

# Pathophysiology of perennial allergic rhinitis

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Allergic rhinitis involves an early phase, largely mediated through mast cells, and a late phase which involves cellular infiltration and mediator release. In the early phase, mast cells release mediators as a result of antigen cross-linking adjacent immunoglobulin E molecules bound to mast cell surfaces. This results in an accumulation of histamine which gives rise to the characteristic symptoms of rhinitis – sneezing, itching, rhinorrhoea and congestion. The late phase of the allergic response (hours after challenge) involves infiltration of the nasal epithelium by eosinophils, basophils, monocytes and T-lymphocytes, which release leukotrienes, kinins, histamine and a host of other mediators. The most important part of the late-phase response is probably mediated via the production of cytokines (IL-4, IL-5, IL-6, IL-8, GM-CSF and RANTES) by mast cells, TH<sub>2</sub> lymphocytes or epithelial cells. The infiltration of tissues by cells normally present only in the blood is brought about by the production of adhesion molecules, such as VCAM-1 and E-selectin, which cause circulating eosinophils, basophils and T-lymphocytes to adhere to endothelial cells before moving through the endothelium into the tissue (diapedesis). Neuronal reflexes also play a role in the allergic response, both by mediating local responses to mediators and possibly playing a part in the activation of T-lymphocytes. The allergic response has also been shown to be less intense in a hot, humid environment, and more marked in a cold, dry environment, possibly due to changes in osmolality of the nasal surface fluid. Similar factors may play a role in the aetiology of non-allergic rhinitis.

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Allergic rhinitis is a common condition in industrialized nations (1), characterized by nasal obstruction, itching, watery rhinorrhoea, sneezing, and occasional anosmia (2). The chronic disease state has been estimated to affect more than 40 million Americans (around 16% of the country's total population) – it interferes with quality of life, gives rise to more than 20 million physician visits annually, and costs the US economy billions of dollars each year (3).

Rhinitis can be classified broadly into allergic (immunoglobulin-E [IgE] mediated) and non-allergic forms. Allergic rhinitis may be further subdivided into perennial and seasonal disease. In the majority of patients, perennial allergic rhinitis can be attributed to three common allergens – house dust mite, animal danders, and mould spores, while seasonal rhinitis is frequently triggered by pollen or outdoor mould spores. Non-allergic rhinitis is considered to be a separate disease category, and

includes disease of infectious aetiology, such as common viral illnesses. With regard to symptoms, infective rhinitis may be difficult to distinguish from allergen-induced disease (2). The non-allergic form of rhinitis can be further categorized into two additional groups, one of which has a recognized aetiology, e.g. drug-induced rhinitis, cold dry air-induced rhinitis, or rhinitis associated with metabolic conditions (such as hormonal imbalance), while the other category has no clear aetiology and includes nasal polyposis, non-allergic rhinitis with eosinophilia, and “vasomotor” rhinitis.

The pathophysiology of allergic rhinitis has been the subject of many investigations, including studies utilizing nasal lavage fluid, nasal scrapings, and biopsies following antigenic and non-antigenic nasal stimulation. Biochemical and cytological information can be obtained relatively easily and pharmacological manipulations can be monitored effectively. This article reviews studies relating to

the pathophysiology of perennial allergic rhinitis and highlights areas where non-allergic stimuli may influence the course of allergic disease.

### The early-phase response

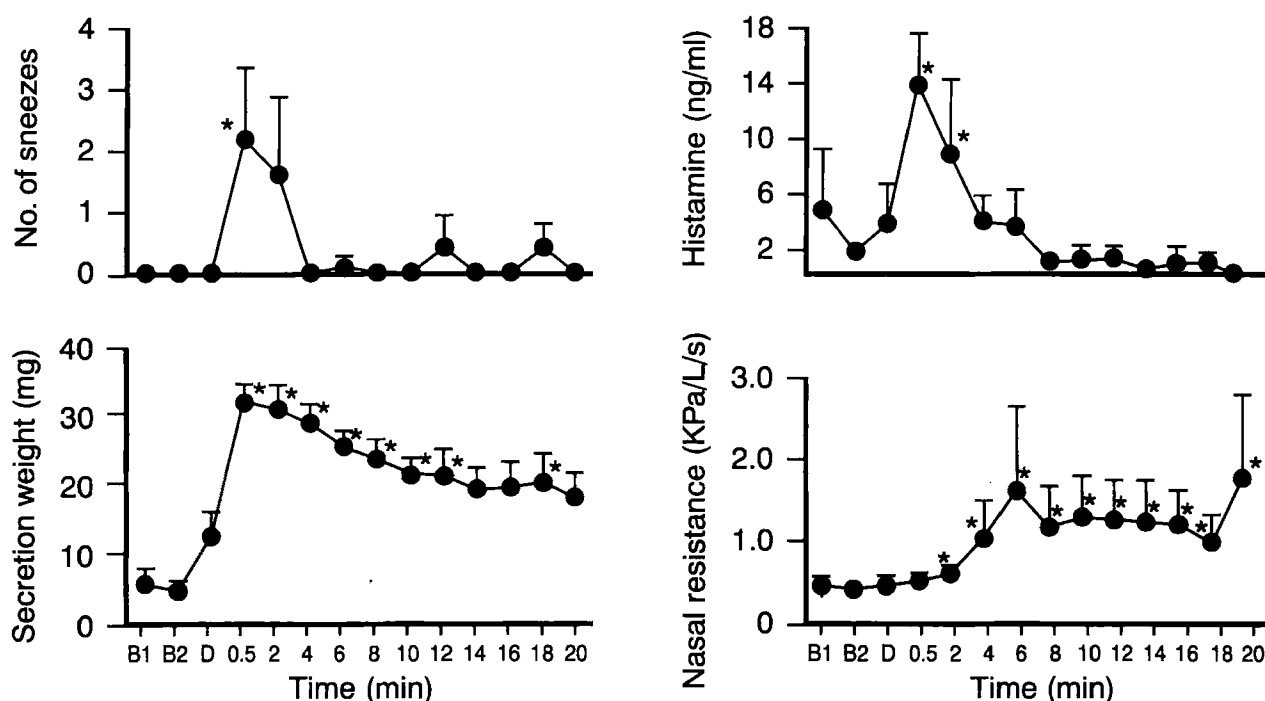
The early-phase response to antigenic stimulation in allergic rhinitis is a well recognized phenomenon, being responsible for the immediate onset of symptoms in sensitized individuals. One of the most important components of the early-phase reaction is mast cell degranulation (4). Tissue mast cells are ubiquitous in the human body, but are particularly abundant in the mucous membranes of the nose, and in pulmonary tissue. In the sensitized host, mast cells residing in the nasal mucosa have IgE antibodies, specific to the offending antigens, bound to the cell surface by high-affinity receptors (FcεR1). Upon subsequent antigen challenge, allergen binds to adjacent IgE antibodies on mast cells, causing cross-linking of the molecules and signaling the subsequent degranulation of the mast cell, with the release of inflammatory mediators, such as histamine. Indeed, activation of mast cells in the nasal epithelium is a consistent finding in patients with both seasonal and perennial allergic rhinitis, and elevated levels of histamine and tryptase can be detected in nasal lavage fluid (5). The increase in histamine levels causes stimulation of blood

vessels, nerves and mucus-producing glands in the nasal mucosa, resulting in the characteristic symptoms of rhinitis – sneezing, itching, rhinorrhoea, and congestion.

Experimental models have illustrated the acute inflammatory reaction that occurs in response to nasal provocation. These studies show that histamine release from mast cells in the nasal mucosa occurs within minutes of antigen challenge. This is coupled with an immediate “sneezing” reaction, which dissipates rapidly (over 2–3 min), a sudden increase in secretion weight (a measure of rhinorrhoea), which decreases more slowly over time, while the increase in nasal airway resistance follows a different time course, occurring minutes after the sneezing and persisting for approximately 20 min (Fig. 1).

### Effect of ambient conditions on the early response to allergen challenge

Many non-allergic factors influence the allergic response. One example is environmental temperature and humidity. This was illustrated in a recent study by Desrosiers et al. (6), in which 10 subjects with allergic rhinitis were placed in an environmental chamber and subjected to antigen challenge on two different days. The tests were carried out outside the pollen season and none of the sub-



\* $P < 0.05$  vs diluent

Fig. 1. The course of histamine production and physiological changes after single-dose antigen challenge. B1 and B2=baseline measurements; D=diluent.

jects were exhibiting any signs of rhinitis. On one day environmental conditions were normal indoor conditions (20°C and 30% relative humidity) and on the other day subjects were exposed to a hot, humid environment (37°C and 90% relative humidity). After 1 h in the environmental chamber, the subjects' response to diluent was determined for use as a baseline comparison, and this was followed by exposure to allergen. The standard allergen challenge comprised 50 µl of either ragweed or mixed grass pollen extract containing 333 protein nitrogen units (PNU) of antigen. The vascular response to antigen challenge was determined by measuring human serum albumin levels in the nasal surface fluid. Since albumin is made in the liver, an increase in albumin in nasal secretions represents an increase in vascular permeability. It was found that the albumin level in nasal surface fluid (i.e. vascular permeability) was significantly lower after exposure to hot, humid conditions ( $242.2 \pm 37.9$  µg) compared with normal environmental conditions ( $389.6 \pm 53.4$  µg) ( $P \leq 0.05$ ). In addition, subjects sneezed less on allergen challenge if they had been exposed to hot, humid air. The mechanisms by which increased humidity and temperature down-regulates the vascular response to antigen challenge is not clear, though it has been suggested that nasal fluid tonicity or changes in the temperature of the nasal mucosa may be involved (6–8).

### Neural interactions

There is evidence to suggest an important role for the autonomic nervous system in the pathophysiology of allergic rhinitis (for a brief review see reference 9). In a study in nine subjects with allergic rhinitis conducted outside the pollen season, single-dose allergen challenge to one nostril resulted in stimulation of the autonomic nervous system, and a subsequent increase in nasal secretion in both the ipsilateral and contralateral nostril. This effect was antagonized by administration of atropine, suggesting that it is parasympathetically mediated (10). When the subjects were challenged with progressively increasing doses of antigen, a dose-dependent association was found between dose of allergen and weight of nasal secretion. Interestingly, there was a dose-dependent increase in secretion weight from the contralateral nostril as well as from the challenged nostril (10). In contrast, a dose-dependent increase in antigen-induced histamine release was found only in the ipsilateral nostril, demonstrating that antigen directly causes mast cell activation. Nasal airway resistance also increased only on the side of challenge, suggesting that it is related to the local inflammatory response on the side of challenge (10).

### The late-phase response

In addition to the early-phase response to antigen stimulation, a late-phase reaction occurs hours rather than minutes after challenge. The late-phase response is typified by a prolongation of symptoms – occasional sneezing, rhinorrhoea, and most predominantly a sustained nasal blockage. Following early stimulation and mast cell activation, the nasal epithelium is infiltrated by eosinophils, basophils, monocytes and T-lymphocytes. A variety of mediators are released by these cells, including leukotrienes, kinins and histamine, all of which may be involved in the continued symptomatology and development of late-phase inflammation (11–14). However, one of the most important processes responsible for orchestrating and regulating the inflammatory response is the production of cytokines. These cytokines possibly include interleukin-4 (IL-4) produced by mast cells (15), IL-3, IL-4, IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) produced by TH<sub>2</sub> lymphocytes, and IL-6 produced by epithelial cells (16). The nasal epithelium itself does not simply act as a barrier – it is also implicated in the production of IL-6, IL-8, GM-CSF, and RANTES (a chemo-attractant for eosinophils) (17). Indeed, the variety of cytokines released has been established via immunohistochemistry and *in situ* hybridization studies, and a late and prolonged increase in cytokine levels has been observed several hours after antigen challenge (18).

### Neurogenic reflexes in the late-phase response

Nasal stimulation studies have been undertaken to determine whether the late-phase response is also associated with neurogenic reflexes. Early and late response to unilateral nasal challenge was examined in a study by Wagenmann et al. (19). Patients with allergic rhinitis were challenged with allergen ( $n=9$ ) or diluent (control;  $n=9$ ) and the response was measured in terms of histamine release. After nasal allergen challenge, elevated levels of histamine were observed on the ipsilateral side, and were significantly higher than control values at all time points ( $P=0.05$ ). An immediate release of histamine was observed (early-phase response) as well as a late peak of histamine release (late-phase response) (Fig. 2). In contrast, on the contralateral side, no immediate release of histamine was observed, but a late increase did occur, although the levels of histamine were lower than those produced on the side of antigen challenge. This study was followed up by a demonstration of an increase in the number of basophils in the opposite nostril hours after the challenge (19).

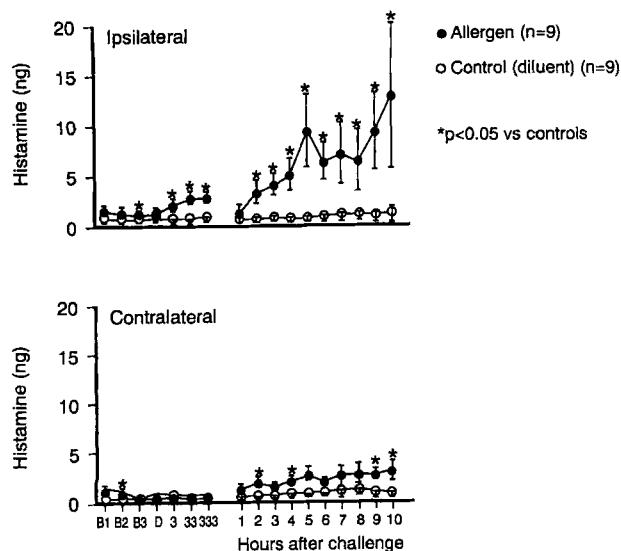


Fig. 2. Early- and late-phase response to unilateral nasal challenge with allergen or diluent. The challenge protocol is displayed on the abscissa, where B=baseline measurements, D=challenge with diluent for the allergen extract, and 3, 33, and 333=antigen dose (PNU). Histamine release was then measured at hourly intervals after antigen challenge (19).

In an extension to the same study (19), the nasal mucosa was examined in 11 patients with allergic rhinitis to determine which cells were the source of late histamine release. Rhinoprobe measurements were conducted before and after antigen challenge on both the ipsilateral and contralateral sides. After 24 h, a significant increase in basophilic cells was observed in the ipsilateral nostril compared with pre-challenge values ( $P < 0.02$ ). In the same patients, allergen challenge resulted in a significant increase in basophils on the contralateral side ( $P = 0.06$ ), although the absolute basophil count was lower than in the ipsilateral nostril. When the same experiment was undertaken after a sham challenge, an increased basophil count was not observed (19). Combined, these studies suggest that neurogenic mechanisms contribute to the influx of basophils in patients with allergic rhinitis. The mechanism by which a unilateral challenge causes an influx of basophils and a release of histamine in the opposite nostril is unknown.

Antigen challenge studies have also demonstrated T-lymphocyte activation during the late-phase response, possibly by neurogenic involvement (unpublished observations). In 16 patients with seasonal allergic rhinitis, nasal biopsies were obtained and stained for CD25-positive cells using immunohistochemistry. Antigen challenge resulted in a significant increase in the mean number of CD25-positive cells/mm<sup>2</sup> (a marker for activated T-lymphocytes) in the ipsilateral nostril ( $P < 0.05$ ), as well as a lower but significant increase in the

contralateral nostril ( $P < 0.05$ ), compared with 12 non-challenged seasonal allergic rhinitic patients out of season and 12 non-allergic individuals (Fig. 3). These experiments suggest that neurogenic mechanisms may be contributing more than a bilateral secretory response to the pathophysiology of allergic rhinitis.

### Mechanism of leucocyte-endothelial cell adhesion

The inflammatory cells involved in the acute and late-phase response to antigen challenge infiltrate the nasal mucosa by a selective recruitment process. Endothelial antigenic stimulation causes circulating eosinophils, basophils and T-lymphocytes to adhere to the surface of the vascular endothelium; they then diapedese between endothelial cells and migrate into the tissue in response to chemotactic stimuli (20). The initial recruitment at the vascular endothelium probably occurs in response to cytokine-induced upregulation of leucocyte adhesion molecules and cell surface ligands. An immunohistochemical study of allergic rhinitis patients 24 h after antigen challenge has revealed dense staining at the vascular endothelial surface, suggesting upregulation of the expression of vascular cell adhesion molecule-1 (VCAM-1) (21). Comparison of adhesion molecule expression in allergic ( $n = 10$ ) and non-allergic subjects (controls;  $n = 13$ ) 24 h after antigen challenge shows significant upregulation of VCAM-1 and E-selectin on the side of challenge in the allergic individuals compared with the controls ( $P < 0.05$ ; Fig. 4). E-selectin was significantly higher in the allergic subjects than in the non-allergic subjects. This molecule is involved early in the migration process and thus this increase, although small, probably reflects the timing of the biopsy. ICAM-1 is the most predominantly expressed endothelial cell adhesion molecule but in this study expression of ICAM-1 did not increase further after allergen challenge (21).

### Priming effect

Allergic rhinitis does not only involve the early and late response to antigen challenge. In addition, sensitivity to antigen significantly increases following the initial challenge, and this phenomenon is not obligatorily linked to the presence of the late-phase reaction. In allergic rhinitis patients, after a first exposure to antigen, the reactivity of the nasal mucosa to re-challenge with low levels of antigen results in a heightened inflammatory response – known as the priming effect (22). This was well demonstrated in a study in which 13 patients with allergic rhinitis were challenged with increasing

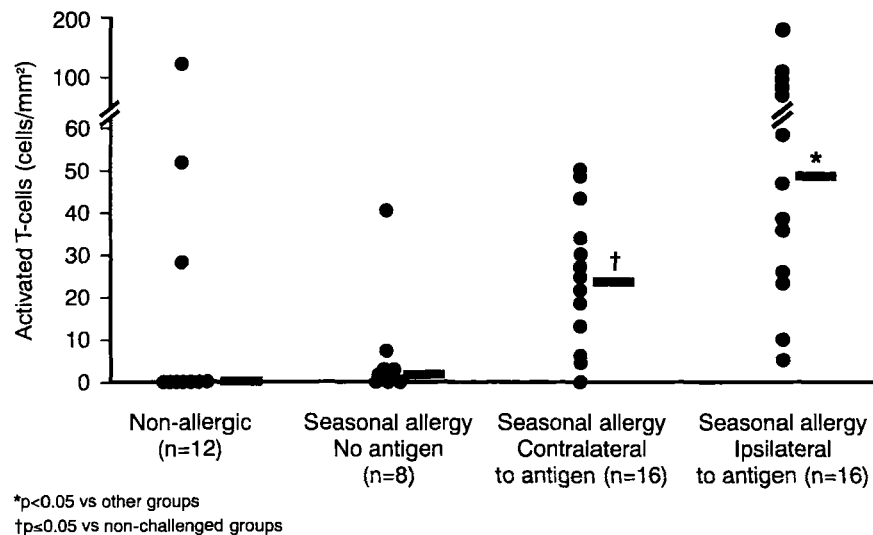


Fig. 3. Number of IL-2 bearing cells ipsilateral and contralateral to antigen challenge in patients with seasonal allergic rhinitis, compared with non-allergic subjects and non-challenged patients with seasonal allergic rhinitis. Horizontal bars are mean values.

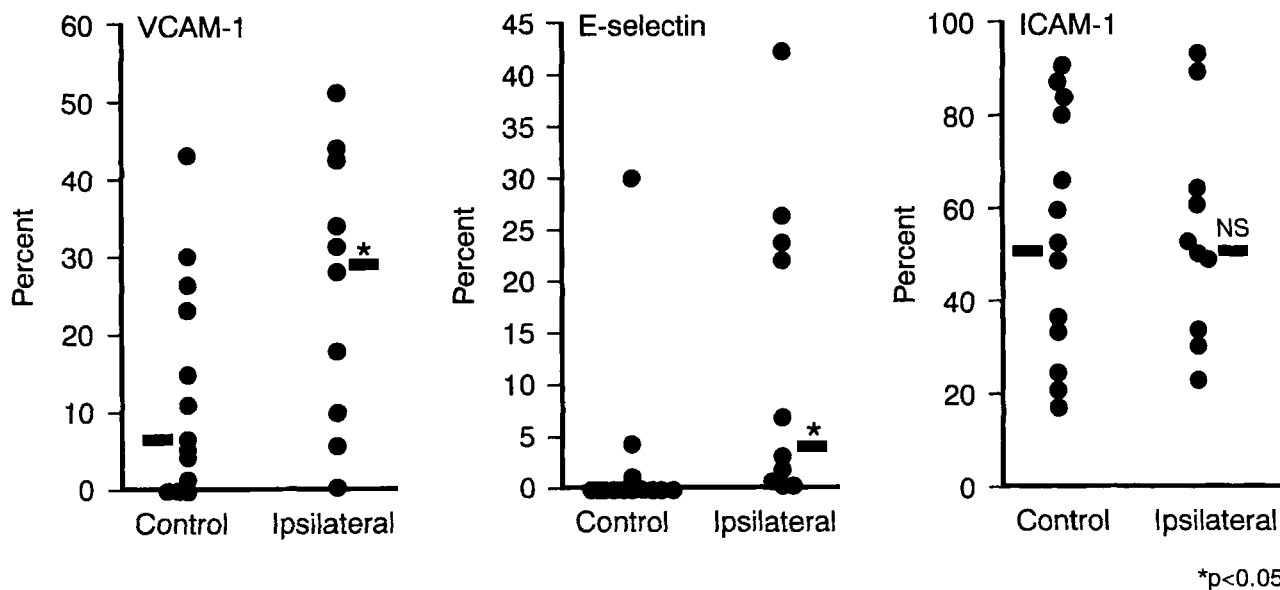


Fig. 4. Comparison of adhesion molecule expression between allergic subjects (n=10) and non-allergic controls (n=13) after antigen challenge (21). Adapted from Lee et al. *J Allergy Clin Immunol* 1994;94(6):1006–16, with permission from Mosby-Year Book, Inc.

doses of antigen (10 PNU, 100 PNU and 1,000 PNU). There was a dose-dependent increase in early histamine release which was not prevented by pretreatment with prednisone (20 mg tid for 2 days) (14). However, when the same patients were challenged 11 h later with the initial lowest dose of antigen (10 PNU), histamine release was significantly augmented ( $P<0.01$ ). In contrast to the immediate response, this priming effect was significantly reduced ( $P<0.05$ ) when patients were pretreated with prednisone, suggesting that systemic corticosteroids can effectively suppress the clinical, biochemical and cellular manifestations of

the antigen-induced late-phase response, but have little effect on the acute-phase response. Topical corticosteroids have a similar effect, but are also capable of suppressing the early reaction to antigen (23).

### Interaction of allergenic and non-allergenic stimuli

A non-allergic form of rhinitis can be induced by nasal inhalation of cold dry air in individuals who report sensitivity to cold and windy environments. Studies on the mechanism of this effect have

detected elevations in the osmolality of nasal secretions following cold dry air challenge. It has been suggested that hyperosmolality of nasal fluid triggers glandular secretion by a neural mechanism (19). Indeed, elevated osmolality has been correlated with an increased release of mediator during the reaction (8), suggesting that nasal fluid tonicity plays a role in the initiation of the reaction. In this study, nine patients who responded to inhalation of cold dry air by developing rhinitis and inflammatory mediator release also had increased osmolality of their nasal fluid. In six subjects who were unaffected by inhalation of cold dry air, however, the osmolality of nasal fluid did not change. In the responders, there were significant correlations between mediator concentrations and osmolality of nasal fluid ( $r_s=0.617$ ,  $P<0.02$  for histamine and  $r_s=0.679$ ,  $P<0.01$  for TAME-esterase).

Besides an increased reactivity to antigen, patients with allergic rhinitis also show hyper-responsiveness to non-antigenic stimuli, such as methacholine and histamine. We sought to determine whether antigen caused an increase in responsiveness to cold dry air. Using TAME-esterase as a marker for secretory activity, a study in 18 patients showed a baseline response to cold dry air that was augmented 24 h after allergen challenge, suggesting an interaction between allergenic and non-allergenic stimuli with respect to nasal reactivity (unpublished observations). In this study, when allergic rhinitis patients were exposed to cold dry air alone, an increase in TAME-esterase activity was observed compared with baseline values. However, 24 h after subsequent allergen challenge, the response to cold dry

air was significantly augmented ( $P=0.008$ ). A further study (unpublished observations) compared the responsiveness to warm moist air and cold dry air in perennial allergic rhinitis patients ( $n=25$ ), non-allergic rhinitis patients ( $n=9$ ), and normal individuals ( $n=10$ ). Those in the control group were the least responsive to these environmental influences, while patients with underlying inflammation, whether allergic or non-allergic in origin, had an increased responsiveness to cold dry air in terms of TAME-esterase activity (Fig. 5). Controlling the inflammation, therefore, would be expected to decrease the hyper-responsiveness to non-antigenic irritants.

## Summary

Allergic rhinitis is an extremely common disease with well recognized symptoms which belie the complexity of the underlying pathophysiological processes. It can be characterized as a two-phase allergic reaction – the initial sensitization phase, where allergen presentation results in antibody (IgE) formation and triggering of the humoral response, and the clinical disease phase, a symptomatologic reaction to subsequent antigen exposure. The clinical condition involves an acute-phase and a late-phase inflammatory reaction, the latter being associated with cellular infiltration and cytokine release in the nasal mucosa. The production of cytokines and the interactions of the various mediators results in an extremely complex orchestrating network, directing adhesion molecule expression, production of chemoattractants, and subsequent recruitment of inflammatory cells. The

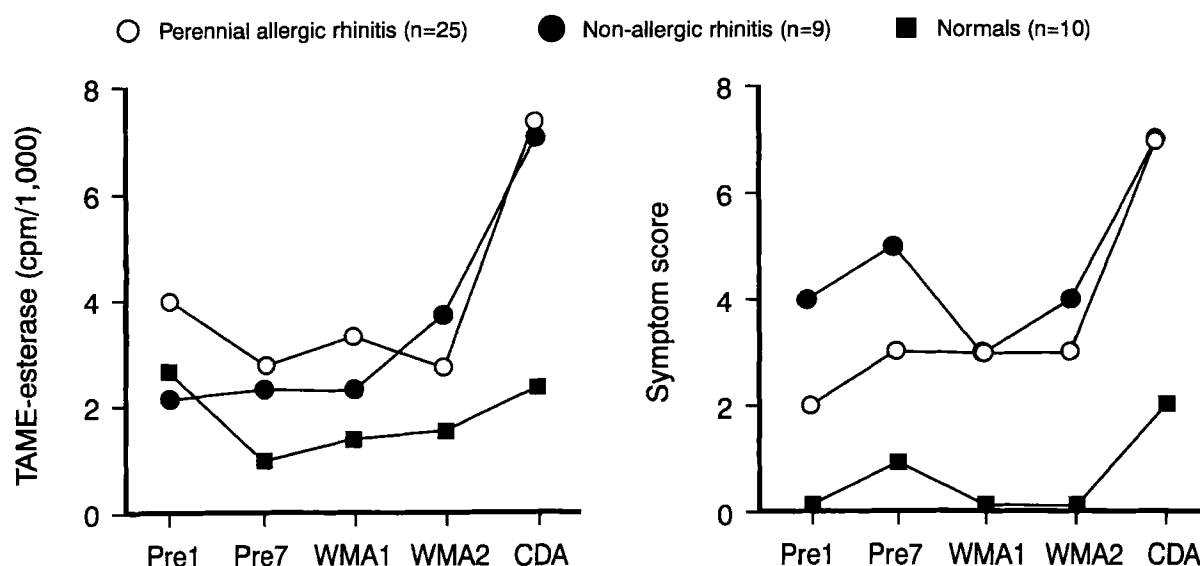


Fig. 5. Effect of underlying inflammation on responsiveness to warm moist air (WMA) and cold dry air (CDA). Pre1 and Pre7 are baseline measurements.

pathophysiology of the disease is further complicated by the involvement of neural reflex mechanisms and the interaction of allergenic and non-allergenic stimuli. It appears that patients with underlying inflammatory disease, such as those with perennial or seasonal allergic rhinitis, are more susceptible to factors which stimulate rhinitis in non-allergic individuals, e.g. cold dry air. Controlling inflammation will therefore greatly benefit our patients.

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