulation.[158]

In rhinitis, comparatively little attention has been paid to the contribution of proteases in disease pathogenesis. However, the recent development of sensitive procedures for the detection of proteases from mast cells, and the discovery of their potent biologic effects has provoked interest in the potential of these enzymes to act as major mediators of allergic disease.[159] Increased levels of proteases have been detected in the nasal secretions of rhinitis patients. Provocation of acute rhinitis with allergen or cold dry air is associated with the rapid release of mast cell tryptase as well as histamine and other mast-cell-derived mediators into nasal fluid.[160] In nasal lavage fluid of perennial allergic rhinitis patients levels of tryptase were elevated only during the immediate phase reaction to provocation with house dust mite extract.[32,42] Tryptase may thus participate in many of the processes of rhinitis and deserves attention beyond its role as a marker for mast cell activation in the airways.

Eicosanoids: Free arachidonic acid may be enzymatically oxygenated by two major pathways: cyclooxygenase and lipoxygenase. The prostaglandins and thromboxane are generated through the cyclooxygenase pathway and leukotrienes are derived via the lipoxygenase pathway.

Cyclooxygenase metabolites. Cyclooxygenase (COX) products have effects on bronchial smooth muscle and vessels. $PGF_{2\alpha}$ and PGD_2 are potent bronchoconstrictors.[161] PGD_2 also has vasoactive properties, causing increase in pulmonary arterial pressure.[162] TxA_2 has bronchoconstrictor properties,[163] stimulates airway smooth muscle cell proliferation,[164] and causes vasoconstriction and platelet aggregation.[165] PGE_2 and PGI_2 are broncho- and vasodilators.[162] However, inhaled PGI_2 may have bronchoconstrictor properties in some mild allergic asthmatics,[166] this paradox has not been resolved. PGD_2, PGE_2 and PGI_2 inhibit platelet aggregation.[165] $PGF_{2\alpha}$, PGE_2 and PGI_2 are potent inducers of cough, perhaps through stimulation of irritant receptors and C-fibres.[167] PGE_2 inhibits phagocytosis, mediator function and cytotoxicity of macrophages, chemotaxis of macrophages and neutrophils and several lymphocyte functions.[168]

COX has two isoforms: COX1 and COX2. COX1 is constitutively expressed and involved in prostaglandin synthesis in cellular 'housekeeping functions'. COX2 expression is inducible and involved in inflammatory processes.[169] COX2 is expressed in lung tissue, but whether COX2 plays a role in rhinitis is not known.

Increased concentrations of PGD_2 and TxA_2 were found in bronchoalveolar lavage fluid after antigen-induced bronchoconstriction in atopic asthmatics.[170] In addition to constrictor/dilator properties, prostanoids have also been demonstrated to induce airway hyperreactivity in asthma.[171]

PGD_2 was released into nasal secretions during the immediate response to nasal challenge with pollen antigen, though not during the late phase response.[172] Only a release of PGD_2 during the immediate allergic response to allergen challenge of perennial allergic rhinitis patients was found.[42,173] In another study with allergic rhinitis patients, increased concentrations of PGD_2 were reported to occur within minutes of an allergen-induced early nasal response.[174]

Lipoxygenase metabolites. LTC_4, LTD_4 and LTE_4 have potent bronchoconstrictor properties, and increase microvascular permeability in the airways and decrease blood pressure.[175] LTB_4 is a potent chemoattractant for neutrophils and

monocytes, but is less effective for eosinophils.[176] LTB_4 also stimulates the release of lysosomal enzymes from macrophages and neutrophils,[177] increases vascular permeability and releases oxygen radicals from neutrophils.[178] 5- and 15-HETE modestly contracted human bronchial muscle,[179] and HETEs are chemotactic for neutrophils and eosinophils.[180] Neutrophils are degranulated by 5- and 12-HETE.[181]

Increased concentrations of LTC_4, LTD_4 and LTE_4 were found in nasal lavages of rhinitis patients allergic to ragweed during allergen-induced early nasal response.[174] During the immediate allergic reaction to allergen provocation of perennial allergic rhinitis patients an increase of cysteinyl leukotrienes was found.[42,173]

As a consequence of their activity, the eicosanoids have been implicated as potential candidates in the pathogenesis of rhinitis.

Platelet activating factor: PAF is a potent *in vitro* activator of eosinophil, platelet, neutrophil, monocyte and macrophage chemotaxis and superoxide anion production, and an activator of the release of arachidonic acid metabolites, such as LTC_4, by neutrophils, eosinophils and macrophages.[182–184] PAF has been shown to be a potent mucus secretagogue for human airways *in vitro*[185] and to stimulate the secretion of chloride ions and, thus, allow the movement of water toward the lumen.[186] Basophils are activated by PAF and, thereafter, release histamine and LTC_4 by a rise in calcium influx.[187] Intravenous injections of PAF to guinea-pigs leads to a bronchoconstriction and hypotension[188] as well as bronchial hyperreactivity to serotonin,[189] histamine or acetylcholine.[190] In humans PAF induces bronchial hyperreactivity to methacholine in non-asthmatics.[191] This is in contrast with other investigators, who found that PAF failed to induce hyperreactivity to methacholine in normal subjects[192] and asthmatic patients.[193]

Lyso-PAF-acether, but almost no PAF was significantly increased in nasal secretions from allergic patients in the immediate reaction to antigen challenge.[194] In a study with perennial allergic rhinitis patients a 15-fold increase from baseline of PAF after allergen provocation was demonstrated, which tended to decrease after treatment with a corticosteroid.[42,173] Topical pretreatment with PAF of seasonal allergic rhinitis patients induced only minor changes in nasal respiratory peak flow rate and symptom score as compared with placebo. However, it induced an increase in responsiveness of the nasal vasculature to allergen challenge, measured as increased symptoms and nasal peak flow, but other parameters, such as sneezes and secretion remained identical.[195] Nasal challenge with PAF induced nasal obstruction, rhinorrhoea and itching in allergic rhinitis patients, but no increase in histamine levels was observed in nasal lavages. No changes were seen after challenge with lyso-PAF.[196] Topical nasal application of PAF induced an increase in eosinophils in the nasal lavage fluid and brushes of allergic rhinitis patients, but did not produce any changes in methacholine-induced secretory responsiveness.[197] Thus, PAF may have pathogenetic and clinical relevance in allergic rhinitis.

Eosinophil-derived granule proteins: Activation of granulocytes, including eosinophils, can result in the release of granule contents, providing the cells with a very potent mechanism of inflammatory action. Degranulation of these cationic proteins has been correlated to several of the symptoms of asthma and rhinitis and hyperresponsiveness. MBP is toxic to many mammalian cells, such as human lung epithelium,[198] and induces mast cell and basophil histamine release. The EPO can stimulate mast cell secretion,[199] inactivate mediators of immediate hypersensitivity,[200] and is cytotoxic to various target cells. ECP can inhibit T-lymphocyte proliferation in a non-cytotoxic fashion, but the mechanisms involved are unclear.[201]

Eosinophil cationic protein. Motojima *et al.*[202] found that ECP caused dope-dependent damage to guinea-pig tracheal epithelium *in vitro*. However, ECP had no effect on bronchoconstrictor or airway hyperresponsiveness of cynomolgus monkeys.[203]

Increased serum levels of ECP occur in allergen-provoked asthma.[204] Elevated levels of ECP have been found in bronchoalveolar lavage fluid of asthmatics obtained during the late phase reaction after allergen-inhalation challenge of asthmatics, as well as in unchallenged patients with chronic asthma.

In both allergic and nonallergic rhinitis increased serum levels of ECP are observed.[122] Lavage fluid from allergic rhinitis patients showed marked elevations of ECP after segmental bronchial antigen challenge.[205] In nasal lavage fluid of perennial allergic rhinitis patients levels of ECP were elevated only during the late phase reaction to provocation with house dust mite extract.[32,42,206] An increased number of eosinophils and raised levels of ECP were found on the nasal mucosal surface during natural allergic rhinitis patients.[207] These changes were not accompanied by an increased secretory responsiveness of the nasal mucosa to methacholine.[208] In the lavage fluid of the patients with a late phase reaction, a significant eosinophilia was found, com-

pared with controls and those patients who only demonstrated early responses. This suggested that eosinophils and their mediators might be involved in the development of the late phase reaction.

Cytokines: Cytokines modulate reactions of the host to foreign antigens or injurious agents by regulating the growth, mobility and differentiation of leukocytes and other cells. Normal resting cells must be stimulated to produce cytokines, and therefore usually no cytokines are normally present in serum. Many cytokines are simultaneously produced by activated cells.

Some cytokines have direct histamine-releasing properties, such as IL-3, GM-CSF and IL-1 from basophils and mast cells.[209] Cytokines can prime basophils for enhanced histamine release in response to other secretagogues, such as anti-IgE and FMLP. This priming effect has been documented for IL-1-3,[210,211], IL-5,[98] IL-11, GM-CSF[212] and IFN-γ.[213] Some of these priming cytokines, such as IL-5, also upregulate adhesion molecules in nasal mucosa, including E selectin, P selectin, ICAM-1, ICAM-2 and VCAM-1.[214] The inducible expression of these molecules on endothelium directs the focal adherence of leukocytes to endothelium for extravasation at sites of inflammation.

Several investigators have suggested that cytokines may contribute to the occurrence of degranulation of cells in bronchial mucosa of asthmatics.[215] Durham *et al.*[216] showed with *in situ* hybridization messenger ribonuclear acid (mRNA) for IL-3, IL-4, IL-5 and GM-CSF in nasal biopsies 24 h after allergen challenge, which is correlated with the number of activated T-cell and eosinophils. In addition to the work in nasal mucosal tissue, attempts have been made to quantitate cytokines in nasal secretions following antigen challenge.[217] In general, little success has been reported in nasal lavages, with some cytokines such as IL-1β, IL-2 and IL-6 being detectable in higher levels than prechallenge fluids only in a subset of allergic subjects. Increased levels of IL-1β and GM-CSF have been detected by using strips of filter paper to collect secretions from the nose.[217] Of these cytokines, IL-5 is highly important, because IL-5 alone is capable of inducing eosinophil degranulation in the absence of a ligand and greatly enhancing ligand-stimulated eosinophil degradation.[218]

Interleukin-5. IL-5 promotes the proliferation and differentiation of B-cells and promotes the antibody production by B-cells, particularly of the IgA isotype. IL-5 has modest mitogenic effects on T-cells. In addition, it induces the differentiation of bone marrow precursors into eosinophils and supports the growth of eosinophilic cell lines and induction of cytotoxic T-cells. IL-5 enhances eosinophil development and differentiation[219] and prolongs survival of eosinophils.[220] IL-5 can alter functional and immunologic properties of eosinophils. Data from patients with eosinophil-related disorders suggest that IL-5 produces 'activated' eosinophils.[221] It has been observed that IL-5 increases eosinophil, but not neutrophil, adherence to vascular endothelium[222] and IL-5 is chemotactic for eosinophils.[223] Eosinophils can be primed by IL-5 for chemotaxis towards PAF.[224]

Although the T-lymphocyte is considered to be a major source of IL-5, eosinophils contribute to the production of IL-5 in allergic airway inflammation.[225] This raises the possibility of an autocrine mechanism whereby stimulated eosinophils may both release and respond to cytokines, such as IL-5. Thus, there is the potential for a self-perpetuating cycle, with continuous eosinophil infiltration and activation and consequently chronic inflammation.

In humans, elevated serum IL-5 was noted in symptomatic asthmatics in association with activated T-lymphocytes and eosinophilia.[226] In allergic rhinitis patients, IL-5 levels were elevated 48 h after antigen challenge and found to correlate strongly with eosinophil number, eosinophil granule proteins and LTC_4 levels.[205] IL-5 levels were increased in nasal lavages during both the immediate and the late phase response to allergen challenge of perennial allergic rhinitis patients. Treatment with a corticosteroid decreased the evoked IL-5 levels in the late phase reaction.[42,206] Application of recombinant human IL-5 onto the nasal mucosa of patients allergic to pollen increased the numbers of eosinophils, epithelial cells, ECP and IgA in the nasal lavage fluid. Also the number of eosinophils in both the epithelium and lamina propria as well as in the lumens of the blood vessels in the nasal mucosa were increased. The response to histamine was also enhanced after the application.[227]

Nitric oxide: NO generated by intact endothelium not only induces smooth-muscle relaxation, but also appears to serve to inhibit further adhesion and aggregation of normal platelets, which suggests protective effects against inflammation.[228] NO has the ability to suppress leukocyte adherence and T-lymphocyte proliferation and to regulate the mitogen responses.[229] NO can modulate the release of histamine from mast cells.[230]

NO has been shown to be a potent bronchodilator in isolated guinea-pig trachea smooth muscle and in humans.[178] Probably, NO mediates

airway smooth muscle relaxation by inhibiting the release of acetylcholine from nerve terminals.[231] NO also leads to the production of cAMP.[232] The products of NO are extremely cytotoxic. Because epithelial damage is related to the development of bronchial hyperreactivity,[233] NO may be greatly responsible for hyperresponsiveness in asthmatics. This is supported by Golden, who found that inhalation of nitrogen dioxide and ozone increases bronchial reactivity in healthy humans[234] and by Barnes, who suggested that free oxygen radicals from inflammatory cells increases the breakdown of NO, thus leading to exaggeration of the cholinergic reflex bronchoconstriction.[231]

Inhalation of ozone of allergic rhinitis patients caused an increase in symptoms after allergen challenge. Also, an increase in nasal lavage neutrophils, eosinophils, mononuclear cells and epithelial cells was observed. The histamine and albumin concentration in lavage fluid increased on the ozone exposure day. NO metabolites (measured as nitrite + nitrate) were present in nasal lavage fluid of both controls and perennial allergic rhinitis patients.[42,235] However, the level gradually increased with time and treatment with fluticasone propionate did not affect initial production of NO nor production following provocation with allergen. These findings do not suggest that NO is associated with rhinitis nor hyperreactivity.

Pharmacotherapy

Antihistamines, corticosteroids, mast cell stabilizers, decongestants and anticholinergics are the major topical drugs used in the treatment of allergic rhinitis. Although H_1 antihistamines are effective in controlling sneezing, pruritus and rhinorrhea, they are not useful for alleviating congestion. Some H_1 receptor antagonists (terfenadine, cetirizine) inhibit mediator release from basophils and mast cells and decrease recruitment of inflammatory cells. Intranasal corticosteroids, such as fluticasone propionate, may be the most effective treatment of rhinitis. They decrease vasodilatation, oedema and inflammation and decrease symptoms, including nasal blockage. Mast cell stabilizers constitute a class of drugs, such as cromolyn sodium, that prevent degranulation and mediator release from mast cells. Cromolyn is more helpful for sneezing, rhinorrhoea and nasal itching than for nasal obstruction. Nasal decongestants (vasoconstrictor sympathomimetic agents) reduce blood flow, oedema and blanching of the nasal mucosa. They are very effective for short-term use to increase nasal airway patency, but they do not improve rhinorrhea, sneezing or nasal pruritis. The anticholinergic ipratropium bromide has been shown to be effective for perennial allergic rhinitis.[236–238]

Concluding Remarks

Several inflammatory cells, such as mast cells, basophils, lymphocytes and eosinophils and their mediators released after specific or nonspecific stimuli, have been demonstrated during the nasal allergic processes. Although some of these mediators, such as histamine, prostaglandins and leukotrienes may be biologically active in allergic rhinitis, the role of others, such as PAF, IL-5 and nitric oxide still needs clarification. The interaction between these different cellular components to induce the clinical symptoms of allergic rhinitis remains unclear. Also the relationship between the inflammatory infiltration, cellular activation and hyperreactivity needs further establishment. We have particularly reviewed the role of tryptase, as a marker of activated mastcells, ECP, as a marker of activated eosinophils, and further more histamine, $LTC_4/D_4/E_4$, PGD_2, PAF, IL-5 and NO, which may be involved in the immediate and late phase nasal reaction to allergen challenge, in hyperreactivity and in therapeutic intervention. Intranasal corticosteroid is the most effective treatment of allergic rhinitis, because not only are the symptoms improved but nasal inflammation is also decreased.

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