

Original article

Mechanisms of vasomotor rhinitis

Summary Nonallergic non-infectious perennial rhinitis (NANIPER) is a heterogeneous disorder comprising several pathophysiological entities. The etiology of some of these disorders (e.g. drug-induced rhinitis, nonallergic rhinitis with eosinophilia syndrome [NARES], occupational rhinitis, hormonal rhinitis, emotion-induced rhinitis, physical/chemical irritant-induced rhinitis) is well established. In contrast, the aetiology of idiopathic forms of rhinitis (also known as vasomotor rhinitis) is largely unknown. Mechanistic studies have suggested that non-IgE-mediated inflammatory and/or neurogenic processes may be involved. There is evidence that localized inflammation is the underlying cause of symptoms in drug-induced rhinitis and NARES, since eosinophilia is an important pathophysiological component in these conditions. In contrast, neurogenic reflex mechanisms initiated by environmental factors appear to be involved in idiopathic rhinitis. It has been suggested that there may be an imbalance of the sympathetic and parasympathetic nervous systems, with parasympathetic hyper-activity and sympathetic hypo-activity resulting in nasal congestion and rhinorrhoea. Indirect evidence suggests that C-fibres may also play an important role in the pathophysiology of idiopathic rhinitis.

R. Garay

INSERM U400, Faculté de Médecine de Créteil,
France

Key words: Vasomotor rhinitis; drug-induced rhinitis; NANIPER; NARES; idiopathic rhinitis; nasal reflex; C-fibres; eosinophilia

R. Garay
INSERM U400
Faculté de Médecine de Créteil, France
E-mail: Garayperso@aol.com

Introduction

Nonallergic noninfectious perennial rhinitis (NANIPER), is a heterogeneous disease, which is characterized by nasal hyperreactivity that results in symptoms of nasal blockage, rhinorrhoea, and sneezing, which are often indistinguishable from nasal symptoms of allergic rhinitis. Diagnosis of the disease is established on the basis of persistent symptoms throughout the year after exclusion of infection (as indicated by a clear and watery nasal discharge, as compared with a purulent discharge produced in infectious rhinitis), any anatomical or medical disorder of the nose, and negative skin prick testing for IgE-mediated sensitivity to relevant aeroallergens. Although negative skin prick testing is necessary to confirm diagnosis of nonallergic rhinitis, it is important to note that irrelevant aeroallergens may occasionally result in positive skin prick testing (1).

NANIPER comprises several forms of rhinitis, in which the aetiology and/or pathophysiology is established only for some minor forms of the disease, in particular drug-induced rhinitis and nonallergic rhinitis with eosinophilia syndrome (NARES). In contrast, the aetiology is largely unknown for a majority of about 75–80% of the individuals, in whom the disease is classified as being idiopathic or vasomotor rhinitis. Although other more minor forms of rhinitis (e.g. occupational rhinitis, non-allergic hormonal rhinitis, food-induced rhinitis, emotion-induced rhinitis, physical/chemical irritant-induced

rhinitis, and rhinitis of the elderly) (2–5) have also been defined on the basis of limited information on aetiological and pathological factors, only drug-induced rhinitis, NARES, and idiopathic rhinitis will be discussed in greater detail to illustrate the general mechanisms that may be important in NANIPER.

Drug-induced rhinitis

A wide range of medications including: aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), reserpine, hydralazine, guanethidine, phentolamine, methyldopa, angiotensin-converting enzyme (ACE) inhibitors, β -blockers, α -adrenoceptor antagonists, chlorpromazine, oral contraceptives, topical nasal decongestants and psychotropic agents have been shown to induce symptoms of rhinitis (2, 3), which result either as side-effects of the drug, or directly as a consequence of hypersensitivity to the drug. Reserpine, guanethidine, methyldopa, angiotensin-converting enzyme (ACE) inhibitors, some α - and β -adrenoceptor antagonists, chlorpromazine, and oral contraceptives have been implicated in causing nasal obstruction as a side-effect. In contrast, aspirin and other NSAIDs produce rhinorrhoea, which is either isolated or as part of the “aspirin-triad” involving chronic rhinosinusitis, nasal polyps and asthma, in aspirin sensitive individuals. Persistent over-use of the topical nasal

decongestants and abuse of psychotropic drugs such as cocaine may lead to nasal hyperreactivity and hypertrophy of the nasal mucosa, a condition known as “rhinitis medicamentosa”.

In order to gain an understanding of the mechanisms underlying the generalized effects of these drugs as inducers of rhinitis, these drugs may arbitrarily be sub-grouped into three main types; (i) the local inflammatory type, which elicit a localized inflammatory reaction that eventually results in the symptoms of rhinitis; (ii) the neurogenic type, which elicit their effects via a neural mechanism; and (iii) other types, for which there is little or no information on the underlying mechanisms.

Local inflammatory type

Aspirin and NSAIDs are classic examples of the types of drugs that may induce rhinitis in sensitized individuals by production of a local inflammation in the nasal mucosa. Although the precise mechanism of aspirin sensitivity is not entirely clear, it has been hypothesized that increased production of leukotrienes and activation of mast cells and eosinophils may play a central role. It has been suggested that inhibition of cyclooxygenase pathway by aspirin may shift arachidonic acid metabolism through the lipoxygenase pathway, thus resulting in increased amounts of leukotrienes. Although the majority of studies have investigated the effects of aspirin sensitivity in the lower airways, studies in the upper airways have demonstrated that aspirin challenge results in the increased levels of leukotriene C₄ (LTC₄), prostaglandin E₂ (PGE₂), PGF_{2 α} and histamine in nasal secretions of aspirin-sensitive individuals, but not in healthy and aspirin-insensitive individuals (6, 7). More recent evidence suggests that the increased production of LTC₄ in aspirin-sensitive individuals is likely to be as a consequence of over-expression of LTC₄ synthase, compared with expression of this enzyme in normal controls (8).

Similarly, studies investigating the release of chemical mediators of anaphylaxis from mast cells and other cells in aspirin-sensitive individuals have also mostly investigated the lower airways. Studies investigating the role of mast cells in aspirin-sensitive individuals have demonstrated that aspirin challenge leads to increased levels of plasma histamine levels and appearance of mast cell tryptase in serum, and that the increase in these mediators may be associated with moderate to severe respiratory reactions (9, 10). One study demonstrated that endobronchial aspirin challenge lead to decreased mast cell numbers, presumably as consequence of activation and degranulation, and increased eosinophil activation in bronchial biopsies of aspirin-sensitive asthmatics (11). Similarly, there is some evidence that direct nasal challenge also leads to mast cell and eosinophil activation in the nasal mucosa of aspirin-sensitive individuals, as indicated by an increase in histamine, tryptase, and

eosinophil cationic levels and an increase in the number of eosinophils in nasal lavage samples obtained from these individuals (10, 12).

Neurogenic type

The vasoactive drugs such as guanethidine, methyl dopa, and the α and β -adrenoceptor antagonists, are principally sympatholytic and elicit their effects by down-regulating the activity of the sympathetic nervous system, which in the nasal airways leads to congestion. Indeed, neuroanatomical examination has demonstrated that the airways are innervated by the sensory, parasympathetic/cholinergic and sympathetic/adrenergic nervous systems, of which the distribution of adrenergic nerves is predominantly concentrated in the nasal vessels, bronchial vessels and to a lesser extent in glands. Immunostaining studies have demonstrated that the adrenergic neurons contain norepinephrine and neuropeptide Y (NPY), a potent vasoconstrictor, which acts as a cotransmitter to amplify the effects of norepinephrine on release from the sympathetic neurons (13). Other functional studies have demonstrated that NPY also acts directly via NPY₂-receptors to modulate cholinergic transmission in postganglionic cholinergic nerves.

NARES

NARES is also an example of a form of nonallergic rhinitis in which production of a local inflammation appears to be the main underlying pathological mechanism. NARES was originally described by Jacobs and colleagues, who characterized 52 patients with perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhoea, and pruritus of the nasopharyngeal mucosa in an “on-again-off-again” symptomatic pattern (14). Additionally, these patients had a profound nasal eosinophilia ($\geq 20\%$ of the granulocytic or mononuclear cells present excluding nasal epithelial cells), which was not associated with allergic disease, as indicated by negative skin-prick testing and no evidence for increased levels of either total or specific IgE in the nasal secretions of these patients. Indeed, 42% of the patients could not associate any specific trigger factor with the acute onset of their nasal symptoms, whilst 31% of patients associated their symptoms with weather changes, 15% with odours, and 12% with noxious or irritating substances. Other studies have suggested that this condition may be prevalent in up to one third of adults with nonallergic rhinitis, and although it usually occurs as an isolated disorder, in severe cases it may be associated with non-IgE-mediated asthma, aspirin intolerance and nasal polyps (1).

Although the nasal cytology of NARES is characterized by eosinophilia, which ranges from mild to massive and is frequently associated with basophilic and/or metachromatic cell infiltration, the precise

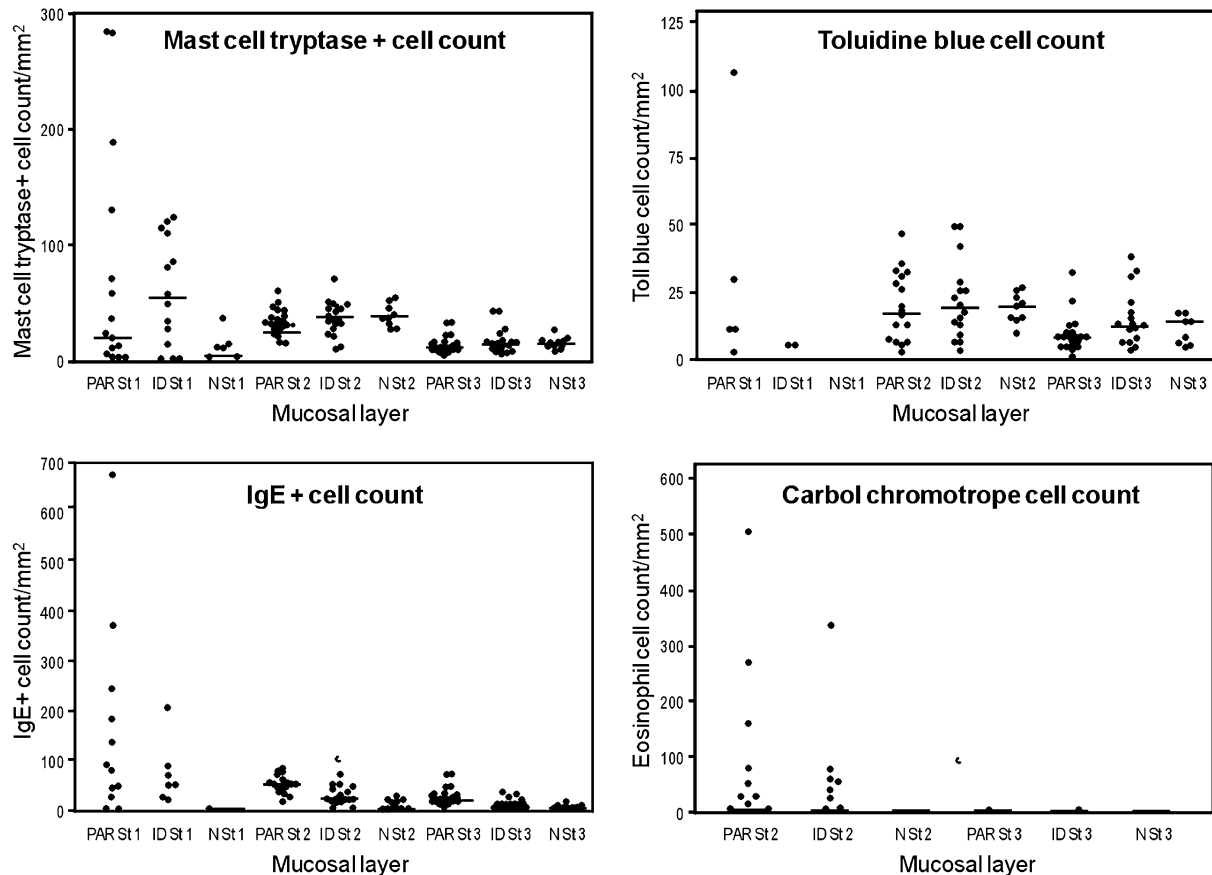


Figure 1. Mean mast cell, toluidine blue staining, IgE⁺ and eosinophil cell counts/mm² nasal biopsy tissues collected from patients with perennial allergic (PAR) and idiopathic (ID) rhinitis, and normal nonrhinitic subjects (N). (Horizontal bar + median counts; St1 = counts in epithelium; St2 = counts in superficial submucosa; St3 = counts in deep submucosa.) (Modified from Powe et al. 2001 (15) and reprinted with kind permission.)

pathophysiology of the condition is not clearly understood. Powe and colleagues (15) have recently demonstrated that the number of mast cells, IgE⁺ cells, and eosinophils are significantly increased in the nasal mucosa of perennial allergic and idiopathic rhinitis patients, compared with normal nonrhinitic patients (Fig. 1). Since mast cells and IgE⁺ cells play a key role in the Th₂ IgE-mediated inflammatory response, these findings suggest that inflammation in nonallergic rhinitis may be a consequence of localized IgE-mediated reactions, which do not involve systemic Th₂ responses or atopy.

However, it has been suggested that eosinophilia in NARES may contribute to nasal mucosal dysfunction, since major basic protein (MBP) and eosinophil cationic protein (ECP) released from the eosinophil granules are capable of damaging the nasal ciliated epithelium and prolonging mucociliary clearance (1). Prolonged or delayed mucociliary clearance itself may increase the propensity towards infection and predispose the individual to the development of nasal polyps. Nevertheless, the presence of eosinophilia in NARES is an important predictor for response to treatment with topical anti-

inflammatory therapy, such as intranasal steroids and azelastine nasal spray.

Idiopathic rhinitis

Unlike drug-induced rhinitis and the other minor forms of nonallergic rhinitis (occupational, nonallergic hormonal, food-induced, emotion-induced rhinitis and physical/chemical irritant-induced rhinitis) for which there is some aetiological information, the aetiology of idiopathic rhinitis is unknown and diagnosis is generally established by exclusion. It has, however, been demonstrated that careful determination of the intensity of symptoms combined with modern diagnostic tools such as nasal provocation with cold dry air, which results in increased mucus production and nasal blockage in a dose-dependent manner in idiopathic rhinitis patients (16), can be used to discriminate between idiopathic rhinitis patients and normal healthy subjects.

Several mechanisms have been postulated to explain the pathophysiology of idiopathic rhinitis, of which:

(i) increased permeability of the nasal epithelium; (ii) non-IgE-mediated inflammatory responses; and (iii) neurogenic responses are the most plausible (4). It has been suggested that an increase in the nasal epithelial permeability, resulting as a consequence of epithelial damage by irritants, infection or cellular components such as eosinophil MBP/ECP, might lead to increased access of stimuli to the sensory nerve endings, vessels and secretory glands and become manifest as the symptoms of rhinitis. However, many of these events are not different from those observed in the bronchi of asthmatics, and are thus unlikely to exclusively explain the pathological features of idiopathic rhinitis.

Although non-IgE-mediated inflammatory responses have been shown to be present in the nasal airways of idiopathic rhinitis patients by some authors (15), others have not been able to demonstrate inflammation in their group of patients (17). Also a major difficulty with the few studies demonstrating inflammation in nonallergic rhinitis has been that a clear distinction was not made between idiopathic rhinitis and NARES in the patient groups investigated, of which the latter could account for the observed inflammation. Similarly, inconsistent results have been demonstrated for the efficacy of anti-inflammatory treatments such as corticosteroids and

antihistamines in the treatment of this condition, suggesting that inflammation may not be an important underlying mechanism.

In contrast, there is increasing evidence that neurogenic mechanisms are likely to be involved in the pathophysiology of rhinitis symptoms (18). Neural regulation in the upper airways is maintained by the sensory (peptidergic), sympathetic (adrenergic), and parasympathetic (cholinergic) nervous systems, which innervate and interact in the nasal mucosa to regulate epithelial, vascular, and glandular processes in particular. Under normal conditions the sympathetic nervous system constitutes the main vasoactive mechanism, ensuring vascular tone. The sympathetic nerve fibres that innervate the nose originate from the first and second thoracic segments of the spinal cord and synapse in the superior cervical ganglion. Post-ganglionic fibres enter the nose accompanying branches of the carotid artery and innervate mainly the vasculature and to a lesser extent the secretory glands, where they discharge norepinephrine (Nor) and NPY to cause predominantly vasoconstriction and a decrease in nasal secretion (Fig. 2a). This normal sympathetic tone has the net effect of increasing nasal patency.

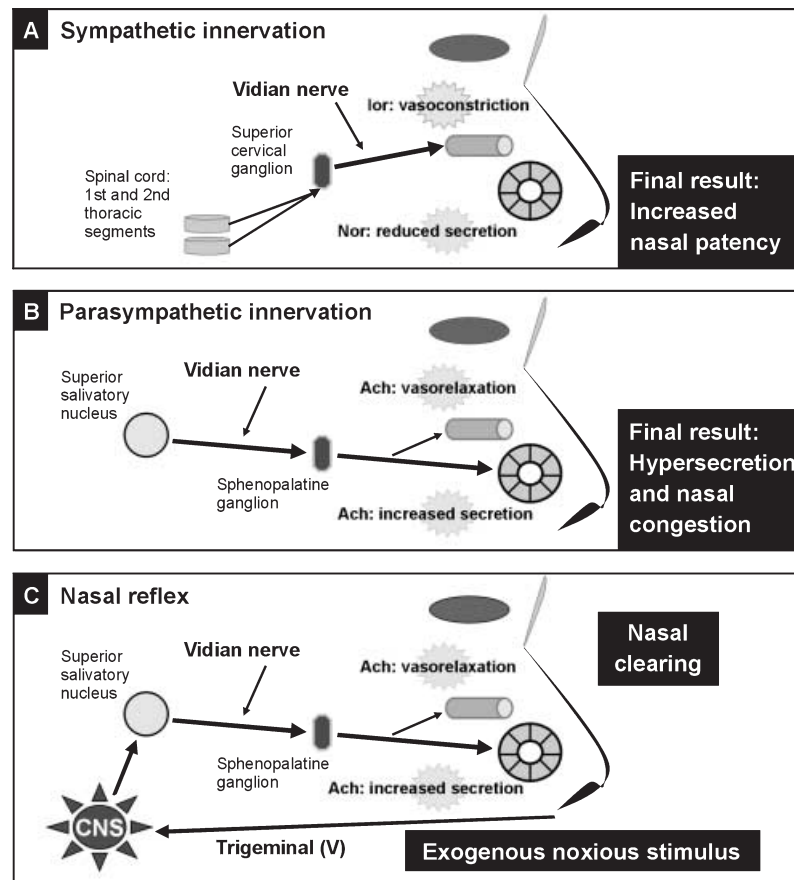


Figure 2. Effects of: (A) sympathetic innervation; (B) parasympathetic innervation; and (C) nasal reflex on nasal function.

In contrast, preganglionic parasympathetic fibres leave the superior salivatory nucleus and join the postganglionic sympathetic fibres to form the vidian nerve, prior to synapsing with the sphenopalatine ganglion. Post-ganglionic parasympathetic fibres then innervate both the blood vessels and the exocrine (seromucous and serous) glands of the nasal mucosa, of which innervation of the glands appears to be more important. The parasympathetic nerve fibres release predominantly acetylcholine (ACh), and other neuropeptide transmitters such as vasoactive intestinal peptide (VIP), which increase nasal secretion and vasorelaxation, leading to nasal congestion under extreme conditions (Fig. 2b). Although the parasympathetic tone is not as prominent as the sympathetic tone under normal conditions, it has been demonstrated that, in conjunction with sensory neurons, the parasympathetic neurons play an essential role in “protective” nasal clearing reflexes such as sneezing, secretion and congestion, in response to exogenous noxious stimuli. Stimulation of sensory mechanoreceptors and/or chemo-sensitive receptors in the nose leads to excitation of the parasympathetic reflex, via stimulation of the trigeminal nerve connected to the central nervous system (Fig. 2c).

However, it has been suggested that there is a balance between the sympathetic and parasympathetic tones, which under normal conditions is biased towards the sympathetic tone and results in increased nasal patency and low mucus production. In contrast, some mechanistic studies in idiopathic rhinitis have suggested that this balance becomes biased towards the parasympathetic system, i.e., hypo-reactivity of the sympathetic system and hyper-reactivity of the parasympathetic system; resulting in functional abnormality of the nasal end organs in these patients (4).

Other studies have suggested that the functional abnormality in idiopathic rhinitis may be associated with abnormal sensory afferent nerves and/or C-fibre stimulation. C-fibres are unmyelinated parts of the sensory neurons that originate from the ethmoidal and posterior nerves and innervate the vessels, glands and epithelium of the mucosa. C-fibres are unspecialized sensory nerve endings, which induce local antidromic spreading of the action potential in peripheral branches of the sensory neurons and local release of neuropeptides on stimulation by noxious agents. Neuropeptides such as substance P (SP), in particular, and calcitonin gene-related protein (CGRP) are released from C-fibres and cause a localized increase in vascular permeability and nasal secretion. Under normal conditions this acts as a protective nose clearing reflex mechanism similar to that described above for the parasympathetic reflex. However, there are several reports, which suggest that increased C-fibre activity may lead to nasal dysfunction in idiopathic rhinitis. Several studies have demonstrated that capsaicin, the pungent agent in red peppers, predominantly stimulates C-fibres to induce burning,

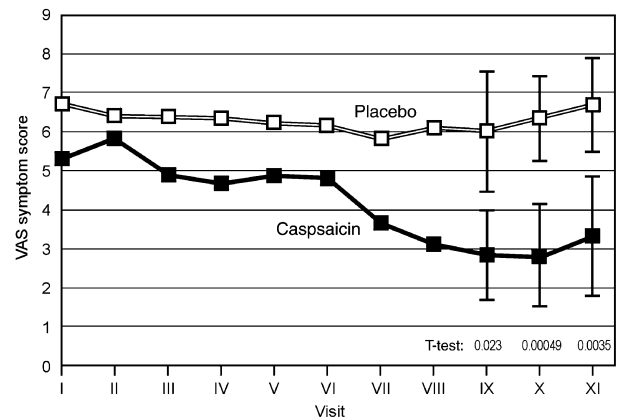


Figure 3. Effect of repeated provocation with capsaicin or placebo on nasal complaints in idiopathic rhinitis patients, as indicated by a symptom score measured on a VAS of 0–10 cm. (Modified from Blom et al. 1997 (23) and reprinted with kind permission.)

rhinorrhoea, and nasal congestion (19, 20). Similarly, several studies have demonstrated that repeated nasal provocation with capsaicin significantly reduces nasal complaints in patients with idiopathic rhinitis (21–24) (Fig. 3), suggesting that this may be a consequence of either C-fibre desensitization or degeneration, although this remains to be confirmed in human models. However, reports on the involvement of C-fibre-mediated inflammatory processes as underlying mechanisms are conflicting, because although some studies have demonstrated capsaicin-induced neurogenic inflammation in patients with allergic rhinitis (20), this has been shown not to be the case in idiopathic rhinitis (23, 24).

Conclusion

It is clear that nonallergic noninfectious rhinitis is a heterogeneous disorder comprising several aetiological and/or pathophysiological entities. The aetiology of some minor forms such as drug-induced rhinitis and nonallergic rhinitis with eosinophilia syndrome [NARES], and some even more minor forms such as occupational rhinitis, nonallergic hormonal rhinitis, emotion-induced rhinitis, physical/chemical irritant-induced rhinitis, and rhinitis of the elderly is well established, but is unknown in a majority of the patients who present idiopathic forms of the disease. Studies of the mechanisms underlying the pathophysiology of this disorder have suggested that these may involve non-IgE-mediated inflammatory and/or neurogenic processes. Certainly, evidence from studies in patients suffering from drug-induced rhinitis and NARES points to localized inflammation as the underlying cause of symptoms, since eosinophilia has been shown to be an important pathophysiological component in these conditions. In contrast, idiopathic rhinitis appears to be

consequent to neurogenic reflex mechanisms initiated by environmental factors. It is likely that the homeostasis between the sympathetic and parasympathetic nervous systems is disturbed, specifically towards parasympathetic hyper-activity and sympathetic hypo-activity,

which results in nasal congestion and rhinorrhoea. There is some indirect evidence that C-fibres may also play an important role in the pathophysiology of idiopathic rhinitis, although direct evidence to this effect is lacking.

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General discussion

Bachert: Of course the classification of disease as you have indicated is very appropriate from the academic point of view, but is there evidence from a patient's history which suggests that a high parasympathetic tone means a classification of the "runner" type and a low or complete lack of

sympathetic tone means a classification of the "blocker" type? How can you actually differentiate a particular type? *Garay:* Classically speaking, you are right, but parasympathetic hyperactivity seems to play a more important role in idiopathic rhinitis than reduced sympathetic

activity. Also, these systems are interdependent and since there is a lot of controversy with respect to the role of C-fibres, then I do not think that they should be classified as separate entities.

Bachert: So you would put them under the umbrella of idiopathic form, and is there any sort of diagnostic tool that you can use in these forms?

Garay: One can use the skin prick test when the agonist is applied on the skin, to look for heightened activity. For example, you can look at the effect of a cholinergic or an adrenergic agonist in the skin. However, there is a very real difference for some but not all vasomotor rhinitis patients. Thus, I think that this type of a test is of limited value.

Delegate: I have two questions. Firstly, what do you think of the cellular components involved in idiopathic rhinitis patients, particularly with regard to the role of neutrophils? Secondly, do you think that we should be classifying these nonallergic rhinitis patients as just vasomotor rhinitis patients or just idiopathic rhinitis patients?

Garay: To answer your second question first, these patients are clearly not all idiopathic, because there is at least some information on the aetiology and the mechanisms underlying the pathophysiology in some cases. Subsequently, it may possibly be better to classify them as nonallergic noninfectious perennial rhinitis (NANIPER) patients. In practice, they are vasomotor rhinitis patients, but perhaps the term NANIPER is more accurate because it gives some indication of the pathophysiology of this condition. With respect to your question about the cellular components, then again if you look in the literature you cannot find much in this regard. Not only for the neutrophils, but also for mast cells, which would give support for the use of antihistamines such as azelastine, which incidentally is the only antihistamine to have been licensed for treatment of this condition. However, I think that from the cellular infiltrate, the most important cell may be the eosinophil, because if you can find higher than 20–25% eosinophils, then at least you have a defined entity (NARES) for sure.

Bachert: You said that drug-induced rhinitis could be subdivided into major two subclasses, and I completely agree with that. However, I wonder why you see only very

few patients suffering from rhinitis medicamentosa, because we actually find quite a lot of patients still suffering from this disease. It is possible that we see more of these patients since we ask our patients to use a combination spray of dexamethasone and a decongestant regularly on the basis that dexamethasone might control their disease more effectively. What do you think?

Garay: That is very interesting, and it is possible that the reason why you do see a lot more patients with rhinitis medicamentosa is precisely for the reason that you have indicated, i.e. more frequent and generalized use of the nasal decongestant.

Delegate: What do you think of the classification of “blocker” type with both rhinorrhoea and nasal congestion?

Garay: That is an interesting question. There is a lot of controversy about this type of classification, which is very arbitrary, and for this reason I have reservations about this classification. I prefer to classify the disease on the basis of parasympathetic and sympathetic activities/tones. Although I discussed the extremes of high parasympathetic and low sympathetic tones in idiopathic disease, of course there are intermediate situations, like the one you describe, which are more difficult to assess and classify. However, I think that in at least 30% of these patients, one can classify their disease without much difficulty on the basis of pathophysiological mechanisms.

Delegate: Some authors believe that the idiopathic form of rhinitis is a nonexistent entity and that this is really a form of allergic rhinitis expressed under different conditions. What are your thoughts about this?

Garay: I think that a neurological component is indeed involved in the pathophysiology of nonallergic rhinitis, which is not seen in allergic rhinitis. Although this is only academic research based evidence, I think that it can be clinically important nevertheless.

Bachert: I would also argue against this hypothesis on the basis that there is no inflammation in the nasal mucosa of idiopathic rhinitis patients, although they clearly have the symptoms. This is in marked contrast to allergic rhinitis, in which the symptoms are dependent on inflammatory changes in the nose, and therefore I clearly think that there is something like nonallergic/idiopathic rhinitis.