Chronic and recurrent nasal symptoms

M.J.J.S. Crobach

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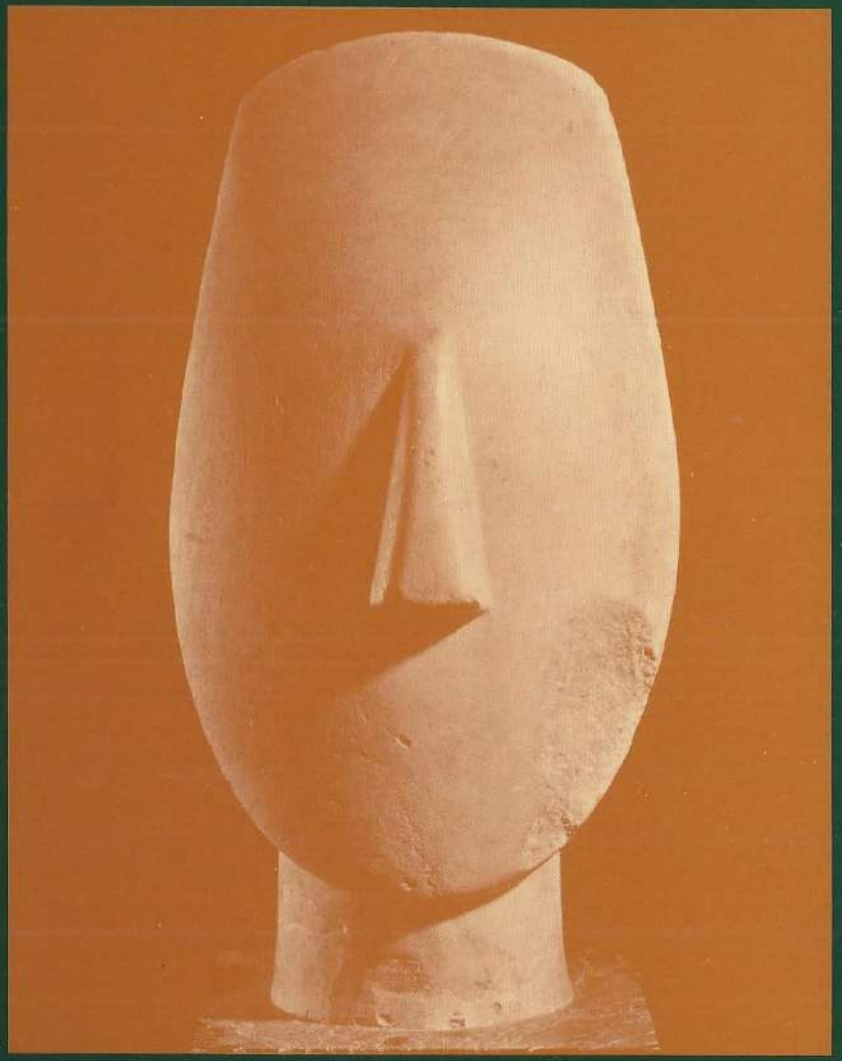
A diagnostic study in general practice with special reference to allergic rhinitis



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Cover illustration: Head of an idol. Circa 2000 B.C. Marble; height 27 cm.
From the isle of Amargos, Cyclades, Greece.
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Aan: Paola,
Yara, Cecile en Lucas

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Chapter 1

General introduction

1.1. Introduction

Throughout history the nose has appealed to the imagination of writers, artists, and physicians. Cleopatra definitely had a nose for politics, Cyrano de Bergerac could not help sticking his nose into other people's affairs, and Pinocchio followed his nose a little too far. It was not always the size of the nose that made it famous. For instance, there is a well-known painting showing a nasal disorder: Domenico Ghirlandaio's portrait of the Florentine banker Sassetti, who had a rhinophyma (circa 1490; Louvre). For centuries, physicians, too, have been intrigued by nasal disorders. In the Works of Hippocrates, a collection of books which were probably written by several different authors associated with the Medical School of Cos (circa 400 B.C.), there is a detailed description of a technique for the removal of nasal polyps.[1] Allergic rhinitis, however, has a very short history. In 1819 Bostock formulated the first full description of a case of hay fever (his own), which he called 'summer catarrh'.[2] It took him nine years to collect another 28 cases for a second article.[3] Later the lay term 'hay-fever' was coined, as it came during the haymaking season. Its etiology remained uncertain until 1873, when Blackley, in an extremely well-designed study, identified pollen as the culprit.[4] There is strong evidence that since that time the prevalence of allergic rhinitis has increased dramatically,[5, 6] so that today it is the most frequent cause of chronic and recurrent nasal symptoms.[7]

Virtually everyone occasionally experiences some form of nose trouble. And yet most people with nasal symptoms never consult a physician.[8] Symptoms arising from the common cold generally disappear within a week, with or without the benefit of home remedies such as steaming.[9]

In contrast, chronic and recurrent nasal symptoms form a much greater problem. The patient's quality of life may be considerably reduced.[10] Patients experience not only nasal symptoms but also systemic symptoms, sleep disturbances, curtailment of activities, practical problems, and emotional distress.[10, 11] In population studies, the prevalence of self-reported 'hay fever and hay-fever-like diseases' ranges from 10% to 15%.[12] Due to the direct and indirect costs, the problem concerns not only these patients, but also society as a whole. In the USA 17% of the population, or 35 million people, are affected by allergic diseases, predominantly allergic rhinitis and asthma, at a cost per annum of 1.5 billion dollars, as well as a loss of 5 million working days and 589 million dollars in wages.[13]

In the United Kingdom, the Netherlands, Denmark, Norway, and Finland, patients need a referral from their general practitioner to obtain specialist care. This means that the general practitioner is the main provider of care for the majority of all medical problems, including chronic and recurrent nasal symptoms.[14] In the Netherlands, for example, only 2-4% of patients with allergic rhinitis are referred to a specialist.[15, 16] The general practitioner may choose to prescribe medication without undertaking further diagnostic efforts. However, if there is reason to believe that specific causes are involved, additional testing may be necessary to identify these causes. This may be especially useful in the case of allergic rhinitis, because, wherever feasible, the patient should minimize exposure to the causal allergen.[17]

In view of the above, it is perhaps surprising that in general practice the management of these complaints is based on such limited scientific knowledge. It is unclear whether it is possible in general practice to distinguish between different types of nasal pathology, and what the diagnostic value is of the medical history, the physical examination, and additional tests.[18] Any diagnostic policy for the general practitioner should be based on diagnostic studies performed in populations that are representative for general practice. It was in an effort to provide some of the missing information that the present study was performed. On the basis of the results of this study, diagnostic guidelines can be formulated which will help the general practitioner to make correct diagnoses and choose the appropriate management.

1.2. Aims of the study

The aims of this study were:

1. To investigate whether it is possible to distinguish between different types of nasal pathology in patients with chronic or recurrent nasal symptoms in general practice.
2. To assess the diagnostic value of the medical history, the physical examination, and additional tests that can be carried out by the general practitioner for the different types of nasal pathology.

In order to obtain results that would be representative of patients who consult their general practitioner because of chronic or recurrent nasal symptoms, great care was taken to include as many eligible patients as possible and, if at all possible, to avoid refusals. As asking patients to go to the hospital for further examination would lead many patients to refuse to take part, it was decided to examine the patients in the office of their general practitioner or at home. The additional tests performed were selected on the basis of the literature and the practicability in general practice. Because these tests included skin tests and venipuncture, which children might find scary, we arbitrarily chose to exclude patients under the age of 12.

In the absence of a universally accepted system for the terminology of nasal pathology, we opted for that proposed by Mygind.[19] With a few adaptations, it comprised the following 8 diagnostic categories: 'allergic rhinitis' (divided into 14 different allergies), 'vasomotor rhinitis', 'infectious rhinitis', 'rhinitis medicamentosa', 'nasal polyps', 'anatomical obstructions', 'other diseases', and 'non-specific hyperreactivity'. Special attention was given to allergic rhinitis, because of the practical consequences of making this diagnosis, namely, the possibility to reduce exposure to the causal allergens.

The first aim of the study was approached by obtaining expert opinion on the presence of the different types of nasal pathology in each patient. In a modified Delphi consensus method, three experts tried to reach consensus on the presence of each of the diagnostic categories (See Appendix 3); their judgments were based on all the symptoms and signs, and the results of the additional tests as presented on a written format. The

resulting 'consensus diagnoses' were used as the reference diagnoses, which were necessary to achieve the second aim of the study.

From the beginning of the study, it was anticipated that the methodology chosen would result in a higher degree of agreement among the experts on the presence of allergic rhinitis than on the presence of most of the non-allergic nasal disorders. Nevertheless, in stead of focusing on allergic rhinitis only, it was decided to study all the common nasal disorders.

The research questions of this study were:

1. Is it feasible to make use of a modified Delphi consensus method in order to obtain reference diagnoses of different types of nasal pathology in patients aged 12 or over with chronic or recurrent nasal symptoms?
2. What is the diagnostic value of the medical history and the physical examination for the different types of nasal pathology?
3. What is the diagnostic value of all the various combinations of medical history, physical examination, ultrasonography, nasal smear eosinophilia, total IgE, the Phadiatop test, radioallergosorbent tests (RASTs), and skin prick tests for the different types of nasal pathology?
4. How does the Phadiatop ratio compare with a panel of radioallergosorbent tests?

1.3. A guide to the reader

In **Chapter 2** the literature is reviewed with respect to the epidemiology and etiology of chronic and recurrent nasal symptoms as well as the diagnosis and management of nasal pathology, with special reference to allergic and non-allergic rhinitis.

In **Chapter 3** an outline of the study is given, including the results of a pilot study. The characteristics of the patient population and the diagnostic procedure are also described.

Chapter 4 compares the Phadiatop test and the Phadiatop ratio with a panel of radioallergosorbent tests. A third outcome for the Phadiatop is proposed: 'inconclusive'.

Chapter 5 describes the methodology and results of the consensus procedure used to obtain the expert 'consensus diagnoses', that served as the references. The prevalence of the different types of nasal pathology is presented.

In **Chapter 6** the diagnostic value of the medical history and the physical examination for allergic rhinitis is examined. Quite a limited case history is proposed, to which the physical examination contributes no relevant information.

In **Chapter 7** the diagnostic value of the various combinations of the medical history with skin prick tests or with radioallergosorbent tests for allergic rhinitis are compared. Simple diagnostic criteria are presented, with the aid of which nasal allergies can be diagnosed with a high degree of certainty.

In **Chapter 8** the diagnostic values of the Phadiatop test and the total IgE for allergic rhinitis are compared.

Chapter 9 presents the diagnostic value of nasal smear eosinophilia for allergic rhinitis and the prevalence of eosinophilic non-allergic rhinitis.

In **Chapter 10** the diagnostic value of the medical history and the physical examination for the non-allergic types of nasal pathology is discussed; the additional tests make no relevant contribution.

Chapter 11 consists of a general discussion and a proposal for a diagnostic policy.

This thesis is composed of a number of chapters that have previously been published or submitted as articles. These articles are presented in their entirety, with no adaptations to the content. Adapting the chapters in order to omit the repetition of certain sections, notably those concerned with the methods, was an option. However, we preferred to present the articles unchanged. In this way, moreover, the reader is free to read a single chapter, without having to go through the whole thesis.

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Chapter 2

The literature on allergic and non-allergic rhinitis

2.1. Introduction

This Chapter consists of an overview of current opinion on the definition, the classification, and the pathophysiology of nasal pathology, with special reference to allergic and non-allergic rhinitis. Current knowledge on the epidemiology and diagnostic procedures in general practice is also discussed. Therapy is addressed only briefly.

2.2. Definition and classification

Chronic or recurrent nasal symptoms can be caused by a variety of disorders. Unfortunately, there is no generally accepted system for the definition and classification of nasal pathology. There have been many proposals for classification, most of which make a clear distinction between rhinitis, defined as a group of disorders of the nasal mucous membrane, and other causes, such as anatomical abnormalities. Some proposals for the classification of rhinitis are based predominantly on the cytology of nasal smears,[1] others on symptomatic criteria combined with skin tests.[2, 3]

It was not until quite recently, in 1994, that a consensus report was drawn up by leading clinicians and researchers in the fields of allergy and otorhinolaryngology, representing ten different countries. In this 'International Consensus Report on the Diagnosis and Management of Rhinitis', which is intended principally for use by the primary care physician, the chapter on definition and classification consists of a list of terms and a single sentence: 'Rhinitis is defined as an inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and itching'.[4] No attempt was made to attach time criteria or criteria for the severity of the symptoms, or to define the many terms listed. This classification, too, makes a clear distinction between rhinitis and non-inflammatory nasal pathology. The classification proposed in the consensus report is presented in Table 2.1.

From a practical point of view, differentiating between various types of nasal pathology is useful only if this has consequences for the management. In this regard, certain remarks on Table 2.1 are in order. First, it is often impossible to differentiate between seasonal and perennial allergic rhinitis because many patients have perennial symptoms with seasonal exacerbations.[5] It would appear to be of more importance to differentiate between different causal allergens, since, wherever feasible, the patient should minimize exposure to the causal allergens.[6] Second, it is probably not necessary to identify all the different types of non-allergic rhinitis in order to determine the appropriate management.[7] Third, in general practice, the prevalence of many types of rhinopathy is extremely low, and making the diagnosis of, for instance, a granuloma is virtually impossible. Therefore, instead of checking a list of differential diagnoses, it would seem more practical for the general practitioner to be able to recognize 'alarm signals' that require referral to a specialist for further examination. In conclusion, for use in general practice Table 2.1. should be adapted, to make it more practical. The proposed adaptations are discussed in Chapter 3.

Table 2.1. Classification of nasal pathology, proposed by the International Rhinitis Management Working Group[4] (see the text for comment)

rhinitis	allergic	seasonal	
		perennial	
	infectious	acute	
		chronic	specific
			non-specific
	other	idiopathic	
		NARES	
		occupational	
		hormonal	
		drug-induced	
		irritants	
		food	
		emotional	
		atrophic	
nasal polyps			
mechanical factors	deviated septum		
	hypertrophic turbinates		
	adenoidal hypertrophy		
	anatomical variants in the ostiomeatal complex		
	foreign bodies		
	choanal atresia		
tumours	benign		
	malignant		
granulomas	Wegener's granulomatosis		
	sarcoid		
	infectious (tuberculosis, leprosy)		
	malignant-midline destructive granuloma		
cerebrospinal rhinorrhoea			

It should be noted that some terms that have been widely used are not mentioned in Table 2.1. The term 'hay fever' was first used by the general public in the 19th century, since the symptoms appeared during the haymaking season. In 1873, the cause was found to be grass pollen rather than hay, while fever was not described as a symptom. Nevertheless, 'hay fever' is still more frequently used than 'pollinosis' or 'pollen allergy'. The term 'seasonal rhinitis' is also used, although, strictly speaking this term would apply also to symptoms occurring every year in the autumn or winter. Again, the clearest nomenclature seems to be one that indicates the specific cause, e.g., 'allergic rhinitis: to grass pollen'.

The terms 'vasomotor rhinitis' and 'non-allergic rhinitis' are both used for idiopathic rhinitis, even though there is no evidence for the existence of a 'vasomotor pathogenesis', and 'non-allergic' is confusing because it excludes only one of many possible other disorders.[8] 'Hyperreactivity' usually indicates non-specific hyperreactivity - in contrast to specific hyperreactivity, or allergy - to non-allergic stimuli, such as cigarette smoke, perfume, rapid changes in temperature, and fog. Hyperreactivity is often seen as characteristic for idiopathic rhinitis. However, by no means all patients with idiopathic rhinitis have a history of hyperreactivity, while many patients with allergic rhinitis are also hyperreactive.[9] Therefore, hyperreactivity should not be seen as a distinct disorder, but rather as a clinical manifestation that may be present in different types of rhinitis.[10]

A special type of non-allergic rhinitis is called 'non-allergic rhinitis with eosinophilia syndrome' (NARES) or 'eosinophilic non-allergic rhinitis' (ENR).[11, 12] These patients are found to have nasal eosinophilia, although they have been diagnosed as having non-allergic rhinitis on the basis of the medical history and skin tests. Identifying patients with ENR may be useful in choosing medication, as nasal corticosteroids have proved highly effective.[13]

'Rhinitis of pregnancy' has long been accepted as a distinct pathologic entity. From the scarce data available, however, it appears that rhinitis attributable solely to pregnancy may not exist as a primary entity.[14] Finally, instead of the term 'drug-induced rhinitis', the term 'rhinitis medicamentosa' is often used; for some this indicates a rhinitis caused by prolonged use of topical vasoconstrictors, while for others it also includes the nasal symptoms that sometimes occur as a side effect of systemic medication.

In the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined), the following definition is given for allergic rhinitis, including hay fever:[15]
- three of the following on a chronic or seasonal basis:
  (a) sneezing
  (b) nasal obstruction
  (c) clear nasal discharge
  (d) watering eyes
  (e) edema of the nasal mucosa.

There are no criteria listed for other chronic nasal disorders, such as chronic upper respiratory tract infection (URTI), deviated septal septum, or nasal polyps. The criteria for allergic rhinitis appear to be inadequate: on the one hand, they are too strict (e.g., house dust mite allergic rhinitis may cause nasal obstruction only); on the other hand,

they are not precise enough (patients with non-allergic rhinitis may show the same symptoms). From a pathophysiologic point of view, inclusion of determination of specific IgE would seem to create more appropriate criteria.

2.3. Pathophysiology

Like allergic asthma, allergic rhinitis is a clinical manifestation of atopy, which is characterized by IgE-mediated allergic responses to common inhalant allergens. These include tree pollen, grass pollen, weed pollen, house dust mites, cockroaches, and mammals, such as cats, dogs, and horses.[4] T and B lymphocytes play a major role in the production of specific IgE antibodies. When allergens reach the nasal mucosa of sensitized individuals, the allergens react with specific IgE antibodies bound to mast cells, causing the mast cells to degranulate. A range of chemical mediators is secreted, each of which produces a different effect. In nasal provocation tests, the immediate symptoms, i.e., sneezing, itching, watery discharge, and nasal congestion, which occur within minutes, are caused mainly by mediators such as histamine, leukotrienes, and prostaglandines. A late-phase reaction, characterized by an influx of activated eosinophils, occurs about 6 to 8 hours after exposure, causing nasal blockage, loss of smell, and hyperreactivity.[4, 16] Unlike provocation tests, natural exposure is often prolonged, causing the acute and late-phase reactions to overlap and making it difficult to distinguish between the two phases.

Although the nature of hereditary factors is obvious, the complex pattern of the relationship has not yet been clarified.[17, 18] The increasing prevalence of hay fever during the last two centuries has given rise to a number of speculations on external factors that may play an important role[18, 19, 20, 21]. There is accumulating evidence for a major role of indoor and outdoor pollution, as well as increased exposure to allergens.[22, 23, 24] It is widely accepted that irritant damage to mucous membranes acts as an aggravating factor in allergic disease. In fact, the historical data relating to hay fever suggest that without chemical damage hay fever would occur very rarely, if at all.[22] It is also likely that exposure to allergens has increased during the last few decades. For instance, energy-conservation measures have included a reduction in the air-exchange rate, leading to an increase in both air humidity and the prevalence of house dust mites.[25] Furthermore, there are findings that support the hypothesis of a 'sensitive' period in the first months of life during which allergen exposure is more likely to prime for an allergy later in life.[26]

When repeated nasal provocations are performed in patients with allergic rhinitis to grass pollen, the number of pollen grains required to elicit a positive response is markedly reduced.[27] This 'priming effect' may cause patients who are allergic to tree pollen to develop marked grass-pollen-induced symptoms, even following exposure to very low pollen counts.

Few studies have focused on the non-allergic types of rhinitis. Most of the terms presented in Table 2.1 refer to the presumed causes and will not be discussed here. For

further information on the pathophysiology of rhinitis, the reader is referred to the literature.[4, 6, 10, 28]

2.4. Epidemiology

Population studies

There are no reliable data on the prevalence of chronic and recurrent nasal symptoms in the general population. This is not surprising, considering that there is a continuum in the frequency and severity of nasal symptoms.[4] Little is known about the prevalence of the different types of nasal pathology, since there are no explicit criteria to distinguish physiologic findings from pathologic findings. Moreover, changing patient behaviour, diagnostic fashion, and research methods may explain much of the variation in the prevalence of rhinitis both between populations and over time. With regard to allergic rhinitis, there is strong evidence that the prevalence is actually increasing.[19, 20]

Of the different types of nasal pathology, allergic rhinitis has most often been the object of study. When comparing epidemiologic data on allergic rhinitis, a distinction must be made between studies dealing exclusively with the presence of sensitization, e.g., by means of skin tests, and other studies in which both the prevalence of nasal symptoms and skin test reactivity are registered.

As regards the prevalence of skin test reactivity, there have been two large studies in the United States in a general population sample; these revealed skin test reactivity to the common aeroallergens in 20% (the NHANES II study; N=16,204) to 34% (the Tucson study; N=3101) of subjects.[29, 30] Peak reactivity occurred during the second and third decade, falling rapidly past age 50. One study found a slightly higher prevalence in males than in females.[29] When present, reactions tended to be multiple, and more frequent among those in the higher socioeconomic strata. In the NHANES II study, prevalence was higher in urban than in rural areas. Because both studies document the prevalence of sensitization, also referred to as 'atopy', which does not necessarily imply clinical symptoms, the prevalence of the different inhalant allergies remains uncertain.

Of more interest are the studies that report both symptoms and skin test reactivity. In a continuation of the Tucson study, patients were asked whether they had 'hay fever or any other allergy that makes your nose runny or snuffy, apart from colds'. Of the patients with completely negative skin tests, 31% affirmed such an 'allergy'; however, the majority of these subjects were probably suffering from non-allergic rhinitis. Of the patients with very strong positive tests, 15% said they did not have allergic rhinitis.[31] In two other studies, the prevalence of allergic rhinitis, based on questionnaires, ranged from 9% (in patients ≥ 15 years old) to 13% (all ages).[32, 33] In a random selection, only two-thirds of those who claimed to suffer from 'allergic rhinitis' displayed positive skin tests.[32] In a study involving adults, the positive predictive value of a history of hay fever was 42% for the presence of serum specific IgE; the positive predictive value of a history of perennial rhinitis was only 27%. Of those patients with a negative history, 15% displayed specific IgE.[34] In Uppsala, 1050 medical students were examined in 10 years:

29% reported allergic symptoms affecting the nose or eyes; of these, 64% had positive skin tests.[35] In a London general practice, 39% of all adults responded to a postal questionnaire: the estimated minimum prevalence of chronic or recurrent nasal symptoms was 24%; of these patients, 3% had seasonal symptoms only, 13% perennial symptoms only, and 8% perennial symptoms with seasonal exacerbations. Samples from subjects with and without symptoms were tested: positive skin tests were found in 63% of the symptomatic subjects, while 34% of subjects without symptoms also displayed positive skin tests.[5] In conclusion, these studies make it clear that skin test reactivity may be present without allergic symptoms, and vice versa.

The problem of discrepancies between the history and in vivo or in vitro tests has never been completely solved. Nevertheless, it appears to be generally accepted that negative tests for the common aeroallergens rule out an allergic cause with an acceptable degree of certainty.[4] However, the presence of positive skin tests or specific IgE without clearly correlated symptoms is more troublesome. Individuals with positive tests but without symptoms have been referred to as 'latent sensitized'. In some cases, this term is probably appropriate: in a prospective study in 114 latent-sensitized school children, 53% developed manifest allergic rhinitis within 4 years.[36]

In addition to these two groups, there is a third group of individuals whose condition is difficult to interpret: those sensitized for an allergen, and with nasal symptoms, but without an obvious relation between the symptoms and exposure to the allergen in question. In the case of perennial allergens, in particular, the medical history is often regarded as unreliable.[37] There are a number of reasons why the patient may be unaware of a relation between exposure to allergens and the occurrence of symptoms. First, if the symptoms are of relatively short duration, causal influences or seasonal variation may not be immediately clear to the patient. This is often a problem, especially in the case of tree pollen allergy, where the exposure may vary considerably from year to year.[38] Second, a late-phase type-I allergic reaction may be dominant, especially in perennial nasal allergy, causing non-acute symptoms or non-specific hyperreactivity.[6, 10] Third, allergens may come from 'hidden sources'. In one study, cat allergens were found in high concentrations in the dust from floors in schools.[39] In another study, house dust mite was found in 99% of homes, and animal allergens in 100%; many homes without pets contained high concentrations of pet allergens.[40] It has been suggested that the difference between the huge dose of allergen needed to provoke immediate symptoms in the least sensitive persons and the tiny amount necessary to induce inflammation, hyperreactivity, and chronic symptoms in highly sensitive patients may be as high as 10^{12}.[37] Fourth, in the presence of non-allergic nasal pathology, or in cases where both seasonal and perennial allergens cause rhinitis in the same patient, the precise relation to exposure may be less clear to the patient. In the absence of a generally accepted 'standard', these problems remain unsolved.

It must be concluded from the above that the prevalence of allergic rhinitis in the general population is still unclear. Nevertheless, it may be roughly estimated at somewhere between 5% and 15%.

The relationship between allergic rhinitis and asthma has been studied: the prevalence of allergic rhinitis was 4 to 6 times greater in individuals with asthma than in

the general population.[33] Asthma is more likely to precede allergic rhinitis than to follow it.[33]

Studies in general practice

The annual period prevalence of patients consulting their general practitioner for 'hay fever' (including other types of allergic rhinitis) has been registered in large morbidity surveys. In the United Kingdom this prevalence increased from 5.1 per 1000 registered patients in 1955 to 10.6 in 1970 and 19.7 in 1981.[41] It is believed that the registered increase represents a real increase, and cannot be accounted for by changes in diagnostic preference.[41] In the Netherlands, prevalence increased from 3.5 in 1967 to about 13 in 1985-1988.[42, 43, 44] A Danish study likewise recorded a prevalence of 13; this same study showed that in urban regions the prevalence rate was more than twice as high as in rural areas.[45]

An interesting finding of the Danish study was that only 20-25% of patients with allergic rhinitis had symptoms at the time they consulted their general practitioner.[45] The rate of consultation for symptomatic allergic rhinitis increased at the start of the tree pollen season (March/April), rose still further at the start of the birch pollen season (April/May), and was at its height during the grass pollen season (mid-May to mid-July). Two-thirds of all consultations for symptomatic allergic rhinitis took place within a period of 10 weeks: from the beginning of May up to mid-July.[46] The same researchers studied the relation between allergic rhinitis and asthma: 17% of the patients with allergic rhinitis also had asthma, while 28% of the patients with asthma also had allergic rhinitis.[47]

The validity of these general practice studies must be questioned: the diagnosis of allergic rhinitis was based on criteria that do not include the assessment of specific IgE, and there was no separate code for non-allergic rhinitis.[48] Therefore, it is likely that many patients with non-allergic rhinitis were coded as 'allergic rhinitis'.

Studies in hospital outpatient departments

In the Netherlands, only 2-4% of patients diagnosed as having 'allergic rhinitis' are referred to a specialist.[43, 49] Presumably, this number is about the same in other countries where patients need a referral from their general practitioner to consult a specialist; these include the United Kingdom, Denmark, Norway, and Finland.[50]

Most publications on outpatients with rhinitis come from university hospitals. In Sweden, 38% of these patients were diagnosed as having allergic rhinitis, 47% vasomotor rhinitis, and 15% other disorders.[9] In the Netherlands, skin test reactivity was assessed for 5 common inhalant allergens in a random sample of patients visiting the outpatient allergy department or the outpatient department of otorhinolaryngology of an academic hospital: 56% showed positive skin test reactivity, 9% a questionable reactivity, and 35% a negative reactivity. Of the patients with a negative reaction to all 5 common inhalant allergens, only 2% showed a positive reaction to an extended panel of 15 allergens.[51]

Selection bias

On the basis of the information presented in the previous sections, it may be concluded that around 10% of all the individuals with allergic rhinitis are known to their general

practitioner, and that about 3% of these patients are referred to a specialist. This process of selection applies to virtually all diseases and is often referred to as the 'iceberg phenomenon'. In the case of the present condition, an even more appropriate representation would be the human body itself: if the body is the whole population, then the individuals with allergic rhinitis are represented by the head, and those known to their general practitioner by the nose; those patients referred to a specialist are represented by no more than a pimple on the nose.

To date, there have been no studies which examined why some patients with chronic or recurrent nasal symptoms visit their doctor, while others refrain from doing so. Nor has any research focused on the general practitioners' reasons for referral. Nevertheless, there is no disguising the fact that some kind of selection is involved in these processes, and that this probably generates patient samples that differ considerably in their composition. Because of this selection bias, it may be inappropriate to extrapolate the results of research in one of these three populations to another. Not only are the predictive values of a diagnostic test likely to differ, because of different prevalences, but also the sensitivity and specificity, as a result of the degree of severity.[52, 53] Therefore, the application of any diagnostic procedure in a certain population should be based on diagnostic studies performed in population samples that were representative for the population in question.

2.5. Diagnostic procedures

Diagnostic studies in general practice

In a MEDLINE search (1980-1993; keyword rhinitis), only one diagnostic study on rhinitis in a primary care setting was found.[54] This study focused on the labels applied to 'rhinitis' by doctors and was part of a community survey among adults. Subjects were asked what label the doctor had given their condition. To exclude patients who never consulted their general practitioner, patients were asked whether they ever consulted their GP with specific complaints about nasal symptoms, without, however, differentiating between acute and chronic nasal symptoms. Moreover, it cannot be ruled out that doctors did diagnose 'rhinitis' but did not mention this term to the patient. Therefore, the authors' conclusion that 'rhinitis', as defined by the authors, was frequently underdiagnosed and misdiagnosed, must be questioned.

In the absence of diagnostic studies performed in a primary care setting, studies carried out in other populations may be useful. However, as noted above, it may be inappropriate to extrapolate the results of such studies to general practice.

Symptoms and signs

Text books and review articles on allergic rhinitis often stress that the medical history is the cornerstone of the diagnosis.[16, 37, 55] Clinical diagnoses are based mainly on a limited number of symptoms: itching, sneezing, discharge, and blockage. It is the context of these symptoms that may help to differentiate between different types of nasal pathology.

Allergic rhinitis should be considered when there appears to be a relation between the exposure to an allergen and the occurrence of symptoms. Consistent obstruction on the same side suggests a polyp, an anatomical abnormality, or, in rare cases, a tumour. However, for the reasons mentioned in section 2.4 (page 16), the medical history is often not all that clear. Well-executed studies on the diagnostic value of the medical history are scarce.[9, 56, 57, 58] Moreover, there are no studies that present the results of regression analysis performed to identify the independent clinical predictors of the different types of nasal pathology.[59] Thus far it is unclear which questions are mandatory, and what the predictive value is of the medical history when it is not accompanied by additional tests.

Physical examination is essential for the diagnosis of anatomical obstructions, nasal polyps, and such rare causes as tumours or foreign bodies. Severe obstructions will cause no diagnostic problem, but there are many people who have a slight septal deviation or a small septal spur or spine. Unfortunately, there are no explicit objective criteria to establish whether an anatomical finding should be seen as a normal variation or as an anatomical abnormality and, in the latter case, whether this is related to the symptoms presented. As regards such findings as the colour and consistency of secretions, and the colour of the mucosa, the same holds true as in the case of the symptoms: there are no reliable studies on the diagnostic value of physical findings for rhinitis.

Skin tests and radioallergosorbent tests

The determination of specific IgE directed against common aeroallergens is now the most important test in the diagnosis of allergic rhinitis. It is carried out by means of skin testing or the assessment of specific IgE in blood serum. For the latter procedure, several methods have been developed, but the radioallergosorbent test (RAST) is seen as the 'gold standard'.[60] Studies have shown that testing with a relatively small number of allergens is capable of detecting the vast majority of inhalant allergies.[51, 61] The allergens should be selected on the basis of their established importance as inhalant allergens in the region.[4, 62]

Allergy skin testing may be performed by the percutaneous route, commonly referred to as 'prick testing' or the intracutaneous route, called 'intradermal testing'. Prick testing is usually preferred, because it is safe, and easy to perform, and the results are highly correlated with clinical disease.[4, 63, 64] In Table 2.2, The characteristics of both tests and those of RASTs are shown in the way they are commonly presented in text books and review articles.[16, 37, 55]

Some remarks with regard to this table are in order. First, the validity of the displayed sensitivities and specificities of the tests may be questioned as they were assessed using different references, while a 'gold standard' is absent. For instance, it is often stated that intradermal tests have a greater sensitivity than skin prick tests.[63] However, it has been shown that in the absence of prick test reactivity, positive intradermal tests do not correlate with either clinical or immunologic evidence of inhalant allergy.[65] In a Dutch multicenter study, a concordance of 83% and 91% was found, as compared with RAST ($\geq$ class 1), and 77% and 86% as compared with clinical history, for intradermal skin test and skin prick test, respectively.[66] In some diagnostic studies, nasal provocation tests have been used as the reference.[56, 57, 67] However, provocation in

the laboratory, which entails the sudden application of a large quantity of allergen, is decidedly not comparable to the natural exposure, which is often prolonged and involves very low concentrations of allergen. Moreover, the results of provocation tests with allergens may be biased, due to non-specific hyperreactivity.[37] In others studies, the diagnoses of an experienced clinician have been used as the reference, without assessing interobserver variation.[9] Another item which influences the test characteristics is the choice of the cut-off point used to define a positive or negative test result. For skin prick tests, mean weal diameters (MWDs) ranging from 2mm to 5.5mm have been advised as the cut-off point.[68] However, even small weals, which measure 1mm to 2mm in diameter and are reproducible, can be taken as positive evidence of immunologic reactivity.[69] It has also been advised to use histamine-equivalent weal sizes (HEWS): the MWD of the weal from the allergen divided by the MWD of the positive control (histamine). In the Dutch multicenter study mentioned above, the optimum HEWS cut-off values were found to be 0.7 for intradermal tests and 0.4 for skin prick tests; however, the correlations with RAST or clinical history did not differ much between HEWS and MWD.[66]

Table 2.2. Comparison of the characteristics of in vitro and in vivo tests for specific IgE (see the text for comment)

test characteristic	RAST	SPT	IDT
sensitivity	+++	+++	++++
specificity	+++	+++	++
costs	+++	+	++
systemic reactions	-	-	±
result immediately available	no	yes	yes
influenced by certain medication	no	yes	yes
influenced by extensive dermatitis	no	yes	yes
experience needed	no	yes	yes

RAST: radioallergosorbent test; SPT: skin prick test; IDT: intradermal test.

Second, the costs of the different tests are somewhat difficult to compare. If we consider only the material needed, RASTs are the most expensive and skin prick tests the cheapest. When the costs of referral to a laboratory or specialist are taken into account, the situation becomes more complex. In the Netherlands, some general practitioners perform skin prick tests themselves; without the need for expensive referrals, the difference in costs between SPTs and RASTs increases still further. However, as the Dutch National Health Service does not reimburse the costs of skin tests performed by the

general practitioner, it is cheaper for him to refer the patient to a laboratory or a specialist. The costs of RASTs may be reduced through the appropriate use of the Phadiatop test, which indicates the presence of specific IgE to one or more of the common inhalant allergens without differentiating between the allergens; if the Phadiatop test is negative, RASTs may no longer be needed, as they will probably be negative as well.[70]

Third, the most impressive disadvantage of skin tests is the small but certain risk of systemic reactions. The American Academy of Allergy and Immunology has detailed information on six fatalities that occurred during skin testing between 1945 and 1984. Five of these patients had asthma, and five were tested for allergens other than inhalant allergens; none of them had hay fever only. All the fatalities occurred during intradermal skin testing.[71] In the United Kingdom, from 1957 to 1986, there was not a single report of anaphylaxis caused by inhalant allergens used as diagnostic skin tests.[72] Therefore, as long as skin prick tests are used with inhalant allergens only, the chance of fatal reactions is probably negligible.

Other reported disadvantages of skin testing are the necessity to withdraw medication that may influence the results,[73] and the need for special knowledge to ensure proper performance and the correct interpretation of the results.[55]

One advantage of skin testing has been suggested, but not yet documented. It concerns the fact that the result is more impressive to the patient, which might be helpful in persuading patients to take measures to contain house dust exposure or to part with their pets.[74]

Despite all these differences, it is generally agreed that in the hands of a well-trained and experienced physician, both skin prick tests and RASTs can be helpful in obtaining an accurate diagnosis of most cases of inhalant allergies.[67, 75] It is often noted that a positive skin test or the demonstration of specific IgE does not necessarily mean that the patient's symptoms are due to an allergy.[4, 37, 55] This warning is based on studies in which skin tests in symptom-free individuals were positive.[5, 31, 34] However, these were population studies, whereas general practitioners will normally perform such tests only in patients who consult their physician because of nasal symptoms. Due to the higher pre-test probability, the likelihood of false-positive results will be lower.[76] Nevertheless, there remains the problem of deciding whether the symptoms are related to the recorded sensitization. It is usually stated that 'the results of these tests must be interpreted appropriately in the light of clinical history and physical examination'.[16, 75, 75] However, it is seldom made explicit how this interpretation should be effected. In one study, involving patients in a department of allergology, a scoring system for the combination of case history and skin tests or RASTs was developed, using nasal provocation as the reference. The medical history was obtained 'according to the routine' and was not documented precisely.[56]

Other diagnostic tests

There are several other tests that may be helpful in the differentiation of the various nasal disorders. First, the total IgE has long been used as the only available laboratory test correlated with atopy. Unfortunately, it does not discriminate very well between atopic

and non-atopic individuals.[37] Blood eosinophilia has been proved to be of no use at all in the diagnosis of nasal allergy.[77] In contrast, nasal eosinophilia may be helpful in differentiating patients with allergic rhinitis from those with non-allergic rhinitis.[77] Neither the total IgE nor nasal eosinophilia indicates the causal allergens, and they are therefore of limited practical value.

Nasal expiratory or inspiratory peak flow, measured by means of a normal peak flow meter, compares well with rhinomanometry.[78] Both techniques, which are mostly regarded research tools, attempt to measure nasal airway resistance. In contrast to asthma, and probably due in part to the absence of muscle tissue in the nose, there is no correlation between nasal airway resistance in histamine provocation tests and nasal symptoms.[79]

Plain X-ray examination of the nose and paranasal sinuses may be helpful if chronic rhinosinusitis is suspected, although its value is limited.[80] Ultrasonography has been suggested as a useful alternative in acute sinusitis,[81, 82] but studies involving patients with chronic nasal symptoms are lacking.

In addition to these tests, there are others that are usually not available for general practitioners. Endoscopy, the examination of the internal nose and throat by means of a flexible fibre-optic endoscope, may be especially useful in detecting sinus pathology, anatomical abnormalities, and small polyps.[4] In one study, fiber-optic rhinolaryngoscopy was performed by general practitioners in patients with chronic nasal symptoms.[83] Because interobserver reliability was not assessed and the results were not compared with those of anterior rhinoscopy, the clinical relevance of this technique in general practice remains uncertain. The costs of the equipment needed were not stated; it is beyond doubt that for most general practitioners these costs will be prohibitive. CT scans or MRI scans may be useful in a few special cases.[4] Nasal provocation tests are seen by some as the gold standard for allergic rhinitis.[84] However, the performance and registration are far from standardized and, as noted above, provocation in the laboratory is not comparable to natural exposure, which is often prolonged, with very low concentrations of allergen.[85] Moreover, when the case history is combined with RAST or skin test results, the provocation test is no longer necessary.[56] For the time being, nasal provocation tests are considered of value only in research situations.[4, 16]

2.6. Treatment

Environmental control measures

As in many other diseases, aggravating factors should be avoided. For allergic rhinitis, this means avoiding exposure to the causal allergens, which may be more difficult for seasonal than for perennial allergens (Table 2.3).[4, 86, 87] Although there is relatively little information available on the efficacy of indoor allergen avoidance measures for allergic rhinitis, there is every reason to believe that they are at least as effective as those for asthma.[87] It must be stressed that after the removal of a pet from the home, it will take months to reduce allergen levels in settled dust to a level found in homes that have

Table 2.3. Environmental control measures[4]

pollen avoidance measures
- monitor pollen forecasts
- avoid high pollen areas
- stay inside house when pollen count is high
- keep windows and doors closed when pollen count is high
- use high efficiency particulate (HEPA) filters in cars
- consider using glasses outside house
house dust mite control measures
the bedroom
- use allergen-impermeable mattress, duvet, and pillow covers on all beds in room
- thoroughly vacuum the mattress, pillows, around the base of the bed, and bedroom floor each week
- remove feather pillows, woollen blankets, and eiderdowns; replace with synthetic ones and wash them weekly at 60°C
- remove carpeting if possible
- wipe all surfaces each week including pelmet tops, window sills, and tops of cupboards with a damp cloth
- have light washable cotton curtains and wash frequently
- use a vacuum cleaner with disposable paper bags and a filter; wear a mask whilst cleaning or preferably get someone else to do it
other rooms
- particular attention should be directed at removal of dust from upholstered furniture; vacuum clean at least twice a week, including headrests, arms and edges of seats
children
- affected children should be out of the room when cleaning is being done and should not return for two hours
- children should not sleep with furry toys in their beds; toys should be vacuumed, tumble-dried or put in the deep-freeze (-20°C) overnight to reduce mites.
pets
- remove pets (if possible); do not replace animal
- no pets in the bedroom at any time; allergic families should avoid having furred or feathered pets since allergic sensitivity to them may develop in time, even if not immediately apparent
- wash pet regularly

never housed a pet.[88] The airborne allergen levels of house dust mite are about ten times higher during sleep than during usual domestic life.[89] This explains the effectiveness of mattress, duvet, and pillow covers that are impermeable to house dust mite allergen.[90] Acaricides (chemicals designed to kill mites) may be effective;[91] however, no safety studies on long-term exposure have yet been undertaken, and application to fabrics with which children are likely to have prolonged close contact is not recommended.[86] Electrostatic precipitators and high-efficiency particle-arresting (HEPA) filters are of limited value,[92] as house dust mite allergens are relatively large and tend to settle rapidly after disturbance.[93] In the case of both allergic and non-allergic rhinitis, non-specific irritants such as cigarette smoke and perfume should be avoided, and indoor ventilation should be accurate.[23, 86]

Medical treatment

A selection can be made from the available medication for allergic rhinitis, on the basis of the profile of the patient's symptoms, and the characteristics of the medication (Table 2.4). The onset of therapeutic effect may play an important role in this choice. Antihistamines take effect immediately, except for astemizole, whose effect may become clear only after several days;[94] topical corticosteroids often take 1 or 2 weeks to reach their maximum effect. The newer, nonsedating antihistamines are often preferred, because of the relatively low incidence of sedation as a side effect.[93, 95] There are no clinical studies that indicate a clinically relevant difference in efficacy or side effects between the various topical corticosteroids.[95] Local irritation from a topical corticosteroid occurs in 10% of patients; no atrophy or systemic side effects were detected in long-term clinical trials.[93, 95, 95] There is no evidence that a single depot injection for allergic rhinitis is superior to other treatments; because of the possible risk of adrenal suppression, it is not recommended.[93, 95] Sodium cromoglycate is a prophylactic drug without side effects; however, it should be administered before the onset of symptoms.[4] In patients with severe symptoms, the combination of a topical corticosteroid with an antihistamine is often more effective than either one used separately.[96] Finally, the patient's preference, based on proper information, will be decisive.

Table 2.4. Comparative effect of medication for allergic rhinitis[4]

medication	itching, sneezing	discharge	blockage
sodium cromoglycate	+	+	±
oral antihistamines	+++	++	±
ipratropium bromide	-	+++	-
topical corticosteroids	+++	+++	++
oral corticosteroids	+++	+++	+++

Patients with rhinitis medicamentosa should stop taking local vasoconstrictors; however, this is always difficult because of the rebound effect. Systemic corticosteroid therapy (25 mg prednisone daily for 7-14 days) may be helpful; during the same period, therapy with a topical corticosteroid can be started and then continued after the oral corticosteroid has been stopped.[97]

Systemic corticosteroid therapy may also be effective in obstructing nasal polyps.[97] However, topical corticosteroids are preferred as the initial therapy.[98]

Little is known about the efficacy of antibiotics in chronic rhinosinusitis.[99] The combination of an antibiotic with a topical corticosteroid is believed to be more appropriate than an antibiotic alone.[100] It is not clear whether topical corticosteroids alone are also effective.[7]

Vasomotor rhinitis may respond to a topical corticosteroid, especially in the presence of nasal eosinophilia. As a rule, topical vasoconstrictors should not be used for longer than 7 days.[4] Oral vasoconstrictors have been shown to improve nasal patency, but only in doses which appear to cause side effects.[101] Encouraging results have been obtained with the anticholinergic drug ipratropium administered as a nasal aerosol, especially for rhinorrhoea.[7]

Immunotherapy

Specific immunotherapy for allergic rhinitis was first documented in 1911.[102] Double blind, placebo-controlled studies have shown its efficacy in the case of grass, tree, and weed pollen, and house dust mite.[103, 104] The treatment provides relief, but is seldom curative. It is probably effective only when a correct selection of patients is made, standardized allergen extracts are used, and correct doses are given continuously for 3 to 5 years.[105] In one study, in which short courses of pre-seasonal injections were given, the clinical efficacy was lower than for topical corticosteroids.[105] Surprisingly, there are no other comparative studies which relate the effect of immunotherapy to topical corticosteroids. Moreover, little is known about the long-term effects. One study showed a steady symptom score 6 years after the termination of therapy; however, there was no comparison with the spontaneous course in patients who were not receiving immunotherapy.[106] In a recent position paper, it was stated that immunotherapy reduces the development of rhinitis into asthma.[103] However, there are no studies that support this statement. Moreover, there is some evidence that asthma is more likely to precede allergic rhinitis than to follow it.[33]

In the United Kingdom, between 1957 and 1986, 26 patients died as a result of anaphylaxis induced by desensitising agents. This occurred mainly in patients with asthma; only one patient was being treated for hay fever.[72] The American Academy of Allergy and Immunology has obtained detailed information on 24 fatalities that occurred during immunotherapy between 1945 and 1984: the majority of these patients had asthma or cardiovascular disease; no detailed information on another 16 cases could be obtained.[71] In the United States, 7 to 10 million allergen injections are administered yearly, so that the risk of a fatal reaction is extremely low. However, no matter what precautions are taken, systemic reactions will inevitably occur at some time in some patients. Therefore, personnel should be trained to cope with such reactions, and the

necessary equipment and reagents should be available.[107]

Operative therapy

In the case of anatomical abnormalities, operative correction may be considered. However, it has been shown that many patients with anatomical obstructions also display allergic or non-allergic rhinitis. Therefore, therapy for rhinitis should be given first. Even when medication does not help, a conservative waiting policy would seem to be an appropriate approach, since nasal obstruction tends to disappear over time.[108] Sinus surgery may be helpful in the case of chronic rhinosinusitis that does not respond to medication.[109] If polyps do not respond to topical corticosteroids administered during one month, they may be removed surgically; long-term post-operative treatment with a topical corticosteroid reduces the frequency of recurrence.[98]

Homoeopathy

In a detailed study, the literature was reviewed on controlled trials using homoeopathy published between 1966 and 1990.[110] There were four trials on hay fever, three of which displayed reasonable to good methodology. All three indicated that homoeopathy had produced a positive result. However, it was stressed that the results of the review may have been complicated by publication bias, especially on such a controversial subject.[110]

Patient education

As in other chronic diseases, patient education is important as a means of enhancing the patient's coping strategies. It is important that the patient is aware of the cause of his disorder, the aggravating and the alleviating factors, and the mode of therapy. Written instructions for environmental control measures and for the use of medication should be provided. If necessary, the correct use of medication should be verified.[4] Finally, it may be beneficial for both the patient and the physician to know that, in addition to local symptoms of rhinoconjunctivitis, patients may experience impairment of the quality of life through systemic symptoms, sleep disturbances, practical problems, activity limitations, and emotional problems.[111]

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Chapter 3

Outline of the study

3.1. Introduction

In this chapter, the general methodology of the study is presented. Considerations that led to the basic design of the study are given, as well as the results of a pilot study that gave rise to certain modifications to the methods. Details of the study population are also given. Some parts of this chapter are repeated in one or more of the following chapters. Thus, the reader may choose to read a single chapter without having to refer back to this chapter.

3.2. Selection of patients

Inclusion and exclusion criteria
The intention was to include a group of patients who reflected as closely as possible the broad spectrum of clinical presentations of chronic and recurrent nasal symptoms in a primary care setting. At the same time it was the intention to include patients who were likely to suffer from any nasal disorder except for common colds. Therefore, both indicators of specific causes and time criteria were incorporated into the inclusion criteria. In the absence of scientific information that could act as a guide in the formulation of time criteria, the ICHPPC-II definitions were employed: 'acute' (4 weeks or less), 'subacute' (4 weeks to 6 months), and 'chronic' (6 months or more).[1] This resulted in the criteria given below. In view of seasonal influences, the selection of patients was performed continuously during exactly one year, between March 1, 1990 and March 1, 1991. The study protocol was approved by the Ethics Committee of the Medical School of Leiden University.

Inclusion criteria:
- 12 years of age or older
- and reason for the encounter:
  - a stuffy nose
  - a runny nose
  - an itchy nose
  - or sneezing
- and symptoms which are:
  - continuous for more than 4 weeks
  - intermittent for more than 6 months
  - seasonal
  - or related to a specific place or contact.

Exclusion criteria:
- linguistic problems
- the patient declines to give informed consent
- or the patient is reluctant to discontinue medication which may influence skin tests.

The reason for the encounter was defined as 'the agreed statement of the reason(s) why a person enters the health care system, representing the demand for care by that person'.[2]

It was stressed that these criteria were to be strictly adhered to by the general practitioners, without regard for the presence or absence of certain types of nasal pathology. The presence of other diseases was not an exclusion criterion. For instance, allergic asthma could be recorded, provided the reason for the encounter were the nasal symptoms. Patients whom the general practitioner knew to be suffering from some type of nasal pathology were also eligible. However, if their reason for the encounter was a repeat prescription only, and they did not consult their general practitioner for nasal symptoms, then they did not meet the inclusion criteria.

Any medication that might influence skin testing was to be withheld for the appropriate period of time.[3] This included: antihistamines (1 week; but astemizole 6 weeks); oral $beta_2$-adrenostimulants (1 day); xanthin preparations (1-2 days); topical corticosteroids applied on the inside of the forearm (3 weeks).

Number of patients to be included

For this diagnostic study, it was decided that as many patients as possible should be included, using the researcher's availability as constraint. It was estimated that the researcher could visit and examine no more than six patients per day. As he was available 3 days a week, this meant a maximum of 18 patients per week (or $\pm$ 70 per month), at the height of the season. According to a Dutch morbidity survey, there is an annual period prevalence of 13.1 for patients consulting for 'hay fever' and other nasal allergies.[4] This would mean about 30 patients per year in a standard practice with 2350 registered patients. On the basis of previous experience, it was estimated that half of these patients consulted their general practitioner in May or June. Again from previous experience, it was estimated that about the same number of patients would consult their general practitioner annually because of non-allergic chronic or recurrent nasal symptoms. This led to the conclusion that in a standard practice some 60 patients would be seen annually, 10 of them in May and another 10 in June. Taking into account the researcher's availability, this would mean a maximum of 7 participating practices. However, experience has shown that the number of patients included in studies always lags behind the number that might be expected on the basis of the morbidity surveys. Moreover, the estimates were far from reliable. Therefore, to be on the safe side, the estimated number of practices needed was tripled to 20. A monthly lower and upper limit of the patients to be included was planned, and this was to serve as a point of reference.

General practitioners

For the selection of the general practitioners who would be asked to participate, a number of points were taken into consideration. First, although it is not entirely clear whether there is a connection between the prevalence of allergic rhinitis and urban or rural residence,[5, 6] we chose to include urban practices as well as rural ones. Second, because all patients were to be examined by a single researcher, the practices had to be situated within reasonable reach. Third, to ensue that the general practitioners were not overloaded with scientific research, no general practitioners were approached who were known to be participating in other research. Finally, the researcher selected a number of general practitioners whom he knew personally and who were believed to be eager to

participate.[7]

Taking into account that a number of general practitioners would drop out, a total of 31 general practitioners in 24 practices were asked to participate. Two months after the start of the study, six general practitioners in five practices had not included a single patient, apparently due to personal circumstances of the general practitioners; for this reason they were excluded from further participation.

Encouragement of the general practitioners and the patients

In order to include as many eligible patients as possible, participation in the study was made attractive for both the general practitioners and the patients.[8]

To enlist the cooperation of the general practitioner, it was considered important to ensure that participation would take hardly any extra time and would not interfere with normal practice procedures. Both these requirements were met: first, the general practitioners needed only a few minutes to include a patient, while the researcher performed all the examinations himself. Second, as soon as the patient had been examined by the researcher, the results that were immediately clear were reported to the general practitioner, who remained responsible for further management. In addition, the general practitioners were given a small financial bonus for each patient, which was less than the cost of a single consultation (DFl 20).

To remind the general practitioners of their part in the study, a desk standard displaying the inclusion criteria was supplied. Moreover, a newsletter was sent every two months, showing not only the total number of patients included, but also the number of patients per practice. For this purpose, the practices were coded and the general practitioners were told only their own code. Finally, as the researcher usually visited and examined the patients in the office of their general practitioner, there was regular personal contact between the researcher and the general practitioners.

From the very start, patients were willing to cooperate, even though they had to make another appointment for the examination, which took about one hour. Many expressed pleasure at being the object of so much attention, and most of them were eager to hear the results of all the tests that had been done. Moreover, participation was free of charge.

3.3. Collection of clinical and paraclinical data

Diagnostic information can be divided into clinical data, i.e., symptoms and signs, and paraclinical data, such as laboratory tests, skin tests, and other additional tests.[9] The complete set of information collected from each patient is presented in Appendix 2. Further considerations on these topics are presented in Chapter 4 and Chapters 6 to 10. Here, a few additional remarks will suffice.

When this study was first designed, it was suggested that the participating general practitioners should collect all the data. However, once a clear insight had been gained into the resulting workload, this was considered impossible. Therefore, it was decided

that the principal researcher (M.C.), who is himself a general practitioner, would visit and examine every patient. An additional advantage of this design was the improved reliability, as all tests would be performed by a single person, who had received special training for this study.

As will be clear from Appendix 2, the questionnaire was very detailed. This was a result of combining the items proposed in the literature[9, 10, 11] with additional items from the questionnaire used at the Department of ENT diseases of the Academic Hospital Leiden, and the questionnaire in use at the Department of Allergology of the Academic Hospital Rotterdam.

In an effort to reflect as closely as possible the practical situation in primary health care, only those tests were selected which would fit into the routine of general practice and could be carried out by general practitioners.[12] Therefore, such tests as the basophil histamine-release test and nasal provocation tests were not performed. For the skin prick tests, two types of tests were available: first, the commonly used 'wet' test, which is a prick with a special disposable lancet through a drop of a standardized allergen extract placed on the surface of the skin, and second, the 'dry' Phazet skin prick test, which consists of a prick with an allergen-coated lancet; the amount of allergen on the tip of the lancet is standardized.[13, 14] For reasons of convenience, the Phazet test was chosen. Moreover, with this test there is no danger of contaminating the site of one test with traces of allergen extract from another test.

At the time, it could not be foreseen that in 1991 the Phazet skin prick test would be withdrawn from the market. This was done for commercial reasons, since it is much more expensive than the 'wet' skin tests (information from the manufacturer). Nevertheless, the results of this study are also valid for other skin prick tests provided standardized allergen preparations are used.[14, 15]

3.4. Reference diagnoses

Classification of nasal pathology

There is no generally accepted system for the classification of nasal pathology. The use of different terms for the same disease and the same term for different diseases has made reports on nasal disorders confusing to read.[16] For the present study, the simple classification proposed by Mygind, et al. was adopted.[16] With a few adaptations, it comprised the following 8 categories: 'allergic rhinitis' (divided into 14 different allergies), 'vasomotor rhinitis', 'infectious rhinitis', 'rhinitis medicamentosa', 'nasal polyps', 'anatomical obstructions', 'other diseases', and 'non-specific hyperreactivity'. The following annotations were attached to these terms.[16]

- Allergic rhinitis is an IgE-mediated rhinitis.
- Vasomotor rhinitis is a chronic non-purulent rhinitis of unknown aetiology, often referred to as 'non-allergic rhinitis'.
- Infectious rhinitis is a purulent rhinitis.
- An anatomical obstruction is a septal deviation, a septal spine or spur, or a hypertrophic turbinate, provided it is assumed to cause the symptoms.
- Non-specific hyperreactivity is the occurrence of nasal symptoms on contact with such non-allergic stimuli as cigarette smoke and fog; it is not a distinct disorder, but a clinical manifestation that may be present in any type of rhinitis.

The definitions used in this classification were not precise enough to determine which of the disorders were present in each of the patients under study. Indeed, this 'classification' did not meet the requirements of a proper classification or taxonomy.[17] Although the terms were accepted as a useful nomenclature, their definitions were considered insufficient to obtain the reference diagnoses needed for this diagnostic study.

Unfortunately, a gold standard, defined as a generally accepted reference test that indicates the true presence or absence of disease, seldom exists. Although this problem may be especially troubling in allergic diseases, it is also common in other medical fields.[18] In the literature, alternative methodological approaches have been documented for assessing diagnostic accuracy in the absence of a 'gold standard'.[18]

On the basis of the literature and discussions with experts in the field of ENT diseases and allergology, it appeared that the lack of gold standards for the different types of nasal pathology was generally agreed on. Nevertheless, in diagnostic as well as therapeutic studies on allergic rhinitis, it was considered acceptable for diagnoses to be made by a single experienced clinician.[19, 20] This is based on the fact that the diagnosis of this disorder can usually be agreed on when history, physical examination, and radioallergosorbent test (RAST) or skin prick test (SPT) results are combined.[21] However, in the case of unclear or contradictory findings, the situation is more complex. Often these 'uncertain' cases are excluded from participation.[20] In the present study, however, it was our intention to study patients who reflected as closely as possible the broad spectrum of clinical presentations of chronic or recurrent nasal symptoms in a primary care setting, whereby many patients display different types of nasal pathology at one and the same time.

'Consensus diagnoses'

Although in the literature the clinical diagnoses of a single experienced clinician are often used as reference diagnoses,[19, 20, 22, 23] we preferred diagnoses provided by several experts by means of a consensus method. Of the various consensus methods used, Delphi has the advantage of giving all the participants an equal opportunity to express their opinion.[24] For application in the present study, a modified Delphi method was developed during a pilot study, on the assumption that acceptable reference diagnoses can be obtained by presenting to experienced clinicians as much clinical and paraclinical data as possible; the clinicians then try to reach consensus on the presence or absence of a disease in each patient. For the selection of the clinicians, it was considered important to include not only expert opinion from the specialties concerned, i.e., otorhinolaryngology and allergology, but also expert opinion from general practice, as specialists in the Netherlands deal only with referred populations.[25, 26] The general practitioner who took part in the consensus procedure was not the researcher himself, because the latter was not blind for the diagnoses of the other experts. All experts were attached to a university. They received a small financial compensation (DFl 3) per patient, roughly the price of a

cup of coffee.

The experts were asked to give their opinion on the presence of each of the nasal disorders in each patient. For this purpose, a 'list of diagnoses' was drawn up (Appendix 3), on the basis of the classification proposed by Mygind, et al.[16] Further details on the consensus procedure are discussed in Chapter 5.

3.5. Pilot study

The pilot study consisted of two parts. First, ten patients completed the entire diagnostic procedure. In some cases, the patient had difficulty in completing the questionnaire, and later, during the real study, it became clear that some patients were illiterate. Where necessary, the researcher read out the questions and then filled in the answers. No other problems presented themselves.

Second, artificial data on 20 patients were presented to the experts, who performed two rounds of the consensus procedure. For this second part of the pilot study, four experts had been selected: an allergologist, an ENT specialist, and two general practitioners. Although it would have been possible to include more experts, in order to obtain diagnoses based on a wider variety of expert opinion, this was not considered feasible, due to the enormous workload each of the experts was given. As it was, the pilot study took 6 months, due to a number of problems. One of the experts, a general practitioner, withdrew from the study because of the workload. After consulting with the remaining three experts, it was decided to continue with the chosen methodology, after certain adaptations designed to simplify the procedure. These adaptations consisted in shortening and rearranging of the list of diagnoses, balancing the advantages of a simpler list against the clinical relevance of more detailed diagnoses. For instance, there was no longer any distinction made between the different types of anatomical obstructions, and eosinophilic non-allergic rhinitis was no longer registered separately. The final list appears in Appendix 3.

It was decided not to include another general practitioner, because he would not have been involved in the study from the start and would need extra time to work up the subject. Moreover, the contribution of a general practitioner's point of view had already been secured. Now that there were three experts instead of four, the criteria on whether or not consensus had been reached, had to be adjusted. When these new criteria were applied to the judgments in the pilot study, the results were virtually the same as those following the previous criteria. The final criteria are presented in detail in Chapter 5.

3.6. Study procedures

Collection of data from the patients

From March 1, 1990 to March 1, 1991, 376 consecutive patients were considered eligible by the general practitioners; they were handed a letter with information on the study (Appendix 1). As soon as a patient was included, certain demographic data were registered, as well as information from the medical history concerning nasal symptoms, which was already known to the general practitioner. Next, the patient was asked to wait while the 'doctor's assistant' - who may be seen as a combination of the British practice nurse and practice assistant - called the researcher by means of a radiophone. An appointment was made and the researcher visited and examined the patient within a few days of inclusion (median: 4 days). If there was enough room in the office of the general practitioner, the examination was performed there. Otherwise, the patient was visited at home.

The researcher travelled from patient to patient by car, carrying all the necessary equipment in two bags. On arrival, he checked to see that the patient met the inclusion criteria. Then the patient was asked to fill in the questionnaire, while the researcher got out the equipment. When the patient had filled in the questionnaire, anterior rhinoscopy was performed with the aid of a nasal speculum and using a head lamp after, if necessary, application of a local vasoconstrictor (xylometazoline). Using a cotton swab, a nasal smear was made; the secretions were spread into a thin layer on a glass slide and allowed to dry. Next, ultrasonography of the maxillary sinuses was performed, by means of portable ultrasonography equipment. A venous blood sample was then taken. Finally, skin prick tests were performed, and a timer was set at 15 minutes. While waiting for the skin test results, the researcher checked the questionnaire for missing or inconsistent answers. As soon as the timer went off, the weals of the skin tests were outlined and transferred to paper by means of transparent tape. The results which were immediately clear were reported to the patient's general practitioner in a letter which was handed to the patient. The patient was asked to contact his general practitioner, who would decide on further management. The whole examination usually lasted about one hour, not including travel time.

Although the chance of anaphylaxis from skin prick tests with inhalant allergens is remote, the researcher always carried an emergency set, which included epinephrine. No systemic reactions occurred.

On the days on which one or more patients were examined, the researcher went to the laboratory of the Academic Hospital Leiden in the evening, to centrifuge the blood; the serum was deep-frozen within 24 hours of collection. Later the nasal smears were stained by the May-Grünwald-Giemsa method, and assessed as reported in detail in Chapter 9.

Each serum sample was divided into three samples, for purposes of the total IgE, the Phadiatop test and a number of radioallergosorbent tests. Details on the assessment of these tests are presented in Chapters 4 and 8.

Performance of the consensus procedure

First, all the information obtained from the patients was rendered anonymous. For each patient, the complete set of information (see Appendix 2) was copied three times, once for each expert. In the first round of the consensus procedure, the experts were asked to give their opinion on the presence of each of the nasal disorders in each patient, on the basis of all the available information. Their judgment was given on a five-point scale (see Appendix 3). The patients were presented in random order. In the second round, the experts were asked to re-judge a selection of the diagnoses on which they had not reached consensus. These two rounds were performed anonymously. For the third and final round, the experts and the researcher met to discuss the remaining discrepancies. Details on this procedure and the results are presented in Chapter 5. The experts were able to judge no more than six patients an hour. The whole consensus procedure took each expert about 80 to 100 hours, over a period of one year.

Statistical analysis

The data were entered in a database by secretaries, using SPSS Data-Entry. Lists of the data were printed and checked for outliers. Then 5% of the data were re-entered by the researcher, which revealed incorrect data in 0.3% of the numbers; this was regarded as acceptable.

Various methods of statistical analysis were used, which will be discussed in the following chapters.

3.7. Study population

A total of 25 general practitioners in 19 general practices took part in the selection of the patients. The practices were situated in urban as well as rural areas in the west of the Netherlands. The registered patient population of these practices was approximately 47,250; of these, 40,350 were 12 years of age or older.

As noted above, every two months the general practitioners were sent a newsletter, which showed by means of a figure the upper and lower limits of the planned number of patients included, together with the actual number of patients included. After 12 months, 365 patients were included in the study (Figure 3.1).

Not all the general practitioners contributed to this result to the same extent. Taking into account the number of registered patients per practice, the number of patients included varied from 2.6 per 1000 to 17.3 per 1000 registered patients (median 7.5). However, these numbers have not been corrected for age.

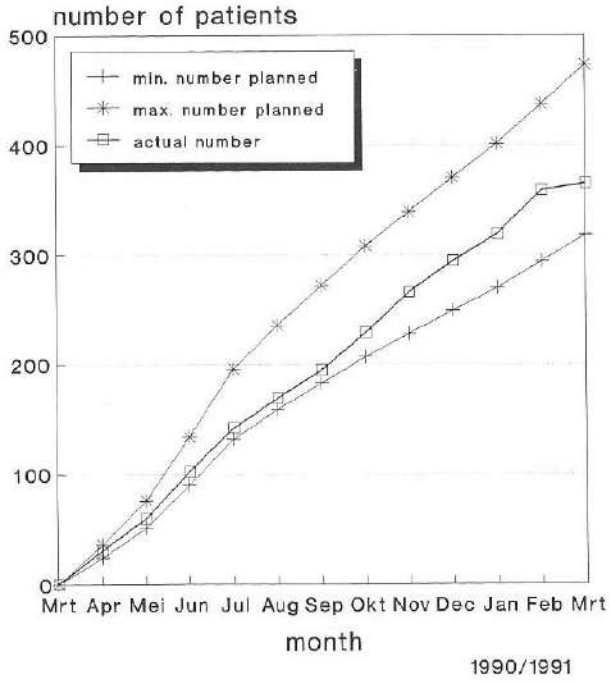

Figure 3.1. Planned number and actual number of patients included.

Of 376 consecutively enlisted patients, 11 were excluded on the following grounds: linguistic problems (n=2), inability to obtain informed consent (n=6), and reluctance to discontinue medication which might have influenced skin prick tests (n=3). A total of 365 patients were ultimately included in the study, representing 9.0 episodes per year of chronic or recurrent nasal symptoms in 1000 patients aged 12 or over. The mean age was 34 (range 12-83); 41 patients (11%) were over 50 years of age. There were 152 men (42%) and 213 women.

The degree of urbanization was recorded as follows: 21% of the patients were rural residents, 45% lived in small towns (up to 100.000 inhabitants), and 34% came from the city of Leiden, which has a population of over 100.000 citizens and is a large city by Dutch standards.

The presence of the main symptoms is presented in Table 3.1. When asked which symptom was experienced as the most annoying, 60% indicated the stuffiness. The majority of the patients (264; 72%) had had such symptoms for more than two years.

Table 3.1. Main symptoms in 365 patients with chronic or recurrent nasal symptoms

symptom	number of patients (%)
stuffy nose	328 (90)
runny nose	240 (66)
itchy nose	194 (53)
sneezing	281 (77)
perennial symptoms only	143 (39)
perennial symptoms and seasonal exacerbation	97 (27)
seasonal symptoms only	88 (24)
none of the above*	28 (8)
missing answers	9 (2)
all patients with seasonal symptoms	185 (51)
spring	88 (24)
summer	85 (23)
autumn	52 (14)
winter	73 (20)

* Patients with symptoms that lasted less than one year.

This study was not intended to explore aspects of quality of life. Nevertheless, to obtain a rough idea on the perceived annoyance and the hindrance experienced in day-to-day life, the patients were asked to indicate these items on a three-point scale (Table 3.2).

Table 3.2. Degree of annoyance and hindrance in day-to-day activities experienced by 365 patients with chronic or recurrent nasal symptoms

annoyance and hindrance	number of patients (%)
- little annoyance	18 (5)
- moderate annoyance	157 (43)
- much annoyance	190 (52)
- I can do everything as usual	232 (64)
- I am hindered	125 (34)
- I cannot carry out my usual activities	8 (2)

Of a total of 365 patients, 185 (51%) reported that they had previously been examined by a physician because of their nasal symptoms. In addition to the physical examination, additional tests had often been performed (Table 3.3).

Table 3.3. Previous examinations and additional tests reported by 365 patients with chronic or recurrent nasal symptoms

	number of patients (%)
examining physician:	
- general practitioner	132 (36)
- ENT-specialist	95 (26)
- allergologist	18 (5)
- paediatrician	3 (1)
- another physician	10 (3)
additional test:	
- skin tests	76 (21)
- X-rays	58 (16)
- blood tests	47 (13)
- echography	4 (1)

Table 3.4. Previous diagnoses reported by 365 patients with chronic or recurrent nasal symptoms

diagnosis	number of patients (%)
hay fever or allergic rhinitis	109 (30)
recurrent sinusitis	81 (22)
nasal polyps	21 (6)
asthma (allergic and non-allergic)	21 (6)
allergic asthma	14 (4)
chronic bronchitis	25 (7)
recurrent middle ear infections	21 (6)
allergic eczema	26 (7)
any other allergic disease	21 (6)

Only 104 patients (29%) reported that this previous examination had revealed the cause of their symptoms. Still, even more patients reported that they had been given one or more diagnoses (Table 3.4). To obtain a rough idea of the therapy previously given to these patients, self-reported therapy and the perceived effect were registered (Table 3.5). For ease of registration, no further specification of the type of medication was included.

Table 3.5. Previous therapy and effect reported by 365 patients with chronic or recurrent nasal symptoms

therapy	number of patients (%)	reported effect: none	moderate	good
nose drops	117 (32)	16	76	25
nasal spray	155 (42)	36	77	42
tablets	68 (19)	11	26	31
antibiotics	81 (22)	10	31	40
injections	25 (7)	9	7	9
homoeopathy	29 (8)	11	12	6
operation	48 (13)	15	16	17

3.8. Presentation of the results

As noted in the Introduction, the main goal of this study was to assess the diagnostic value of the medical history, the physical examination, and additional tests that can be carried out by the general practitioner for the different types of nasal pathology; these results are presented in Chapters 6 to 10. In order to assess the diagnostic values, reference diagnoses were first obtained by means of a modified Delphi consensus method; this is presented in Chapter 5. Before addressing the methodology and the results of the consensus procedure, another item will be discussed, namely the relation between the Phadiatop test and radioallergosorbent tests (Chapter 4). The reference diagnoses were not required to study this relation.

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Chapter 4

The Phadiatop® test compared with RAST, with the CAP system; proposal for a third Phadiatop outcome: 'inconclusive'

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Abstract

In 19 general practices, blood samples were obtained from 361 patients aged 12 years or older with chronic nasal symptoms. The Phadiatop® test and a panel of RASTs to common inhalant allergens were performed on all sera with the recently introduced Pharmacia CAP system. The RAST panel was accepted as the standard. The sensitivity of the Phadiatop was 94% (95% confidence interval (CI): 89-97%), the specificity 98% (95% CI: 95-99%), the positive predictive value 97% (95% CI: 94-99%), and the negative predictive value 95% (95% CI: 91-98%). It is noteworthy that these values are very similar to those found in hospital outpatient departments. It was possible to reduce further the small percentage of false outcomes by replacing the cutoff point of the Phadiatop ratio of 1.00 by the two cutoff points 0.75 and 1.15. This resulted in three possible outcomes: a highly predictive positive outcome, a highly predictive negative outcome, and an 'inconclusive' outcome. Alternatively, the cutoff point of 1.00 may be maintained while attaching the annotation 'borderline' to all positive or negative Phadiatop outcomes where the Phadiatop ratio is between 0.75 and 1.15. By this simple method, physicians are alerted to the possibility of a false outcome; on the basis of the case history and other clinical findings, they can then decide whether further testing should be done.

Introduction

The Phadiatop® test was introduced a few years ago as a single test for specific IgE against common inhalant allergens (21). Although widely used, the test has not been evaluated in general practice patients with chronic nasal symptoms. In the Netherlands, only 2-4% of allergic rhinitis patients who consult their general practitioner are referred to a specialist (9, 18). The selection that occurs in this referral process may generate patient samples that differ considerably from those found in general practice. Because of this referral bias, it may be inappropriate to extrapolate the results of research in hospital outpatient departments to general practice. Not only are the predictive values of a diagnostic test likely to differ, because of other prevalences, but also the sensitivity and specificity, as a result of the type of allergy or degree of severity (16, 23, 25).

The result of the Phadiatop test is expressed as a ratio, namely, the ratio of the percent binding of the patient serum to the percent binding of a reference serum. If the ratio is higher than 1.00, it is current practice to call the outcome positive. If the ratio is 1.00 or below, the outcome is considered to be negative (5). As is always the case when a variable measured on an interval scale is converted into a dichotomous outcome, some information is lost. For instance, the nearer the ratio is to 1.00, the higher the likelihood of a false-negative or a false-positive outcome. To reduce this problem, we can define three ranges of Phadiatop ratio outcomes in such a way that the upper and lower ranges give highly predictive positive or negative outcomes. This leaves a middle range that gives an inconclusive outcome for the Phadiatop. As this method of reducing the number of false outcomes of the Phadiatop has not previously been discussed in the literature, we

investigated this issue.

A new laboratory method has recently been introduced, the Pharmacia CAP system, which can be used for the radioallergosorbent test (RAST), the Phadiatop test, or determination of the total IgE (7). It consists of a new type of solid-phase radioimmunoassay or enzyme immunoassay calibrated against the World Health Organization (WHO) standard for IgE. The solid phase as used in the CAP system has a higher binding capacity than the Phadebas paper disk, resulting in a higher sensitivity (26). This CAP system has been investigated several times for RAST (3, 7, 14, 15, 19, 22, 26, 31), but only once for Phadiatop (6). No study has yet been published that compares Phadiatop with a RAST panel by means of the CAP system.

The aim of this study was to compare Phadiatop with a RAST panel in general practice patients with chronic nasal symptoms, with the Pharmacia CAP system. Our research questions were the following:

1. What are the sensitivity, specificity, and predictive values (PV+ and PV-) of Phadiatop for the presence of specific IgE, a RAST panel to common inhalant allergens being used as the standard?
2. Is it possible to reduce the number of false outcomes of Phadiatop by introducing a third outcome - 'inconclusive' - in addition to positive and negative?

Material and methods

Practices

A total of 25 general practitioners in 19 general practices took part in the selection of patients. The practices were situated in the western Netherlands in urban as well as rural areas. The registered patient population of these practices was approximately 47,250.

Patients

The patients were selected between March 1, 1990 and March 1, 1991 according to the following inclusion criteria. They were 12 years or older and consulted their general practitioner because of a stuffy, runny, or itchy nose, or sneezing. These symptoms had continued for more than 4 weeks, had occurred intermittently for more than 6 months, were seasonal, or were related to a specific place or contact. Eleven patients were excluded on grounds put forward by the general practitioner; these included linguistic problems and inability to obtain informed consent.

A total of 365 consecutive patients who met the inclusion criteria were enroled in the study. A venous blood sample was taken. The blood sample was centrifuged, and the serum deep-frozen within 24 h of collection. In four cases no blood could be obtained: the venipuncture failed three times, and one patient refused to give a blood sample, despite earlier consent. The data in this paper concern the remaining 361 patients. The mean age was 34 years (range 12-83); 41 patients were older than 50 years. There were 152 men (42%) and 209 women.

Laboratory tests

Separate serum samples of each blood sample were prepared and coded for RAST and Phadiatop. The tests were performed 'blindly' in runs of at least 80 sera. All sera were tested with the Pharmacia CAP system, according to the manufacturer's instructions. The CAP system has been described in detail elsewhere (7). All tests were performed with ^{125}I-radiolabeled antibodies. Phadiatop was expressed as the ratio of the percent binding of the patient serum to the percent binding of a reference serum. The Phadiatop test results were given either a negative outcome (ratio $\leq$ 1.00) or a positive outcome (ratio $>$ 1.00). The RASTs were expressed in kU_A/l and were converted to one of seven classes (classes 0-6) (15).

Table 4.1. RASTs used in this study (codes of manufacturer)

RAST panel used as standard:	
house dust mite:	*Dermatophagoides pteronyssinus* (D1)
grass pollen mixture (Gx1):	*Dactylis glomerata* (G3)
	Festuca pratensis (G4)
	Lolium perenne (G5)
	Phleum pratense (G6)
	Poa pratensis (G8)
tree pollen mixture (Tx9):	*Alnus incana* (T2)
	Betula verrucosa (T3)
	Corylus avellana (T4)
	Quercus alba (T7)
	Salix caprea (T12)
weed pollen mixture (Wx3):	*Artemisia vulgaris* (W6)
	Plantago lanceolata (W9)
	Chenopodium album (W10)
	Solidago virgaurea (W12)
	Urtica dioica (W20)
mould mixture (Mx1):	*Penicillium notatum* (M1)
	Cladosporium herbarum (M2)
	Aspergillus fumigatus (M3)
	Alternaria tenuis (M6)
cat dander (E1)	
dog dander (E5)	
Additional RASTs, not part of standard:	
horse dander (E3)	
guinea pig dander (E6)	
rabbit dander (E82)	

There is often some difficulty in applying the terms sensitivity and specificity to allergy, since there is no way to establish unequivocally the presence or absence of disease (7). In this paper the sensitivity and specificity of Phadiatop will not be calculated for the presence or absence of disease, but for the presence or absence of specific IgE antibodies, with a RAST panel as the standard. Because Phadiatop was developed to detect common inhalant allergies (21), we selected a panel of RASTs to the most common inhalant allergens in our region (Table 4.1) (28). This RAST panel was considered to be positive if at least one RAST was class 1 or higher. Moreover, up to three additional RASTs were done if the patient had had regular contact with one or more of three less common allergens (horse, guinea pig, rabbit), or if the patient reported having had symptoms after contact with these allergens. These three RASTs were not included in the panel that was used as the standard.

Approval
The study protocol was approved by the ethics committee of the University Hospital, Leiden, The Netherlands.

Results

The RAST panel was found to be positive in 164 out of 361 patients (45%); 90 of these displayed monosensitization. When the panel was negative, a positive result for one of the additional RASTs was found in 4 patients. The results of the RASTs are presented in Table 4.2.

First, we analyzed Phadiatop as a negative or positive outcome, with the RAST panel results as the standard (Table 4.3). The sensitivity was 94%, the specificity was 98%, and the predictive values were 97% (PV+) and 95% (PV-). There were 10 false-negative Phadiatops; nine of these were recorded for patients with only one positive RAST (6 x D1: 5 x class 1 and 1 x class 2; 1 x E5, class 2; 1 x Gx1, class 2; 1 x Mx1, class 2). One patient had a false-negative Phadiatop and two positive RASTs (E1, class 1; E5, class 2). There were four false-positive Phadiatops; one of these was accompanied by a positive RAST (class 3) for guinea pig dander, which was not a part of the panel we used as the standard.

Second, we studied the relationship between the Phadiatop *ratio* and the RAST panel. As Fig. 4.1 shows, a cutoff point lower than 1.00 leads to fewer false-negative Phadiatops but more false-positive ones. By choosing several cutoff points for the Phadiatop ratio, the sensitivity and specificity can be varied (Table 4.4). This can also be demonstrated in a receiver operating characteristic (ROC) curve (Fig. 4.2) (25).

Table 4.2. Number of positive (≥ class 1) RASTs in 361 patients with chronic nasal symptoms in general practice population

allergen	positive RASTs	(%)	mono-sensitizations
RAST panel			
house dust mite *(D.pt.)* (D1)	100	(28)	54
grass pollen mixture (Gx1)	80	(22)	26
tree pollen mixture (Tx9)	45	(12)	4
weed pollen mixture (Wx3)	33	(9)	1
mould mixture (Mx1)	11	(3)	1
cat dander (E1)	38	(11)	1
dog dander (E5)	28	(8)	3
total panel (patients with ≥ 1 pos. RAST)	164	(45)	90
additional RASTs			
horse dander (E3) (n=19)	4	(21)	0
guinea pig dander (E6) (n=29)	6	(21)	3
rabbit dander (E82) (n=50)	2	(4)	1
all allergens (patients with ≥ 1 pos. RAST)	168	(47)	94

Table 4.3. Relation between Phadiatop and RAST panel in 361 general practice patients with chronic nasal symptoms; panel was used as standard and was considered to be positive if at least one RAST was class 1 or higher

		RAST panel +	RAST panel -	total
Phadiatop	+	154	4	158
	-	10	193	203
	total	164	197	361

sensitivity = 154/164 = 94% (95% CI: 89-97%)
specificity = 193/197 = 98% (95% CI: 95-99%)
PV+ = 154/158 = 97% (95% CI: 94-99%)
PV- = 193/203 = 95% (95% CI: 91-98%)

PV+: positive predictive value.
PV-: negative predictive value.
CI: confidence interval (8).

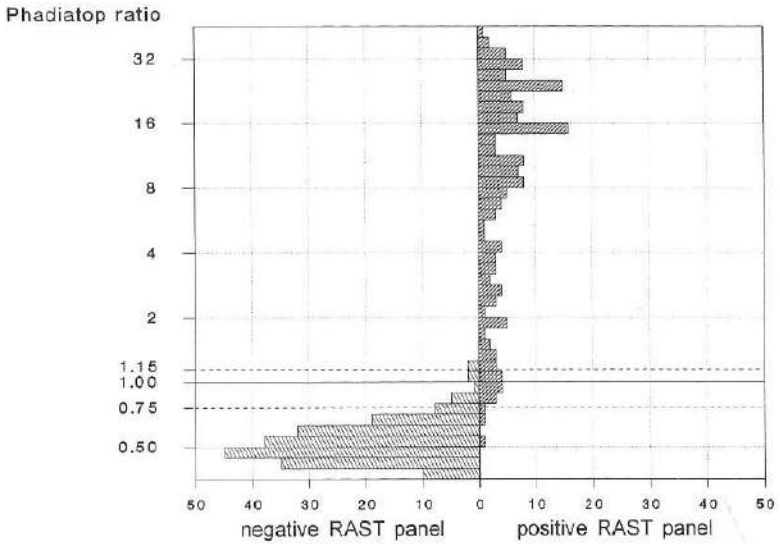

Figure 4.1. Relation between Phadiatop ratio and RAST panel in 361 patients with chronic nasal symptoms in general practice population.

Table 4.4. Sensitivity and specificity of Phadiatop, for several cutoff points of Phadiatop ratio, with a RAST panel as standard

cutoff point Phadiatop ratio	sensitivity (%)	specificity (%)	number of false-negatives	number of false-positives
1.25	90	100	16	0
1.15	91	99	14	1
1.10	92	98	13	3
1.05	93	98	12	3
1.00	94	98	10	4
0.95	96	98	7	4
0.90	96	97	6	5
0.85	98	97	4	6
0.80	98	95	3	10
0.75	99	93	2	14
0.70	99	90	2	20
0.65	99	83	1	34
0.50	100	46	0	107

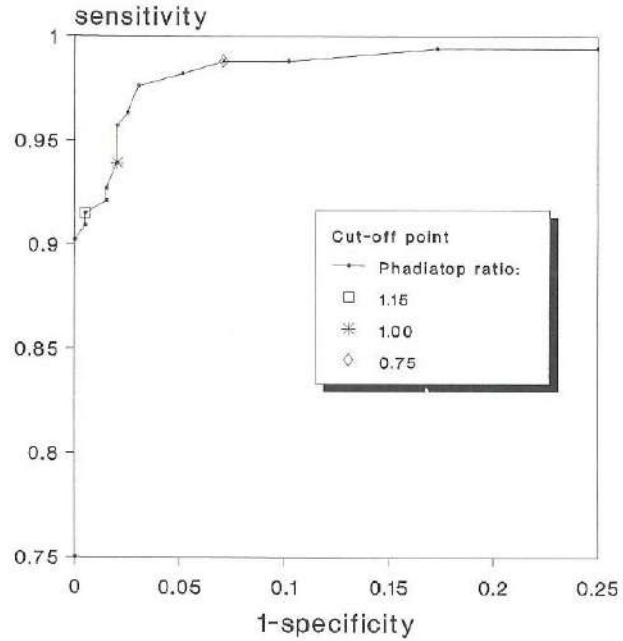

Fig. 4.2. ROC curve, presenting sensitivity and specificity of Phadiatop test, as related to cutoff point of Phadiatop-ratio, with RAST panel as standard. Only upper left quadrant of ROC curve is shown.

Whatever cutoff point is selected, the problem of false-positive or false-negative outcomes remains. Another approach to this problem is to use three ranges of outcomes, as explained in the introduction. We selected three ranges of outcomes of the Phadiatop ratio in such a way that the upper outcome 'positive' produced a posttest probability of 99% for a positive RAST panel outcome (150/151), while the lower outcome 'negative' produced a posttest probability of 99% for a negative RAST panel outcome (183/185). The values of the Phadiatop ratio for the two cutoff points needed proved to be 0.75 and 1.15 (Table 4.5). A Phadiatop ratio result between these two values produced an 'inconclusive' outcome in 25 (7%) of 361 cases; in this group the chances of a positive or negative RAST panel were about even (13 negative and 12 positive panels, displaying the following RAST results: 8 x D1, 6 x class 1 and 2 x class 2; 2 x Gx1, class 1 and 2; 1 x Tx9 class 1; 1 x E1 class 1 combined with E5 class 2). In this way, the number of false outcomes was reduced from 14 to 3.

Table 4.5. Relation between Phadiatop and RAST panel, with three ranges of Phadiatop ratio outcomes (n=361)

Phadiatop (ratio)	RAST panel +	-	total	likelihood ratio (25) (95% CI)	posttest probability (95% CI)
positive (>1.15)	150	1	151	180 (26-1274)	150/151=99% (96-100%)
inconclusive (>0.75, ≤1.15)	12	13	25	1.11 (0.52-2.36)	12/25=48% (28-69%)
negative (≤0.75)	2	183	185	0.013 (0.003-0.052)	2/185=1% (0-4%)*
total	164	197	361		

CI: confidence interval (8).
* Posttest probability for positive RAST panel; posttest probability for negative RAST panel is 183/185 = 99% (95% CI: 96-100%).

Discussion

Our study is the first to evaluate the Phadiatop in general practice patients with chronic nasal symptoms. The sensitivity, specificity and predictive values proved to be very high when a RAST panel was used as the standard. Nevertheless, there was a small percentage of false-positive and false-negative outcomes. We have shown that this problem can be reduced by using three outcomes for the Phadiatop, and two cutoff points for the Phadiatop ratio. In addition to a highly predictive positive or negative outcome, a third outcome - 'inconclusive' - can be given, indicating that the chances of a positive or negative RAST panel are about even. This simple method reduces the problem of false outcomes to a minimum. The price to be paid is low: in our study only 25 (7%) of 365 patients were given the outcome 'inconclusive'.

In evaluation of Phadiatop, it seems to be a problem that the manufacturer will not reveal the exact allergen composition of the Phadiatop. It remains uncertain whether the most complete RAST panel of allergens has been chosen for this comparative study. However, as the test was developed as a test for IgE against common inhalant allergens, the panel to compare with is mainly determined by the allergens which are common in the region where the study is performed. From our results, it can be concluded that the Phadiatop outcome is indeed highly predictive of the RAST outcomes for the common inhalant allergens in our region. The only exception may be moulds: the single patient with a monosensitization (class 2) against moulds displayed a negative Phadiatop. A poor sensitivity of Phadiatop for moulds has already been reported (20, 21).

While Phadiatop was developed as a test for IgE against common inhalant

allergens, we were interested to know whether it could also be used to detect sensitizations to less common allergens. There were four monosensitizations for the additional, less common allergens guinea pig and rabbit dander. Only one of these four patients had a positive Phadiatop; thus, Phadiatop appears to be unsuitable for the detection of monosensitizations to these allergens. Since these monosensitizations occurred in only 1% of the cases, it is probably a minor problem in general practice. Moreover, when the case history indicates a possible monosensitization, it is cost-effective to skip Phadiatop and start with the specific RAST.

There are two other studies that evaluated Phadiatop in general practice, using a RAST panel as the standard (29, 30). These studies concerned only patients on pulmonary medication, and no CAP system was used. One of these two considered the RAST panel to be positive if at least one RAST was class 2 or higher. Nevertheless, our findings are virtually the same as those of these two studies, showing a high sensitivity (98% and 93%) and specificity (100%, 99%).

Another question of external validity is related to the situation in further selected patient populations. In outpatient departments, there have been a number of studies focusing on Phadiatop. Because of methodologic differences, only a few of these can be compared with our study. A major consideration in evaluating Phadiatop is the choice of the standard. There is no such thing as a 'gold standard' for allergy. In a number of studies the clinical diagnosis of atopy, made by a specialist, was used as the standard (2, 4, 6, 10, 12, 17, 24, 32). These included the only study that used the CAP system (6); here the sensitivity was 96% and the specificity 94% for asthma and rhinitis. Since the diagnoses in these studies were not always defined unequivocally, and the between-observer and within-observer variations were unknown, the results may be difficult to interpret. It has been said that the differences in the outcomes of these studies reflect not so much the test performance as the physicians' judgements (13). Therefore, we chose to start by comparing Phadiatop with a RAST panel. The clinical significance of the test can then be assessed by comparing these results with well-defined diagnoses, or diagnoses obtained by means of a consensus of opinion among several experts. We are now performing further research on this point.

Phadiatop has been compared with a RAST panel in outpatient departments; these studies involved both children (10, 11) and adults (5, 21), with both nasal and pulmonary allergies. These studies used not the CAP system but the Phadebas paper disk method. The sensitivities in these studies were 98%, 95%, 94%, and 95%, respectively. The specificities were 95%, 100%, 100%, and 97%, respectively. These results do not differ significantly from our findings.

An important finding of the present study is that the sensitivity and specificity of Phadiatop are the same in general practice and hospital outpatient departments, and in patients with nasal and pulmonary allergies. Apparently, the assumed referral bias does not affect the correspondence of Phadiatop with the RAST panel outcomes. In view of this, our results can be extrapolated to outpatient departments, provided a possible difference in the prevalence of a positive RAST panel is taken into account. If this prevalence is different, the posttest probabilities can be calculated with the help of the likelihood ratios shown in Table 4.5 (25). It is noteworthy that the prevalence of

sensitizations in our study is comparable to those in several outpatient department studies (1, 6, 12).

The clinical relevance of our recommendation to introduce the third Phadiatop outcome 'inconclusive' depends on the clinical relevance of the positive RAST panels. Therefore, in continuation of this study we asked three experts to give their diagnoses for the patients who had an inconclusive Phadiatop outcome and a positive RAST panel. Further data were presented to them on the medical history and skin prick tests. From the preliminary results (data not shown), it appeared that eight of these 12 sensitized patients were diagnosed as being allergic. Therefore, we think our recommendation is indeed clinically relevant.

Further studies involving the clinical significance of Phadiatop are now under way. Obviously, the correlation between Phadiatop and RASTs is favored by the fact that the two assays utilize allergens coming from the same source and utilize the same methods. Therefore, continuation of this study will include comparison of the Phadiatop with case history and skin prick tests. Finally, it must still be established whether the application of Phadiatop is cost-effective.

We investigated Phadiatop as supplied in Europe. The standard used included the inhalant allergens common in our region, i.e., northwestern Europe (27, 28); in southern Europe other allergens are more common (27). The manufacturer also produces two other compositions of Phadiatop, for use in North America and Japan, respectively. Further research should make clear whether the results obtained from our study are valid for other regions.

The practical implications of our study, which are probably also valid for outpatients, are the following. Phadiatop has high predictive values for the presence of specific IgE, as determined by means of a RAST panel to common inhalant allergens. There is a small percentage of false outcomes. Nevertheless, it is possible to reduce this problem still further by replacing the cutoff point of the Phadiatop ratio of 1.00 by the two cutoff points 0.75 and 1.15, resulting in highly predictive positive and negative outcomes, and a third outcome 'inconclusive'. Alternatively, the cutoff point of 1.00 may be maintained, and the designation 'borderline' attached to both positive and negative Phadiatop outcomes where the ratio is between 0.75 and 1.15. In this way, physicians are alerted to the possibility of a false outcome; on the basis of the case history and other clinical findings, they can then decide whether further testing should be done.

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Chapter 5

Use of a consensus method to obtain expert diagnoses as references in patients with chronic or recurrent nasal symptoms

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Submitted.

Abstract

In the absence of generally accepted criteria for the diagnosis of nasal disorders, the feasibility was studied of a consensus method to obtain expert diagnoses in patients with chronic or recurrent nasal symptoms encountered in primary care. In 19 general practices with a total of 47,250 registered patients, 365 consecutive patients aged 12 or over who visited their general practitioner because of chronic or recurrent nasal symptoms between March 1, 1990 and March 1, 1991 were included in the study. Using a modified Delphi technique consisting of three rounds (the first two performed anonymously), three experts gave their diagnoses. After the first round, Cohen's Kappas varied from 0.91 for allergic rhinitis to 0.04 for rhinitis medicamentosa. The second and third rounds were limited to the following nasal disorders (final Kappas given in brackets): allergic rhinitis (0.89-0.94) and 14 different nasal allergies (0.78-0.95); nasal polyps (0.96-1.00); and non-specific nasal hyperreactivity (0.58-0.70). The consensus method has been shown to be feasible to obtain expert diagnoses of nasal pathology. This method may also be useful in other diagnostic studies, especially in situations where a reference test is not available.

Introduction

In diagnostic studies, the lack of a 'gold standard', defined as an accepted reference test which indicates whether a disease is present or absent,[1] is a common problem.[2] To obtain alternative standards or references, several methods are presently in use.

In some cases, patients under study are followed up regarding the natural course or the effect of treatment, using classification based on precisely defined endpoints.[3] However, when the disease is chronic or the expression of the disease is influenced by coexisting conditions, endpoints are virtually impossible to define. The 'next best' reference test has also been used, despite its shortcomings.[4, 5] In many diseases, however, it is generally agreed that the 'clinical diagnosis' should be based not on a single test outcome but on the consideration of both clinical data, i.e., symptoms and signs, and paraclinical data, i.e., outcomes of in vivo or in vitro tests.[6] For this reason, the clinical diagnoses of an experienced clinician are often used as reference.[7, 8, 9] Finally, there are the consensus procedures, in which experts collectively formulate diagnostic guidelines.[10, 11] However, as such guidelines are not based on analyses of diagnoses in patients who are representative for the population under study, most of them are of a general nature, and do not include explicit criteria.

In planning a study, aimed at formulating explicit diagnostic criteria for nasal pathology in patients with chronic or recurrent nasal symptoms in a primary care setting, we first considered the problem of obtaining reference diagnoses. Nasal symptoms are caused by different types of nasal pathology, and there is often more than one nasal disorder present in the same patient. These disorders must be differentiated before the optimum management procedure can be established.[12, 13] While there is no universally accepted system for the definition, classification, and terminology of nasal pathology,[14]

there is general agreement that the clinical diagnosis should be based on the interpretation of both clinical and paraclinical data.[15]

This paper describes the feasibility of a method to obtain reference diagnoses. This method, developed in a pilot study, is based on the assumption that in the absence of an accepted reference test, reference diagnoses can be obtained by presenting to experienced clinicians as much clinical and paraclinical data as possible; these data are obtained from representative patients in a standardized fashion. The clinicians then try to reach consensus on the presence or absence of the disease in each patient.

Materials and methods

Patients

The patients were selected between March 1, 1990 and March 1, 1991 by 25 general practitioners in 19 general practices, situated in both urban and rural areas in the west of the Netherlands. The registered patient population of these practices was 47,250, 40,350 of whom were 12 years of age or older. The following inclusion criteria were used: all the subjects had consulted their general practitioner because of a stuffy nose, a runny nose, an itchy nose, or sneezing, and were 12 years of age or older. Moreover, these symptoms had continued for more than 4 weeks, had occurred intermittently for more than 6 months, were seasonal, or were related to a specific place or contact. Of 376 consecutively enlisted patients, 11 were excluded on the following grounds: linguistic problems (n=2), inability to obtain informed consent (n=6), and the patient's reluctance to discontinue medication which might have influenced skin prick tests (n=3). A total of 365 patients were ultimately included in the study, representing 9.0 episodes per year of chronic or recurrent nasal symptoms in 1000 patients aged 12 or over. The mean age was 34 (range 12-83); 41 patients (11%) were over 50 years of age. There were 152 men (42%) and 213 women. One general practitioner (M.C.), who had received special training for this study, visited and examined each patient within a few days, either at home or in the surgery of the patient's general practitioner.

Data

Information on current medication, previous diagnoses of nasal pathology, response to treatment, and the outcome of referrals to specialists was provided by the general practitioners. Detailed questionnaires, to be filled in by patients, comprised the items proposed in the literature.[6, 13, 16] The completed questionnaires were checked by one of the authors (M.C.) for missing items and inconsistent answers. A physical examination of the nose and throat was performed prior to checking the questionnaires, hence, blinded for the medical history, by one author (M.C.). The findings were recorded on a structured form composed of the items proposed in the literature.[13, 17] Ultrasonography of the maxillary sinuses was performed blinded for the medical history.[18]

Nasal smears were obtained as described elsewhere.[17] Microscopic evaluation was performed blinded by one author (M.C.) and by a laboratory assistant, who independently

assessed the percentage of eosinophils semi-quantitatively on a four-point scale.[19] If the assessments differed, a second laboratory assistant was asked to assess the smear blinded, and the middle outcome of the three was recorded. Using a venous blood sample, the total IgE, the Phadiatop test, and radioallergosorbent tests (RASTs) were performed blinded, using the Pharmacia CAP system.[20] Details on this item have already been published by us.[21] Phazet skin prick tests (SPTs) were performed with a positive control, a negative control, and 14 allergens, including two tree pollen, two grass pollen, two weed pollen, two house dust mites, one mould (*Alternaria*), cat dander, dog dander, horse dander, rabbit dander, and guinea pig dander.[22, 23] Medication that might influence skin prick testing had been withheld for the appropriate period of time.[24] All SPTs were performed unblinded by the first author (M.C.), as described previously.[25] Weals were outlined after 15 minutes and the contours transferred to paper by means of tape.

Terminology of nasal pathology

In the absence of a universally accepted system for the terminology of nasal pathology, we chose that proposed by Mygind.[26] With a few adaptations, it comprised the following 8 categories (definitions by Mygind between brackets): 'allergic rhinitis' divided into 14 different allergies (IgE-mediated rhinitis), 'vasomotor rhinitis' (chronic non-purulent rhinitis of unknown aetiology), 'infectious rhinitis' (purulent rhinitis), 'rhinitis medicamentosa', 'nasal polyps', 'anatomical obstructions', 'other diseases', and 'non-specific hyperreactivity'. It should be noticed that Mygind quite recently proposed an alternative term for vasomotor rhinitis: 'perennial non-allergic rhinitis'.[14] Non-specific nasal hyperreactivity was defined not as a disease but as a clinical manifestation that may be present in any type of rhinitis, characterized by nasal symptoms on contact with non-allergic stimuli.[27] Some findings, e.g. a minor septal deviation, may produce no symptoms. Therefore, it was agreed that diagnoses should be made only if the findings were thought to be clinically relevant.

Consensus method

The Delphi consensus method is an attempt to obtain expert opinion in a systematic manner.[28] Experts are polled individually and anonymously. As a rule, the survey is conducted over three or four rounds; the results are reported to the group after each round. The Delphi is considered complete when there is a convergence of opinion or when a point of diminishing returns is reached.

In our application, expert opinion was obtained on the presence of nasal pathology in patients with chronic or recurrent nasal symptoms encountered in primary care; experts made their diagnoses based on the clinical and paraclinical data on paper. Three experts, an allergologist (P.D.), an ENT specialist (J.H.H.), and a general practitioner (A.P.T.) were selected; the first two are experts in their specialty. The general practitioner was included in order to obtain final diagnoses which also reflected the view of a general practitioner; this was considered important because specialists in the Netherlands deal with referred populations only.[29, 30]

In the first round, the experts were asked to give their opinion on the presence of each of the diagnostic categories in each patient, on the basis of all the available data.

Thus, for each of the 365 patients, the experts gave 8 assessments and, where allergic rhinitis was judged to be present, up to 14 additional assessments. The assessments were scored on a five-point scale: (almost) certainly absent; probably absent; questionable; probably present; (almost) certainly present. For ease of analysis and interpretation, these assessments were recoded to a three-point scale: 1 = (probably) absent; 2 = questionable; 3 = (probably) present. If two experts gave the same assessment on this three-point scale, and the third did not give a contradictory assessment (i.e., 1 versus 3, or 3 versus 1), consensus was considered to have been reached. Thus the outcome was either: 'consensus: disease absent', 'consensus: disease questionable', 'consensus: disease present', or 'no consensus'. The manifestation 'non-specific hyperreactivity' was assessed directly on a three-point scale: 1 = absent; 2 = moderate; 3 = severe; the criteria were as given above. The experts were not informed of the consensus criteria.

In the second round, the intention was to present the data of all patients with a 'no-consensus' outcome to each expert, together with the anonymous assessments of the other two experts given in the first round, and to ask them to reconsider their assessments. However, after the first round it appeared not feasible to ask the experts to reassess all those patients with one or more 'no-consensus' outcomes. Therefore, the second and third rounds were restricted to the 'no-consensus' cases of the diagnoses 'allergic rhinitis' (and all 14 nasal allergies), and 'nasal polyps', and of the manifestation 'non-specific hyperreactivity'.

In the third round, unlike the usual Delphi procedure, all three experts met together, to discuss the remaining 'no-consensus' outcomes, and to reconsider their assessments once again.

Statistical methods

Linear weighted Cohen's Kappas, reflecting the percentage of agreement corrected for agreement by chance,[1] were calculated by means of the statistical programme AGREE.[31] Linear weighing was used to attach less importance to 'minor disagreements' (disease absent or present versus questionable) than to 'strong disagreements' (disease absent versus present). Kappa ranges from -1 (perfect disagreement) to +1 (perfect agreement).

A sensitivity analysis was performed to determine how the results were influenced by the use of different criteria for the attainment of consensus.[2] In the case of less stringent criteria, we considered consensus to have been reached if two experts recorded either '1' or '3' on the three-point scale, regardless of the assessment of the third expert. In the case of more stringent criteria, we considered consensus to have been reached only if two experts recorded the same assessment on the original five-point scale, i.e., '1', or '3', or '5', and the third assessment was not contradictory (for example, a '4' or '5' where the other two had recorded a '1'). As differing criteria would have influenced patient selection for the second and third round, this analysis was performed for the first round only.

Approval

The study protocol was approved by the Ethics Committee of the Academic Hospital, Leiden.

Results

After the first round of the consensus procedure, it was clear that expert consensus on the presence of nasal pathology depended primarily on the particular diagnosis, Cohen's Kappas being the highest for allergic rhinitis (Table 5.1). 'Other diseases' diagnosed by one of the experts included: allergy to fruits (1x), allergy to flowers (1x), eosinophilic non-allergic rhinitis (2x), foreign body or tumour (1x), and anosmia after viral infection (1x by two experts). In this round, each expert recorded almost 6000 assessments, which took each expert over 60 hours to complete.

The sensitivity analysis showed that for all diagnoses the use of less stringent criteria for consensus resulted in an outcome of 'no consensus' in fewer than 5% of patients (Table 5.2). The more stringent criteria had much less influence on the results.

The second and third rounds were restricted to the 'no-consensus' cases of the diagnoses 'allergic rhinitis' (and 14 different nasal allergies), and 'nasal polyps', and of the manifestation 'non-specific hyperreactivity', because it was not feasible to ask the experts to reassess all those patients with one or more 'no-consensus' outcomes. In the second round, these 'no-consensus' cases were reduced from 5.8% to 2.5% for allergic rhinitis, from 2.7% to 0.3% for nasal polyps, and from 1.1% to 0.3% for non-specific hyperreactivity. The results after all three rounds are presented in Table 5.3. For allergic rhinitis, 4.2 episodes per year were registered in 1000 patients aged 12 or over. The single patient in whom one expert diagnosed an occupational allergy worked as a printer.

It should be noted that for most diagnoses, it would be impossible for Cohen's Kappas to reach 1.00, because only those cases with contradictory assessments were reassessed in the second and third rounds, and not those where there was only a slight disagreement. The final Kappas were 0.89-0.94 for allergic rhinitis, 0.96-1.00 for nasal polyps, and 0.58-0.70 for non-specific hyperreactivity. The entire consensus procedure took each expert about 80 to 100 hours.

Table 5.1. Consensus of three experts on the presence of nasal pathology in 365 patients with chronic or recurrent nasal symptoms; results of the first anonymous consensus procedure round

	% consensus				linear weighted Cohen's Kappa*			
	disease absent	disease questionable	disease present	% no consensus	expert 1 versus expert 2	expert 1 versus expert 3	expert 2 versus expert 3	(max. SE)
allergic rhinitis	48.5	1.9	43.8	5.8	0.86	0.91	0.81	(0.03)
vasomotor rhinitis	38.6	0.8	20.5	40.0	0.31	0.47	0.43	(0.05)
infectious rhinitis	65.5	1.1	4.1	29.3	0.15	0.26	0.28	(0.05)
nasal polyps	95.6	0	1.6	2.7	0.55	0.69	0.84	(0.13)
rhinitis medicamentosa	89.9	0.3	0.3	9.6	0.04	0.17	0.47	(0.11)
anatomical obstructions	57.3	1.1	19.7	21.9	0.42	0.55	0.58	(0.04)
other diseases	98.4	0	0	1.6	0.26	**	**	(0.21)
	absent	mild	severe	no consensus				
degree of non-specific nasal hyperreactivity	64.7	26.3	7.9	1.1	0.65	0.69	0.56	(0.04)

max. SE: maximum standard error.

* Assessments on a three-point scale: absent, questionable, present.

** Kappa could not be computed because one expert gave all patients the same assessment.

Table 5.2. Sensitivity analysis for the attainment of consensus of three experts on the presence of nasal pathology in 365 patients with chronic or recurrent nasal symptoms; results of the first consensus procedure round

	less stringent consensus criteria				more stringent consensus criteria			
	% consensus				% consensus			
	disease absent	disease questionable	disease present	% NC	disease absent	disease questionable	disease present	% NC
allergic rhinitis	50.4	1.9	46.0	1.6	47.9	1.9	41.1	9.0
vasomotor rhinitis	55.3	0.8	40.0	3.8	38.6	0.8	16.7	43.8
infectious rhinitis	80.0	1.1	13.7	4.4	61.9	1.1	1.6	35.3
nasal polyps	96.4	0	3.3	0.3	95.6	0	1.6	2.7
rhinitis medicamentosa	95.1	0.3	3.3	1.4	89.6	0.3	0.3	9.9
anatomical obstructions	68.8	1.1	26.8	3.3	56.7	1.1	14.5	27.7
other diseases	99.7	0	0.3	0	98.4	0	0	1.6
	absent	mild	severe	% NC	absent	mild	severe	% NC
degree of non-specific nasal hyperreactivity	64.7	26.3	8.2	0.8	64.7	26.3	7.9	1.1

NC: no consensus.

Table 5.3. Consensus of three experts on the presence of nasal pathology in 365 patients with chronic or recurrent nasal symptoms; results after three consensus procedure rounds

	% consensus			
	disease absent	disease questionable	disease present	% no consensus
allergic rhinitis	49.6	3.0	46.6	0.8
nasal polyps	95.9	0.3	3.8	0
different nasal allergies				
- pollinosis	72.3	2.5	25.2	0
- tree pollen	85.2	1.6	13.2	0
- grass pollen	75.3	1.4	23.3	0
- weed pollen	92.3	0.5	7.1	0
- house dust mite	67.4	3.6	28.2	0.8
- moulds	97.3	0.5	2.2	0
- animals	85.5	1.6	12.6	0.3
- cat	88.2	0.5	11.2	0
- dog	89.6	2.5	7.4	0.5
- horse	97.3	1.4	1.4	0
- rabbit	99.2	0.3	0.5	0
- guinea pig	98.1	0	1.9	0
- other animals	99.5	0.3	0.3	0
- occupational allergy	99.7	0	0	0.3
	absent	mild	severe	no consensus
degree of non-specific nasal hyperreactivity	64.7	27.4	7.9	0

Discussion

The major finding of this study pertains to the feasibility of performing a consensus procedure to obtain expert diagnoses. Although our method was time-consuming, consensus of opinion was reached on the presence of allergic rhinitis in 99% of the patients, and on the presence of nasal polyps and the degree of non-specific nasal hyperreactivity in 100% of the patients. On the basis of the sensitivity analysis, we conclude that using more stringent criteria would not have altered the outcome for the latter two, while in the case of allergic rhinitis only slightly different results would have

occurred in the first round. Therefore, we believe that our method provides acceptable reference diagnoses, particularly in situations where no reference test is available, and the best attainable clinical diagnosis is one based on the interpretation by experts of as much clinical and paraclinical data as possible.

Another finding of this study was that there was considerably more agreement on the presence of allergic rhinitis than on most of the non-allergic conditions. Due to the experts' workload, a decision had to be made as to which diagnoses would be reassessed in the second and third rounds. Another solution would have been to use less stringent criteria. For all diagnoses, this would have resulted in fewer than 5% of patients with a 'no-consensus' outcome. However, in our opinion these criteria would have been not stringent enough.

As noted in the introduction, consensus procedures have been performed, in which experts collectively formulate diagnostic guidelines.[10, 11] Of the various consensus methods used, Delphi has the advantage of giving all the participants an equal opportunity to express their opinion.[28] In consensus procedures experts are usually asked to formulate statements, for instance, on how to diagnose rhinitis. As far as we know, the Delphi method has not previously been used to obtain expert 'consensus diagnoses' in representative patients; a Medline search (1980 to 1993) for 'Delphi technique', or 'observer variation', produced no publications dealing with a comparable method. With this new method, looking only at the input (the data) and the outcome (the consensus diagnoses), the experts were not required to explain their diagnostic processes. This is seen as an advantage, as it is known that there may be little or no direct introspective access to cognitive processes.[32]

We recorded 9.0 episodes per year of chronic or recurrent nasal symptoms, and 4.2 episodes per year of allergic rhinitis in 1000 patients aged 12 or over. In epidemiologic studies in primary care, the prevalence of episodes of 'hay fever/allergic rhinitis' was about 13 per 1000 patients per year (all ages) in the Netherlands,[33, 34] and 20 in Britain.[35] There are several possible explanations for the lower prevalence which we recorded. In the latter two studies, the criteria were based on the case history alone, making it likely that non-allergic rhinitis was included. Moreover, our study did not include patients with a previous diagnosis of rhinitis, who reported no nasal symptoms and only made an appointment in order to request a repeat prescription. Finally, in our study some general practitioners may not have included all the patients who met the inclusion criteria: the number of included patients varied from 2.6 per 1000 to 17.3 per 1000 patients enlisted (median 7.5). However, these numbers are not corrected for age.

Because of the research setting, there were some restrictions on the collection of data: no X-rays or CT-scans were made, nasal endoscopy was not performed, and provocation tests were not done. Nor were the patients sent to the experts for a personal examination: the experts made their diagnoses solely on the basis of the data on paper. If the patients had been asked to visit a specialist, many of them would have refused, resulting in selection bias.[29, 30] As we wanted to study patients who reflected as closely as possible the broad spectrum of clinical presentations of chronic or recurrent nasal symptoms in a primary care setting, we are of the opinion that the absence of a referral bias outweighed the disadvantage of the limitations mentioned above.

What is the validity of our approach, which uses expert consensus diagnoses as the standard? There is no guarantee that an assessment is accurate simply because a group of experts ultimately agree on it.[2] However, it is hoped that consensus techniques, when properly employed, will create a situation in which experts are given the best available information, and will allow their solutions to problems to be more justifiable, valid, and credible than otherwise.[28] In contrast to the usual Delphi method, only three experts participated in our study, due to the considerable amount of work to be done. However, asking more experts to participate would not automatically have increased the validity of the outcome. As there is no 'gold standard', validation of the outcome would appear to be impossible. In fact, the most important aspect of validity which is attainable is the 'face validity',[36] i.e., the opinion of the readers of this article on whether or not the method looks as if it results in an acceptable reference. The outcome of the sensitivity analysis will assist them in making a decision.

The clinical implications of this study have yet to be assessed: having obtained reference diagnoses for the patients under study, we can now analyze the correlations between, on the one hand, the clinical and paraclinical data, and, on the other hand, the expert consensus diagnoses.

In conclusion, performing a consensus procedure to obtain expert diagnoses as reference diagnoses in patients who are representative for the population under study is feasible, if time-consuming. It is especially useful in situations where no reference test is available, the best available clinical diagnosis is based on the interpretation of clinical and paraclinical findings, and the personal opinion of a single expert is insufficient. When this method is used for future diagnostic research, we suggest that the procedure is limited to only one or two diagnoses, and that the results of a sensitivity analysis are reported, in order to assist readers in forming an opinion on the face validity, the most important attainable aspect of validity.

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Chapter 6

Symptoms and signs of allergic rhinitis: correlation with expert diagnoses

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Submitted.

Summary

Background. The medical history and the physical examination are believed to be the cornerstone of the diagnosis of allergic rhinitis. However, little is known about their diagnostic value in general practice.

Aim. This paper aims to identify the most useful symptoms and signs for the diagnosis of allergic rhinitis in a primary care setting.

Method. In 19 Dutch general practices with a total of 47,250 registered patients, data were obtained from 365 consecutive patients aged 12 or over who visited their general practitioner because of chronic or recurrent nasal symptoms between March 1, 1990 and March 1, 1991. Bivariate and multivariate relations were assessed of 271 items from the medical history and 38 items from the physical examination with the 'consensus diagnoses' of allergic rhinitis, differentiated for 14 different allergens. These 'consensus diagnoses' were made by three experts in a modified Delphi consensus method, and were based on all the clinical findings and various additional tests.

Results. Logistic regression analysis showed a maximum of four independent predictors of each of the nasal allergies. The number of independent predictors present was used to assess the probability of the nasal allergies: the maximum predicted probability was around 80% for grass pollen and house dust mite allergy; for the other allergies it was 60% or below; the minimum predicted probability was 3% or less, except for grass pollen allergy (6%) and house dust mite allergy (10%). The physical examination did not contribute to the diagnoses.

Conclusion. In patients with chronic or recurrent nasal symptoms, a strictly limited medical history provides as much information on the presence or absence of the common nasal allergies as an extended history combined with physical examination; making the diagnosis to a sufficiently high degree of certainty is possible for grass pollen allergy only; in many patients, excluding the common nasal allergies is possible, except for house dust mite allergy. The medical history may serve as a guide to select further tests.

Introduction

Allergic rhinitis is thought to be the most common IgE-mediated allergic disease worldwide,[1] although reliable data on prevalence are scarce. In the West, about 6% to 10% of the population are afflicted,[2, 3] while there is some evidence that this percentage is on the rise.[4] The number of patients who consult their general practitioner and are subsequently diagnosed as having allergic rhinitis is 20 per year per 1000 registered patients in Great Britain, and 13 in the Netherlands.[5, 6, 7] Diagnosing allergic rhinitis and identifying causal allergens is of importance for proper counselling, as whenever feasible, the patient should minimize exposure to the causal allergens.[8, 9]

Although most patients are diagnosed and treated by general practitioners, there are few diagnostic studies dealing with allergic rhinitis in a primary care setting.[10, 11] According to allergologists, the diagnosis of this disorder can usually be agreed on when

history, physical examination, and radioallergosorbent test (RAST) or skin prick test (SPT) results are combined.[12] However, the predictive values of symptoms and signs only have yet to be properly assessed. These values are of particular importance in a primary care setting, where many physicians do not ordinarily perform SPTs, while RASTs are time-consuming and relatively expensive. Knowing the likelihood of allergic rhinitis on the basis of clinical data only may be helpful in deciding whether it is necessary to determine specific IgE, either by means of RASTs or SPTs.

The purpose of this study was to determine the most useful symptoms and signs for the diagnosis of allergic rhinitis differentiated for 14 different allergens in general practice. The references used were the 'consensus diagnoses', provided by experts by means of a modified Delphi method; these were based on all clinical findings, i.e., symptoms and signs, and paraclinical findings, such as RASTs and skin prick tests.

Method

Patients

The patients were selected between March 1, 1990 and March 1, 1991, by 25 general practitioners in 19 practices, situated in both urban and rural areas in the west of the Netherlands. The registered patient population of these practices was approximately 47,250. The following inclusion criteria were used: all the subjects had consulted their general practitioner because of a stuffy nose, a runny nose, an itchy nose, or sneezing, and were 12 years of age or older. Moreover, these symptoms had continued for more than 4 weeks, had occurred intermittently for more than 6 months, were seasonal, or were related to a specific place or contact. Of 376 consecutively enlisted patients, 11 were excluded on the following grounds: linguistic problems (n=2), inability to obtain informed consent (n=6), or the patient's reluctance to discontinue medication which might have influenced skin tests (n=3). A total of 365 patients were ultimately included in the study. The mean age was 34 years (range 12-83); 41 patients (11%) were over 50 years of age. There were 152 men (42%) and 213 women. One general practitioner (M.C.), who had undergone special training for this study, visited and examined each patient, either at home or at the surgery of the patient's general practitioner. The study protocol was approved by the Ethics Committee of the Medical School of Leiden University.

Clinical Data

Information on current medication, previous diagnoses of nasal pathology, response to treatment, and the outcome of referrals to specialists was provided by the general practitioners. Detailed questionnaires, to be filled in by the patients, comprised the items proposed in the literature.[13, 14, 15] A total of 271 variables were recorded, including: demographic data; rural or urban area; the patient's own ideas on possible causes; previous diagnostic tests; results of therapy and referrals; family history; kind and degree of symptoms; concomitant symptoms; course of the symptoms; aggravating or alleviating

factors; contact with animals; housing situation; smoking habits. Copies of the questionnaire (translated into English) are obtainable from the first author. The completed questionnaires were checked by one of the authors (M.C.) for missing items and inconsistent answers.

A physical examination of the nose and throat was performed prior to checking the questionnaires, and thus blinded for the medical history, by one author (M.C.). Anterior rhinoscopy was performed, if necessary, after application of a topical vasoconstrictor (xylometazoline). The findings were recorded on a structured form composed of 38 items proposed in the literature.[14, 16]

Reference Diagnoses

In a modified Delphi consensus procedure,[17] three experts endeavoured to reach consensus on the presence or absence of allergic and non-allergic nasal pathology in each patient, using a specified list of diagnoses (In this paper, only the results pertaining to allergic rhinitis differentiated for 14 allergens will be presented). The first two experts, an allergologist and an ENT specialist, were selected for their specialist expertise. The third expert, an experienced general practitioner, was included in order to obtain final diagnoses which also reflected the view of a primary care physician; this was considered important because specialists in the Netherlands deal with referred populations only.[18, 19] The procedure consisted of three rounds, the first two performed anonymously. For each diagnosis, the final outcome was: 'consensus: disease absent', 'consensus: disease questionable', 'consensus: disease present', or 'no consensus'. Further details on this topic are discussed in Chapter 5.

The diagnoses of the experts were based on their interpretation of both clinical and paraclinical findings. For this purpose, the following additional data were obtained from all the patients under study: ultrasonography of the maxillary sinuses;[20] nasal smear eosinophilia;[16] total IgE; the Phadiatop test;[21] seven to ten radioallergosorbent tests (RASTs);[22] Phazet skin prick tests (SPTs) with a positive control, a negative control, and 14 allergens.[23] Medication that might influence skin testing had been withheld for the appropriate period of time.[24] The allergens selected for skin tests and RASTs were the most common inhalant allergens in our region.[25] Details on a number of these topics have already been published by us.[21]

Statistical Analysis

To facilitate analysis and interpretation, we chose to compare only those patients diagnosed as 'consensus: disease present' with those diagnosed as 'consensus: disease absent'; for allergic rhinitis this involved 351 out of the 365 patients. All clinical variables were dichotomized; answers 'uncertain' were recoded as negative. Bivariate analyses were used to assess the correlations of all 309 independent variables with the presence or absence of the consensus diagnoses of allergic rhinitis and the differentiated nasal allergies. Chi-square statistics were calculated. For variables with a high chi-square, likelihood ratios and predictive values are presented.

Multiple logistic regression was performed to identify independent predictors of the 'consensus diagnoses', using a stepwise forward selection procedure.[26] It was not

feasible to use all the 309 variables. So, the most important variables, based on chi-square results, were selected for use in the stepwise logistic regression; for allergic rhinitis this involved 33 variables. The likelihood ratio chi-square test was used to determine the significance of improvement.[26] For bivariate and multivariate analyses, the statistical programme SPSS/PC+ (version 3.0.1) was used.

The whole procedure was performed separately for allergic rhinitis without differentiation and for each of the differentiated nasal allergies. To represent the discriminating power of the multivariate models, areas under the receiver operating characteristic (ROC) curves were assessed.[27] An area under the curve (AUC) of 1.00 means perfect discrimination, an AUC of 0.50 indicates no better performance than chance.

In order to present the resulting models in a more comprehensible way, which is suitable for daily practice, likelihood ratios and predicted probabilities were analyzed for the number of independent predictors present, given the prevalences found in this study. Confidence intervals were calculated using the statistical programme 'Statistics with confidence'.[28]

Results

After the first anonymous round of the consensus procedure, the experts had reached consensus in 92% of the patients on the presence or absence of allergic rhinitis, and in 90% to 100% on the presence or absence of the 14 differentiated nasal allergies. After all three consensus procedure rounds, consensus had been reached in 96% of cases on the presence or absence of allergic rhinitis, and in 96% to 100% on the presence or absence of the differentiated nasal allergies (Table 6.1). In the diagnostic category 'nasal allergy: other animals', only one consensus diagnosis was recorded: an allergy against birds. The single patient in whom one expert diagnosed an occupational allergy worked as a printer.

Bivariate analyses showed that 75 of the 271 items on the questionnaire were significantly correlated ($p < 0.05$) with the 'consensus diagnosis' allergic rhinitis. Of these, 31 had a $p < 0.0001$ (Table 6.2). Only one of the 38 findings from the physical examination showed a $p < 0.05$, i.e., mucus on the inferior turbinate ($p = 0.03$), which was present in only 13 patients and was negatively correlated with allergic rhinitis.

For the differentiated nasal allergies, the number of items from the questionnaire which were significantly correlated with the diagnosis varied from 67 for grass pollen allergy (27 of which had a $p < 0.0001$) to none at all for mould allergy. Of the findings from the physical examination, only two were correlated with grass pollen allergy, i.e., pale turbinate mucosa ($p = 0.02$), and a moderate or severe anatomical obstruction ($p = 0.02$, negatively correlated); one sign was negatively correlated with house dust mite allergy, i.e., turbid mucus ($p = 0.02$). For all other differentiated nasal allergies, no findings from the physical examination were significantly correlated with the diagnosis. These results are not presented in detail.

Table 6.1. Consensus of three experts on the presence or absence of allergic rhinitis in 365 patients with chronic or recurrent nasal symptoms

	patients (%)		
	disease present	disease absent	missing*
allergic rhinitis	170 (46.6)	181 (49.6)	14 (3.8)
differentiated nasal allergies			
- pollinosis	92 (25.2)	264 (72.3)	9 (2.5)
- tree pollen	48 (13.2)	311 (85.2)	6 (1.6)
- grass pollen	85 (23.3)	275 (75.3)	5 (1.4)
- weed pollen	26 (7.1)	337 (92.3)	2 (0.5)
- house dust mite	103 (28.2)	246 (67.4)	16 (4.4)
- mould	8 (2.2)	355 (97.3)	2 (0.5)
- animals	46 (12.6)	312 (85.5)	7 (1.9)
- cat	41 (11.2)	322 (88.2)	2 (0.5)
- dog	27 (7.4)	327 (89.6)	11 (3.0)
- horse	5 (1.4)	355 (97.3)	5 (1.4)
- rabbit	2 (0.5)	362 (99.2)	1 (0.3)
- guinea pig	7 (1.9)	358 (98.1)	- (0)
- other animals	1 (0.3)	363 (99.5)	1 (0.3)
- occupational allergy	- (0)	364 (99.7)	1 (0.3)

*Patients were missing because of a missing consensus diagnosis or a 'consensus: disease questionable' diagnosis.

Stepwise multiple logistic regression revealed only six independent predictors for allergic rhinitis, and a maximum of four for the differentiated nasal allergies (Table 6.3). For practical reasons, the diagnoses 'pollinosis' and 'allergy to animals' were only analyzed for further specified diagnoses. The diagnoses 'rabbit allergy' and 'allergy to other animals' were not analyzed, because of the low prevalences. The diagnostic performance of the logistic regression functions, expressed as AUCs, ranged from 0.77 to 0.92.

Table 6.2. Performance characteristics of clinical findings for allergic rhinitis in 351 patients[a] with chronic or recurrent nasal symptoms; results of bivariate analyses, given a prevalence of 48% for allergic rhinitis (only variables are presented which showed a Chi-square statistic with a p-value < 0.0001)

clinical finding	LR+	LR-	PV+ (%)	PV- (%)	frequency (n)	missing (n)
40 years of age or under	1.3	0.49	55	68	247	-
patient's ideas (any) on causal factors	1.7	0.70	62	60	137	-
previous diagnosis: hay fever or allergic rhinitis	4.2	0.56	80	65	108	-
previous treatment: injections (immunotherapy)	12.2	0.87	92	55	25	-
family: hay fever or allergic rhinitis	1.9	0.74	65	59	110	-
sneezing	1.4	0.26	57	80	270	-
number of sneezes a day > 5	2.2	0.57	66	66	137	23
number of sneezes in a row ≥ 4 sneezes	2.0	0.64	65	63	135	5
itchy nose	1.9	0.47	64	69	185	-
most important complaint: blocked up nose	0.65	1.9	38	36	208	4
itchy eyes	2.8	0.60	72	64	116	4
watery eyes	1.7	0.66	62	61	152	2
red eyes	2.3	0.71	68	60	103	4
symptoms in a certain season only/worse	1.6	0.58	61	65	181	6
symptoms in the spring only/worse	3.0	0.72	74	60	85	-
symptoms in the summer only/worse	3.5	0.70	77	60	82	-
symptoms in May only/worse	3.2	0.69	75	61	89	-
symptoms in June only/worse	3.1	0.71	74	60	86	-
symptoms in July only/worse	2.8	0.76	73	58	77	-
symptoms less: on rainy days	4.5	0.77	81	58	58	-
symptoms less: ashore	3.0	0.81	74	57	61	-
symptoms worse: dry, sunny weather	3.1	0.70	74	60	89	-
symptoms worse: contact with grass	5.1	0.73	83	59	64	-
symptoms worse: contact with house dust	3.4	0.60	76	64	109	1
symptoms worse: making beds or shaking out blankets	3.5	0.72	77	60	78	1
symptoms worse: dusting	3.5	0.71	77	60	81	1
symptoms worse: contact with animals	9.4	0.71	90	60	59	-
symptoms worse: contact with dogs	30.9	0.83	97	56	30	-
symptoms worse: contact with cats	14.6	0.77	93	58	44	-
symptoms worse: contact with plants or flowers	4.7	0.83	81	56	43	-
smoking	0.44	1.4	29	44	99	-

LR+, likelihood ratio among patients with the clinical finding present.

LR-, likelihood ratio among patients with the clinical finding absent.

PV+, positive predictive value.

PV-, negative predictive value.

[a]14 out of 365 patients were missing because of a missing consensus diagnosis or a 'disease questionable' diagnosis.

Table 6.3. Independent clinical predictors of allergic rhinitis, obtained by multiple logistic regression analyses of data from 365 patients with chronic or recurrent nasal symptoms; expert 'consensus diagnoses' based on clinical and paraclinical data were used as references

	number of patients (disease present, absent)[a]	independent clinical predictors	odds ratio	AUC (SE)
allergic rhinitis	346	symptoms worse: contact with house dust or making beds	2.4	0.84
	(167,	symptoms in the spring or the summer only/worse	2.5	(0.02)
	179)	symptoms worse: contact with animals	5.8	
		itchy eyes	2.9	
		40 years of age or under	2.7	
		sneezing	2.8	
differentiated nasal allergies				
- tree pollen	355	itchy eyes	5.3	0.83
	(47,	symptoms in the spring only/worse	3.2	(0.04)
	308)	symptoms worse: dry, sunny weather	2.9	
- grass pollen	356	itchy eyes	5.1	0.82
	(84,	symptoms in the summer only/worse	2.7	(0.03)
	272)	symptoms worse: dry, sunny weather	3.9	
- weed pollen	359	itchy eyes	4.5	0.85
	(26,	symptoms in the summer only/worse	2.0	(0.05)
	333)	symptoms worse: dry, sunny weather	4.2	
- house dust mite	348	symptoms worse: contact with house dust or making beds	3.5	0.77
	(103,	symptoms worse: contact with animals	3.1	(0.03)
	245)	40 years of age or under	2.3	
		sneezing	2.2	
- mould	363	no significant predictor		
	(8, 355)			
- cat	359	symptoms worse: contact with cats	25.0	0.85
	(41, 318)	itchy eyes	2.6	(0.04)
- dog	353	symptoms worse: contact with dogs	14.0	0.89
	(27, 326)	symptoms worse: contact with house dust or making beds	7.4	(0.04)
- horse	360	symptoms worse: contact with horses	264.7	0.80
	(5, 355)			(0.12)
- guinea pig	365	symptoms worse: contact with guinea pigs	262.2	0.92
	(7, 358)			(0.07)

AUC: area under the curve of the receiver operating characteristic (ROC) curve. SE: standard error.
[a]Patients were excluded because of a missing diagnosis, or a missing independent variable.

To present the results of this study in a more comprehensible way, which is suitable for daily practice, scoring models were developed, using the independent predictors that were obtained from the logistic regression analyses. For most of the diagnoses, these predictors showed odds ratios of about the same magnitude. Therefore, by simply counting the number of independent predictors present, the probabilities of the diagnoses could be assessed. An exception was made for the scoring models for cat and dog allergy, as both showed predictors with markedly varying odds ratios; the predictors used in these scoring models were given unequal weights. The scoring models were drawn up in such a way that the patients were stratified as having a high, intermediate, or low probability of allergic rhinitis and the differentiated common nasal allergies (Table 6.4). The diagnostic performance of the scoring models and the logistic regression functions, expressed as AUCs, did not differ significantly.

Discussion

This study is the first to identify the independent clinical predictors of allergic rhinitis in a primary care setting. It was shown that in patients with chronic or recurrent nasal symptoms, a strictly limited medical history provided as much information on the presence or absence of the common nasal allergies as an extended history combined with physical examination.

The symptoms that were identified as the independent predictors are all mentioned in the literature as being related to the differentiated nasal allergies. For instance, tree pollen are known to be the most important cause of pollen allergic rhinitis in the spring, whereas grass pollen are the most important cause in early-summer.[25] The finding that 'itchy eyes' were predominantly related to cat allergy, may be explained by the allergen particle size and buoyancy. The particle size of cat allergens can be extremely small; particles of this size tend to remain airborne for hours after they are produced.[9]

The finding that the medical history is often unreliable, is also supported by the literature.[29] There are a number of reasons why the patient may be unaware of a relation between exposure to allergens and the occurrence of symptoms. First, if the symptoms are of a relatively short duration, causal influences or seasonal variation may not yet be clear to the patient. This may be a problem especially in the case of tree pollen allergy, because the exposure to tree pollen may differ considerably from year to year.[30] Second, a late-phase type I allergic reaction may be dominant, especially in perennial nasal allergy, causing non-acute symptoms or nonspecific hyperreactivity.[8, 31] Third, allergens may come from 'hidden sources': cat allergens have been found in high concentrations in dust from floors in schools;[32] house dust mite was found in 99% of homes, and animal allergens in 100%; many homes without pets contained pet allergens to high concentrations.[33] It has been suggested that there may be a difference as high as 10^{12} between the huge dose of allergen needed to provoke immediate symptoms in the least sensitive persons, and the tiny amount necessary to induce inflammation, hyperreactivity and chronic symptoms in highly sensitive patients.[29] Fourth, in the presence of non-

allergic nasal pathology or when both seasonal and perennial allergens cause rhinitis in the same patient, relation to exposure may be less clear to that patient.

It was remarkable that so few of the symptoms and signs mentioned in textbooks were needed to obtain optimal prediction.[8, 15] This is explained largely by dependency: when the most relevant predictors were known, others no longer contributed any information of importance. However, it was surprising that many predictors mentioned in textbooks were not significantly correlated with the diagnoses (data not shown). The most striking examples were symptoms in the autumn; symptoms at night or upon rising; housing situations; contact with animals; symptoms all year round; symptoms from food; living in a rural or urban area; and all findings from the physical examination not mentioned in the results. This was true for allergic rhinitis as a whole and for the differentiated nasal allergies. Most of these findings are in accordance with the results of a study that compared clinical and paraclinical data in patients referred to an allergy clinic.[13] At this point, it must be emphasized that whereas the physical examination is not useful for the diagnosis of allergic rhinitis, it is usually needed to diagnose non-allergic nasal disorders.

Some additional findings are supported by the results of studies on the correlation between symptoms and the results of RASTs or SPTs. First, although nasal blockage may be more prominent in patients with nonallergic rhinitis,[34] this symptom does not help in excluding allergic rhinitis (data not shown).[13] Second, mould allergy, which displays a very low prevalence, was the only nasal allergy for which there was no clinical predictor at all.[34] Third, reported aggravation of symptoms by nonspecific stimuli did not differentiate between those patients who had been diagnosed as having allergic rhinitis and those who had not (data not shown).[34] This supports the view that nonspecific nasal hyperreactivity should not be seen as a disease, but rather as a clinical manifestation that may be present in any form of rhinitis.[31]

In the absence of a 'gold standard' for allergic rhinitis, defined as an accepted reference test which indicates whether the disease is present or absent, choosing an alternative reference presents a number of problems.[29] Nasal provocation tests are generally regarded inadequate because they do not resemble the natural exposure which is often prolonged with very low concentrations of allergen.[35] The presence of specific IgE indicates only sensitization, which may be found in people who have no symptoms.[36] Therefore, it is generally agreed that the diagnosis must be derived from a consideration of both clinical and paraclinical findings;[29] in the literature, references are often obtained by asking an experienced clinician to diagnose all patients on the basis of the case history and specific IgE tests.[37, 38, 39] Since the diagnoses in these studies are not always defined unequivocally, and the between-observer and within-observer variations are unknown, the results may be somewhat difficult to interpret. To overcome the limitations of using only one expert, we chose three experts to provide consensus diagnoses to serve as references.

It may be seen as a major drawback of this diagnostic study that we did not use an independent reference: the 'consensus diagnoses' were used as references. These were based on all the clinical data (symptoms and signs) and paraclinical data (results from in vitro and in vivo tests) obtained from the patients under study.[40] The same clinical and

Table 6.4. Relation between the number of independent clinical predictors present and the probability of allergic rhinitis; results are based on expert diagnoses in 365 patients with chronic or recurrent nasal symptoms

	number of independent clinical predictors present[a]	patients (n)[b]			likelihood ratio (95% CI)	predicted probability[c] (95% CI)	AUC (SE)
		disease absent	disease present	inconclusive diagnosis			
allergic rhinitis	0 - 1	81	10	4	0.13 (0.07-0.26)	11 (5-19)	0.77
	2 - 4	96	109	9	1.22 (0.86-1.72)	53 (46-60)	(0.03)
	5 - 6	2	48	1	25.7 (6.16-108)	96 (86-100)	
differentiated nasal allergies							
- tree pollen	0	167	4	4	0.16 (0.06-0.44)	2 (1-6)	0.81
	1 - 2	126	22	2	1.14 (0.66-1.98)	15 (9-21)	(0.04)
	3	15	21	-	9.17 (4.42-19.0)	58 (41-75)	
- grass pollen	0	170	11	2	0.21 (0.11-0.40)	6 (3-11)	0.80
	1 - 2	94	44	3	1.52 (0.98-2.34)	32 (24-40)	(0.03)
	3	8	29	-	11.7 (5.17-26.7)	78 (62-90)	
- weed pollen	0	182	1	-	0.07 (0.01-0.52)	1 (0-3)	0.84
	1	87	5	1	0.74 (0.28-1.97)	5 (2-12)	(0.05)
	2 - 3	64	20	1	4.00 (2.11-7.60)	24 (15-34)	
- house dust mite	0 - 1	114	12	5	0.25 (0.13-0.47)	10 (5-16)	0.74
	2 - 3	125	61	11	1.16 (0.79-1.70)	33 (26-40)	(0.03)
	4	6	30	-	11.9 (4.81-29.4)	83 (67-94)	
- cat	0	215	6	1	0.22 (0.09-0.52)	3 (1-6)	0.84
	1	85	9	1	0.82 (0.38-1.76)	10 (4-17)	(0.04)
	2	18	26	-	11.2 (5.66-22.2)	59 (43-74)	
- dog	0	229	1	4	0.05 (0.01-0.39)	0 (0-2)	0.89
	1	83	11	6	1.60 (0.76-3.36)	12 (6-20)	(0.04)
	2	14	15	1	12.9 (5.66-29.6)	52 (33-71)	
- horse	0	353	2	4	0.40 (0.08-2.09)	1 (0-2)	0.80
	1	2	3	1	106 (14.5-783)	60 (15-95)	(0.12)
- guinea pig	0	350	1	-	0.15 (0.02-1.19)	0 (0-2)	0.92
	1	8	6	-	38.4 (10.5-140)	43 (18-71)	(0.07)

CI: confidence interval. AUC: area under the curve of the receiver operating characteristic (ROC) curve. SE: standard error.

[a]The independent clinical predictors are presented in Table 6.3; for cat and dog allergy, the predictor 'symptoms worse: contact with cats/dogs' counts double, while the maximum score is regarded as 2.

[b]Patients were excluded from analysis because of a missing consensus diagnosis, a 'disease questionable' diagnosis, or a missing independent variable; the former two categories are reported as 'inconclusive diagnosis'.

[c]Posttest probability, given the pretest probability, i.e., the prevalence, in the study population.

paraclinical data were analyzed for their 'predictive value' of the expert diagnoses. Consequently, there was no independent, 'blind' comparison with a 'gold standard' of diagnosis, which is usually seen as a prerequisite for diagnostic research.[40] Including the variables under study in the reference standard may lead to an 'incorporation bias', which will result in estimates that are either too high or too low, and is generally advised against.[40] It has even been stated that by allowing this type of bias, the investigator works out a 'sure bet' arrangement.[41]

However, assessment of diagnostic values is no more than an approximation of the true values which remain unknown because of the impossibility to determine 'true disease'. The aim of diagnostic studies is to make the best estimation of the true values. Generally, this includes choosing an independent reference. However, problems arise if there is no generally accepted independent reference. Choosing an independent reference that is generally regarded as insufficiently valid, may result in estimates of the 'true' diagnostic values that are worse than the estimates that are obtained by using a dependent reference which is, however, generally accepted as a more valid one. In other words, the bias that results from choosing an independent but improper reference may be larger than the incorporation bias that results from using a dependent but more valid reference. In our opinion, for the diagnosis of allergic rhinitis this is indeed the case. There is no acceptable reference that does not include both clinical and paraclinical findings.

Because of the research setting, there were some restrictions on the collection of data: no X-rays or CT-scans were made, nasal endoscopy was not performed, and no provocation tests were done. Nor were the patients sent to the experts for a personal examination; the experts made their diagnoses solely on the basis of the data on paper. If the patients had been asked to visit a specialist, many of them would undoubtedly have refused, resulting in selection bias.[18, 19] As we wanted to study patients who reflected as closely as possible the broad spectrum of clinical presentations of chronic or recurrent nasal symptoms in general practice, we are of the opinion that the absence of a referral bias outweighed the disadvantages of the limitations mentioned above.

The clinical implications of this study are as follows. On the one hand, making the diagnosis of the common nasal allergies based on the medical history only, emerges to be tied to uncertainty. The highest degree of certainty was achieved for house dust mite and grass pollen allergy. However, especially in the case of house dust mite allergy where minimizing exposure is expensive and difficult, an even higher degree of certainty will usually be required. On the other hand, the medical history showed to be very useful for identifying large groups of patients who are unlikely to have most of the common nasal allergies. For these patients, further testing would appear less advisable. The only exception concerns house dust mite allergy, which was still present in 10% of those identified as having a low probability. Considering that these patients have chronic symptoms which may improve remarkably from environmental control measures,[42] it seems adequate to do further testing for sensitization against this allergen in all patients with chronic or recurrent nasal symptoms, regardless of the further history. The medical history may serve as a guide to select tests for sensitization against the other allergens. Testing for sensitization against weed pollen is not advised, as this occurred only in patients who were sensitized against grass pollen (data not shown) and differentiating

between these two allergies is irrelevant for choosing management, leaving immunotherapy aside. The proposed diagnostic management is represented in Table 6.5.

Table 6.5. Diagnostic management for allergic rhinitis in patients with chronic or recurrent nasal symptoms; selection of tests

medical history	RAST or SPT to be performed
- NR	house dust mite
- symptoms in the spring - or symptoms in dry, sunny weather - or itchy eyes	tree pollen
- symptoms in the summer - or symptoms in dry, sunny weather - or itchy eyes	grass pollen[a]
- symptoms worse on contact with cats - or itchy eyes	cat
- symptoms worse on contact with dogs - or symptoms on contact with house dust or when making beds	dog
- symptoms worse on contact with other animals	animal in question

RAST: radioallergosorbent test. SPT: skin prick test. NR: not relevant.
[a]Grass pollen allergy is highly probable if all three symptoms are present; in that case, RAST or SPT is not necessary.

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Chapter 7

Which combinations of history and tests are of most value to the general practitioner in diagnosing allergic rhinitis?

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Submitted.

Summary

The aim of this study was to identify the most useful combinations of medical history and additional tests for the diagnosis of allergic rhinitis. In 19 general practices, data were obtained between March 1, 1990 and March 1, 1991 from 365 consecutive patients aged 12 or over who visited their general practitioner because of chronic or recurrent nasal symptoms. A prospective comparison was made of symptoms and results from skin prick tests and radioallergosorbent tests (RASTs) with 7 different nasal allergies; the references used were the 'consensus diagnoses' provided by three experts using a modified Delphi method. Diagnostic criteria could be drawn up that combined the findings from the medical history with those from either RASTs or skin prick tests, resulting in a near-perfect discrimination between patients diagnosed as having allergic rhinitis and patients diagnosed as not having allergic rhinitis. This discrimination was significantly better than that provided by the history alone. Most of the diagnostic criteria combined only a single item from the history with either RAST or SPT. For nearly all nasal allergies both the negative predictive value and the positive predictive value were 97% or more. With the aid of simple diagnostic criteria that combine results from a strictly limited medical history with results from either RASTs or skin prick tests, the common nasal allergies can be diagnosed with a very high certainty.

Introduction

Allergic rhinitis is a very common disorder, which is illustrated by the prevalence in general practice of 13 to 20 per 1000.[1, 2, 3] In northwestern Europe, allergic rhinitis is predominantly caused by one or more of seven common inhalant allergens. These are, in order of relative frequency: house dust mite, grass pollen, tree pollen, cat dander, dog dander, weed pollen, and mould.[4] Diagnosing allergic rhinitis and identifying causal allergens is of importance for proper counselling, because, where feasible, the patient should minimize exposure to the causal allergens.[5]

Despite the high prevalence of allergic rhinitis, there have been very few diagnostic studies in general practice.[6, 7] In Chapter 6, we have shown that in patients with chronic or recurrent nasal symptoms, a quite limited medical history provides as much information on the presence or absence of the common nasal allergies as an extended history combined with physical examination. Based on the medical history only, making the diagnosis to a sufficiently high degree of certainty is possible for grass pollen allergy only; in many patients, excluding the common nasal allergies is possible, except for house dust mite allergy (See Chapter 6). Additional testing is often required to obtain more certainty on the presence of allergic rhinitis and to identify the causal allergens. Thus far, there have been no studies that properly investigated the diagnostic value of radioallergosorbent tests (RASTs) or skin prick tests (SPTs) for allergic rhinitis in general practice. Although SPTs are not generally performed in general practice, their presumed higher sensitivity in comparison with RASTs makes it relevant to study both.[8, 9]

In this study, the best combinations of findings from the medical history and results from RASTs and skin prick tests were identified for the diagnosis of 7 different nasal allergies in general practice patients with chronic or recurrent nasal symptoms. The references used were the 'consensus diagnoses' provided by experts using a modified Delphi method.

Methods

Patients

The patients were selected between March 1, 1990 and March 1, 1991 by 25 general practitioners in 19 general practices, situated in both urban and rural areas in the west of the Netherlands. The registered patient population of these practices was approximately 47,250; of these, 40,350 were 12 years of age or older. The following inclusion criteria were used: all the subjects had consulted their general practitioner because of a stuffy nose, a runny nose, an itchy nose, or sneezing, and were 12 years of age or older. Moreover, these symptoms had continued for more than 4 weeks, had occurred intermittently for more than 6 months, were seasonal, or were related to a specific place or contact. Of 376 consecutively enlisted patients, 11 were excluded on the following grounds: linguistic problems (n=2), inability to obtain informed consent (n=6), or the patient's reluctance to discontinue medication which might have influenced skin prick tests (n=3). A total of 365 patients were ultimately included in the study. The mean age was 34 (range 12-83); 41 patients (11%) were over 50 years of age; 152 of the patients were men (42%) and 213 women. One general practitioner (M.C.), who had received special training for this study, visited and examined each patient, either at home or in the surgery of the patient's general practitioner.

Medical history, radioallergosorbent tests, and skin prick tests

Detailed questionnaires, filled in by the patients, comprised the items proposed in the literature.[5, 10, 11] In Chapter 6, it was shown that there were only a small number of independent clinical predictors of each of the common nasal allergies. For all allergies together, these predictors are as follows: 40 years of age or under; sneezing; itchy eyes; symptoms worse on contact with house dust or when making beds; symptoms worse on contact with animals; symptoms in the spring or summer only or worse at these times; and symptoms worse on dry, sunny days.

Using a venous blood sample, seven RASTs were performed blinded, using the Pharmacia CAP system.[12] If the case history indicated additional causal allergens, up to three additional RASTs were performed. The outcome was expressed in classes 0 to 6.[13] Details on this topic have already been published by us.[14]

Phazet skin prick tests (SPTs) were performed with a positive control, a negative control, and 14 allergens: tree pollen (birch, alder), grass pollen (cocksfoot, timothy), weed pollen (mugwort, plantain), house dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*), mould (*Alternaria*), cat dander, dog dander, horse dander, rabbit dander, and guinea pig dander.[15, 16] Medication that might influence skin testing had been withheld for the appropriate period of time.[17] All SPTs were performed unblinded by the first author (M.C.) on the ventral side of both arms, with a minimum distance between two tests of 4 cm. Weals were outlined after 15 minutes and the sizes were transferred to paper by means of tape.

The allergens selected for SPTs and RASTs were the most common inhalant allergens in our region.[18]

Reference diagnoses

In a modified Delphi consensus procedure,[19] three experts endeavoured to reach consensus on the presence or absence of allergic and non-allergic nasal pathology in each patient, using a specified list of diagnoses, including allergic rhinitis and 12 different nasal allergies. In this paper, only the results on the 7 nasal allergies which showed the highest prevalences (those mentioned in the introduction) will be presented. Two experts, an allergologist and an ENT specialist, were selected for their specialist expertise. The third expert, a general practitioner, was included in order to ensure final diagnoses which also reflected the view of a primary care physician; this was considered important because specialists in the Netherlands deal with referred populations only.[20, 21] The procedure consisted of three rounds, the first two performed anonymously. For each diagnosis, the final outcome was 'consensus: disease absent', 'consensus: disease questionable', 'consensus: disease present', or 'no consensus'. Further details have been described in Chapter 5.

The diagnoses of the experts were based on their interpretation of both clinical findings, i.e., symptoms and signs, and paraclinical findings, such as the results from the RASTs and skin prick tests. In addition to the findings mentioned above, the following findings were also presented to them: a copy of the completed questionnaire, comprising 271 items; findings from a physical examination of the nose and throat;[5, 11] ultrasonography of the maxillary sinuses;[22] nasal smear eosinophilia;[11, 23] total IgE; and the Phadiatop test.[14]

Data analysis

To facilitate analysis and interpretation, we chose to compare only those patients diagnosed as 'consensus: disease present' with those diagnosed as 'consensus: disease absent'; for most allergies, this involved 98% or more of the patients.

All clinical and paraclinical variables were dichotomized. From the symptoms, only the ones mentioned in the section 'medical history' were eligible for the regression analysis; items registered as 'uncertain' were recoded as negative. On the basis of bivariate analyses, which will be shown in the results, the RASTs were considered positive if class 1 or higher. All SPTs were recorded in two ways: first, as the mean weal diameter (MWD), i.e., the mean of the largest diameter and the perpendicular diameter through the middle of the largest one; second, as the histamine-equivalent weal diameter (HEWD), i.e., the ratio of the MWD of the reaction against the allergen to the MWD of the reaction against the histamine control. In the case of both MWD and HEWD, when a negative control showed a reaction equal to or larger than the reaction to the allergen, the

outcome '0' was noted. Where two allergens were used for the same diagnosis, e.g., alder and birch pollen for tree pollen allergy, the maximum outcome was recorded. On the basis of the results, which are shown below, the SPTs were considered positive if the mean weal diameter (MWD) was 3 mm or larger.

Multiple logistic regression analyses were performed to find the best combinations of variables to discriminate between patients diagnosed 'nasal allergy present' and patients diagnosed 'nasal allergy absent'.[24] For each of the nasal allergies, four models were assessed, using the following combinations of data: medical history only; medical history and RAST; medical history and SPT; and medical history, RAST, and SPT. For multivariate analyses, the statistical programme SPSS/PC+, 3.0.1 was used.

To compare the diagnostic power of these models, various cut-off points were chosen for each model, resulting in various combinations of sensitivity and specificity. These were then combined in a 'Receiver Operating Characteristic' (ROC) curve.[25] The area under this curve (AUC) served as an instrument to express the discriminative power of the model: the higher the AUC, the better the discrimination between patients diagnosed 'nasal allergy present' and those diagnosed 'nasal allergy absent'; an AUC of 1.00 signifies a perfect discrimination, an AUC of 0.50 indicates a performance comparable to chance.[25]

As regression functions are difficult to apply in daily practice, we wanted to draw up simple diagnostic criteria that would be easier to use, but would still have a diagnostic power similar to the power of the regression functions. On the basis of the regression models, the RAST and SPT outweighted the medical history. Therefore, we started by drawing up criteria that used RAST or SPT only. Next, by studying the false outcomes in detail, we found that using a single item from the medical history in the case of a RAST class 1 or an SPT of 3 mm resulted in the best attainable simple diagnostic criteria. Only in the case of house dust mite allergy were more items from the history required, including items that had not been found to be independent predictors by the logistic regression analysis.

These simple diagnostic criteria were drawn up in such a way that the patients could be stratified as having a high, medium, or low probability of being diagnosed by the experts as having a nasal allergy. Likelihood ratios and posttest probabilities were analyzed for these three outcomes, using the prevalences found in this study. Confidence intervals were calculated using the statistical programme 'CIA'.[26]

Ethics

The study protocol was approved by the Ethics Committee of the Academic Hospital, Leiden.

Results

First, we examined the relationship between the RASTs and skin prick tests on the one hand, and the expert diagnoses on the other, without taking into account the medical

Table 7.1. Comparison of radioallergosorbent tests (RASTs) with expert consensus diagnoses of nasal allergies in 361 patients with chronic or recurrent nasal symptoms*

	expert consensus diagnoses of nasal allergy															
	tree pollen		grass pollen		weed pollen		housedust mite		mould		cat dander		dog dander	
RAST class	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	307	4	272	6	328		243	7	349	1	317	5	324	2		
1	1	2	1	2	5	2		10	2		1	6		4		
2		18		18		19		20		5		12		11		
3		15		20		4		27		2		14		8		
4		5		18		1		24				3		1		
5		1		8				12				1				
6		2		12				2								
total	308	47	273	84	333	26	243	102	351	8	318	41	324	26		
excl.**	6		4		2		16		2		2		11			

* from 4 out of 365 patients, no blood sample was obtained.

** patients were excluded from analysis if the experts did not reach consensus on the presence or absence of the nasal allergy.

history. It proved possible to select a single cut-off point for all diagnoses which resulted in a small number of false outcomes. For the RASTs, this was ≥ class 1 (Table 7.1), and for the skin prick tests MWD ≥ 3 mm (Table 7.2). For all diagnoses, there was a tendency for the mean weal diameter to show a better performance than the histamine-equivalent weal diameter, although the difference was not statistically significant (See Appendix 4, Table 10 and Table 11). The dichotomized outcomes of RASTs and skin prick tests were used for the logistic regression analyses.

Next, the diagnostic power of the different combinations of history and additional tests was studied for each nasal allergy, by assessing the areas under the receiver operating characteristic curves (AUC) of the logistic regression models. The results for house dust mite allergy, which showed the highest prevalence, are given in detail. When the medical history only was used, the diagnostic power of the logistic regression model was 0.77 (95% confidence interval (CI): 0.71 - 0.83). When either RAST or SPT was added, the diagnostic power improved significantly to 0.989 (95% CI: 0.975-1.000). Combining the medical history with both tests led to the highest achievable diagnostic power of 1.000 (95% CI: 0.998-1.000), which was not, however, significantly better than the models that used only one of the two tests.

Table 7.2. Comparison of skin prick tests, expressed as mean weal diameters (MWD), with expert consensus diagnoses of nasal allergies in 365 patients with chronic or recurrent nasal symptoms

	expert consensus diagnoses of nasal allergy															
	tree		grass		weed		housedust				cat		dog	
MWD	pollen		pollen		pollen		mite		mould		dander		dander	
(mm)	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	284	5	254	1	325	13	210	2	343	2	307	5	299	3
1	11	1	5		3		15		4		3	3	11	1
2	12	2	11	3	6	2	16	1	7		10	2	12	3
3	2	4	3	6	3	3	2	11	1	1	2	5	5	5
4	2	3	2	4		4	1	16		1		9		8
5-9		25		41		4	2	55		3		15		7
10-14		7		26				18		1		2		
15-24		1		4										
total	311	48	275	85	337	26	246	103	355	8	322	41	327	27
excl.*	6		5		2		16		2		2		11	

* patients were excluded from analysis if the experts did not reach consensus on the presence or absence of the nasal allergy.

Likewise, findings were recorded for the other 6 nasal allergies under study (Table 7.3). Three findings emerge from this table. First, for most allergies, combining information from the medical history with either RAST or SPT led to a significantly better discrimination than the use of the medical history only. Second, for all the diagnoses, there was no significant difference between the performance of the medical history when combined with RAST, and the performance of the medical history when combined with SPT, although there was a tendency for the combination with RAST to display a better discrimination. Third, performing both tests on the same patient did not produce significantly better results than performing only one test.

As alternatives for the complex regression functions, simple diagnostic criteria for the diagnosis of the nasal allergies were drawn up, which combine items from the medical history with either RAST or SPT (Figure 7.1 and Table 7.4). The diagnostic power of these criteria is given in the form of AUCs in Table 7.5. A comparison of these AUCs with those in Table 7.3 showed that the diagnostic power of the simple criteria did not differ significantly from the diagnostic power of the regression models.

Table 7.3. Diagnostic power, expressed as the area under the curve (AUC) of the receiver operating characteristic curve, of multiple logistic regression functions, using expert consensus diagnoses of nasal allergies as references

	expert consensus diagnoses of nasal allergy															
components of the logistic regression function	tree pollen		grass pollen		weed pollen		house dust mite		mould		cat dander		dog dander	
	AUC	(SE)	AUC	(SE)	AUC	(SE)	AUC	(SE)	AUC	(SE)	AUC	(SE)	AUC	(SE)
MH	0.83	(0.04)	0.82	(0.03)	0.85	(0.05)	0.77	(0.03)	*		0.85	(0.04)	0.89	(0.04)
MH + RAST	0.97	(0.02)	0.99	(0.01)	0.99	(0.01)	0.99	(0.01)	0.93	(0.06)	0.97	(0.02)	1.00	(0.01)
MH + SPT	0.97	(0.02)	0.98	(0.01)	0.90	(0.04)	0.99	(0.01)	0.87	(0.08)	0.92	(0.03)	0.95	(0.03)
MH, RAST, and SPT	1.00	(0.00)	1.00	(0.00)	1.00	(0.01)	1.00	(0.00)	1.00	(0.01)	1.00	(0.00)	1.00	(0.00)

SE: standard error. MH: medical history. RAST: radioallergosorbent test. SPT: skin prick test.

* for mould allergy, there were no predictors from the medical history.

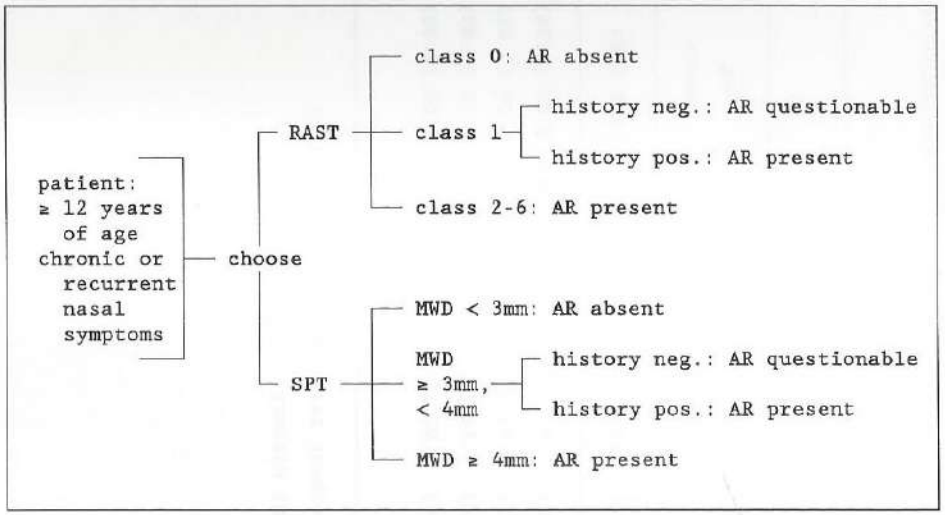

Figure 7.1. Diagnostic criteria for the diagnosis of allergic rhinitis (AR) in patients with chronic or recurrent nasal symptoms; see the Methods for details on the radioallergosorbent test (RAST), the skin prick test (SPT) and the mean weal diameter (MWD); see Table 7.4 for details on the history.

Table 7.4. Items from the medical history that are part of the diagnostic criteria for the diagnosis of allergic rhinitis (See Figure 7.1)

nasal allergy	occurrence of nasal symptoms
tree pollen	in the spring only/worse
grass pollen	in the spring or summer only/worse
weed pollen	in the summer only/worse
house dust mite	on contact with house dust, when making beds, when staying in the bedroom, or when staying indoors
mould	(no positive history)
cat dander	on contact with cats
dog dander	on contact with dogs

Finally, in order to present the value of the diagnostic criteria in a more comprehensible way, likelihood ratios and posttest probabilities for the three outcomes of all criteria are also presented in Table 7.5. For the 'RAST criteria' the posttest

probability of a negative outcome was 2% or lower, except for house dust mite (3%); the posttest probability of a positive result was for all allergies 100%, except for weed pollen (90%). A comparison between the posttest probabilities of the 'RAST criteria' and the posttest probabilities of the 'SPT criteria' showed that there was a tendency for most 'RAST criteria' to perform better. However, this difference reached statistical significance only in the case of weed pollen allergy.

Discussion

This study is the first to compare the diagnostic value of radioallergosorbent tests (RASTs) with that of skin prick tests (SPTs), in combination with the medical history, for the diagnosis of allergic rhinitis in general practice. Combining the medical history with either RASTs or SPTs resulted in a near-perfect discrimination of patients with and patients without the common nasal allergies; this discrimination was significantly better than that provided by the medical history only. Moreover, this discrimination, which was obtained by using complex logistic regression functions, could be obtained equally well with the aid of simple diagnostic criteria, applicable in daily practice.

Our finding that a RAST class 1 indicated a potential clinical relevance, and class 2 or higher a clinically relevant sensitization, is in accordance with a recently published review on testing for inhalant allergy in asthma.[27]

Another interesting finding of this study was that SPTs did not perform better than RASTs; this has been suggested by some authors,[8, 9] but rejected by others.[28] Most of the 'RAST criteria' showed a tendency to perform better, which may be due to the use of the recently introduced CAP system for RAST, which has a greater sensitivity than the paper disk method.[12] It should be noted that in this study the SPTs were performed and read by a single experienced physician; in the hands of less experienced persons, this might result in a lower reliability. Other disadvantages of SPTs are the need to suspend medication that might influence skin testing, and a lack of reliability in patients with significant eczema. The advantage of SPTs most often stressed is the lower cost in comparison with RASTs. However, if the performance of SPTs demands referral to a specialist, RASTs may prove to be cheaper. In addition, it has been suggested that performing RASTs only in those patients who show a positive Phadiatop test, would lead to a reduction in costs.[27] The remaining advantages of SPTs may be a quicker test result and a more impressive result in the eyes of the patient. Because the performance and interpretation of SPTs requires experience and special knowledge, these should be used only by physicians who are willing to invest a certain amount of time. For them, it may be useful to know that the assessment of the HEWD, which is preferred by some physicians because it is believed to correct for the non-specific hyperreactivity of the skin,[29] did not produce any better results than the easier assessment of the MWD. This agrees with the findings of other researchers.[30]

Table 7.5. Performance of diagnostic criteria (as documented in Figure 7.1 and Table 7.4) for nasal allergies; results are based on expert diagnoses in 365 patients with chronic or recurrent nasal symptoms in general practice

nasal allergy	test chosen for the diagnostic criteria	outcome of the diagnostic criteria	patients (n)* disease absent	patients (n)* disease present	likelihood ratio (95% CI)	% predicted probability** (95% CI)	AUC (SE)
tree pollen	RAST	-	307	4	0.09 (0.03-0.24)	1 (0-3)	0.96 (0.02)
		?	1	-	0.00 (***)	0 (***)	
		+	-	43	∞ (***)	100 (92-100)	
	SPT	-	307	8	0.17 (0.08-0.36)	3 (1-5)	0.91 (0.03)
		?	1	1	6.48 (0.40-105)	50 (1-99)	
		+	3	39	84.2 (25.0-283)	93 (81-99)	
grass pollen	RAST	-	272	6	0.07 (0.03-0.17)	2 (1-5)	0.96 (0.01)
		?	1	1	3.25 (0.20-52.5)	50 (1-99)	
		+	-	77	∞ (***)	100 (95-100)	
	SPT	-	270	4	0.05 (0.02-0.13)	1 (0-4)	0.97 (0.01)
		?	3	2	2.16 (0.04-13.1)	40 (5-85)	
		+	2	79	128 (30.8-531)	98 (91-100)	
weed pollen	RAST	-	328	-	0.00 (***)	0 (0-1)	0.99 (0.01)
		?	2	-	0.00 (***)	0 (0-84)	
		+	3	26	111 (31.5-391)	90 (73-98)	
	SPT	-	334	15	0.58 (0.30-1.12)	4 (2-7)	0.71 (0.06)
		?	1	-	0.00 (***)	0 (***)	
		+	2	11	71.3 (15.0-339)	85 (55-98)	
house dust	RAST	-	243	7	0.07 (0.03-0.15)	3 (1-6)	0.97 (0.01)
		?	-	5	∞ (***)	100 (48-100)	
		+	-	90	∞ (***)	100 (96-100)	
mite	SPT	-	241	3	0.03 (0.01-0.10)	1 (0-4)	0.98 (0.01)
		?	2	1	1.19 (0.11-13.3)	33 (1-91)	
		+	3	99	78.8 (24.4-254)	97 (92-99)	
mould	RAST	-	349	1	0.13 (0.02-1.01)	0 (0-2)	0.94 (0.06)
		?	2	-	0.00 (***)	0 (0-84)	
		+	-	7	∞ (***)	100 (59-100)	
	SPT	-	354	2	0.25 (0.05-1.19)	1 (0-2)	0.87 (0.08)
		?	1	1	44.4 (2.54-774)	50 (1-99)	
		+	-	5	∞ (***)	100 (48-100)	
cat dander	RAST	-	317	5	0.12 (0.05-0.31)	2 (1-4)	0.94 (0.03)
		?	1	1	7.76 (0.48-126)	50 (1-99)	
		+	-	35	∞ (***)	100 (90-100)	
	SPT	-	320	10	0.25 (0.12-0.50)	3 (1-6)	0.88 (0.04)
		?	1	-	0.00 (***)	0 (***)	
		+	1	31	243 (32.4-1831)	97 (84-100)	
dog dander	RAST	-	324	2	0.08 (0.02-0.33)	1 (0-2)	0.96 (0.03)
		?	-	3	∞ (***)	100 (29-100)	
		+	-	21	∞ (***)	100 (84-100)	
	SPT	-	322	7	0.26 (0.11-0.61)	2 (1-4)	0.87 (0.05)
		?	5	1	2.42 (0.27-21.5)	17 (0-64)	
		+	-	19	∞ (***)	100 (82-100)	

CI: confidence interval. AUC: area under the curve of the receiver operating characteristic (ROC) curve. SE: standard error.

* Patients were excluded from analysis if no blood sample was obtained or if the experts did not reach consensus on the presence or absence of the nasal allergy.

** Posttest probability, given the pretest probability, i.e., the prevalence, in the study population.

*** Cannot be calculated.

In the case of all the allergies studied, the performance of both RASTs and SPTs resulted in a virtually perfect discrimination of patients with and without nasal allergy. However, the criteria that used either RAST or SPT already performed extremely well; combining both tests did not result in a statistically significant improvement and was clinically irrelevant.

When performing diagnostic studies on allergic rhinitis, choosing the reference is a problem, because there is no single test that indicates whether allergic rhinitis is present or not.[8] The presence of specific IgE merely indicates sensitization; and this may be found in people who have no symptoms.[31] Therefore, it is generally agreed that the diagnosis must be derived from a consideration of both the clinical and the paraclinical findings.[8] To overcome the limitations of using only one expert, we chose three experts to provide consensus diagnoses to serve as references.

In future research, the diagnostic criteria may be used in general practice studies on allergic rhinitis. As they comprise explicit components, these criteria should be very useful as objective diagnostic tools for the diagnosis of the common nasal allergies.

The clinical implications are the following. Chronic or recurrent nasal symptoms may be caused by allergic rhinitis; in order to identify the causal allergens and to minimize exposure, additional testing will be desired. The diagnostic criteria, presented in this study, provide a simple tool for general practitioners to improve diagnostic certainty with respect to the presence or absence of the common nasal allergies in patients with chronic or recurrent nasal symptoms.

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Chapter 8

The Phadiatop® test for the diagnosis of allergic rhinitis: total IgE no longer functional

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Submitted.

Summary

Background. The Phadiatop test and total IgE are available as an aid to diagnose inhalant allergies. Their value in the diagnosis of allergic rhinitis has not yet been evaluated in general practice.

Aim. To assess the diagnostic values of the Phadiatop test and total IgE for allergic rhinitis in general practice.

Method. Prospective comparison of test results with 'consensus diagnoses' made by three experts in a modified Delphi method, in 361 patients aged 12 or over who visited their general practitioner because of chronic or recurrent nasal symptoms between March 1, 1990 and March 1, 1991.

Results. The prevalence of allergic rhinitis, as assessed by the experts, was 49%. For the Phadiatop, the positive predictive value for allergic rhinitis was 99% (95% confidence interval (CI) 96%-100%), and the negative predictive value 93% (95% CI 88%-96%). By using a third Phadiatop outcome 'borderline', 11 of the 14 false-negative Phadiatop results could be detected. For the total IgE, the positive predictive value was 83% (95% CI 76%-89%), and the negative predictive value 71% (95% CI 65%-77%). If the Phadiatop was known, the total IgE did not contribute any additional relevant information.

Conclusion. The Phadiatop test is a useful tool for the diagnosis of allergic rhinitis in patients with chronic or recurrent nasal symptoms. Provided the Phadiatop test is available, total IgE is irrelevant.

Introduction

Allergic rhinitis is present in about half of the patients with chronic or recurrent nasal symptoms.[1] The medical history is often insufficient to make the diagnosis, especially in patients with perennial symptoms; detection of specific IgE in the patient's serum by means of a panel of radioallergosorbent tests (RASTs) is a useful but expensive aid in confirming the diagnosis.[2] Two types of less expensive laboratory tests are available that assess the serum level of IgE, without identifying the allergen specificity: first, the assessment of total IgE, i.e., the total amount of specific and non-specific IgE,[3] and second, tests that measure the combined amount of specific IgE against inhalant allergens only. An example of the latter type is the Phadiatop test.[4] Thus far, there are no data on the diagnostic value of either of these tests for allergic rhinitis in general practice.

The aim of this study was to assess the predictive values of total IgE and the Phadiatop test for the presence of allergic rhinitis in patients who consulted their general practitioner because of chronic or recurrent nasal symptoms. The references used were 'consensus diagnoses', provided by experts by means of a modified Delphi method; these were based on all clinical findings, i.e., symptoms and signs, together with paraclinical findings, such as RASTs and skin prick tests.

Method

Patients

The patients were selected between March 1, 1990 and March 1, 1991, by 25 general practitioners in 19 practices, situated in both urban and rural areas in the west of the Netherlands. The registered patient population of these practices was approximately 47,250. The following inclusion criteria were used: all the subjects had consulted their general practitioner because of a stuffy nose, a runny nose, an itchy nose, or sneezing, and were 12 years of age or older. Moreover, these symptoms had continued for more than four weeks, had occurred intermittently for more than six months, were seasonal, or were related to a specific place or contact. Of 376 consecutively enlisted patients, 11 were excluded on various grounds.

One general practitioner (M.C.), who had received special training for this study, visited and examined each patient, either at home or at the surgery of the patient's general practitioner. A venous blood sample was taken; after clotting, the blood was centrifuged, and the serum was deep-frozen within 24 h of collection. No blood sample could be obtained from four patients: in three cases the venipuncture failed, and one patient refused to give a blood sample, despite earlier consent. The mean age of the remaining 361 patients was 34 years (range 12-83); 41 patients (11%) were over 50 years of age. There were 152 men (42%) and 209 women.

The study protocol was approved by the Ethics Committee of the Medical School of Leiden University.

Total IgE and the Phadiatop test

Each serum sample was divided into two samples which were coded independently for assessment of total IgE and the Phadiatop test. The tests were performed 'blind' in runs of at least 80 sera. All sera were tested with the recently introduced Pharmacia CAP system,[5] according to the manufacturer's instructions. All tests were performed with ^{125}I-radiolabeled antibodies. Total IgE was determined in duplicate, according to the manufacturer's instructions, and the result was expressed as the mean in kU/l. For assessment of the predictive values, the cut-off point mentioned in the manufacturer's manual was adopted: a total IgE $>$ 100 kU/l was considered positive. The Phadiatop test was expressed as the ratio of the percentage binding of the patient serum to the percentage binding of a reference serum. The Phadiatop test results were given either a negative outcome (ratio $\leq$ 1.00) or a positive outcome (ratio $>$ 1.00).

Reference Diagnoses

In a modified Delphi consensus procedure,[6] three experts endeavoured to reach consensus on the presence or absence of allergic and non-allergic nasal pathology in each patient, using a specified list of diagnoses (In this paper, only the results pertaining to allergic rhinitis are presented). The first two experts, an allergologist and an ENT specialist, were selected for their specialist expertise. The third expert, an experienced general practitioner, was included in order to obtain final diagnoses which also reflected the view of a primary care physician; this was considered important because specialists in the

Netherlands deal with referred populations only.[7, 8] The procedure consisted of three rounds, the first two performed anonymously. For each diagnosis, the final outcome was 'consensus: disease absent', 'consensus: disease questionable', 'consensus: disease present', or 'no consensus'. Further details on this topic are presented in Chapter 5.

The diagnoses of the experts were based on their interpretation of symptoms, signs, and the results of additional tests; in addition to the total IgE and the Phadiatop results, the following data were obtained from all the patients under study: detailed questionnaires, filled in by the patient, comprising the items proposed in the literature;[2, 9, 10] the results of a physical examination of the nose and throat;[9, 11] ultrasonography of the maxillary sinuses;[12] nasal smear eosinophilia;[11, 13] seven to ten radioallergosorbent tests (RASTs);[5] Phazet skin prick tests with a positive control, a negative control, and 14 allergens.[14] The allergens selected for skin tests and RASTs were the most common inhalant allergens in our region.[15]

Statistical Analysis

To facilitate analysis and interpretation, we chose to compare only those patients diagnosed as 'consensus: allergic rhinitis present' with those diagnosed as 'consensus: allergic rhinitis absent'; this comprised 348 (96%) of the 361 patients. The predictive values of the total IgE and the Phadiatop test for the presence or absence of allergic rhinitis were assessed, using the cut-off points given above. Confidence intervals were calculated using the statistical programme 'CIA'.[16]

As we have shown, the Phadiatop test is highly predictive for the presence or absence of positive RASTs against the common inhalant allergens; most of the false negative results could be detected by the introduction of a third Phadiatop outcome 'borderline'.[17] In this study we also investigated whether the use of a third Phadiatop outcome led to a reduction in the number of false-negative Phadiatop outcomes for allergic rhinitis; this third Phadiatop outcome, 'borderline', was defined as a Phadiatop ratio $>$ 0.75 and $\leq$ 1.00. Thus, when this third outcome was used, the Phadiatop outcome 'negative' was defined as a Phadiatop ratio $\leq$ 0.75.

For the diagnosis of allergic asthma, another method to detect false negative Phadiatop test results has been proposed in the literature: in the case of patients whose Phadiatop test is negative and the history questionable or positive, the total IgE may be a useful test.[18, 19] However, this sequential use of the Phadiatop test and the total IgE has not yet been documented. We evaluated this policy for allergic rhinitis.

Cases have been reported in the literature of false-positive specific IgE tests caused by binding of non-specific IgE in patients with very high levels of total IgE; this phenomenon did not occur at concentrations of total IgE less than 2000 kU/l.[20] In the present study, it was investigated whether false-positive Phadiatop test results were associated with a very high level of total IgE.

Results

The experts diagnosed allergic rhinitis in 169 (48.6%) of 348 patients. Both total IgE and the Phadiatop test results were highly significantly correlated with the expert diagnoses. However, the predictive values of the Phadiatop test (positive predictive value 99%; negative predictive value 93%) were significantly higher than those of the total IgE (positive predictive value 83%; negative predictive value 71%): Table 8.1 and Table 8.2.

For the 14 patients whose Phadiatop outcome was 'borderline', the results are presented here in detail. Eleven patients were diagnosed as having allergic rhinitis; 8 of them showed one or more RASTs class 1 or higher (3 x class 1 and 1 x class 2 against house dust mite; 1 x class 2 against grass pollen; 1 x class 1 against cat dander; 1 x class 2 against dog dander; 1 x class 3 and 1 x class 4 against guinea pig dander). The 3 other patients who had been diagnosed as having allergic rhinitis displayed no positive RAST; all three had a positive skin prick test against house dust mite. The remaining 3 patients had been diagnosed as not having allergic rhinitis; they displayed no positive RAST. In conclusion, with the use of the Phadiatop outcome 'borderline', 11 of the 14 false-negative Phadiatop outcomes were identified as 'borderline', as against only 3 true-negative outcomes. The resulting newly-defined Phadiatop outcome 'negative' was true-negative in (177-3)/(191-14)=98% (95% confidence interval: 95%-100%).

To investigate the use of sequential testing, the predictive values of the total IgE were assessed only in those patients who displayed a negative Phadiatop (Table 8.3). This method proved to be less capable of detecting false-negative Phadiatop results than the use of the 'borderline' Phadiatop outcome.

Table 8.1. The correlation between total IgE and allergic rhinitis in 348 patients with chronic or recurrent nasal symptoms*

		allergic rhinitis present	allergic rhinitis absent	total
total IgE (kU/l)	> 100	104	22	126
	≤ 100	65	157	222
	total	169	179	348

sensitivity=104/169=62% (95% CI: 54%-69%)
specificity=157/179=88% (95% CI: 83%-93%)
PV+ =104/126=83% (95% CI: 76%-89%)
PV- =157/222=71% (95% CI: 65%-77%)
PV+: positive predictive value; PV-: negative predictive value; CI: confidence interval.
* Data from 13 patients were excluded from analysis because of a missing 'consensus diagnosis'.

Table 8.2. The correlation between the Phadiatop test and allergic rhinitis in 348 patients with chronic or recurrent nasal symptoms*

		allergic rhinitis present	allergic rhinitis absent	total
Phadiatop test	positive	155	2	157
	negative**	14 (11)	177 (3)	191
	total	169	179	348

sensitivity=155/169=92% (95% CI: 87%-95%)
specificity=177/179=99% (95% CI: 96%-100%)
PV+ =155/157=99% (95% CI: 96%-100%)
PV- =177/191=93% (95% CI: 88%-96%)
PV+: positive predictive value; PV-: negative predictive value; CI: confidence interval.
* Data from 13 patients were excluded from analysis because of a missing 'consensus diagnosis'.
** Between brackets: number of patients with a 'borderline' Phadiatop result (ratio >0.75 and ≤1.00).

Table 8.3. The correlation between total IgE and allergic rhinitis in 191 patients who displayed a negative Phadiatop test result

		allergic rhinitis present	allergic rhinitis absent	total
total IgE (kU/l)	> 100	4	20	24
	≤ 100	10	157	167
	total	14	177	191

sensitivity= 4/14 =29% (95% CI: 8%-58%)
specificity=157/177=89% (95% CI: 84%-93%)
PV+ = 4/ 24=17% (95% CI: 5%-37%)
PV- =157/167=94% (95% CI: 89%-97%)
PV+: positive predictive value; PV-: negative predictive value; CI: confidence interval.

In the 2 patients who displayed a false-positive Phadiatop test result, the total IgE was 512 and 1023. These patients, who were diagnosed as not having allergic rhinitis, had perennial symptoms and no positive RASTs; one patient had no positive skin prick tests, and the other a questionable skin reaction to grass pollen.

Discussion

This study is the first to assess the diagnostic value of total IgE and the Phadiatop test for the diagnosis of allergic rhinitis in general practice. It was shown that the Phadiatop test displayed significantly better predictive values than the total IgE. These results are in agreement with the findings in other populations, i.e., in the general population and in outpatient departments.[3, 18, 19, 21, 22, 23]

An interesting additional finding was that the use of a third Phadiatop outcome 'borderline' (Phadiatop ratio >0.75 and ≤ 1.00) led to the identification of most of the false-negative Phadiatop outcomes. In this way, the percentage of false-negative Phadiatop outcomes, which was already very low (7%), was reduced to only 2%.

Once the result of the Phadiatop test was known, the total IgE did not contribute any additional relevant information. In contrast to what is suggested in the literature, total IgE was not useful in detecting false-negative or false-positive Phadiatop results.

The experts' 'consensus diagnoses' were used as the references; these were based on symptoms, signs, and the results of the additional tests. The latter included the Phadiatop test and the total IgE. Consequently, there was no independent 'blind' comparison with a 'gold standard' of diagnosis, which is usually seen as a prerequisite for diagnostic research.[24] Inclusion of the variables under study in the reference standard may have led to an 'incorporation bias', which may have resulted in estimates that were either too high or too low.[24] Not presenting the results of these tests to the experts, was an option. However, the research question of the present paper was part of an investigation which included several other research questions; to be able to answer all these research questions, it was considered important to obtain reference diagnoses with the highest attainable validity under the circumstances of the study. Therefore, we preferred to present all the results from history, physical examination, and additional tests to the experts. Besides, we are of the opinion that the incorporation bias in the present paper is probably negligible, because the experts' diagnoses could be reproduced 100% correctly by combining the results of the history, RASTs, and skin prick tests regardless of the results of Phadiatop and total IgE (Table 7.3).

The clinical implications of this study are the following. In patients who consult their general practitioner because of chronic or recurrent nasal symptoms, the predicted probability of the common nasal allergies as assessed by means of the medical history alone, will often be too low to warrant difficult and expensive environmental control measures. The Phadiatop has now proven to be a useful test to identify patients with allergic rhinitis. If the Phadiatop is positive, RASTs against the common inhalant allergens should be performed in order to identify causal allergens. To reduce the small

percentage of false-negative Phadiatop outcomes even further, in patients displaying a 'borderline' Phadiatop (ratio > 0.75 and ≤ 1.00), performing RASTs may be considered.

An important advantage of the Phadiatop test would appear the lower cost, since fewer RASTs are required: in patients who display a negative Phadiatop result, no RASTs need be performed. However, this presumed cost-effectiveness has never been investigated in detail. Three factors must be taken into account: the ratio of the costs of the Phadiatop test to the costs of the RAST, the number of RASTs required in the case of a positive Phadiatop outcome, and the prevalence of a positive Phadiatop outcome. As these factors will differ from place to place, no general conclusion can be drawn. In our situation, where the costs of one Phadiatop test were about the same as the costs of one RAST, the number of RASTs to be performed in the case of a positive Phadiatop outcome was estimated at 4, and the prevalence of a positive Phadiatop outcome was about 45%, costs would be reduced by about 30%.

In conclusion, the Phadiatop test is a useful and in all probability cost-effective tool for the diagnosis of allergic rhinitis in patients with chronic or recurrent nasal symptoms. Provided the Phadiatop test is available, total IgE is irrelevant.

Acknowledgements

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Chapter 9

Nasal smear eosinophilia for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis

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Submitted.

Summary

Objectives. To evaluate nasal smear eosinophilia for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis in general practice.
Methods. Nasal smears were obtained from 363 consecutive patients aged 12 or over who visited their general practitioner because of chronic or recurrent nasal symptoms between March 1, 1990 and March 1, 1991. Two observers, and if necessary a third, independently judged the percentage of eosinophils on a four-point scale. The results were compared with 'consensus diagnoses' made by three experts in a modified Delphi method; these were based on all the clinical findings and various additional tests.
Results. The two observers showed agreement on the percentage of eosinophils in 315 (87%) of 363 patients; the linear weighted Cohen's Kappa was 0.33. The prevalence of allergic rhinitis, as assessed by the experts, was 49%. The positive predictive value of nasal smear eosinophilia ($\geq$ 10% eosinophils) for allergic rhinitis was 30/37=81% (95% confidence interval (CI): 65-92%), the negative predictive value 172/312=55% (95% CI: 50-61%). Addition of the result of nasal smear eosinophilia to the information that was already obtained from the medical history, resulted in a significant, however, very small improvement of the discrimination between patients with and without allergic rhinitis. The prevalence of eosinophilic non-allergic rhinitis was 7/349=2.0% (95% CI: 0.8-4.1%).
Conclusions. Nasal smear eosinophilia contributes significantly to the diagnosis of allergic rhinitis; however, this contribution is very small and considered clinically irrelevant. Eosinophilic non-allergic rhinitis has a low prevalence; identifying this disorder is of minor importance. In conclusion, assessment of nasal smear eosinophilia appears to be not functional in general practice.

Introduction

Nasal smear eosinophilia has been recommended as a useful tool for the diagnosis of allergic rhinitis.[1, 2, 3, 4, 5, 6] The advantages of this test compared with others, such as skin tests or radioallergosorbent tests, are: it is inexpensive, the result is available within minutes, and there is no need to refer the patient to a laboratory or specialist. Nevertheless, the impression exists that this test is hardly ever performed by general practitioners. This seems appropriate, since, before recommending any test to general practitioners, its validity and reliability should have been documented in general practice. For nasal smear eosinophilia, this has not been done yet.

In addition to the diagnosis of allergic rhinitis, nasal smear eosinophilia has been suggested to be useful for the diagnosis of a special type of non-allergic rhinitis. Among patients with non-allergic rhinitis, diagnosed as such because of perennial symptoms and negative skin tests against inhalant allergens, patients can be identified who have many eosinophils in nasal secretions.[7] This phenomenon has been called "eosinophilic non-allergic rhinitis" (ENR).[8] It is thought to be associated with nasal polyps, but the pathophysiologic background is unclear.[8] Identifying patients with ENR may be useful for

choosing medication, as it has been proven that topical corticosteroids are extremely effective.[9]

In this study, we assessed (a) the diagnostic value of nasal smear eosinophilia for allergic rhinitis and (b) the prevalence of ENR in patients who consulted their general practitioner because of chronic or recurrent nasal symptoms. The references used were the 'consensus diagnoses', provided by experts by means of a modified Delphi method; these were based on clinical data, i.e., symptoms and signs, and paraclinical data, e.g., results from skin prick tests and radioallergosorbent tests (RASTs).

Methods

Patients

The patients were selected between March 1, 1990 and March 1, 1991, by 25 general practitioners in 19 practices, situated in both urban and rural areas in the west of the Netherlands. The registered patient population of these practices was approximately 47,250. The following inclusion criteria were used: all the subjects had consulted their general practitioner because of a stuffy nose, a runny nose, an itchy nose, or sneezing, and were 12 years of age or older. Moreover, these symptoms had continued for more than four weeks, had occurred intermittently for more than six months, were seasonal, or were related to a specific place or contact. Of 376 consecutively enlisted patients, 11 were excluded on the following grounds: linguistic problems (n=2), inability to obtain informed consent (n=6), or the patient's reluctance to discontinue medication which might have influenced skin tests (n=3). A total of 365 patients were ultimately included in the study. The mean age was 34 years (range 12-83); 41 patients (11%) were over 50 years of age. There were 152 men (42%) and 213 women. One general practitioner (M.C.), who had received special training for this study, visited and examined each patient within a few days from inclusion, either at the surgery of the patient's general practitioner or at home. The study protocol was approved by the Ethics Committee of the Medical School of Leiden University.

Nasal smear eosinophilia

Anterior rhinoscopy was performed, if necessary after application of a local vasoconstrictor (xylometazoline 0.1%). With a tightly wound cotton swab, a smear was made from the posterior part of the lower or middle turbinate, as described elsewhere.[2] The secretions were spread out to a thin layer on a glass slide and dried in air.[2] Later, the smear was stained by the May-Grünwald-Giemsa method.[2]

Microscopic evaluation was performed blinded by a general practitioner (M.C.) and by a laboratory assistant, who independently judged the percentage of eosinophils semi-quantitatively on a four-points scale.[1] If the judgments differed, a second laboratory assistant was asked to judge the smear blinded, and the median of the three outcomes was chosen as the final result. The general practitioner and the first laboratory assistant received a special training of half a day; the second laboratory assistant was experienced

in evaluating nasal smears.

Reference Diagnoses

In a modified Delphi consensus procedure,[10] three experts endeavoured to reach consensus on the presence or absence of allergic and non-allergic nasal pathology in each patient, using a specified list of diagnoses (Appendix 3). In this paper, only the results pertaining to the presence or absence of allergic rhinitis will be presented. The first two experts, an allergologist and an ENT specialist, were selected for their specialist expertise. The third expert, an experienced general practitioner, was included in order to obtain final diagnoses which also reflected the view of a primary care physician; this was considered important because specialists in the Netherlands provide care for referred populations only.[11, 12] The procedure consisted of three rounds, the first two performed anonymously. Further details on this topic are discussed in Chapter 5.

The diagnoses of the experts were based on their interpretation of all clinical and paraclinical data obtained from the patients under study. For this purpose, in addition to the nasal smear eosinophilia, the following data were obtained: information on current medication, previous diagnoses of nasal pathology, response to treatment, and the outcome of referrals to specialists; detailed questionnaires, filled in by the patient, comprising the items proposed in the literature;[2] results of a physical examination of the nose and throat; ultrasonography of the maxillary sinuses;[13] total IgE; the Phadiatop test;[14] seven to ten radioallergosorbent tests (RASTs);[14, 15] and Phazet skin prick tests with a positive control, a negative control, and 14 allergens.[16] Medication that might influence skin testing had been withheld for the appropriate period of time.[17] The allergens selected for skin tests and RASTs were the most common inhalant allergens in our region.[18]

ENR was not presented as a separate diagnosis on the list, that was used by the experts to give their diagnoses. We presumed this disorder to be present if nasal smear eosinophilia was found in combination with the absence of allergic rhinitis, as agreed by the experts.

Statistical Analysis

First, we assessed the agreement of the general practitioner and the first laboratory assistant on the nasal smear eosinophilia. This agreement was expressed as linear weighted Cohen's Kappa, reflecting the percentage of agreement corrected for the agreement that was to be expected by chance.[19] Linear weighing was used to attach less importance to minor disagreements than to strong disagreements. A Kappa of 1.00 indicates perfect agreement; a Kappa of 0.00 indicates no more agreement than by chance.

Next, the predictive values of nasal smear eosinophilia for the presence or absence of allergic rhinitis were assessed. To identify independent predictors of allergic rhinitis from the combined findings of the medical history and nasal smear eosinophilia, stepwise logistic regression analysis was performed.[20] For this purpose, we combined the dichotomized nasal smear eosinophilia ($< 10\%$ eosinophils; $\geq 10\%$ eosinophils)[2] with the independent predictors from the medical history. These were: sneezing; itchy eyes; 40

years of age or under; more symptoms on contact with animals; more symptoms on contact with house dust or when making beds; and symptoms in the spring or summer (unpublished data, 1995).

Assessment of the predictive values of nasal smear eosinophilia for ENR would be incorrect, because the finding of nasal smear eosinophilia was a built-in part of the definition of ENR. Doing so, would have led to an incorporation bias.[19] Therefore, for ENR we assessed the prevalence only.

Confidence intervals (CIs) were calculated using the statistical programme 'Confidence Interval Analysis'.[21]

Results

The two observers showed agreement on the percentage of eosinophils in 315 (87%) out of 363 patients; two out of the 365 patients refused the smear despite earlier consent. The linear weighted Cohen's Kappa was 0.33. The two observers agreed that nasal smear eosinophilia was less than 5% in 311 (86%) out of the 363 patients; in 48 out of the remaining 52 patients, the two observers gave different judgments (Table 9.1). The third observer judged all these 48 smears, and agreed with the first observer in 21 patients, and with the second observer in 3 patients. Therefore, half of the smears that were evaluated by all three observers, were given three different judgments. Nasal smear eosinophilia, defined as ≥ 10% eosinophils,[2] was concluded to be present in 38 (10.5%) of the 363 patients.

Table 9.1. The agreement between two observers on the percentage of eosinophils in nasal smears of 363 patients with chronic or recurrent nasal symptoms

	observer 2				
observer 1	< 5%	≥ 5% < 10%	≥ 10% < 50%	≥ 50%	total
< 5%	311	5	1	1	318
≥ 5%, < 10%	3	0	0	0	3
≥ 10%, < 50%	22	5	2	0	29
≥ 50%	5	2	4	2	13
total	341	12	7	3	363

The experts had reached consensus on the presence or absence of allergic rhinitis in 349 (96%) out of the 363 patients. For ease of interpretation and analysis we choose to study the findings of these 349 patients only; in this group, the prevalence of allergic rhinitis was 49%. The correlation of the percentage of nasal smear eosinophilia with the diagnosis of allergic rhinitis is presented in Table 9.2. Using the dichotomized outcome, the positive predictive value of nasal smear eosinophilia was found to be 30/37 = 81% (95% CI: 65-92%), the negative predictive value 172/312 = 55% (95% CI: 50-61%).

Table 9.2. Nasal smear eosinophilia in allergic rhinitis; 349 patients with chronic or recurrent nasal symptoms[a]

nasal smear	allergic rhinitis		
eosinophilia	absent	present	total
< 5%	168	132	300
≥ 5%, < 10%	4	8	12
≥ 10%, < 50%	4	24	28
≥ 50%	3	6	9
total	179	170	349

[a]Data from 14 of 363 patients were excluded from analysis because the experts did not reach consensus on the presence of allergic rhinitis.

For practical reasons, it is interesting to know whether nasal smear eosinophilia does contribute to the diagnostic information that can be obtained from the medical history alone. Stepwise logistic regression analysis revealed that nasal smear eosinophilia did contribute significantly to the medical history in the distinction between patients with and patients without allergic rhinitis. However, in the stepwise analysis all six predictors from the medical history were selected prior to the nasal smear eosinophilia, the latter showing the least significant contribution of all (Model Chi-Square improved from 136 to 142; 7 degrees of freedom; p=0.02). Moreover, adding nasal smear eosinophilia to the medical history would not change the positive predictive value of 75%, while the negative predictive value would change from 79 to 75%, which is not statistically significant.

Finally, from Table 9.2 it was concluded that seven out of the 349 patients displayed nasal smear eosinophilia while the experts agreed that these patients did not have allergic rhinitis. Therefore, the prevalence of ENR was estimated at 7/349 = 2.0% (95% CI: 0.8-4.1%). Nasal polyps were found in 14 patients; none of these displayed nasal smear eosinophilia.

Discussion

This study is the first to assess the diagnostic value of nasal smear eosinophilia, additionally to the medical history, for the diagnosis of allergic rhinitis in general practice. Although nasal smear eosinophilia appeared to improve the distinction between patients with and without allergic rhinitis, this improvement was so small, that it should be considered clinically irrelevant.

The percentage of agreement among the observers and the Kappa seem in contrast with each other: agreement was present in 87%, while the Kappa of 0.33 indicated only moderate agreement. This seemingly contradiction is caused by the very low prevalence of nasal smear eosinophilia, causing Kappa to be low. Therefore, a better representation may be given by means of the following text: the observers showed high agreement on the absence of nasal smear eosinophilia, while no reliable conclusion can be made on the degree of agreement on the presence, due to the low prevalence.

A low agreement for the presence would have been in agreement with the statement of others that evaluating nasal smears is difficult and should be done by experienced investigators only.[2] However, if the test's main advances, namely, being quick and inexpensive, should remain standing, it should be evaluated in circumstances that are representative for daily practice. Therefore we did not ask experienced laboratory assistants to judge all smears. To resemble the situation in daily practice, we preferred judgments by less experienced persons, who received a short training.

There may be several other explanations for the low positive predictive value of nasal smear eosinophilia for allergic rhinitis, found in this study. First, we investigated patients who consulted their general practitioner because of chronic or recurrent nasal symptoms. Many of these patients did not have symptoms at the moment they consulted their general practitioner: from a Danish study, it is known that only 20%-25% of the allergic rhinitis patients had symptoms when they consulted their general practitioner.[22] As eosinophilia is correlated with exposure to allergens, it has been recommended to ask asymptomatic patients to return when experiencing symptoms. Moreover, to obtain a higher sensitivity, it has been advised to take three smears on separate occasions.[23] Second, nasal eosinophilia is negatively influenced by viral or bacterial infections.[24] Some patients with allergic rhinitis probably consulted their general practitioner because of an exacerbation of symptoms, caused by an infection. Third, the use of topical corticosteroids reduces the percentage of eosinophils.[25] Some patients in this study already used topical corticosteroids at the time they were included. However, as we choose to evaluate this test under circumstances that were representative for daily practice, we did not want to influence these factors.

For allergic rhinitis, the experts' 'consensus diagnoses' were used as the references; these were based on symptoms, signs, and the results of the additional tests. The latter included nasal smear eosinophilia. Consequently, there was no independent 'blind' comparison with a 'gold standard' of diagnosis, which is usually seen as a prerequisite for diagnostic research.[19] Inclusion of the variable under study in the reference standard may have led to an 'incorporation bias', which may have resulted in estimates that were either too high or too low.[19] Not presenting the results of the nasal smears to the experts, was an option. However, the research question of the present paper was part of an investigation which included several other research questions; to be able to answer all these research questions, it was considered important to obtain reference diagnoses with the highest attainable validity under the circumstances of the study. Therefore, we preferred to present all the results from history, physical examination, and additional tests to the experts. Besides, we are of the opinion that the incorporation bias in the present paper is probably negligible, because the experts' diagnoses could be reproduced 100% correctly by combining the results of the history, RASTs, and skin prick tests regardless of the results of the nasal smears (Table 7.3).

Eosinophilic non-allergic rhinitis (ENR) was found in only 2% of the patients. A correlation between ENR and nasal polyps, as found by others,[8] could not be confirmed. It must be stressed that diagnosing ENR is possible only if skin prick tests are shown to be negative. The only advantage of assessing nasal smear eosinophilia in patients with negative skin tests, is the knowledge that topical corticosteroids are much more effective, compared with non-allergic rhinitis without eosinophils.[9] However, for any type of non-allergic rhinitis, often topical corticosteroids will be prescribed on a trial-basis, making the detection of ENR irrelevant.

A final interesting finding, which was unexpected and therefore not recorded systematically, was the patients' experience. Many patients spontaneously expressed there discomfort when the smear was made. This was seen as far more annoying than the venipuncture or the skin tests. We feel this topic deserves more attention in future studies.[26]

In conclusion, nasal smear eosinophilia is a finding with a low prevalence. For the diagnosis of allergic rhinitis, its contribution to the knowledge already obtained from the medical history is clinically irrelevant. Diagnosing ENR, a disorder which is very seldom, does not have practical consequences. Finally, patients perceive the nasal smears as very annoying. Therefore, nasal smear eosinophilia is not recommended for use in general practice.

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Chapter 10

The diagnosis of non-allergic nasal disorders

10.1. Introduction

As noted in Chapter 1, the aim of this study was twofold: to investigate whether it is possible to distinguish between different types of nasal pathology in patients with chronic or recurrent nasal symptoms in general practice, and to assess the diagnostic value of the medical history, the physical examination, and additional tests that can be carried out by the general practitioner. In the previous chapters, the emphasis was on allergic rhinitis; in this chapter, non-allergic nasal disorders will be discussed.

The problem of choosing reference diagnoses has already been discussed in Chapters 3 and 5. In short, the references chosen were 'consensus diagnoses', provided by three experts by means of a modified Delphi consensus method; these diagnoses were based on all the clinical and paraclinical data obtained from the patients under study. The experts were asked to give their judgments on the presence or absence of allergic rhinitis and the following non-allergic nasal disorders: vasomotor rhinitis, infectious rhinitis, nasal polyps, rhinitis medicamentosa, anatomical obstructions, and 'other diseases'.

After the first round of the consensus procedure, it was clear that the experts displayed far less agreement on the presence of non-allergic nasal disorders than on the presence of allergic rhinitis (Table 5.1). It was decided to restrict the consensus procedure for non-allergic disorders to this first round, which meant that for many patients there was no consensus on the presence of the non-allergic disorders. Accordingly, patients were classified in one of three groups: 'disease present', 'disease absent', and 'no consensus'. A fourth group, 'consensus: disease questionable', was so small that it was excluded from further analysis (See Chapter 5 for further details).

Because the consensus procedure was limited to one round, the first aim of the study was in effect restricted. Because the experts were not given the opportunity to complete the consensus procedure, we do not know whether they would have reached consensus on the non-allergic nasal disorders in many more patients. In addition, the second aim of the study could not be met for all the patients involved in the study. The lack of certain 'consensus diagnoses' meant that the diagnostic value of the medical history, the physical examination, and additional tests for non-allergic nasal disorders was difficult to assess.

It was noteworthy that the experts showed so little agreement on the presence of the non-allergic nasal disorders, and this fact was seen as an indication of the need for further research. It was considered interesting to identify the variables that differentiated between the two groups of patients, diagnosed as either 'disease present' or 'disease absent'. However, the results of such an analysis would not be valid for the whole study population. Therefore, an assessment of the variables that discriminated between the patients diagnosed as 'disease present', and the combined group of patients diagnosed as 'disease absent' or 'no consensus', was also carried out. It was anticipated that the first analysis would yield results that would be more valid to distinguish between two clearly different diagnostic categories, while the results of the second analysis would be more appropriate for application to the whole population presenting with chronic or recurrent nasal symptoms.

In section 10.2, the general methodology pertaining to both these analyses will be

discussed. In section 10.3, the results will be presented and discussed for each of the non-allergic nasal disorders separately: infectious rhinitis, anatomical obstructions, nasal polyps, rhinitis medicamentosa, and vasomotor rhinitis. The diagnostic group 'other diseases' consisted of only 6 patients, whose findings appeared in Chapter 5. The diagnosis of eosinophilic non-allergic rhinitis has already been discussed in Chapter 9. In section 10.4, the phenomenon 'nasal hyperreactivity' will be examined.

10.2. Methods

The methodology concerning the population sample, the collection of data, and the consensus procedure has been presented in detail in previous chapters.

As explained in section 10.1, two problems were studied for each of the non-allergic nasal disorders. The first one concerned the question of which variables discriminated between the categories 'disease present' and 'disease absent'. The second problem pertained to the question of which variables discriminated between the category 'disease present' and the combined group of patients classified as 'disease absent' or 'no consensus'; in other words, can how to detect the category 'disease present' be detected in the whole population of patients with chronic or recurrent nasal symptoms.

For each of the non-allergic disorders, both problems were studied twice: once on the basis of the symptoms and signs alone, and once with the addition of the results from the additional tests. These included nasal smear eosinophilia and the results from ultrasonography. Of the laboratory tests and skin tests, only the Phadiatop test was chosen as the object of study in this chapter, because it was found to be highly predictive for the presence of specific IgE directed against the common inhalant allergens (Chapter 4).

Bivariate analyses were carried out to assess the correlations of the symptoms, the signs, and the results of the additional tests, with the diagnostic outcome classes. Chi-square statistics were performed to select the variables that were eligible for a regression analysis. Multiple logistic regression was performed to identify independent predictors of the 'consensus diagnoses', using a stepwise forward selection procedure.[1] The likelihood ratio chi-square test was used to determine the significance of improvement.[1] For bivariate and multivariate analyses, the statistical programme SPSS/PC+, version 3.0.1, was used.

Only the resulting independent predictors will be presented. For most of the diagnoses, these predictors had about equal odds ratios. Consequently, the number of independent predictors that were positive could be used as a predictor of the actual classification of each patient. This relation will be presented in a table, providing a simple aid for the general practitioner who, by counting the number of independent predictors that are positive, can determine the likelihood that a particular diagnosis is correct. An exception was made in the case of excessive differences between the odds ratios; in that case, unequal weights were given to the independent predictors.

10.3. Results and discussion

The results are presented and discussed for each of the non-allergic nasal disorders. The expert 'consensus diagnoses' are also presented in Tables 5.1 and 5.3. An additional general discussion is held in Chapter 11, including the problem of the incorporation bias.

10.3.1. Infectious rhinitis

Results

All 365 patients were judged by the experts on the presence of infectious rhinitis in the first round of the consensus procedure only: 15 patients (4%) were diagnosed as 'infectious rhinitis present' and 239 patients (66%) as 'infectious rhinitis absent'. In 107 patients (29%), no consensus was reached. The remaining 4 patients (1%), diagnosed as 'consensus: infectious rhinitis questionable', were excluded from analysis.

First, the symptoms and signs were identified that discriminated independently between the patients diagnosed as having infectious rhinitis and those diagnosed as not having infectious rhinitis. Four variables were identified (Table 10.1, upper left quadrant). The correlation of the number of predictors present with the consensus diagnoses is presented in Table 10.2 (upper left quadrant).

Second, this analysis was repeated after adding the results of the additional tests. The Phadiatop test and nasal smear eosinophilia did not contribute to the distinction between the two groups of patients. When the results of ultrasonography were added, the two discriminating signs were substituted in the regression function for a single finding from ultrasonography, i.e., 'backwall echo', which indicates the presence of fluid in the maxillary sinus (Table 10.1, lower left quadrant). The relation between the number of independent predictors that were present and the consensus diagnoses is presented in Table 10.2 (lower left quadrant).

Third, the symptoms and signs were identified that discriminated independently between, on the one hand, the patients diagnosed as having infectious rhinitis and, on the other hand, the group consisting of patients diagnosed as not having infectious rhinitis and those on whom no consensus was reached. Analysis identified four independent symptoms and signs, which were identical to those found in the first analysis (Table 10.1, upper right quadrant). The relation between the number of the predictors that were present and the outcome classes was different (Table 10.2, upper right quadrant).

Fourth, the third analysis was repeated after adding the results of the additional tests. Again, the Phadiatop test and nasal smear eosinophilia were irrelevant for the distinction between the two groups, whereas ultrasonography did provide additional information (Table 10.1, lower right quadrant). The relation between the number of independent predictors present and the outcome classes is presented in Table 10.2 (lower right quadrant).

Table 10.1. Symptoms, signs, and additional tests found to be independent predictors of infectious rhinitis; expert 'consensus diagnoses' based on clinical and paraclinical data were used as the references

	IR present (n=15) versus IR absent (n=239)	IR present (n=15) versus IR absent/no consensus (n=346)
symptoms and signs indicative of IR	- history of yellow or green nasal secretion - history of coughing up phlegm - AR: mucus on the inferior turbinate - AR: vivid red turbinates	- history of yellow or green nasal secretion - history of coughing up phlegm - AR: mucus on the inferior turbinate - AR: vivid red turbinates
symptoms, signs, and results from ultra-sonography indicative of IR	- history of yellow or green nasal secretion - history of coughing up phlegm - ultrasonography: backwall echo	- history of yellow or green nasal secretion - history of coughing up phlegm - AR: mucus on the inferior turbinate - AR: vivid red turbinates - ultrasonography: backwall echo

IR: infectious rhinitis. AR: anterior rhinoscopy.

Discussion

In almost one third of the patients, the experts did not reach consensus on the presence of infectious rhinitis in the first round of the consensus procedure; this finding is in accordance with the lack of literature on infectious rhinitis: although this disorder is often mentioned, original articles focusing on diagnosis are extremely scarce. Because the experts were not given the opportunity to perform the second and third round for this diagnosis, we do not know whether they would have diagnosed more patients as having infectious rhinitis. Nevertheless, by comparing the patients in whom consensus was reached, it was possible to infer the main discriminating variables; these consisted of two symptoms (yellow or green nasal secretion and coughing up phlegm) and two signs (mucus on the inferior turbinate and vivid red turbinates). The same symptoms and signs were found to discriminate between, on the one hand, the patients diagnosed as having infectious rhinitis and, on the other hand, the group consisting of the patients diagnosed as not having infectious rhinitis and the patients in whom no consensus was reached.

*Table 10.2. Relation between the number of independent predictors present and expert 'consensus diagnoses' of infectious rhinitis**

	number of independent predictors present	number of patients according to expert diagnoses		number of patients according to expert diagnoses	
		IR present (n=15)	IR absent (n=239)	IR present (n=15)	IR absent/NC (n=346)
symptoms and signs	0	1	204	1	266
	1	3	33	3	67
	2	6	2	6	12
	3	4	0	4	1
	4	1	0	1	0
symptoms, signs, and additional tests	0	0	164	0	181
	1	2	70	1	124
	2	8	5	4	35
	3	5	0	6	5
	4			3	1
	5			1	0

IR: infectious rhinitis. NC: no consensus.
* See Table 10.1 for the independent predictors.

Looking at the left side of Table 10.2, one might conclude that it is relatively easy to make the diagnosis infectious rhinitis. However, when the whole population sample was studied (the right side of Table 10.2), the situation was less simple. A diagnosis of infectious rhinitis was considered highly probable when 3 or 4 of the symptoms and signs mentioned were present. This was the case in only 5 of the 15 patients diagnosed as having infectious rhinitis. In another 6 patients, in whom 2 of the symptoms and signs were present, the likelihood of infectious rhinitis was estimated at 33%, which is still significantly higher than the prevalence (or pre-test probability) of 4%. The addition of the results from the tests did not appreciably alter the outcome.

The symptom 'yellow or green mucus' and the sign 'mucus on the inferior turbinate' have been found to be significantly related to acute maxillary sinusitis;[2] in that particular study, the colour of the turbinates was not mentioned. Because the lining of the nose and the sinus form a continuum, it is understandable that the more of these predictors that are present, the higher the chance of an infectious 'rhinosinusitis'. In the present study, 'pain on bending' and 'beginning with a common cold', which are significantly related to acute sinusitis,[2] were not found to be discriminating variables of

infectious rhinitis. This may be explained by the inclusion criteria: only patients with chronic or recurrent nasal symptoms were included.

The results of ultrasonography require a closer examination, as the diagnostic value of this technique for the diagnosis of chronic sinusitis or rhinosinusitis has not been documented before. For the diagnosis of acute maxillary sinusitis, this diagnostic tool has proven to be a reliable alternative for radiography.[3, 4] A 'backwall echo' indicates fluid in the sinus. It might be hypothesized that in the case of chronic rhinosinusitis less mucus is produced than in acute sinusitis. This may mean that the sinus contains air, and that a backwall echo may not be present. Moreover, such a backwall echo only indicates the presence of fluid, which is not necessarily infected. In patients with chronic rhinosinusitis, in particular, mucus may also be produced by non-infectious types of rhinitis, and the mucous membranes may be swollen even without infection. Based on the findings presented in Table 10.2, it may be concluded that the addition of this technique does not contribute appreciably to the diagnosis of chronic infectious rhinitis or 'rhinosinusitis'.

Another point which is deserving of attention concerns the method used to gather the data for this study. The experts did not see the patients themselves. Instead, the researcher reported his findings to the experts on paper. He had received special training at an ENT department in performing anterior rhinoscopy and ultrasonography. The reliability and validity of the researcher's findings have not been assessed, and it cannot be ruled out that the findings of an experienced ENT specialist would have been more reliable or valid. Nevertheless, the symptoms in Table 10.1 were highly correlated with the findings from anterior rhinoscopy and ultrasonography, which were obtained blind for the medical history.

On the basis of the present findings, it must be concluded that as yet little is known about the prevalence of infectious rhinitis in patients with chronic or recurrent nasal symptoms in general practice: the experts agreed on the presence of this disorder in 4%, but did not reach consensus in another 29%. Nevertheless, in the light of the results, the following policy is proposed: infectious rhinitis may be considered to be probably present when two or more of the following symptoms and signs are present: a history of yellow or green nasal secretion, a history of coughing up phlegm, mucus on the inferior turbinate, and vivid red turbinates. In all other patients, infectious rhinitis may be considered absent. However, it should be borne in mind that even in the absence of all these four symptoms and signs, the experts did not reach consensus on 62 patients (17%). Therefore, if the chosen management does not lead to an improvement, the diagnosis should be reconsidered.

10.3.2. Anatomical nasal obstructions

Results

Four types of anatomical abnormalities identified by anterior rhinoscopy were recorded: septal deviation, septal spine, septal spur, and hypertrophic turbinates. The findings were

presented to the experts on a four-point scale: absent; small (no obstruction); moderate (obstructive); severe (complete obstruction or a septal spine that is impacting into the inferior turbinate). On the basis of all the reported clinical and paraclinical findings, the experts agreed in 72 (20%) of the 365 patients on the presence of an anatomical obstruction; 209 (57%) were diagnosed as 'consensus: anatomical obstruction absent'; and in 80 patients (22%), no consensus was reached. The remaining 4 patients (1%), diagnosed as 'consensus: anatomical obstruction questionable', were excluded from further analysis. For further analyses, the variables were all dichotomized: positive if 'moderate' or 'severe'; negative if 'small' or 'absent'.

Analogous to the previous section, those symptoms and signs were identified that discriminated independently between the patients diagnosed as having an anatomical obstruction and those diagnosed as not having an anatomical obstruction. Logistic regression analysis identified four variables (Table 10.3, left side). The relation between the number of predictors present and the consensus diagnoses is presented in Table 10.4 (left side). A history of predominantly unilateral blockage was highly correlated (p=0.01) with the outcome, but was not an independent predictor; in other words, it did not contribute any relevant information, once the other four variables were known.

Table 10.3. Symptoms, and signs found to be independent predictors of anatomical nasal obstructions; expert 'consensus diagnoses' based on clinical and paraclinical data were used as the references

	ANO present (n=72) versus ANO absent (n=209)	ANO present (n=72) versus ANO absent/no consensus (n=289)
symptoms and signs indicative of ANO	- symptoms all year round - AR: moderate or severe septal deviation - AR: moderate or severe septal spine - AR: moderate or severe septal spur	- symptoms all year round - AR: moderate or severe septal deviation - AR: moderate or severe septal spine - AR: moderate or severe septal spur

ANO: anatomical nasal obstructions. AR: anterior rhinoscopy.

This analysis was repeated with addition of the results from the additional tests. The Phadiatop test, nasal smear eosinophilia, and the results from ultrasonography did not contribute to the distinction between these two groups of patients.

Next, the symptoms and signs were identified that discriminated independently between the patients diagnosed as having an anatomical obstruction and the group

consisting of the patients diagnosed as not having an anatomical obstruction and the patients on whom no consensus was reached. Logistic regression analysis identified four independent symptoms and signs, which were exactly the same as those found in the first analysis (Table 10.3, right side). However, the relation between the number of predictors present and the outcome classes was different (Table 10.4, right side). This analysis was repeated with the addition of the results from the additional tests. Again, all three additional tests were irrelevant for the distinction between the two groups concerned.

*Table 10.4. Relation between the number of independent predictors present and expert 'consensus diagnoses' of anatomical nasal obstructions**

	number of independent predictors present	number of patients according to expert diagnoses		number of patients according to expert diagnoses	
		ANO present (n=72)	ANO absent (n=209)	ANO present (n=72)	ANO absent/NC (n=289)
symptoms	0	0	82	0	96
and	1	3	120	3	155
signs	2	41	6	41	36
	3	22	1	22	2
	4	6	0	6	0

ANO: anatomical nasal obstructions. NC: no consensus.
* See Table 10.3 for the independent predictors.

Discussion

It must be emphasized that the experts made their diagnoses on the basis of the findings of anterior rhinoscopy, as performed and reported by the researcher. Although the researcher had received special training for this study, the reliability of the researcher's anterior rhinoscopy has not been assessed. Nevertheless, the findings 'symptoms all year round' and 'predominantly unilateral blockage' were highly correlated with the findings from anterior rhinoscopy, which were obtained blind for the medical history, thus supporting the validity of the researcher's diagnostic skills.

It might be suggested that the experts based their diagnoses predominantly on the reported signs, without the interpretation of other clinical findings, although they had been instructed to make the diagnosis only if they believed that there was a relation between the anatomical abnormality and the reported symptoms. However, it is clear from the results presented in Table 10.4, that even in the presence of two or three of the four independent predictors, in some cases the experts agreed on the absence of clinically

relevant anatomical obstructions.

An unexpected finding was that the sign 'hypertrophic turbinates' was not an independent predictor, despite its high correlation with the expert diagnoses ($p<0.0001$). This was due to the high correlation with the signs 'septal deviation' and 'septal spine'. However, these latter correlations remain unexplained.

Despite the fact that the experts were not given the opportunity to perform the whole consensus procedure for this diagnosis, the results clearly indicate which symptoms and signs are most relevant. While a history of nasal symptoms all year round may be indicative of a clinically relevant anatomical obstruction, this diagnosis must also be based on one or more of the following three findings from anterior rhinoscopy: a moderate or severe septal deviation, a moderate or severe - impacting - septal spine, and a moderate or severe septal spur. When three or all four findings are present, the diagnosis is highly probable; when two findings are present, the likelihood is still more than 50% that there is a clinically relevant anatomical obstruction.

It must be emphasized that in many patients with nasal symptoms, there may be anatomical obstructions without clinical relevance, the symptoms being caused by other nasal disorders that are present at the same time. A major problem is the fact that there are no objective criteria as to whether an anatomical abnormality is small (and clinically irrelevant) or moderate (and possibly clinically relevant). Here it must be emphasized that even in the presence of nasal obstructions presumed to be clinically relevant, a conservative waiting policy would appear to be the appropriate approach, as symptoms from nasal obstruction tend to disappear over time.[5]

10.3.3. Nasal polyps

Results

In the case of nasal polyps, all three consensus procedure rounds were performed. This resulted in 14 patients (4%) being diagnosed as 'consensus: nasal polyps present', while for 350 patients (96%) consensus was reached on the absence of nasal polyps. In only one case was the outcome 'consensus: nasal polyps questionable'; this patient was excluded from further analysis. Because there were no patients for whom no consensus was reached, the analysis concerned only the differentiation between two groups.

The only three variables that were significantly correlated with the diagnosis of nasal polyps were 'older than 40 years', 'ultrasonography: backwall echo', and 'anterior rhinoscopy: nasal polyp'. The latter variable was the only independent predictor: in all 14 patients in whom the researcher reported nasal polyps, the experts agreed that they were present. In 2 of these patients, polyps were found on both sides.

Nasal smear eosinophilia was present in 10.5% of all the patients, but absent in the 14 patients diagnosed as having nasal polyps (Chapter 9).

The Phadiatop test was not significantly correlated with the presence of nasal polyps: they were found in 4.5% of the patients with a positive Phadiatop test and in 3.4% of the patients with a negative Phadiatop test.

Discussion

The experts agreed on the presence of nasal polyps on the basis of the information they were given. Again, it must be stressed that this information consisted of the reported findings from anterior rhinoscopy, which was performed by the researcher. This may largely explain the high degree of agreement among the experts. It has been shown that endoscopy, the examination of the internal nose and throat by means of a flexible fibre-optic endoscope, is especially useful in the detection of small polyps.[6] As no such examination was performed in the present study, it cannot be ruled out that there were more patients with nasal polyps.

An interesting finding pertains to the relation between nasal polyps and allergic rhinitis. In the past, it was generally believed that nasal polyps were a sign of allergic rhinitis. On the basis of well-designed studies, the association is now known to be coincidental.[7,8] The results of the present study support the idea that there is no relation, either positive or negative, between these two disorders. It has also been suggested that nasal polyps are part of a triad, consisting of nasal polyps, intrinsic asthma, and intolerance for acetylsalicylic acid.[7] This relation could not be confirmed in the present study.

Despite the methodological problems noted above, it may be concluded that the diagnosis of nasal polyps must be based on the results of anterior rhinoscopy. This may give the impression of stating the obvious; however, it may be more clear now that there are no symptoms that are indicative of nasal polyps, and that performing anterior rhinoscopy may be worthwhile in every patient with chronic or recurrent nasal symptoms. A positive diagnosis can be made if typical nasal polyps are seen: these are pale or grey rounded masses with a smooth surface, more mobile and less sensitive than swollen turbinates when touched with a probe.[9] However, in patients showing unexplained chronic nasal blockage, nasal polyps that cannot be detected by means of anterior rhinoscopy may still be present, and further examination may be considered.

10.3.4. Rhinitis medicamentosa

Results

After the first round of the consensus procedure, the experts reached consensus on the presence of rhinitis medicamentosa in one patient (0.3%). This patient reported the present use of a topical vasoconstrictor more than eight times a day for over a year. In 328 patients (90%), the experts agreed on the absence of rhinitis medicamentosa. In one patient (0.3%) they agreed that this diagnosis was questionable, and in 35 patients (10%) they did not reach consensus. For ease of analysis, these two latter groups were combined with the single patient diagnosed as 'rhinitis medicamentosa present'. This new group was compared with those patients diagnosed as 'consensus: rhinitis medicamentosa absent'.

The following variables were highly correlated with the combined outcome ($p<0.01$): 'frequent use of a topical vasoconstrictor'; 'use of a topical vasoconstrictor for more than 2 weeks'; 'frequent use of a topical vasoconstrictor less than two weeks ago'.

Multiple logistic regression revealed that only the first two variables were independent predictors. The correlation of these two variables with the expert diagnoses is presented in Table 10.5.

Two patients reported the occurrence of nasal symptoms after taking oral medication: one after non-steroidal anti-inflammatory drugs (NSAIDs), the other after NSAIDs or acetylsalicylic acid. The latter patient also experienced shortness of breath.

Table 10.5. Relation between history and expert 'consensus diagnoses' of rhinitis medicamentosa (RM)

	number of patients according to expert diagnoses	
history	RM present or uncertain (n=37)	RM absent (n=328)
none of the findings mentioned below:	2	239
frequent use of a topical vasoconstrictor,	4	62
use of topical vasoconstrictor for > 2 weeks,	0	1
both of these findings	31	26

Discussion

Because of the lack of consensus among the experts on the presence of rhinitis medicamentosa, little can be said about the relevant symptoms or signs. Nevertheless, it is clear which factors determined whether or not this diagnosis was considered by one or more of the experts. The possibility of rhinitis medicamentosa should be considered when a patient reports the frequent use of topical vasoconstrictors for more than 2 weeks at a time. Patients hardly ever attributed their nasal symptoms to oral medication. Although the experts were given information on all the medication used by the patients, they never indicated causal medication that had not already been suggested by the patient.

10.3.5. Vasomotor rhinitis

Results

All 365 patients had been judged by the experts on the presence of vasomotor rhinitis only during the first round of the consensus procedure: 75 patients (21%) were diagnosed

as 'consensus: vasomotor rhinitis present' and 141 (39%) as 'consensus: vasomotor rhinitis absent'; in 146 cases (40%) no consensus was reached. The remaining 3 patients (1%), diagnosed as 'consensus: vasomotor rhinitis questionable', were excluded from analysis.

First, the symptoms and signs were identified that discriminated independently between the patients diagnosed as having vasomotor rhinitis and those diagnosed as not having vasomotor rhinitis. Logistic regression analysis identified seven variables (Table 10.6, upper left quadrant). Most of these were negatively correlated with the diagnosis of vasomotor rhinitis. In other words, the more symptoms and signs present, the higher the

Table 10.6. Symptoms, signs, and additional tests found to be independent predictors of the absence of vasomotor rhinitis; expert 'consensus diagnoses' based on clinical and paraclinical data were used as the references

	VMR present (n=75) versus VMR absent (n=141)	VMR present (n=75) versus VMR absent/no consensus (n=287)
symptoms and signs indicative of the *absence* of VMR	- symptoms on contact with animals - symptoms on contact with housedust/when making beds - itchy eyes - use of a topical vaso-constrictor > 2 weeks - symptoms *not* worse from tension or stress - *no* history of post nasal drip - AR: moderate or severe septal deviation	- symptoms on contact with animals - use of a topical vaso-constrictor > 2 weeks - *not* smoking cigarettes - AR: moderate or severe septal deviation
symptoms, signs, and additional tests indicative of the *absence* of VMR	- use of a topical vaso-constrictor > 2 weeks - positive Phadiatop test	- use of a topical vaso-constrictor > 2 weeks - AR: moderate or severe septal deviation - positive Phadiatop test

VMR: vasomotor rhinitis. AR: anterior rhinoscopy.

chance that the experts had judged vasomotor rhinitis to be absent. For ease of presentation, the only two variables that were positively correlated with vasomotor rhinitis were recoded so that they were also negatively correlated: 'symptoms *not* worse as a result of tension or stress' and '*no* history of postnasal drip'. This made it possible to present the relation between the number of independent predictors present and the consensus diagnoses (Table 10.7, upper left quadrant).

Second, this analysis was repeated with the addition of the results from the additional tests. The Phadiatop test emerged as highly predictive: only one symptom remained as an additional independent predictor (Table 10.6, lower left quadrant). Based on these two predictors, which were both negatively correlated with the diagnosis of vasomotor rhinitis, the distinction between the two groups of patients in question improved. Because the Phadiatop test contributed much more to this distinction than the symptom (Table 10.7, lower left quadrant), a positive Phadiatop test was given double

*Table 10.7. Relation between the number of independent predictors that are present and expert 'consensus diagnoses' of vasomotor rhinitis**

	number of independent predictors present	number of patients according to expert diagnoses		number of patients according to expert diagnoses	
		VMR present (n=75)	VMR absent (n=141)	VMR present (n=75)	VMR absent/NC (n=287)
symptoms and signs	0	3	0	39	111
	1	31	11	32	110
	2	31	35	4	54
	3	8	40	0	12
	4	2	39	0	0
	5	0	12		
	6	0	4		
	7	0	0		
symptoms, signs, and additional test	0	72	16	65	69
	1	2	5	8	48
	2	1	105	2	113
	3	0	14	0	47
	4			0	6

VMR: vasomotor rhinitis. NC: no consensus.
* See Table 10.6 for the independent predictors; a positive Phadiatop test counts double.

weight. Nasal smear eosinophilia and ultrasonography did not contribute to the distinction between these two groups of patients.

Third, the symptoms and signs were identified that discriminated independently between the patients diagnosed as having vasomotor rhinitis and the combined group consisting of the patients diagnosed as not having vasomotor rhinitis and the patients in whom no consensus was reached. Logistic regression analysis identified four independent symptoms and signs. Only one of these had not been found in the first analysis, i.e., '*not* smoking cigarettes' (Table 10.6, upper right quadrant). Compared with the patients studied in the first analysis, the two groups of patients studied in this analysis showed considerably more overlap with respect to the number of the predictors that were present (Table 10.7, upper right quadrant).

Fourth, the third analysis was repeated after adding the results from the additional tests. Again, the Phadiatop test was an independent predictor, while nasal smear eosinophilia and ultrasonography emerged as irrelevant for the distinction between the two groups concerned (Table 10.6, lower right quadrant). The relation between the number of independent predictors present and the outcome classes improved when the result of the Phadiatop test was added (Table 10.7, lower right quadrant).

The high correlation of the Phadiatop with the outcome 'vasomotor rhinitis absent' can also be illustrated by its bivariate results: of all 157 patients with a positive Phadiatop test, 119 were diagnosed as 'vasomotor rhinitis absent', and 1 as 'vasomotor rhinitis present', while in 37 patients no consensus was reached.

Of the 75 patients diagnosed as having vasomotor rhinitis, 62 reported both a stuffy nose and a runny nose or sneezing, 7 sneezing or a runny nose only, and 6 a stuffy nose only. When they were asked to indicate the most annoying symptom, 42 indicated the nasal obstruction and 28 indicated the runny nose or sneezing; 5 could not answer the question.

In these 75 patients, the experts sporadically diagnosed other nasal disorders: allergic rhinitis in 2 patients, infectious rhinitis in 1 patient, nasal polyps in 1 patient, rhinitis medicamentosa in 1 patient, and an anatomical obstruction in 8 patients.

Discussion

In contrast to the diagnoses of the other nasal disorders, the diagnosis of vasomotor rhinitis was characterized by an inverse relation with most of the independent predictors: the more predictors present, the higher the chance that the experts had agreed on the *absence* of vasomotor rhinitis. These independent predictors were related to the following nasal disorders: allergic rhinitis, rhinitis medicamentosa, and anatomical obstructions. These findings are in accordance with the generally agreed concept that the diagnosis of vasomotor rhinitis should be based on the exclusion of other nasal disorders, a so-called 'diagnosis by exclusion'.[10, 11] Recently, it has been suggested that the name 'idiopathic rhinitis' would be more appropriate than 'vasomotor rhinitis', because its etiology is unknown (See Chapter 2).[10]

The only discriminating variables that were positively related to vasomotor rhinitis were 'symptoms worse as a result of tension or stress', 'history of post nasal drip', and 'smoking cigarettes'. The latter might indicate a causal or aggravating role for smoking

cigarettes. Because these variables emerged as independent predictors in only one out of the four analyses, the significance of these findings remains unclear.

As a consequence of the need to exclude other nasal disorders, something which is often difficult to do with any certainty, a diagnosis of vasomotor rhinitis is in itself uncertain. This is reflected in the results, presented on the right side of Table 10.7.

Another interesting finding was that nasal hyperreactivity, i.e., symptoms on exposure to non-specific irritants, was not an independent predictor of vasomotor rhinitis. This is in accordance with the findings from others,[12] and supports the view that nasal hyperreactivity is not characteristic of vasomotor rhinitis, as has often been stated,[10] but may be present in other types of rhinitis as well.[13]

It has been suggested that patients with vasomotor rhinitis form a heterogeneous group consisting of 'blockers', patients with mainly nasal obstruction, and 'runners', patients whose main complaint is a runny nose or sneezing.[10] The type of symptoms may serve as a guide in choosing a therapy (see Chapter 2). In this study, most patients reported both types of symptoms. When asked to indicate which one they perceived as the most annoying, two groups could be identified. However, the clinical relevance of this grouping is unclear, as the patients may have felt pressed to choose just one symptom.

On the basis of the above findings, it may be concluded that, on the one hand, excluding vasomotor rhinitis appears to be acceptable in patients with symptoms and signs that are indicative of other nasal disorders, and especially in patients with a positive Phadiatop test. On the other hand, it is unclear how the diagnosis of vasomotor rhinitis can be established.

10.4. Nasal hyperreactivity

Nasal hyperreactivity is used to indicate an overreaction to non-allergic stimuli such as cigarette smoke, perfume, rapid changes in temperature, and fog. It should not be seen as a distinct disorder, but as a clinical manifestation that may be present in any type of rhinitis.[13] Because it is often present in patients with allergic rhinitis also, it does not actually belong in this chapter on the non-allergic nasal disorders. Nevertheless, the results pertaining to this phenomenon will be discussed here. Only the 'clinical hyperreactivity', which is based on the medical history, is considered here; no nasal provocation tests were performed.

Results

The presence of nasal hyperreactivity was registered on a three-point scale: absent; moderate; severe. For this topic, all three consensus procedure rounds were carried out, resulting in consensus on all 365 patients: nasal hyperreactivity was judged to be severe in 29 patients, moderate in 100 patients and absent in 236 patients.

Logistic regression analysis was performed twice, in order to find the discriminating variables between, first, the patients judged to be severely hyperreactive and all other patients and, second, between the patients judged to be moderately or

severely hyperreactive and the patients judged to be not hyperreactive. The two analyses identified almost the same variables (Table 10.8). Other provoking factors, which do not appear in this Table, were highly correlated with the expert judgments, but were not independent predictors. These were cooking or baking odours; physical exercise or sport; and tension or stress.

Table 10.8. Symptom-provoking factors found to be independent predictors of nasal hyperreactivity; expert 'consensus judgments' based on clinical and paraclinical data were used as the references

	HR severe (n=29) versus HR moderate/absent (n=336)	HR severe/moderate (n=129) versus HR absent (n=236)
provoking factors indicative of HR	- cigarette smoke - perfume - smog - smell of paint	- cigarette smoke - perfume - smog - smell of paint - rapid change in temperature

HR: nasal hyperreactivity.

*Table 10.9. Relation between the number of independent predictors present and expert 'consensus judgments' on nasal hyperreactivity**

number of independent predictors present	number of patients according to expert judgments		number of patients according to expert judgments	
	HR severe (n=29)	HR moderate/absent (n=336)	HR severe/moderate (n=129)	HR absent (n=236)
0	0	197	4	125
1	0	84	14	97
2	7	44	51	13
3	14	11	36	1
4	8	0	19	0
5			5	0

HR: nasal hyperreactivity.
* See Table 10.8 for the independent predictors.

Discussion

It may be concluded from the results that it is fairly easy to discriminate between patients with nasal hyperreactivity, as judged by experts, and patients without nasal hyperreactivity. Moreover, patients with severe nasal hyperreactivity can also be identified with a reasonable degree of certainty.

However, what is the practical use of identifying patients with moderate or severe nasal hyperreactivity in general practice? On the basis of the results shown for each of the non-allergic nasal disorders in this chapter and the results for allergic rhinitis shown in Chapter 6, it was concluded that a history of aggravation of nasal symptoms on exposure to non-specific irritants did not contribute to any of these diagnoses. This is in agreement with the findings of others.[12] Therefore, the presence or absence of nasal hyperreactivity does not help in diagnosing any of the nasal disorders.

It has been suggested that the clinical relevance of nasal hyperreactivity lies not in its diagnostic value, but in its prediction of the effect of treatment: in the case of nasal hyperreactivity, topical corticosteroids have been shown to be very effective.[10] However, in most studies, the assessment of nasal hyperreactivity was based not on the medical history, but on results from nasal provocation tests with histamine or metacholine. Although, in selected patients, a significant relation has been shown to exist between the hyperreactivity resulting from a provocation test and a history of nasal hyperreactivity,[14] this relation has not yet been clarified extensively. Moreover, in choosing medication, there are several other factors that may play a role, such as the presence of a blocked-up nose, the presence of symptoms from the eyes, the duration of the symptoms, whether the symptoms occur intermittently, whether the symptoms occur unexpected, and finally, the patient's preference. In conclusion, the clinical significance of a history of hyperreactivity is probably limited.

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Chapter 11

General discussion and conclusions

11.1. Introduction

General practitioners are frequently consulted by patients who complain of chronic or recurrent nasal symptoms.[1, 2, 3, 4] The majority of these patients are given advice or treatment by the general practitioner on the basis of his diagnosis, and are not referred to a specialist.[3, 5] However, because there are virtually no diagnostic studies in general practice, the general practitioner lacks a scientific foundation for his diagnostic policy. Results from studies in other populations, such as outpatient departments, may not be applicable in general practice, due to bias.[6, 7] This thesis aims at providing information that can be used to formulate guidelines for the diagnostic management of patients with chronic or recurrent nasal symptoms in general practice.

In section 11.2, the major results of the study will be considered. In section 11.3, the limitations and strengths of this study will be discussed; some minor aspects that have already been discussed in the previous chapters will not be reiterated here. In section 11.4, the practical implications of this study will be discussed and a diagnostic policy proposed. Finally, in section 11.5, a number of recommendations for future research will be made.

11.2. The major results

As noted in Chapter 1, the first aim of this study was to investigate whether it was possible to distinguish between different types of nasal pathology in patients with chronic or recurrent nasal symptoms in general practice. The distinction between different types of pathology is the subject matter of classification: the recognition of similarity and the grouping of objects or persons into identifiable classes. The characteristics of classification are:[8]

1) There must be something to perceive or to identify, e.g., symptoms, signs, and the results of tests.
2) We must be able to place these identified elements (e.g., patterns of symptoms and signs) into a class of similar elements (e.g., diseases).
3) We have to know how these classes are interrelated; e.g., how can we distinguish one disease from another, related disease which has analogous patterns.

We found that there was confusion in the literature concerning disease definition and disease classification. Unanimity in the description of the various diseases would appear to be a distant goal. Therefore, we had no clearly documented 'gold standard' on which to base any diagnosis of nasal pathology.

However, for the purpose of our research question - Which symptoms, signs, and tests contribute to the identification of nasal disorders and to what degree do they do so? - diagnoses had to be assigned to the cases in our patient population. Having considered the various taxonomic methods, we selected the consensus method as the method of choice. With the cooperation of three experts in the field, we endeavoured to reach consensus on the presence or absence of nasal disorders in 365 patients, based upon their symptoms and

signs, and the results from in vivo and in vitro tests presented in a written format.

After the first round of the modified Delphi consensus method,[9] consisting of at most three rounds, it was clear that there was considerable agreement on the presence or absence of allergic rhinitis, but less so on the remaining types of nasal pathology. In order to keep the experts' workload within feasible limits, it was decided to restrict the consensus procedure to the first round for most of the non-allergic disorders. Consequently, the first objective, namely, to investigate whether it was possible to distinguish between different types of nasal pathology, was not fully met for all nasal disorders: as the experts were not given the opportunity to perform all three rounds of the consensus procedure for the non-allergic nasal disorders, it remained uncertain whether consensus would have been reached in many more patients. In the case of allergic rhinitis, all three consensus rounds were performed, resulting in agreement in 99% of the patients; a diagnosis of allergic rhinitis was established in 47% of cases.

The second goal of the study was to assess the diagnostic value of the medical history, the physical examination, and in vivo and in vitro tests for the different types of nasal pathology. For this purpose, the expert 'consensus diagnoses' were used as references.

The emphasis was on the diagnosis of allergic rhinitis and its differentiation according to the causal allergens. First, the diagnostic value of the symptoms and signs was analyzed. It appeared that with the aid of a medical history comprising only six questions the estimation of the probability of allergic rhinitis was just as reliable as when the information from all 271 items from the medical history and 38 items from physical examination was used. With the exception of house dust mite allergy, the medical history was very useful in identifying large groups of patients who were unlikely to have a nasal allergy. Only in the case of grass pollen allergy was it possible to establish the diagnosis on the history.

The addition of the findings from either radioallergosorbent tests (RASTs) or skin prick tests resulted in a virtually perfect distinction between patients with and without allergic rhinitis. This distinction was significantly better than that obtained using the medical history only. For most of the nasal allergies, the predictive values, both positive and negative, were 97% or higher.

The Phadiatop test was highly predictive of RAST results: the positive predictive value was 97%, the negative predictive value 95%. Both values could be improved by using two cut-off points for the Phadiatop ratio, resulting in both a negative and a positive predictive value of 99% and a third Phadiatop outcome designated as 'inconclusive'. The predictive values of the Phadiatop for a clinical diagnosis of allergic rhinitis were comparable: the positive predictive value was 99%, the negative predictive value 93%. The latter could be improved by using a second cut-off point, alongside the usual cut-off point for the Phadiatop ratio, resulting in a negative predictive value of 98% and a third Phadiatop outcome 'borderline'. It may be cost-effective to perform RASTs only in the case of a positive or borderline Phadiatop test.

The performance of the total IgE was much less satisfactory than the Phadiatop test; provided the Phadiatop test is available, the total IgE does not contribute to the diagnosis of allergic rhinitis.

Although nasal smear eosinophilia did make a significant contribution to the information from the medical history in the diagnosis of allergic rhinitis, this contribution was so small that it was regarded as clinically irrelevant.

For the non-allergic nasal disorders, the assessment of the diagnostic value of the symptoms, signs, and additional tests was complicated by the fact that in many patients the experts could not reach consensus. Nevertheless, for most diagnoses it was possible to identify the main discriminating variables. By performing two analyses, one for the cases in whom consensus was reached and one for all the patients, two outcomes were obtained. It may be speculated that the results that would have been obtained if the experts had performed the whole consensus procedure would be somewhere in between these two outcomes.

For each of the diagnoses infectious rhinitis, rhinitis medicamentosa, nasal polyps, and anatomical obstructions, a maximum of four symptoms and signs were identified as being most relevant. For infectious rhinitis, in particular, only a rough estimate could be made of the predictive value of the clinical findings. None of the in vivo or in vitro tests, including ultrasonography, contributed appreciably to the diagnosis of these four disorders.

Vasomotor rhinitis was the diagnosis which proved to be most difficult: confirmation of this diagnosis was problematic, while it was relatively simple to exclude if there was a positive Phadiatop test. This reflects the definition of vasomotor rhinitis, which is a diagnosis by exclusion;[10, 11] as a consequence of the need to exclude other nasal disorders, something which is often difficult to do with any certainty, a diagnosis of vasomotor rhinitis is in itself uncertain.

It was fairly easy to discriminate patients with moderate or severe nasal hyperreactivity, as judged by the experts, from patients without nasal hyperreactivity. However, nasal hyperreactivity, defined as the patient's reported overreaction to non-allergic stimuli, such as cigarette smoke, perfume, smog, the smell of paint, and rapid changes in temperature, may be present as a clinical manifestation in any type of rhinitis. Its presence or absence did not help in diagnosing any of the nasal disorders.

11.3. Limitations and strengths of the study

The patients

This investigation is the first to study the diagnostic value of symptoms, signs, and in vivo and in vitro tests in patients with chronic or recurrent nasal symptoms in general practice. Special attention was given to the inclusion of a large group of patients who reflected as closely as possible the broad spectrum of clinical presentations of chronic and recurrent nasal symptoms in a primary care setting. A total of 19 practices were selected for participation, in rural as well as urban areas. In the absence of reliable data on the prevalence of chronic or recurrent nasal symptoms in general practice, estimating the number of patients that were expected to be included was, to a large extent, a matter of guesswork. Nevertheless, the estimation based on the available data proved realistic. Only

11 out of 376 patients were excluded by the general practitioners. Judging by the variation in the numbers of patients included per practice, however, it seems likely that some general practitioners did not include all eligible patients. The distribution of the diagnoses per general practitioner and the frequent personal contacts of the investigator with the general practitioners provided no indication that this exclusion was correlated to the outcome, i.e., certain diagnoses. Therefore, the conclusions drawn are not likely to be biased by this exclusion, except for the exact number of patients who consult their general practitioner because of chronic or recurrent nasal symptoms: this is probably somewhat higher than 9.0 per year in 1000 patients aged 12 or over.

The data

Another focus of attention concerned the method used to collect the data. The experts did not see the patients themselves; instead, the researcher, who was specially trained for the physical examination and the performance of the tests, reported his findings to them on paper. As he was the sole observer, a degree of observer bias cannot be excluded, especially with respect to the physical signs. In the view of the experts, the data appeared both complete and reliable for allergic rhinitis. The high correlation between results from skin prick tests and RASTs and between certain symptoms and findings from anterior rhinoscopy and ultrasonography appear to reflect the validity of the observations. Whether clinical judgments based on written documentation differ significantly from those based on personal observations, is a matter of debate. In the literature on clinical decision-making, judgments based on well-documented written stories appear to be more accurate than those based on the 'flair clinique' of the practising physician.[8] In the case of allergic rhinitis, we are proceeding on the assumption that the method employed here is adequate and valid.

The consensus procedure

As a rule, consensus methods are used to define levels of agreement on controversial subjects. The characteristics of several major methods have been published elsewhere.[9, 12] For the present study, Delphi was selected because it has the advantage of giving all the participants an equal opportunity to express their opinion. Moreover, being a structured indirect-interaction technique, it should provide more accurate judgments than those from an unstructured technique (brainstorming), a semi-structured direct-interaction technique (the procedure used by the Dutch College of General Practitioners: NHG), or a structured direct-interaction technique (Nominal Group Technique: NGT; U.S. National Institutes of Health: NIH; or the Dutch National Organization for Quality Assurance in Hospitals: CBO).[12] Finally, Delphi is especially useful for use by experts from different backgrounds and with different levels of expertise. Past criticism of Delphi was based mainly on studies which departed from the original intentions of the Delphi technique.[12]

In our study, the Delphi technique was also modified. First, instead of asking experts to express their opinion on a general problem, i.e., how to diagnose nasal disorders in general practice, they were asked to express their opinion on the presence of these disorders in a number of patients representative of general practice. Second, because of practical reasons, the number of experts was restricted to three. Due to these

modifications, which were necessary in order to obtain expert consensus diagnoses in real patients, it is difficult to assign the properties of the original Delphi technique to our modified procedure.

Finally, no matter which consensus method is used, there is no guarantee that an assessment is accurate simply because a group of experts ultimately agree on it.[13] However, it is hoped that consensus techniques, when properly employed, will create a situation in which experts are given the best available information, and will make their solutions to problems more justifiable, valid, and credible than otherwise.[9] In order to optimize the circumstances and to increase the chances of achieving the hopes of consensus, before this study started the experts were asked whether they considered our method appropriate, with regard to which data were to be obtained, how to obtain the data, how to present the results to the experts, how to register their opinion on the presence of the different nasal disorders and, in particularly, which nasal disorders were to be judged as being present or absent. For all these items, proposals were formulated on the basis of the literature; if necessary, modifications were made in the light of the experts' comments. This method also resulted in the nomenclature used in this study (Appendix 3). It will be clear that the criteria for deciding whether consensus had been reached were not made known to the experts.

In the literature, a distinction is often made between seasonal allergic rhinitis and perennial allergic rhinitis;[11, 14] some readers may find it surprising that such a distinction was not made in the present study. However, it appeared from the symptoms reported by the patients in this study that this distinction is far from clear: over one fourth of the patients experienced perennial symptoms with seasonal exacerbations, while another 10% could not indicate any relation, for instance, because the symptoms lasted less than a year. Moreover, of the patients with seasonal symptoms, many indicated that autumn or winter was the season with the most symptoms, whereas exacerbation in the spring and summer was related only to allergic rhinitis. Therefore, the classification of allergic rhinitis should not be based on the seasonality of the symptoms. Instead, a classification that indicates the causal allergens would appear more appropriate; it is clinically more relevant, as it is in accordance with the concept that reduction of the exposure to the causal allergens is the first goal of management.

From a general practitioner's point of view, it may seem a bit peculiar that not a single patient was given the consensus judgment 'no nasal disorder'. Each general practitioner probably knows some patients who frequently consult for symptoms which are unlikely to be caused by a disorder, but are more likely to be normal physiologic phenomena, experienced by the patient as abnormal. In the design of this study, where the experts' diagnoses were based on written data from patients unknown to them, it would be impossible to recognize such patients; they were probably diagnosed as 'vasomotor rhinitis', as this is a diagnosis by exclusion.

The reproducibility of the experts' judgments has not been examined. Although this may appear to be an interesting issue, it was not considered relevant for the conclusions of this study because the final product of the consensus procedure was the result of a maximum of three rounds and judgments from three experts. To change a patient's diagnosis in a study on reproducibility, all three experts would have to change

their judgment at the same time. On the assumption that each expert would give a contradictory judgment ('1' or '2' instead of '4' or '5' or vice versa; see Chapter 5) in 1 out of 10 patients if he had to diagnose them for the second time, without knowing his first judgment, the chances of this happening are $(1/10)^3=0.001$. Even if all three experts were to give a contradictory judgment in 1 out of 5 patients, the chances of a patient being given a contradictory diagnosis would be $(1/5)^3=0.008$.

As there is no 'gold standard', validation of the outcome of the consensus procedure would appear to be impossible. In fact, the most important aspect of validity which is attainable is the 'face validity', i.e., the opinion of the readers of this thesis on whether or not the method would appear to result in an acceptable reference. The outcome of the sensitivity analysis (Chapter 5), will assist them in making a decision.

The references

It may be seen as a major drawback of this diagnostic study that we did not use an independent reference; the 'consensus diagnoses' were the references. These were based on all the clinical data (symptoms and signs) and paraclinical data (results from in vitro and in vivo tests) obtained from the patients under study.[15] The same clinical and paraclinical data were analyzed for their 'predictive value' with respect to the expert diagnoses. Consequently, there was no independent, 'blind' comparison with a 'gold standard' of diagnosis, which is usually seen as a prerequisite for diagnostic research.[15] Including the variables under study in the reference standard may lead to an 'incorporation bias', resulting in estimates that are either too high or too low, and this is generally considered inadvisable.[15] It has even been maintained that by allowing this type of bias, the investigator works out a 'sure bet' arrangement.[16]

However, the design of this study was a well-considered choice, based on the view that there were no appropriate independent references available. As mentioned in the introduction of Chapter 5, various independent references were judged to be inappropriate. These included the outcomes of a follow-up study, in which the natural course or the outcome of therapy would have been investigated. As we wanted to investigate a number of different nasal disorders at the same time, several problems would have to be solved first: most of these disorders are chronic, making it virtually impossible to define endpoints, and many patients were expected to suffer from more than one nasal disorder at the same time. At this point, it must be noted that at the time of this study, quality-of-life instruments for allergic rhinitis had not yet been evaluated; in future studies, such instruments may serve as an important aid. Of the other alternative references, the choice a single independent test was likewise rejected. There is no diagnostic test that can be used as a single indicator of the presence of nasal disorders, in particular allergic rhinitis;[11] specific IgE only indicates sensitization and may be present in patients without symptoms,[17] while nasal provocation tests are regarded as insufficiently standardized for general use as a diagnostic tool.[11]

In the absence of a definitive standard, consensus procedures have been suggested to obtain reference diagnoses from experts.[16] It is generally accepted that the diagnosis of nasal disorders, in particular allergic rhinitis, should be based on a consideration of both clinical and paraclinical findings.[11, 18] For this reason, we opted to present symptoms,

signs, and the results of the additional tests to the experts, who used these data to assess the reference diagnoses; these in turn were used to assess the predictive values of the clinical and paraclinical findings.

The assessment of diagnostic values is no more than an approximation of the true values, which remain unknown because of the impossibility of determining 'true disease'. The aim of diagnostic studies is to make the best possible estimation of the true values. As a rule, this includes choosing an independent reference. However, problems arise if there is no generally accepted independent reference. Choosing an independent reference that is generally regarded as insufficiently valid may result in estimates of the 'true' diagnostic values that are less accurate than those obtained by means of a dependent reference, which is generally considered more valid. In other words, the bias that results from choosing an independent but improper reference may be greater than the incorporation bias that results from using a dependent but more valid reference. In our opinion, this is indeed the case where the diagnosis of allergic rhinitis is concerned. There is no acceptable reference that does not include both clinical and paraclinical findings.

One might maintain that because of the incorporation bias, we are not justified in referring to 'diagnostic values'. However, proceeding on the assumption that diagnostic values are no more than an approximation of the true predictive values, which remain unknown because of the impossibility of establishing 'true disease', it follows that the occurrence of any bias, whether an incorporation bias or another type, does not automatically make the results inaccurate. In other words, whether or not the results are called 'diagnostic values', does not depend on the presence of a certain type of bias, but on the magnitude of this bias. Whether our method leads to a larger or smaller bias than other methods, remains a question for debate, focusing on the validity of the expert 'consensus diagnoses'.

It might be said that our study has merely identified the variables that were used by experts in their diagnostic processes. This may be true, although we deliberately made no effort to open the black box of their mental processes; we merely tried to reproduce the outcome, i.e., the diagnoses. In our opinion, the analysis of expert diagnoses in true patients is considerably more relevant than simply asking experts how the diagnosis should be performed: it has been shown that clinicians are not fully aware of their own diagnostic processes, and that doctors do not always think the way they think they do.[19] When asked to recall these unknown processes, they tend to theorize. Nevertheless, it should be stated that our study merely reproduces the diagnoses made by experts. As mentioned in Chapters 3 and 5, in diagnostic as well as therapeutic studies on allergic rhinitis, it was accepted that the diagnoses were made by a single experienced clinician;[20, 21, 22, 23] this may be explained by the generally approved statement that the diagnosis of allergic rhinitis can usually be agreed on when history, physical examination, and radioallergosorbent test (RAST) or skin prick test (SPT) results are combined.[24] On the basis of these points and the remarks mentioned in the previous sections, we consider our method to be adequate and valid for allergic rhinitis.

In contrast, in the case of the non-allergic nasal disorders, the validity of our results should be questioned. First, these diagnoses were based predominantly on the

physical signs obtained by the researcher; these signs may be less valid or reliable than the symptoms and the results from in vivo and in vitro tests used for the diagnosis of allergic rhinitis. Second, in the first round of the consensus procedure the experts displayed considerably less agreement on the presence of the non-allergic disorders, probably indicating a lower validity and reliability for these diagnoses. Third, in order to reduce the experts' workload, it was decided to restrict the consensus procedure for the non-allergic disorders to one round; consequently, the results were less accurate. We could have chosen to omit the results on the non-allergic nasal disorders. Instead, we considered it relevant to present our findings, not only to stress the problematic diagnosis of these disorders, but also to inform other interested researchers concerning the problems we encountered.

As mentioned above, due to the absence of a 'gold standard', the validation of the results is restricted mainly to the 'face validity', which can also be applied to the results of the analyses. In the case of the nasal allergies, it may appear strange that once the RAST or skin prick test (SPT) was clearly positive, the history did not influence the diagnosis. This seems in conflict with the finding that elevated levels of specific IgE may be found in people who have no symptoms.[17, 25] However, such findings come from population-based studies, whereas the patients included in the present study all suffered from chronic or recurrent nasal symptoms. It will be clear from Appendix 4, Table 8, that most of the patients diagnosed as having a nasal allergy did indeed have a medical history that was more or less compatible with the sensitization involved. Only a minority of patients had symptoms that were not clearly related to the sensitization; in these rare cases, the validity of the experts' diagnoses might be questioned. It can not be completely ruled out that some of these patients had elevated levels of specific IgE combined with nasal symptoms that were related not to this IgE, but rather to a non-allergic disorder. However, in section 2.4, a number of reasons are discussed that are likely to explain why a patient may not recognize the relation between the exposure to the allergen and the occurrence of symptoms. In conclusion, sensitization without correlated symptoms is not an issue in patients who consult their general practitioner because of chronic or recurrent nasal symptoms; as a consequence, the positive predictive value of radioallergosorbent tests and skin prick tests is extremely high. Our finding that a RAST class 1 indicates a potential clinical relevance, and class 2 and above indicate a clinically relevant sensitization, is in agreement with a recently published review on testing for inhalant allergy in asthma.[26]

Quality of life

A somewhat surprising result concerns the annoyance reported by patients and the hindrance they experienced as a result of the nasal symptoms. Most patients reported a great deal of annoyance but, at the same time, the majority answered that they were able to go about their usual business. This apparent contradiction may be explained by the limited validity of the two relevant questions. After the start of the present study, a quality of life questionnaire, evaluated especially for allergic rhinitis, became available.[27] On the basis of a recently published study on adolescents, it appears that they experience important problems doing their work at school and during recreation.[28]

External validity

The external validity of the results of this study is limited to patients aged 12 or over who consult their general practitioner because of chronic or recurrent nasal symptoms. Moreover, in the case of allergic rhinitis, the results are limited to the countries of northwestern Europe, where the most common inhalant allergens are the same.[29] Pollen exposure may differ considerably from year to year, and the prevalence of tree and grass pollen allergy may vary accordingly. This prevalence is influenced by the duration of pollen exposure and the daily pollen concentration in the air; the number of days with 'peak exposure' are particularly important. The year in which the patients entered the study may be characterized as follows: for tree pollen, there was an elevated total exposure and an elevated number of 'peak exposure' days; for grass pollen, the total exposure was normal but there were relatively few days with 'peak exposure'; for weed pollen, the total exposure was high (personal communication, FThM Spieksma, Leiden).[30] Therefore, it can be inferred that in years with a higher number of days with grass pollen 'peak exposure', the positive predictive value of the medical history for grass pollen allergy will be even higher, whereas in years with a more normal tree or weed pollen exposure, the positive predictive values of tree and weed pollen allergy will be lower than those reported in Chapter 6.

11.4. Practical implications

On the basis of the findings of this study, a proposal can be formulated for diagnostic guidelines in patients with chronic or recurrent nasal symptoms in general practice. The clinical relevance and feasibility of such guidelines are factors that must be taken into account. From a practical point of view, differentiating between various types of nasal pathology is important only if this has consequences for therapeutic management. Therefore, to illustrate the clinical relevance, proposals for therapeutic management, based on the literature, will also be presented. Ultimately, the choice of a particular management will also depend on the preferences of both patient and general practitioner.

At this point, it must again be stressed that our findings concerning the non-allergic nasal disorders may be less valid than those concerning allergic rhinitis. As a consequence, the proposed diagnostic guidelines for the non-allergic nasal disorders should be handled with caution; further studies will be needed in order to assess the validity of these guidelines. The proposal for the management consists of the following steps, all of which must be completed, as more than one nasal disorder may be present in the same patient (See also Tables 11.1 and 11.2):

1. If a patient reports the frequent use of a topical vasoconstrictor longer than two weeks, the diagnosis **rhinitis medicamentosa** is made. Oral medication may be of importance if the patient himself observed a possible relation.
   The patient should stop the medication; to reduce the symptoms of the rebound effect of the topical vasoconstrictor, a topical corticosteroid or a short course of oral prednisolon can be given.[31]

Table 11.1. Diagnostic management of general practice patients with chronic or recurrent nasal symptoms; part 1: non-allergic nasal disorders

medical history	physical examination	criteria	diagnosis
- frequent use of a topical vasoconstrictor, >2 weeks	- NR	- NR	rhinitis medicamentosa
- yellow or green nasal secretion - coughing up phlegm	- mucus on the inferior turbinate - vivid red turbinates	- ≥2 out of 4	infectious rhinitis
- symptoms all year round	- septal deviation - septal spine - septal spur	- ≥2 out of 4	anatomical obstruction
- NR	- nasal polyp	- NR	nasal polyp
- NR	- NR	- none of the above diagnoses and no AR	vasomotor rhinitis

NR: not relevant. AR: allergic rhinitis, see Table 11.2.

2. If a patient reports two or more of the following symptoms and signs, **infectious rhinitis** is probably present: a history of yellow or green nasal secretion, a history of coughing up phlegm, mucus on the inferior turbinate, and vivid red turbinates. In all other patients, infectious rhinitis may be considered absent. However, this diagnosis is accompagnied by a considerable degree of uncertainty.
   As in the case of acute sinusitis,[32, 33, 34] the effectiveness of antibiotics in chronic rhinosinusitis is questionable. The combination of an antibiotic with a topical corticosteroid is usually appropriate.[35] It is not yet clear whether topical corticosteroids alone are also effective. If a patient does not improve as a result of therapy, nasal endoscopy by means of a flexible fibre-optic endoscope will be required; sinus surgery may be helpful.[36]
3. A history of nasal symptoms all year round may be indicative of a clinically relevant **anatomical obstruction**. Yet this diagnosis must also be based on one or more of the following three findings from anterior rhinoscopy: a moderate or severe septal deviation, a moderate or severe - impacting - septal spine, and a

*Table 11.2. Diagnostic management of general practice patients with chronic or recurrent nasal symptoms; part 2: selection of tests for allergic rhinitis**

medical history	RAST or SPT to be performed
- NR	house dust mite
- symptoms in the spring - or symptoms in dry, sunny weather - or itchy eyes	tree pollen
- symptoms in the summer - or symptoms in dry, sunny weather - or itchy eyes	grass pollen**
- symptoms worse on contact with cats - or itchy eyes	cat
- symptoms worse on contact with dogs - or symptoms on contact with house dust or when making beds	dog
- symptoms worse on contact with other animals	animal in question

RAST: radioallergosorbent test. SPT: skin prick test. NR: not relevant.
* This table is identical to Table 6.5; it is replicated in this concluding chapter for the sake of convenience. The interpretation of the test results is explained in the text.
** Grass pollen allergy is highly probable if all three symptoms are present.

moderate or severe septal spur. When three or even all four findings are present, the diagnosis is highly probable; when two findings are present, there is still a 50% likelihood of a clinically relevant anatomical obstruction.
It must be emphasized that many patients with nasal symptoms have anatomical obstructions without clinical relevance. Even in the presence of nasal obstructions presumed to be clinically relevant, a conservative waiting policy would appear to be the appropriate approach, since the symptoms of nasal obstruction tend to disappear over time.[37] Topical corticosteroids may be helpful in reducing the symptoms of nasal blockage.
4. Typical **nasal polyps** can be found by properly performed anterior rhinoscopy: pale or grey rounded masses with a smooth surface, more mobile and less

sensitive than swollen turbinates when touched with a probe.
Most cases respond to topical corticosteroids, given for a month. If not, the polyps may be removed surgically, followed by topical corticosteroids to reduce the chance of recurrence.[38]

5. **Allergic rhinitis** from an allergy against grass pollen is highly probable if a patient reports all three of the following: symptoms in the summer, symptoms in dry, sunny weather, and itchy eyes. For the diagnosis of all other nasal allergies, additional tests are needed. Radioallergosorbent tests (RASTs) and skin prick tests (SPTs) provide the same information. RASTs are more expensive, but the performance and interpretation of skin prick tests requires experience and special knowledge. The selection of the tests that are required can be based on the medical history, as presented in Table 11.2. If three or more RASTs are required, the Phadiatop test may be more cost-effective: in the case of a negative Phadiatop test, RASTs are not needed, as they are also likely to be negative. This is even more certain when the cut-off point of the Phadiatop ratio for a negative Phadiatop outcome is changed from 1.00 to 0.75.
Alternatively, the Phadiatop test can be performed in all patients who consult for chronic or recurrent nasal symptoms. In the case of a positive Phadiatop outcome, all 5 RASTs mentioned in Table 11.2 are performed. This method is much easier for the general practitioner. Whether the cost of this method will be significantly higher remains uncertain: more tests are performed, but in both cases all patients are referred to the laboratory, and this referral itself contributes greatly to the cost.
The results of the RASTs are interpreted as follows. A positive outcome (RAST class ≥ 2) indicates the presence of allergic rhinitis to the allergen in question. The outcome 'questionable' (RAST class 1) means 'allergic rhinitis questionable' or, in the case of a clearly positive case history, 'present'. A negative outcome (RAST class 0) indicates the absence of allergic rhinitis for the allergen in question. For the interpretation of the results of skin prick tests, the reader is referred to Chapter 7.
The therapeutic management of allergic rhinitis is twofold: a reduction in exposure to the causal allergen and topical or oral medication. Both are discussed in Section 2.6.

6. The exclusion of **vasomotor rhinitis** would appear to be justified in those patients in whom other nasal disorders are judged to be present. On the other hand, it is still unclear how to establish the diagnosis of vasomotor rhinitis. If none of the nasal disorders mentioned above are likely to be present, then vasomotor rhinitis may be present.
A topical corticosteroid may be helpful, alone or in combination with an antihistamine.[10] However, often medication is of little help for this disorder and it should be explained to patients that although the symptoms may be bothersome and may persist for a long period, the disorder is benign and there are no complications.

7. All patients should be asked whether they smoke, and those who do should be encouraged to give up smoking, as this may improve their symptoms regardless of the diagnosis.[39]

In general practice, serious diseases causing nasal symptoms, such as malignancies, granulomas, and others mentioned in Table 2.1, are very rare. Normally, the general practitioner will not consider diagnoses other than the ones mentioned in Tables 11.1 and 11.2. However, in the case of pain, haemorrhagic secretions, or unilateral symptoms that do not improve after therapy, referral for nasal endoscopy should be considered.

Finally, it must be stressed that, as in other chronic diseases, patient education is important in order to enhance the patient's coping strategies. It is important that the patient is aware of the cause of his disorder, the aggravating and the alleviating factors, and the mode of therapy. He should be given written instructions for environmental control measures and the use of medication. If necessary, the correct use of medication should be verified.

11.5. Recommendations for future research

The lack of agreement among the experts on the presence of most of the non-allergic nasal disorders is in accordance with the lack of knowledge on the epidemiology and the pathophysiology of non-allergic nasal disorders; further research on these aspects should be encouraged. The quality of life instruments recently developed for allergic rhinitis may serve as an important tool in further diagnostic or therapeutic studies for the non-allergic nasal disorders as well: the natural course or the effect of treatment can now be adequately measured.[27, 28]

In the future, a study should be performed in general practice patients with a history suggestive of chronic rhinosinusitis, in order to compare the effect of a topical corticosteroid with the effect of the combination of a topical corticosteroid and an antibiotic. In patients diagnosed as having chronic rhinosinusitis, the combination of an antibiotic with a topical corticosteroid is more effective than an antibiotic alone.[35] This may be explained by the inhibitory effect of topical corticosteroids on the inflammation: reducing the swelling of the nasal mucosa may interrupt the vicious circle of inflammation causing swollen mucosa to obstruct the middle meatus, which predisposes to sinus infection, which in turn causes more inflammation.[40] It may be postulated, as in the case of purulent phlegm in patients with an exacerbation of asthma, that a corticosteroid would be as effective alone as in combination with an antibiotic. Assuming that this is true, it may be further theorized that the presence of bacteria should not be seen as the cause of the symptoms or the target of the treatment. Rather, non-specific nasal hyperreactivity may play a more important role here. It may well emerge that differentiating between 'chronic rhinosinusitis' and 'vasomotor rhinitis' is not useful in general practice, as the only medication that would be more or less effective is a topical corticosteroid.

Another interesting question that has not been studied yet is whether immunotherapy is more effective than topical corticosteroids in allergic rhinitis.

Moreover, the importance of the main advantage of immunotherapy, i.e., shortening of the duration of the allergy, remains uncertain as long as there are no long-term comparative studies and little is known about the natural cause of allergic rhinitis. In the future, methods of immunotherapy that cause less serious side effects are likely to become available, thus increasing the popularity of this kind of therapy.[11]

Finally, it has been shown that performing a consensus procedure to obtain expert diagnoses is feasible, if time-consuming. For future diagnostic studies, applying such a procedure may be useful in situations where no reference test is available and the personal opinion of a single expert is insufficient. It is advisable to limit the procedure to one or two diagnoses only, and the results of a sensitivity analysis should be added.

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Summary

Summary

General practitioners are frequently consulted by patients who complain of chronic or recurrent nasal symptoms. The majority of these patients are given advice or treatment by their general practitioner, on the basis of his diagnosis, and are not referred to a specialist. However, the general practitioner lacks scientifically based guidelines that can serve as an aid in making a correct diagnosis and choosing appropriate management. Guidelines that are based on results from studies in other populations, such as hospital outpatients, are not likely to be applicable in general practice, due to bias. This thesis aims at providing information that can be used to formulate guidelines for the diagnostic management of patients with chronic or recurrent nasal symptoms in general practice.

It is clear from the literature that there are two important problems. First, there is no generally accepted classification of nasal pathology. Although there seems to be a reasonable degree of agreement on a nomenclature for different types of nasal disorders, there are no explicit definitions attached to these terms. Therefore, it is unclear whether it is possible to distinguish between different types of nasal pathology. Second, virtually no diagnostic studies on the subject have been performed in a general practice population.

In **Chapter 1**, a general introduction is given, and the background of the subject described in brief. The aim of this thesis was twofold: to investigate whether it is possible to distinguish between different types of nasal pathology in patients with chronic or recurrent nasal symptoms in general practice, and to assess the diagnostic value of the medical history, the physical examination, and in vivo and in vitro tests for the different types of nasal pathology.

In **Chapter 2**, a review of the literature is given. It is shown that there is no proper classification of nasal pathology. Although there is abundant literature on the pathophysiology, much remains to be clarified, especially with respect to the non-allergic types of rhinitis. On the basis of the literature on the epidemiology of nasal disorders it would appear that the 'iceberg phenomenon' is an important factor, one which causes the results from studies that were not performed in primary care to be invalid in general practice. There is virtually no literature on the diagnostic value of symptoms, signs, and tests in general practice. Even in other populations, it remains unclear which items from the medical history are mandatory and what their predictive value is. Much has been written about the comparison of in vivo and in vitro tests; nevertheless, it is unclear whether one method is more valid than the other. Therapy, which was not an object of this thesis, is addressed briefly. For allergic rhinitis, environmental control measures are considered to be a major instrument in therapeutic management; therefore, it is important to identify causal allergens.

In **Chapter 3**, the general methodology of the study is presented. Considerations that led to the basic design of the study are given, as well as the results of a pilot study that gave rise to certain modifications to the methods. Details of the study population are also given. Care was taken to design the study in such a way that participation would be attractive for both the patients and the general practitioners. Between March 1, 1990 and March 1, 1991, 365 consecutive patients aged 12 years or older who consulted their general practitioner because of chronic or recurrent nasal symptoms were included in the

study; they represented 25 practitioners in 19 general practices, situated in both urban and rural areas in the west of the Netherlands (Leiden, Alphen aan den Rijn, and the surrounding villages). The patients were all visited and examined by one general practitioner (M.C.), who obtained the following data: symptoms, signs (including results from anterior rhinoscopy), and results from ultrasonography of the maxillary sinus, nasal smear eosinophilia, total IgE, the Phadiatop test, 7 to 10 radioallergosorbent tests (RASTs), and skin prick tests with 14 allergens (Appendix 2).

In the absence of a classification for nasal pathology, there was no clearly documented reference on which to base a diagnosis. Because it is generally agreed that a diagnosis of nasal pathology should be based on the interpretation of both clinical data, i.e., symptoms and signs, and paraclinical data, i.e., in vivo and in vitro tests, it was decided to obtain 'consensus diagnoses' from experts in the field to serve as references. From the various consensus methods, Delphi was chosen because it has the advantage of giving all participants equal opportunity to express their opinion. For application in the present study, Delphi was modified.

In **Chapter 4**, a comparison is made between the results of the Phadiatop test and the results of a panel of 7 RASTs for the common inhalant allergens; the RAST panel was accepted as the standard. The sensitivity of the Phadiatop was 94%, the specificity 98%, the positive predictive value 97%, and the negative predictive value 95%. It was possible to further reduce the small percentage of false outcomes by replacing the single cut-off point of the Phadiatop ratio, 1.00, by the two cut-off points, 0.75 and 1.15. This resulted in three possible outcomes: a highly predictive positive outcome, a highly predictive negative outcome, and an 'inconclusive' outcome.

In **Chapter 5**, the consensus procedure is discussed, which was performed in order to obtain the 'consensus diagnoses' for use as references in the following chapters. Using a modified Delphi technique consisting of three rounds (the first two performed anonymously), three experts (an allergologist, an ENT specialist, and a general practitioner) gave their diagnoses, based upon the patient's symptoms and signs, and the results of in vivo and in vitro tests as presented in a written format. For this purpose, a list of diagnoses was drawn up (Appendix 3). After the first round, Cohen's Kappas varied from 0.91 for allergic rhinitis to 0.04 for rhinitis medicamentosa. In order to keep the experts' workload within acceptable limits, the second and third rounds were limited to the following nasal disorders (final Kappas given in brackets): allergic rhinitis as a whole (0.89-0.94) and differentiated for 14 different nasal allergies (0.78-0.95); nasal polyps (0.96-1.00); and non-specific nasal hyperreactivity (0.58-0.70). The final prevalences in the study population were: allergic rhinitis 47% (in addition 4% inconclusive); and nasal polyps 4% (0% inconclusive). Non-specific hyperreactivity was judged to be mild in 27% of the patients and severe in 8%. For the other diagnoses, which were made by the experts during only one round of the consensus procedure, the results were: vasomotor rhinitis 21% (41% inconclusive); anatomical obstructions 20% (23% inconclusive); infectious rhinitis 4% (29% inconclusive); and rhinitis medicamentosa 0.3% (10% inconclusive).

In **Chapter 6**, the most useful symptoms and signs for the diagnosis of allergic rhinitis, differentiated for 9 different allergens, are identified from among 271 items from the medical history and 38 items from the physical examination. Logistic regression analysis showed a maximum of four independent predictors for each of the nasal allergies. The maximum predicted probability was around 80% for grass pollen and house dust mite allergy; for the other allergies it was 60% or below; the minimum predicted probability was 3% or less, except for grass pollen allergy (6%) and house dust mite allergy (10%). The physical examination did not contribute to the diagnoses. It was concluded that on the basis of the medical history the diagnosis could be established with a sufficiently high degree of certainty only in definite cases of grass pollen allergy, while in many patients, it was possible to exclude all the common nasal allergies except house dust mite allergy. The medical history was proposed as a guide in the selection of further tests.

In **Chapter 7**, the most useful combinations of medical history and RASTs or skin prick tests are identified for the diagnosis of allergic rhinitis, differentiated for 7 allergens. Diagnostic criteria were drawn up that combined the findings from the medical history with those from either RASTs or skin prick tests, resulting in a near-perfect discrimination between patients diagnosed as having allergic rhinitis and patients diagnosed as not having allergic rhinitis. This discrimination was significantly better than that provided by the history alone. For most of the nasal allergies, the diagnostic criteria combined only a single item from the history with either a single RAST or SPT. For nearly all nasal allergies, both the negative predictive value and the positive predictive value were 97% or more.

In **Chapter 8**, the diagnostic values of the Phadiatop test and total IgE for allergic rhinitis are assessed. For the Phadiatop test, the positive predictive value was 99%, and the negative predictive value 93%. By using a third Phadiatop outcome, 'borderline', (Phadiatop ratio >0.75 and ≤ 1.00) it was possible to reduce the percentage of false-negative Phadiatop results from 7% to 2%. For the total IgE, the positive predictive value was 83%, and the negative predictive value 71%. Where the Phadiatop was known, the total IgE contributed no additional relevant information.

In **Chapter 9**, nasal smear eosinophilia is evaluated for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis. Two and, where necessary, three observers independently judged the percentage of eosinophils on a four-point scale. The first two observers agreed on the percentage of eosinophils in 315 (87%) out of 363 patients; the linear weighted Cohen's Kappa was 0.33. The positive predictive value of nasal smear eosinophilia ($\geq$ 10% eosinophils) for allergic rhinitis was 30/37 = 81%, the negative predictive value 172/312 = 55%. When the results of nasal smear eosinophilia were added to the information that had been obtained from the medical history, this resulted in a significant but very small improvement in the discrimination between patients with and without allergic rhinitis; this improvement was considered clinically irrelevant. The prevalence of eosinophilic non-allergic rhinitis was 7/349 = 2.0%; this diagnosis was judged to be inconsequential. Therefore, nasal smear eosinophilia was not recommended for use in general practice.

In **Chapter 10**, the remaining non-allergic nasal disorders are discussed. In most cases, it was difficult to analyze the results related to these disorders because of missing 'consensus diagnoses', due to the restriction of the consensus procedure to one round. Nevertheless, for each of the non-allergic nasal disorders it was possible to infer the main

discriminating variables. Infectious rhinitis was likely to be present when two or more of the following symptoms and signs were present: a history of yellow or green nasal secretion, a history of coughing up phlegm, mucus on the inferior turbinate, or vivid red turbinates. Ultrasonography did not make any significant contribution to this diagnosis. An anatomical obstruction was likely to be present when at least three of the following findings were present: a history of nasal symptoms all year round, a moderate or severe septal deviation, spine, or spur. Nasal polyps were detected only by anterior rhinoscopy. The possibility of rhinitis medicamentosa should be considered of when a patient reports the frequent use of a topical vasoconstrictor for more than 2 weeks. Vasomotor rhinitis could be excluded in patients in whom any of the other nasal disorders was considered to be present, and especially in patients with a positive Phadiatop test; it was not clear how the diagnosis of vasomotor rhinitis could be to established. Nasal hyperreactivity could be predicted fairly accurately; however, the clinical significance of this assessment is probably limited.

Chapter 11 consists of a general discussion of the major results, as well as the limitations and the strengths, of the study. A proposal is made for a diagnostic policy, together with recommendations for future research.

Samenvatting

Samenvatting

Huisartsen worden regelmatig geconsulteerd door patiënten met chronische of recidiverende neusklachten. De meerderheid van deze patiënten krijgt advies of therapie van hun huisarts, gebaseerd op diens diagnose, zonder verwijzing naar een specialist. Het ontbreekt de huisarts echter aan wetenschappelijk gefundeerde richtlijnen voor het stellen van de juiste diagnose en het kiezen van een daarbij passend beleid. Richtlijnen die gebaseerd zijn op onderzoek in andere populaties, zoals patiënten op poliklinieken, zijn, ten gevolge van bias, waarschijnlijk niet van toepassing in de huisartspraktijk. Dit proefschrift heeft als doel het leveren van informatie waarmee richtlijnen kunnen worden opgesteld voor het diagnostisch beleid bij patiënten met chronische of recidiverende neusklachten in de huisartspraktijk.

Uit de literatuur blijkt dat er twee belangrijke problemen spelen. Ten eerste is er geen algemeen geaccepteerde classificatie van neusaandoeningen. Er lijkt weliswaar een ruime mate van overeenstemming te bestaan over de nomenclatuur van de verschillende neusaandoeningen, maar er zijn geen eenduidig geformuleerde definities van de gebruikte termen. Daarom is het vooralsnog onduidelijk of het mogelijk is onderscheid te maken tussen verschillende neusaandoeningen. Ten tweede is in de huisartpraktijk vrijwel geen diagnostisch onderzoek naar neusdoeningen uitgevoerd.

In **Hoofdstuk 1** wordt een algemene inleiding gegeven. De achtergrond van het onderwerp van studie wordt beschreven en het doel van het proefschrift wordt gepresenteerd. Dit doel was tweevoudig: - onderzoeken of het mogelijk is onderscheid te maken tussen verschillende vormen van neusaandoeningen bij patiënten met chronische of recidiverende neusklachten in de huisartspraktijk, en - het bepalen van de diagnostische waarde van de anamnese, het lichamelijk onderzoek en aanvullend onderzoek (in vivo en in vitro tests) voor de verschillende neusaandoeningen.

In **Hoofdstuk 2** wordt een overzicht van de literatuur gegeven. Er bleek geen degelijke classificatie van neusaandoeningen te zijn. Alhoewel er veel literatuur bestaat over de pathofysiologie, is er nog veel onverklaard, met name voor de niet-allergische neusaandoeningen. Uit de literatuur over de epidemiologie van neusaandieningen blijkt dat het "ijsberg-fenomeen" een belangrijk punt is, waardoor resultaten van onderzoek dat niet in de eerstelijn werd uitgevoerd, waarschijnlijk niet van toepassing zijn in de huisartspraktijk. Er is vrijwel geen literatuur over de diagnostische waarde van de anamnese, het lichamelijk onderzoek en aanvullend onderzoek in de huisartspraktijk. Zelfs voor andere populaties is het onduidelijk welke onderdelen van de anamnese noodzakelijk zijn en wat daarvan de diagnostische waarde is. Er is veel geschreven over de vergelijking van in vivo en in vitro tests; desondanks is het onduidelijk of de ene methode valider is dan de andere. De therapie van neusaandoeningen was geen onderwerp van onderzoek maar wordt wel kort genoemd. Voor allergische rhinitis vormt de vermindering van de expositie aan de oorzakelijke allergenen een belangrijk onderdeel van het beleid; daarom is het identificeren van de oorzakelijke allergenen belangrijk.

In **Hoofdstuk 3** wordt de methode van het onderzoek gepresenteerd. De overwegingen bij het ontwerp van de studie worden genoemd, evenals de resultaten van een pilot study, naar aanleiding waarvan de methoden werden aangepast. Ook worden

hier de kenmerken van de onderzoekspopulatie beschreven. Bij de opzet van het onderzoek was veel aandacht besteed aan de aantrekkelijkheid van deelname voor zowel de patiënten als de huisartsen. Tussen 1 maart 1990 en 1 maart 1991 werden 365 patiënten van 12 jaar of ouder, die hun huisarts bezochten wegens langdurige of recidiverende neusklachten, ingesloten door 25 huisartsen in 19 huisartspraktijken, gelegen zowel in de stad als op het platteland in Zuid-Holland (Leiden, Alphen aan den Rijn en de omliggende dorpen). Eén huisarts (M.C.) bezocht alle patiënten en verzamelde de volgende gegevens: de antwoorden op een uitgebreide vragenlijst en de resultaten van lichamelijk onderzoek, echo van de sinus maxillaris, eosinofilie van het neusslijmvlies, totaal IgE, de Phadiatop test, 7 tot 10 radioallergosorbent tests (RASTs) en huid prik tests voor 14 allergenen (Appendix 2).

Door het ontbreken van een classificatie van neusaandoeningen, was er geen goed gedocumenteerde referentie waar de diagnose op gebaseerd zou kunnen worden. Omdat het algemeen aanvaard is dat de diagnose van neusaandoeningen gebaseerd moet zijn op interpretatie van zowel klinische parameters (klachten en bevindingen van lichamelijk onderzoek) als paraklinische parameters (aanvullend onderzoek), werd besloten aan referenties te komen door deskundigen op het gebied 'consensus diagnosen' te laten maken. Uit de diverse consensus methoden werd de Delphi techniek gekozen omdat deze het voordeel heeft dat alle deelnemers gelijke kansen krijgen om hun mening te uiten. Voor toepassing in dit onderzoek werd de Delphi methode gewijzigd.

In **Hoofdstuk 4** worden de resultaten van de Phadiatop test vergeleken met die van een RAST panel voor 7 veel voorkomende inhalatie allergenen. Het RAST panel diende als referentie. De sensitiviteit van de Phadiatop was 94%, de specificiteit 98%, de positief voorspellende waarde 97% en de negatief voorspellende waarde 95%. Het geringe percentage fout-negatieve en fout-positieve uitkomsten kon nog verder worden verminderd door het afkappunt van de Phadiatop-ratio (1.00) te vervangen door twee afkappunten: 0.75 en 1.15. Dit resulteerde in drie mogelijke uitkomsten: een zeer hoog voorspellende positieve uitkomst, een zeer hoog voorspellende negatieve uitkomst en een uitkomst 'onzeker'.

In **Hoofdstuk 5** wordt de consensus procedure besproken waarmee de 'consensus diagnosen' werden verkregen die als referentie zouden dienen in de volgende hoofdstukken. Door middel van een gemodificeerde Delphi techniek die bestond uit drie ronden (waarvan de eerste twee anoniem), gaven drie deskundigen (een allergoloog, een KNO-arts en een huisarts) hun diagnosen, gebaseerd op de klachten, de bevindingen van het lichamelijk onderzoek en de resultaten van de in vivo en in vitro tests, alle op papier weergegeven. Voor dit doel was een lijst met diagnosen samengesteld (Appendix 3). Na de eerste ronde variëerde Cohens Kappa van 0.91 voor allergische rhnitis tot 0.04 voor medicamenteuze rhinitis. Om de belasting voor de deskundigen binnen redelijke grenzen te houden, werd besloten de tweede en derde ronde te beperken tot de volgende diagnosen (uiteindelijke Kappa's tussen haakjes): allergische rhinitis als geheel (0.89-0.94) en gedifferentiëerd voor 14 verschillende allergieën (0.78-0.95); neuspoliepen (0.96-1.00); en aspecifieke nasale hyperreactiviteit (0.58-0.70). De uiteindelijke prevalenties in de studiepopulatie waren: allergische rhinitis 47% (daarnaast 4% onzeker); en neuspoliepen 4% (0% onzeker). Aspecifieke nasale hyperreactiviteit was matig in 27% en ernstig in

8% van de patiënten. Voor de andere diagnosen, die door de deskundigen alleen in de eerste ronde werden beoordeeld, waren de resultaten: vasomotore rhinitis 21% (41% onzeker); anatomische obstructies 20% (23% onzeker); infectieuze rhinitis 4% (29% onzeker); en medicamenteuze rhinitis 0.3% (10% onzeker).

In **Hoofdstuk 6** wordt onderzocht welke klachten (uit een lijst van 271 punten) en bevindingen van lichamelijk onderzoek (uit een lijst van 38 punten) het best voorspellen voor allergische rhinitis, gedifferentiëerd voor 9 verschillende allergenen. Met logistische regressie werden voor iedere allergie maximaal 4 onafhankelijk voorspellende variabelen gevonden. De maximale voorspellende waarde was rond 80% voor graspollen en huisstofmijt allergie; voor de andere allergiëen was dit 60% of minder. De minimale voorspellende waarde was 3% of minder, behalve voor graspollen (6%) en huisstofmijt allergie (10%). Het lichamelijk onderzoek droeg niet bij tot de diagnose. Er werd geconcludeerd dat het stellen van de diagnose aan de hand van de anamnese alleen voor graspollen allergie met voldoende zekerheid mogelijk was, terwijl bij veel patiënten de veel voorkomende allergiëen konden worden uitgesloten, met uitzondering van huisstofmijt allergie. Er werd geadviseerd de anamnese te gebruiken voor de selectie van aanvullend onderzoek.

In **Hoofdstuk 7** wordt onderzocht welke combinaties van klachten en resultaten van RASTs of huid prik tests het best voorspellen voor allergische rhinitis, gedifferentiëerd voor 7 verschillende allergenen. Het bleek mogelijk diagnostische criteria op te stellen, die de anamnestische bevindingen combineerden met de resultaten van òf RASTs òf huid prik tests, resulterend in een vrijwel perfect onderscheid tussen patiënten met de diagnose allergische rhinitis en patiënten waarbij die diagnose afwezig werd verondersteld. Dit onderscheid was significant beter dan het onderscheid, gebaseerd op alleen anamnestische gegevens. Deze diagnostische criteria combineerden voor de meeste allergiëen slechts een enkel anamnestisch gegeven met òf een RAST òf een huid prik test. Voor vrijwel alle allergiëen waren de positief en de negatief voorspellende waarden 97% of hoger.

In **Hoofdstuk 8** wordt de diagnostische waarde van de Phadiatop test en het totaal IgE voor allergische rhinitis bepaald. Voor de Phadiatop test was de positief voorspellende waarde 99% en de negatief voorspellende waarde 93%. Door invoer van een derde Phadiatop uitkomst 'onzeker' (Phadiatop ratio >0.75 en ≤ 1.00) kon het percentage fout-negatieve Phadiatop resultaten worden gereduceerd van 7% naar 2%. Voor het totaal IgE was de positief voorspellende waarde 83% en de negatief voorspellende waarde 71%. Als het resultaat van de Phadiatop test bekend was, droeg het totaal IgE geen relevante informatie meer bij.

In **Hoofdstuk 9** wordt eosinofilie in een uitstrijkje van het neusslijmvlies geëvalueerd voor de diagnostiek van allergische rhinitis en van eosinofiele niet-allergische rhinitis. Twee onderzoekers, en zo nodig een derde, beoordeelden het percentage eosinofielen op een vier-puntenschaal. De eerste twee onderzoekers vertoonden overeenstemming over het percentage eosinifielen in 315 (87%) van 363 patiënten; de lineair gewogen Kappa was 0.33. De positief voorspellende waarde van neusslijmvlies eosinofilie ($\geq$ 10% eosinofielen) was voor allergische rhinitis 30/37 = 81%, de negatief voorspellende waarde 172/312 = 55%. Toevoeging van de resultaten van neusslijmvlies

eosinofilie aan de informatie die al van de anamnese bekend was, resulteerde in een significante maar erg kleine verbetering van het onderscheid tussen patiënten met en zonder allergische rhinitis; deze verbetering werd niet klinisch relevant geacht. De prevalentie van eosinofiele niet-allergische rhinitis was 7/349 = 2.0%; het vaststellen van deze diagnose werd niet van belang geacht. Bepaling van neusslijmvlies eosinofilie werd niet aanbevolen voor toepassing in de huisartspraktijk.

In **Hoofdstuk 10** worden de resterende niet-allergische neusaandoeningen behandeld. Analyse van de resultaten van de meeste van deze aandoeningen was moeilijk vanwege ontbrekende 'consensus diagnosen' als gevolg van de beperking van de consensus procedure tot de eerste ronde. Desondanks kon voor ieder van de niet-allergische neusaandoeningen worden afgeleid welke de belangrijkste onderscheidende variabelen waren. Infectieuze rhinitis was waarschijnlijk aanwezig indien twee of meer van de volgende klachten en bevindingen van lichamelijk onderzoek aanwezig waren: anamnestisch geel of groen neussecreet, anamnestisch ophoesten van slijm, secreet op de concha inferior of felrode conchae. Echo-onderzoek droeg niet belangrijk bij tot deze diagnose. Een anatomische obstructie was waarschijnlijk aanwezig indien minstens drie van de volgende bevindingen aanwezig waren: anamnestisch klachten het hele jaar door en bij lichamelijk onderzoek een matige of ernstige septum deviatie, spina septi of crista septi. Neuspoliepen werden alleen gevonden door middel van rhinoscopia anterior. Aan medicamenteuze rhinitis zou moeten worden gedacht indien de patiënt vertelt regelmatig een locaal decongestivum te gebruiken gedurende meer dan twee weken. Het uitsluiten van vasomotore rhinitis was mogelijk bij patiënten bij wie een van de andere neusaandoeningen aanwezig werd verondersteld en met name bij patiënten met een positieve Phadiatop uitkomst; hoe de diagnose vasomotore rhinitis bevestigd kon worden, bleef onduidelijk. Nasale hyperreactiviteit kon tamelijk goed worden voorspeld; echter, de klinische betekenis hiervan is waarschijnlijk beperkt.

In **Hoofdstuk 11** wordt een algemene discussie gehouden over de belangrijkste resultaten en de beperkingen en de sterke punten van het onderzoek. Een voorstel voor een diagnostisch beleid wordt gepresenteerd. Ten slotte worden aanbevelingen gegeven voor toekomstig onderzoek.

Appendix 1

Information for the patient

Informatie voor de patiënt

To the patients who are eligible
for participation in the study
'Nasal symptoms in general practice'

Leiden, February 1990

Dear Sir or Madam,

You have visited your general practitioner because of nasal symptoms. There are various causes of nasal symptoms, such as allergies (for example, hay fever), nasal polyps, a deviated nasal septum, and many others. It is important to establish the cause of your symptoms, in order to be able to choose the proper treatment. Unfortunately, we do not yet know which questions and which tests are most appropriate, since this area has not yet been studied thoroughly.

Research is necessary to determine the best method of identifying the causes of nasal symptoms in general practice. This research is being carried out by us, but we need your cooperation. You will have the advantage of being examined thoroughly. Many tests will be performed and all the results will be considered by four experts: an allergologist, an ENT specialist, and two general practitioners. On the basis of these results, your general practitioner will be able to choose the best treatment. We would like to stress that, even if the cause seems to be clear in your case, participation may be of importance in identifying or excluding other causes.

The examination will take about three quarters of an hour to one hour. The following will be done:

- You will complete a questionnaire.
- Your nose will be examined from the inside and some mucus will be collected with a cotton swab; later, this will be examined for 'allergy cells'.
- The sinus will be checked for inflammation using ultrasonography.
- A blood sample will be taken and tested for several allergies.
- Skin tests will be performed for several allergies. By means of very short needles, punctures 1mm in depth will be made in the skin of the lower arms. (This area is much less sensitive than the fingers.)

The examination is free of charge.

Your participation is, of course, voluntary. Your answers and the test results will be analyzed anonymously. Your general practitioner will receive the results only in order to be able to choose the best treatment for you.

If you want to participate, the practice assistant will make an appointment for you. The examination will be performed in the surgery of your general practitioner or, if necessary, at your home.

I hope that you will understand the importance of this investigation, for yourself and for all future patients who consult their general practitioner for nasal symptoms. I look forward to seeing you soon for an examination,

Sincerely,

M.J.J.S. Crobach, general practitioner

P.S. If you have any questions, you may contact your own general practitioner or call me (Telephone: 071-275318).

RIJKSUNIVERSITEIT TE LEIDEN

FACULTEIT DER GENEESKUNDE

INSTITUUT VOOR HUISARTSGENEESKUNDE

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2301 CB LEIDEN

TELEFOON : 071 - 272727
DOORKIESNR. : (27) 5306/5318
FAX : 071 - 275325

UW REF. :

ONZE REF. : Cr/424/90
III.A.8.

ONDERWERP :

Aan de patiënten
die mee kunnen doen aan het
onderzoek "Neusklachten in de
huisartspraktijk"

LEIDEN, februari 1990

Geachte heer/mevrouw,

U bent naar uw huisarts gekomen wegens neusklachten. Er zijn veel oorzaken van neusklachten, zoals allergieën (met name hooikoorts), poliepen in de neus, een scheef neustussenschot en nog veel meer. Het is belangrijk om te weten wat de oorzaak van uw klachten is, zodat de beste behandeling kan worden gekozen. Helaas is het nog niet duidelijk met welke vragen en welk onderzoek uw huisarts het beste achter de oorzaak kan komen. Dit is namelijk nooit goed uitgezocht.

Om er achter te komen hoe de huisarts in de toekomst op de beste manier de oorzaak van neusklachten kan achterhalen, moet onderzoek gebeuren. Dit onderzoek voeren wij uit. Wij hebben daarvoor uw medewerking nodig. U zelf heeft daarbij het voordeel dat uw klachten grondig worden uitgezocht. Er wordt uitgebreid onderzoek verricht en alle uitslagen worden door 4 deskundigen beoordeeld (een allergoloog, een keel-, neus- en oorarts en twee huisartsen). Met deze bevindingen kan uw huisarts de beste keuze voor de behandeling maken. Met nadruk willen wij er op wijzen dat ook als de oorzaak bij u al duidelijk lijkt te zijn, dit onderzoek voor u van belang is om andere tegelijkertijd aanwezige oorzaken op te sporen of uit te sluiten.

Het onderzoek duurt in totaal ongeveer 3 kwartier à 1 uur. Het volgende zal dan plaats vinden:
- u vult een lijst in met vragen over uw klachten,
- er zal in uw neus gekeken worden en met een wattenstaafje zal wat slijm uit de neus worden genomen (later wordt daarin naar "allergie-cellen" gezocht),
- er zal met een echo gekeken worden of de neusbijholten ontstoken zijn,
- er zal wat bloed worden afgenomen (voor onderzoek naar diverse allergieën).
- er zullen huidtests gedaan worden voor diverse allergieën. Daarbij wordt met heel korte naaldjes één millimeter in de huid van de onderarmen geprikt. Dit is veel minder gevoelig dan de zogenaamde "vingerprik".

Dit onderzoek zal helemaal gratis gebeuren.

Uw medewerking aan dit onderzoek is geheel vrijwillig. Uw antwoorden en de uitslagen zullen anoniem worden verwerkt. Alleen uw huisarts ontvangt de uitslagen zodat hij de beste behandeling voor u kan kiezen.

Als u mee wilt werken, zal de assistente een afspraak voor u maken. Dit onderzoek zal in de praktijk van uw huisarts plaats vinden of eventueel bij u thuis.

Ik hoop dat u het belang van dit onderzoek inziet voor uzelf èn voor alle patiënten die in de toekomst met neusklachten bij de huisarts zullen komen. Ik hoop u dan ook binnenkort te mogen ontmoeten voor het onderzoek,

met vriendelijke groeten,

M.J.J.S. Crobach, huisarts

P.S. Als u nog vragen heeft kunt u zich wenden tot uw eigen huisarts of tot mij (tel. 071-275318).

Appendix 2

Information obtained from each patient

Informatie van iedere patiënt verkregen

1. Medication and medical history provided by the general practitioner

Present medication.
Medication that has been discontinued temporarily because of its influence on skin tests.
Previous encounter because of the same symptoms:
- (a) previous examination and results
- (b) previous therapy and effect
- (c) referral to a specialist (specialty; results; therapy; effect).

Degree of urbanization:
- (a) rural
- (b) small town or urbanized rural area
- (c) town with a population over 100,000.

2. Questionnaire

The questionnaire has not been translated literally; instead, only the issue dealt with in each question is presented here.

Date of the examination; date of birth; age; sex; insurance; civil status.
Question 1. The patient's own ideas on causal factors.

Previous examination or treatment
Question 2. Previous examination (by whom; kind of examination; diagnosis).
Question 3. Previous diagnoses made by any physician:
- (a) hay fever or allergic rhinitis
- (b) nasal polyps
- (c) recurrent middle ear infections
- (d) recurrent sinusitis
- (e) asthma: allergic or non-allergic
- (f) chronic bronchitis
- (g) allergic eczema
- (h) any other allergy.

Question 4. Atopic eczema.
Question 5. Over-the-counter medication that was effective.
Question 6. Frequent use of a topical vasoconstrictor (how long; until when; how many times per day).
Question 7. Previous therapy prescribed by any physician, and its effect (nose drops; nose spray; tablets; homeopathic medication; antibiotics; injections (immunotherapy); operation; any other therapy).

Family history

Question 8. Relatives with:
- (a) allergic asthma
- (b) allergic rhinitis or hay fever
- (c) atopic eczema
- (d) allergy to food
- (e) any other allergy.

Nasal symptoms

Question 9. Stuffy nose (both sides; mainly left; mainly right).
Question 10. Runny nose (watery or viscous; clear, both turbid and white, or yellowish-green; with or without blood).
Question 11. Post-nasal drip.
Question 12. Number of handkerchiefs or tissues per day.
Question 13. Sneezing (times per day; number of sneezes in a row).
Question 14. Itchy nose.
Question 15. Loss of sense of smell.
Question 16. Most annoying symptom:
- (a) stuffy nose
- (b) runny nose
- (c) sneezing
- (d) itchy nose.

Question 17. Degree of annoyance; degree of hindrance.

Concomitant symptoms

Question 18.
- (a) itchy eyes
- (b) burning eyes
- (c) runny eyes
- (d) red eyes
- (e) itchy throat
- (f) itchy palate
- (g) itchy ears
- (h) nettle rash
- (i) frontal headache when bending forward
- (j) sore throat
- (k) earache
- (l) coughing (with phlegm; without phlegm)
- (m) wheezy breathing
- (n) shortness of breath
- (o) shivering
- (p) fever
- (q) fatigue.

Course of the nasal symptoms

Question 19. Age at onset.
Question 20. Duration > 2 years (progression of symptoms; unchanged symptoms; regression of symptoms).
Question 21. Seizures of symptoms.
Question 22. Symptom-free days.
Question 23. Duration of current symptoms.
Question 24. Previous periods of symptoms (number of periods per year; usual duration of the periods; duration of the symptom-free periods).
Question 25. Symptoms in the winter.
Question 26. Symptoms all year round.
Question 27. Symptoms mainly or exclusively in a certain season (which season; which month).

Factors that aggravate or alleviate the nasal symptoms

Question 28. Decrease in symptoms:
- (a) on rainy days
- (b) in the mountains
- (c) at the coast.

Question 29. Increase in symptoms:
- (a) on rising; duration
- (b) during the day
- (c) at night
- (d) on dry, sunny days
- (e) on contact with grass.

Question 30. Increase in symptoms:
- (a) outside; suspected cause
- (b) inside; suspected cause
- (c) in the bedroom
- (d) on contact with house dust
- (e) when making beds or shaking out blankets
- (f) when dusting
- (g) when vacuuming.

Question 31. Increase in symptoms on contact with animals:
- (a) dog
- (b) cat
- (c) guinea pig
- (d) hamster
- (e) rabbit
- (f) horse
- (g) cow
- (h) sheep
- (i) goat
- (j) parakeet

(k) canary
(l) parrot
(m) other.

Question 32. Increase in symptoms on contact with plants or flowers.
Question 33. Increase in symptoms due to food or drink.
Question 34. Increase in symptoms due to:
(a) sudden change in temperature
(b) fog
(c) cigarette smoke
(d) smell of paint
(e) perfume
(f) baking or frying odours
(g) other irritants
(h) physical exertion or sport
(i) emotional strain
(j) common colds (usual number of days with coloured nasal discharge).
Question 35. Increase in symptoms due to an analgesic (name of the analgesic; with or without sudden shortness of breath).
Question 36. Increase in symptoms due to other medication.
Question 37. Employment:
(a) kind of employment (housekeeping; pupil or student; none; other).
(b) aggravation of symptoms when at work; suspected cause
(c) irritants at former place of employment.
Question 38. Increase in symptoms due to a hobby (kind of hobby; suspected cause).
Question 39. For women only:
(a) influence of menstrual cycle on nasal symptoms
(b) when pregnant: period; influence on nasal symptoms.
Question 40. Any other aggravating or alleviating factor not previously mentioned.

Environment

Question 41. Contact with animals (regardless of any effect on the symptoms):
(a) type of contact: hobby or sport; occupation; other
(b) kind of animal (See question 31).
Question 42. Dwelling (damp; moist spots on the walls; mildew on the wall; a rotten or repaired floor; mouldy smell; poor ventilation; year of construction; renovated; moist soil or water under the dwelling; kind of heating; period of residence in the present dwelling).
Question 43. If the symptoms first appeared in another dwelling: characteristics of that dwelling (See question 42; difference between the symptoms in the former and the present dwelling).
Question 44. Interior of the bedroom (floor covering; bedding; drapery; age of the mattress; stuffing of the mattress).
Question 45. Interior of the living room (floor covering; furniture; drapery).
Question 46. If ever a resident of another country: date of move to the Netherlands; previous country of residence.
Question 47. Smoking habits:
(a) smoker; never smoked; gave up smoking
(b) cigarettes, cigars, or a pipe; number per day; since when.
Question 48. Smoking by others in the regular environment.
Question 49. Any additional information thought to be relevant.

3. Physical examination

Inspection

General speech with a blocked-up nose; breathing through the mouth; runny nose or sniffing.
Eyes swollen lids; red eyes; wet eyes; purple skin around the eyes.
Mouth hypertrophic tonsils; tonsillitis without exudate; tonsillitis with exudate; red throat; post-nasal drip; fetor from the mouth.
External nose crooked nose; collapse of the nasal bridge; nasal rim (transverse line on the nose).

Anterior rhinoscopy:

I. mucus:
(a) quantity and site: - none (dry mucous)
- little (wet mucous)
- moderate
- much (blocking the nasal passage)
- especially on the inferior turbinate
(b) quality of the mucus: - watery
- viscous
- crusted
(c) colour: - clear
- both white and turbid
- yellowish-green.

II. nasal septum:
(a) no deviation
(b) slight deviation (no blockage of nasal passage); direction
(c) moderate deviation (moderate blockage of nasal passage); direction
(d) severe deviation (severe blockage of nasal passage); direction.

III. septal spur:
(a) none
(b) small (no blockage of nasal passage); side
(c) moderate (moderate blockage of nasal passage); side
(d) severe (severe blockage of nasal passage); side.

IV. septal spine:

(a) none
(b) small; side
(c) moderate; side
(d) severe (impacting); side.

V. turbinates:
(a) size:
- normal
- atrophic; side
- slightly hypertrophic (no blockage of nasal passage); side
- moderately hypertrophic (moderate blockage of passage); side
- severely hypertrophic (severe blockage of nasal passage); side

(b) colour:
- normal (pink/light red)
- reddish
- bright red
- somewhat pale
- pale
- violet.

VI. polyps:
(a) none
(b) small (no blockage of nasal passage); side
(c) moderate (moderate blockage of nasal passage); side
(d) large (severe blockage of nasal passage); side.

VII. other findings.

Palpation
Maxillary sinus:
(a) not painful
(b) moderately painful
(c) very painful.

Ultrasonography of the maxillary sinus
findings compatible with:
(a) normal sinus (front wall echo within 2cm and possible repetitive echos)
(b) swollen mucous (front wall echo between 2cm and 3cm); side
(c) sinusitis (back wall echo between 4cm and 6cm); side
(d) cyst or large polyp (double echo between 4cm and 6cm); side
(e) unclear result (sketch); side.

4. Nasal smear eosinophilia

(a) no eosinophilia (<5% eosinophils)
(b) minor eosinophilia (5% to 10% eosinophils)
(c) moderate eosinophilia (10 to 50% eosinophils)
(d) strong eosinophilia (>50% eosinophils).

5. In vitro tests

Total-IgE (kU/l) (normal value: < 100kU/l).
Phadiatop test (positive; negative).
Radioallergosorbent tests (RASTs) (class 0-4):
- tree pollen mixture
- grass pollen mixture
- weed pollen mixture
- mould mixture
- house dust mite
- cat
- dog
- horse
- guinea pig
- rabbit.

6. Skin prick tests (Phazet)

In order not to influence the interpretation of the results, the weals were outlined and the size transferred to paper by means of tape (see overleaf). On this side of the paper, you may note your own interpretation. The presence or absence of erythema is indicated as '+' or '-'.

- positive control
- negative control
- trees:
  - alder
  - birch
- grasses:
  - cocksfoot
  - timothy
- weeds:
  - mugwort
  - plantain
- mould:
  - *Alternaria*
- house dust mite:
  - *Dermatophagoides pteronyssinus*
  - *Dermatophagoides farinae*
- animals:
  - cat
  - dog
  - horse
  - guinea pig
  - rabbit

Rijksuniversiteit Leiden
Leids Instituut voor Huisartsgeneeskunde

Erasmus Universiteit Rotterdam
Afdeling Huisartsgeneeskunde

Patiëntcode:

ONDERZOEK NEUSKLACHTEN IN DE HUISARTSPRAKTIJK

INHOUD:

---

1. MEDICATIE EN VOORGESCHIEDENIS.

Huisartscode: ....

(Informatie van de huisarts)

Huidige medicatie: .....

.....

I.v.m. huidtests tijdelijk gestaakte medicatie:.....

.....

Eerder bezoek aan de huisarts i.v.m. de huidige neusklachten: ja ☐ nee ☐

- eerder onderzoek en bevindingen: .....

.....

- eerdere therapie: .....

effect: .....

- verwijzing naar specialist: specialisme: .....

diens bevindingen: .....

diens therapie: .....

effect: .....

Urbanisatiegraad van de woonplaats van de patiënt:

plattelandsgemeente..... ☐

gemeente met een stedelijk karakter of verstedelijkte plattelandsgemeente.. ☐

gemeente met meer dan 100.000 inwoners..... ☐

Patiëntcode:

ONDERZOEK NEUSKLACHTEN IN DE HUISARTSPRAKTIJK

VRAGENLIJST VOOR DE PATIENT

Toelichting:

Deze vragenlijst bevat verschillende soorten vragen. Uw antwoorden zijn belangrijk voor het opsporen van de oorzaak van uw neusklachten.

- Soms moet u iets aankruisen. Kruis dan aan wat bij u van toepassing is.

  Voorbeeld: Bent u ouder dan 10 jaar? Ja ☐ Nee ☐

  Als u zich vergist, verandert u als volgt:

  Bent u ouder dan 10 jaar? Ja ☐ Nee ☐

  wordt:

  Bent u ouder dan 10 jaar? Ja ☐ Nee ☐

- Soms kunt u kiezen uit "ja", "nee" of "?". **Kruis het vraagteken alleen aan als u het ècht niet weet.**

- Soms wordt u gevraagd iets op te schrijven. Doe dit dan zo kort mogelijk.

- Als er staat "zo ja ..." hoeft u alleen verder te lezen als u de vraag met "ja" beantwoordde. Zo niet, dan kunt u doorgaan met de volgende vraag.

- Maakt u zich geen zorgen als u een vraag onduidelijk of moeilijk vindt. Probeer het antwoord te geven dat het best uw mening weergeeft en ga door naar de volgende vraag. U kunt zo nodig een toelichting geven.

ALGEMENE GEGEVENS

Vul in / kruis aan:

datum van het onderzoek: .....-.....-.....

geboortedatum : .....-.....-.....

leeftijd : ..... jaar

geslacht : man ☐ vrouw ☐

Verzekering : particulier ☐
ziekenfonds ☐

Burgerlijke staat (kruis één antwoord aan):

gehuwd..... ☐
gescheiden..... ☐
ongehuwd..... ☐
samenwonend..... ☐
weduwe/weduwnaar... ☐
anders:..... ☐ namelijk:.....

Vraag 1. Heeft u zelf een vermoeden waar uw neusklachten door ontstaan?..... ja ☐ nee ☐

Zo ja: a. waardoor?.....
.....
.....

b. waarom denkt u dat?.....
.....
.....

Eerst volgt een aantal vragen over onderzoek of behandeling van uw neusklachten in het verleden. Daarna enkele vragen over een aantal andere aandoeningen.

Vraag 2. Is er wel eens eerder onderzoek gedaan in verband met uw neusklachten?..... ja ☐ nee ☐

Zo ja: a. door wie? (meerdere antwoorden mogelijk)

huisarts..... ☐
kinderarts..... ☐
keel-, neus-, oorarts.. ☐
allergoloog..... ☐
een ander..... ☐ nl:
.....
.....

b. wat voor onderzoek? (meerdere antwoorden mogelijk)

bloedonderzoek..... ☐
röntgenfoto's..... ☐
echo..... ☐
huidtests..... ☐
ander..... ☐ nl:
.....
.....

c. werd er toen een oorzaak van de klachten gevonden? (kruis één antwoord aan)

nee..... ☐
dat weet ik niet meer.. ☐
ja..... ☐ nl:
.....
.....
.....

Vraag 3. Is u ooit door een arts verteld dat u last heeft of had van:
(U kunt antwoorden met "ja", "nee" of "?". **Kruis het vraagteken alleen aan als u het écht niet weet.**)

	ja	?	nee
a. hooikoorts of allergische neusklachten?	☐	☐	☐
b. neuspoliepen?	☐	☐	☐
c. regelmatig middenoorontstekingen?	☐	☐	☐
d. regelmatig neusbijholte-ontstekingen?	☐	☐	☐
e. astma?	☐	☐	☐
zo ja, allergisch astma?	ja ☐		nee ☐
f. chronische bronchitis?	☐	☐	☐
g. allergisch (contact) eczeem?	☐	☐	☐
h. een nog niet genoemde allergische aandoening?	☐	☐	☐

zo ja, waarvoor en met welke klachten?.....

.....

.....

.....

Vraag 4. Had u als kind last van constitutioneel eczeem (dauwworm)?

ja	?	nee
☐	☐	☐

Vraag 5. Heeft u zelf wel eens iets van apotheek of drogist gebruikt waar uw neusklachten minder van werden?

ja ☐ nee ☐

Zo ja, wat?.....

.....

.....

Vraag 6. Gebruikt(e) u regelmatig één of meer van de volgende neusdruppels of neussprays: Otrivin, Xylometazoline, Nafazoline, Nasivin, Privine, Rhinospray, Argyrophedrine of Vicks Sinex? ja ☐ nee ☐

Zo ja:

a. hoe lang gebruikt u het of heeft u het gebruikt? ..... weken

b. tot wanneer? (vul de datum in) .....-.....-.....

c. hoeveel keer per dag?..... ..... keer

Vraag 7. Bent u al eens door een arts behandeld voor uw neusklachten?..... ja ☐ nee ☐

Zo ja: (Kruis aan wat van toepassing is. Meerdere antwoorden zijn mogelijk.)

hoe?		naam van geneesmiddel? (indien bekend)	effect? geen/beetje/goed
- neusdruppels.....	☐	.....	☐ ☐ ☐
		.....	
- neusspray.....	☐	.....	☐ ☐ ☐
		.....	
- tabletten.....	☐	.....	☐ ☐ ☐
		.....	
- homeopatisch middel.	☐	.....	☐ ☐ ☐
		.....	
- antibiotica.....	☐	.....	☐ ☐ ☐
		.....	
		voor allergie tegen...?	
- injectie-kuur (hyposensibilisatie)	☐	.....	☐ ☐ ☐
		.....	
		soort operatie?	
- operatie.....	☐	.....	☐ ☐ ☐
		.....	
- anders.....	☐	nl:.....	☐ ☐ ☐

Nu volgen een aantal vragen over uw familie. U kunt antwoorden met "ja", "nee" of "?". **Kruis het vraagteken alleen aan als u het écht niet weet.**

Vraag 8. Heeft er in uw familie iemand last (gehad) van: ja ? nee

a. allergisch astma..... ☐ ☐ ☐

zo ja, wie? vader..... ☐
moeder..... ☐
broer(s)/zus(sen) ☐ aantal:.....
kind(eren)..... ☐ aantal:.....

ja ? nee

b. allergische neusklachten / hooikoorts..... ☐ ☐ ☐

zo ja, wie? vader..... ☐
moeder..... ☐
broer(s)/zus(sen) ☐ aantal:.....
kind(eren)..... ☐ aantal:.....

ja ? nee

c. constitutioneel eczeem (dauwworm)..... ☐ ☐ ☐

zo ja, wie? vader..... ☐
moeder..... ☐
broer(s)/zus(sen) ☐ aantal:.....
kind(eren)..... ☐ aantal:.....

ja ? nee

d. voedselallergie..... ☐ ☐ ☐

zo ja, wie en waarvoor?.....

.....

ja ? nee

e. andere allergie..... ☐ ☐ ☐

zo ja, wie en wat voor allergie?.....

.....

f. Hoeveel broers en zussen heeft u? .....broers en zussen.

g. Hoeveel kinderen heeft u?..... .....kinderen

Nu volgen enkele vragen over uw neusklachten. **Ze gaan alleen over de periode(n) waarin u last heeft van neusklachten.**

Vraag 9. Heeft u last van een verstopte neus?..... ja ☐ nee ☐

Zo ja: (kruis één keuze aan)

aan beide kanten (al of niet afwisselend)..... ☐
voornamelijk links..... ☐
voornamelijk rechts..... ☐

Vraag 10. Heeft u last van een loopneus?..... ja ☐ nee ☐

Zo ja, hoe ziet het slijm er uit? (kruis telkens één keuze aan)

a. waterig..... ☐
taai..... ☐

b. helder (doorzichtig).... ☐
troebel-wit..... ☐
geel/groen..... ☐

c. met bloed er door..... ☐
zonder bloed er door.... ☐

Vraag 11. Voelt u regelmatig slijm van achter in de neus in uw keel lopen?..... ja ☐ nee ☐

Vraag 12. Hoeveel zakdoeken gebruikt u ongeveer per dag? ..... zakdoeken.

Gebruikt u vooral papieren of stoffen zakdoeken?.. papieren ☐
(kruis één keuze aan)
stoffen ☐
geen ☐

De vragen op deze bladzijde gaan alleen over de periode(n) met neusklachten.

Vraag 13. Heeft u last van niezen?..... ja ☐ nee ☐

Zo ja:
a. hoe vaak niest u ongeveer per dag? ..... keer per dag.

b. hoe vaak niest u achter elkaar? (kruis één keuze aan)

meestal 3 keer of minder..... ☐
buien van 4 tot 10 keer achter elkaar... ☐
buien van 10 keer of meer achter elkaar. ☐

Vraag 14. Heeft u last van jeuk in de neus?..... ja ☐ nee ☐

Vraag 15. Heeft u last van reukverlies?..... ja ☐ nee ☐

Vraag 16. Geef nu uw belangrijkste (meest vervelende) klacht aan (kruis één keuze aan):

verstopte neus..... ☐
loopneus..... ☐
niezen..... ☐
jeuk in de neus..... ☐

Vraag 17.a. Hoeveel last heeft u van uw neusklachten? (kruis één keuze aan)

weinig..... ☐
matig..... ☐
veel..... ☐

b. In hoeverre wordt u door uw neusklachten belemmerd in uw dagelijkse bezigheden? (kruis één keuze aan)

ik kan alles normaal blijven doen..... ☐
ik word gehinderd in mijn dagelijkse bezigheden..... ☐
ik kan mijn dagelijkse bezigheden niet meer doen..... ☐

De vragen op deze bladzijde gaan alleen over de periode(n) met neusklachten.

Vraag 18. Heeft u **samen met uw neusklachten** ook last van:

a. jeukende ogen?..... ja ☐ nee ☐
b. brandende ogen?..... ja ☐ nee ☐
c. tranende ogen?..... ja ☐ nee ☐
d. rode ogen?..... ja ☐ nee ☐
e. jeuk in de keel?..... ja ☐ nee ☐
f. jeuk aan het verhemelte?..... ja ☐ nee ☐
g. jeuk in de oren?..... ja ☐ nee ☐
h. netelroos (jeukende bulten op de huid)?... ja ☐ nee ☐
i. hoofdpijn, aan de voorzijde van het hoofd, die toeneemt bij voorover bukken?..... ja ☐ nee ☐
j. keelpijn?..... ja ☐ nee ☐
k. oorpijn?..... ja ☐ nee ☐
l. hoesten?..... ja ☐ nee ☐

zo ja: (kruis één keuze aan)
hoesten met veel slijm..... ☐
hoesten met weinig of geen slijm..... ☐

m. piepen bij de ademhaling?..... ja ☐ nee ☐
n. kortademigheid?..... ja ☐ nee ☐
o. rillerig gevoel?..... ja ☐ nee ☐

Vervolg van vraag 18. Heeft u **samen met uw neusklachten** ook last van:

p. koorts?..... ja ☐ nee ☐

q. moeheid?..... ja ☐ nee ☐

Nu volgen enkele vragen over het beloop van uw neusklachten.

Vraag 19. Hoe oud was u ongeveer toen uw neusklachten begonnen? ..... jaar

Vraag 20. Duren uw neusklachten langer dan 2 jaar?..... ja ☐ nee ☐

Zo ja, hoe was het beloop van de klachten in de loop der jaren?
(kruis één keuze aan)

de klachten zijn toegenomen..... ☐

de klachten zijn ongeveer hetzelfde gebleven ☐

de klachten zijn afgenomen..... ☐

Vraag 21. Komen de neusklachten plotseling, als aanvallen?..... ja ☐ nee ☐

Vraag 22. Heeft u in de periode met neusklachten dagen waarop u helemaal geen last heeft?

ja ☐ nee ☐

Vraag 23. Hoe lang duren uw neusklachten nu (vrijwel) ononderbroken?
(Indien u eerder perioden last had: hoe lang duren uw klachten deze keer?)

..... dagen

..... weken

..... maanden

..... jaren

Vraag 24. Heeft u eerder perioden met dezelfde neusklachten gehad?

ja ☐ nee ☐

Zo ja,

a. hoeveel perioden per jaar heeft u last? ..... periode(n)

b. hoe lang duren die perioden gewoonlijk? ..... dagen

..... weken

..... maanden

c. hoe lang bent u tussen die perioden klachtenvrij?
(kruis één keuze aan)

meestal korter dan een maand ☐

meestal langer dan een maand ☐

Vraag 25. Heeft u 's winters neusklachten?..... ja ☐ nee ☐

Vraag 26. Heeft u het hele jaar last?..... ja ☐ nee ☐

Vraag 27. Heeft u in een bepaald seizoen **(meer)** last?.. ja ☐ nee ☐

Zo ja: a. in welk(e) seizoen(en)?..... lente... ☐

zomer... ☐

herfst.. ☐

winter.. ☐

b. probeer aan te geven in welke maanden u **(meer)** last heeft:..... januari.. ☐

februari. ☐

maart.... ☐

april.... ☐

mei..... ☐

juni..... ☐

juli..... ☐
augustus. ☐
september ☐
oktober.. ☐
november. ☐
december. ☐

Nu volgen enkele vragen over situaties of dingen die uw klachten mogelijk beïnvloeden. U kunt antwoorden met "ja", "nee" of "?". **Kruis het vraagteken alleen aan als u het ècht niet weet.**

Vraag 28. Worden uw neusklachten **minder erg:**

	ja	?	nee
a. op regenachtige dagen?.....	☐	☐	☐
b. bij verblijf in de bergen? (hooggebergte).....	☐	☐	☐
c. bij verblijf aan de kust?.....	☐	☐	☐

Vraag 29. Worden uw neusklachten **erger:**

	ja	?	nee
a. 's ochtends bij het opstaan?.....	☐	☐	☐

Zo ja, Hoe lang duren de klachten meestal?
korter dan 1 uur ☐
langer dan 1 uur ☐

b. overdag?.....	☐	☐	☐
c. 's nachts?.....	☐	☐	☐
d. bij droog, zonnig weer?.....	☐	☐	☐
e. bij contact met gras?.....	☐	☐	☐

(Kruis het vraagteken alleen aan als u het ècht niet weet.)

Vraag 30. Worden uw neusklachten **erger:**

	ja	?	nee
a. buiten?.....	☐	☐	☐

zo ja: (kruis één keuze aan)
zonder een waarschijnlijke oorzaak ☐
met een waarschijnlijke oorzaak... ☐ nl:....
.....
.....

b. binnen?.....	☐	☐	☐

zo ja: (kruis één keuze aan)
zonder een waarschijnlijke oorzaak ☐
met een waarschijnlijke oorzaak... ☐ nl:....
.....
.....

c. op de slaapkamer?.....	☐	☐	☐
d. bij contact met huisstof?.....	☐	☐	☐
e. bij bedden opmaken of dekens uitkloppen?.....	☐	☐	☐
f. bij afstoffen?.....	☐	☐	☐
g. bij stofzuigen?.....	☐	☐	☐

(Kruis het vraagteken alleen aan als u het écht niet weet.)

Vraag 31. Worden uw neusklachten erger: ja ? nee

bij contact met dieren?.....

Zo ja, kruis aan welke dieren:

hond.....
kat.....
cavia....
hamster..
konijn...
paard....
koe.....
schaap...
geit.....
parkiet..
kanarie..
papegaai.
andere... nl:

.....

Vraag 32. Worden uw neusklachten erger: ja ? nee

bij contact met planten of bloemen?.....

Zo ja, welke? .....

.....

Vraag 33. Worden uw neusklachten erger: ja ? nee

door bepaald voedsel of bepaalde dranken?.....

Zo ja, welk(e)?.....

.....

(Kruis het vraagteken alleen aan als u het écht niet weet.)

Vraag 34. Worden uw neusklachten erger: ja ? nee

a. bij overgang van warmte naar kou of andersom?...

Zo ja: (kruis één keuze aan)
ook bij kleine verschillen in temperatuur..
alleen bij grote verschillen in temperatuur

b. bij mist?.....

c. door sigaretterook?.....

d. door verflucht?.....

e. door parfum?.....

f. door bak- en braadluchten?.....

g. door andere prikkelende stoffen?.....

Zo ja, welke?.....

.....

h. door lichamelijke inspanning (sport)?.....

i. door spanning, stress?.....

j. door verkoudheden?.....

Zo ja, als u verkouden bent, hoeveel dagen heeft u dan meestal last van geel of groen slijm uit de neus?

..... dagen

(Kruis het vraagteken alleen aan als u het écht niet weet.)

Vraag 35. Worden uw neusklachten erger: ja ? nee
door bepaalde pijnstillers (bijvoorbeeld Aspirine, Aspro, enz.)?.....

Zo ja: a. welke?.....

.....

b. (kruis één keuze aan)
met aanvallen van kortademigheid...
zonder aanvallen van kortademigheid

Vraag 36. Worden uw neusklachten erger: ja ? nee
door andere geneesmiddelen?.....

Zo ja, welke?.....

.....

Vraag 37. a. Wat voor werk doet u?
huishouden.....
scholier/student.....
geen.....
anders..... nl:

.....

ja ? nee
b. Nemen uw neusklachten daarbij toe?.....

zo ja: (kruis één keuze aan)
zonder een waarschijnlijke oorzaak
met een waarschijnlijke oorzaak... nl:....

.....

ja ? nee
c. Bent u vroeger bij uw werk in contact geweest met stoffen waardoor uw neusklachten toenamen?

Zo ja, welke?.....

(Kruis het vraagteken alleen aan als u het écht niet weet.)

Vraag 38. Worden uw neusklachten erger: ja ? nee
tijdens het uitoefenen van een hobby?.....

zo ja: a. welke hobby?.....

.....

b. (kruis één keuze aan)
zonder waarschijnlijke oorzaak.
met een waarschijnlijke oorzaak nl:

.....

.....

Vraag 39. Alleen voor vrouwen:

ja ? nee
a. is het tijdstip in de menstruatiecyclus van invloed op de klachten?.....

Zo ja, hoe?.....

.....

b. Bent u zwanger?.....

Zo ja: a. hoe lang?.....

b. de klachten zijn in de zwangerschap:
(kruis één keuze aan)
toegenomen.....
gelijk gebleven
afgenomen.....

Vraag 40. Worden uw neusklachten erger: ja ? nee
door andere nog niet genoemde invloeden of op nog niet genoemde plaatsen?.....

Zo ja, welke?.....

.....

.....

Nu volgen een aantal vragen omtrent uw omgeving.

Vraag 41. Heeft u contact met dieren (ongeacht of u daar wel of geen klachten bij krijgt)?..... ja ☐ nee ☐

Zo ja, (meerdere antwoorden mogelijk)

a. als huisdier of bij hobby (sport)... ☐

beroepsmatig..... ☐

anders..... ☐ nl:.....

.....

b. kruis aan welke dieren: hoelang (jaartal)?

hond.....	☐	sinds.....
kat.....	☐	sinds.....
cavia....	☐	sinds.....
hamster..	☐	sinds.....
konijn...	☐	sinds.....
paard....	☐	sinds.....
koe.....	☐	sinds.....
schaap...	☐	sinds.....
geit.....	☐	sinds.....
parkiet..	☐	sinds.....
kanarie..	☐	sinds.....
papegaai.	☐	sinds.....
andere...	☐	nl:.....

.....sinds.....

(Kruis het vraagteken alleen aan als u het écht niet weet.)

Vraag 42. In wat voor huis woont u?

	ja	?	nee
a. In een vochtig huis?.....	☐	☐	☐
b. Zijn er vochtplekken?.....	☐	☐	☐
c. Is er zichtbare schimmel?.....	☐	☐	☐
d. Zijn er houten vloeren die rot of gerepareerd zijn?.....	☐	☐	☐
e. Ruikt het huis muf?.....	☐	☐	☐
f. Wordt het goed geventileerd?.....	☐	☐	☐

g. Wanneer is het huis ongeveer gebouwd? jaar:.....

h. Is het huis gerenoveerd?.....	☐	☐	☐
i. Woont u op vochtige grond of is er water onder het huis?.....	☐	☐	☐

j. Hoe wordt het huis verwarmd? (meerdere keuzen mogelijk)

centrale verwarming (radiatoren)... ☐

vloerverwarming..... ☐

luchtverwarming..... ☐

losse kachels..... ☐

anders..... ☐ nl:

.....

k. Hoe lang woont u in dit huis?..... .....jaar

(Kruis het vraagteken alleen aan als u het ècht niet weet.)

	ja	?	nee
Vraag 43. Zijn uw klachten begonnen toen u nog in een ander huis woonde?	☐	☐	☐
Zo ja, wat voor huis was dat?			
a. Een vochtig huis?	☐	☐	☐
b. Waren er vochtplekken?	☐	☐	☐
c. Was er zichtbare schimmel?	☐	☐	☐
d. Waren er houten vloeren die rot of gerepareerd waren?	☐	☐	☐
e. Rook het huis muf?	☐	☐	☐
f. Werd het goed geventileerd?	☐	☐	☐
g. Wanneer was het huis ongeveer gebouwd? jaar:.....			
h. Was het huis gerenoveerd?	☐	☐	☐
i. Woonde u op vochtige grond of was er water onder het huis?	☐	☐	☐

j. Hoe werd het huis verwarmd? (meerdere keuzen mogelijk)

- centrale verwarming (radiatoren)... ☐
- vloerverwarming..... ☐
- luchtverwarming..... ☐
- losse kachels..... ☐
- anders..... ☐ nl:

.....

k. Heeft u verschil in klachten gemerkt tussen beide huizen? (kruis één keuze aan)

- nee..... ☐
- ja, in het huis waarin ik nu woon minder klachten ☐
- ja, in het huis waarin ik nu woon meer klachten.. ☐

Vraag 44. Hoe is uw slaapkamer ingericht? (kruis telkens één keuze aan)

a. vloerbedekking:
- alleen hard (zeil, parket)..... ☐
- alleen zacht (vaste vloerbedekking, kleden) ☐
- beide..... ☐

b. kussen, dekens/dekbed:
- alleen synthetisch..... ☐
- ook dons of wol..... ☐
- onbekend..... ☐

c. gordijnen/jalouzieën:
- hard of glad..... ☐
- van stof..... ☐

d. hoe oud is uw matras ongeveer?..... .....jaar

e. waarmee is de matras gevuld?
- kapok/wol..... ☐
- kunststof..... ☐
- onbekend..... ☐

Vraag 45. Hoe is uw woonkamer ingericht? (kruis telkens één keuze aan)

a. vloerbedekking:
- alleen hard (zeil, parket)..... ☐
- alleen zacht (vaste vloerbedekking, kleden) ☐
- beide..... ☐

b. meubels:
- alleen hard, glad materiaal..... ☐
- ook gestoffeerd..... ☐

c. gordijnen/jalouzieën:
- hard of glad..... ☐
- van stof..... ☐

Vraag 46. Heeft u altijd in Nederland gewoond?..... ja ☐ nee ☐

Zo nee,
a. wanneer bent u in Nederland komen wonen? In 19.....

b. waar woonde u daarvoor?.....

.....

.....

Vraag 47. Rookt u? (kruis één keuze aan)

ja..... ☐

nee, nooit gerookt.... ☐

nee, gestopt..... ☐ sinds 19.....

Zo ja, (meerdere keuzen mogelijk)

wat?		hoeveel?	hoe lang?
sigaretten/shag	☐	.....per dag,	sinds 19.....
sigaren.....	☐	.....per dag,	sinds 19.....
pijp.....	☐	.....per dag,	sinds 19.....

Vraag 48. Wordt er in uw omgeving regelmatig gerookt?.. ja ☐ nee ☐

Vraag 49. Heeft u zelf nog aanvullingen die belangrijk kunnen zijn bij het opsporen van de oorzaak van uw neusklachten?

ja ☐ nee ☐

Zo ja, welke?.....

.....

.....

.....

.....

LICHAMELIJK ONDERZOEK Patiëntcode:

INSPECTIE:

Algemeen : nasale spraak..... ☐ (gesloten neusspraak) mondademhaling ☐ loopneus/snuiven ☐

Ogen : gezwollen oogleden ☐ rode ogen ☐ tranende ogen ☐ allergic shiners (periorbitaal paarse huid) ☐

Mond : hypertrofische tonsillen... ☐ toegenomen roodheid van de keel ☐
tonsillitis zonder exsudaat ☐ postnasal drip ☐ foetor ex ore ☐
tonsillitis met exsudaat... ☐

Neus, uitwendig:
opvallende scheefstand ☐ naar: L / R opvallend ingezakte neusrug ☐
dwarse streep/plooi neusrug ☐

Rhinoscopia anterior:

I. Secreet: a. hoeveelheid/plaats:
geen (droog slijmvlies).... ☐
weinig (vochtig slijmvlies) ☐
matig..... ☐
veel (vult neusgang)..... ☐
vooral op concha inferior... ☐

b. samenstelling:
n.v.t. (geen secreet) ☐
dun (waterig)..... ☐
taai..... ☐
met korsten..... ☐

c. kleur:
n.v.t. (geen secreet) ☐
geen (helder)..... ☐
wit (troebel)..... ☐
geel/groen..... ☐

II. Septum: normaal..... ☐
lichte deviatie (geen belemmering doorgang) ☐
matige deviatie (belemmering doorgang)..... ☐ anterior. ☐ naar L / R
ernstige deviatie (afsluiting doorgang).... ☐ posterior ☐ naar L / R

III. Crista septi:
geen..... ☐
gering (geen belemmering doorgang) ☐ L / R
matig (belemmering doorgang)..... ☐ L / R
ernstig (afsluiting doorgang)..... ☐ L / R

IV. Spina septi:
geen..... ☐
geringe..... ☐ L / R
matige (net niet impacterend) ☐ L / R
ernstige (impacterend)..... ☐ L / R

V. Conchae: a. hypertrofie:

geen (normaal).....	☐	
juist atrofie (erg wijde doorgang)	☐	L / R
gering (geen belemmering doorgang)	☐	L / R
matig (belemmering doorgang).....	☐	L / R
ernstig (afsluiting doorgang).....	☐	L / R

b. kleur:

normaal (rose/licht rood)	☐
matig rood.....	☐
erg rood.....	☐
matig bleek.....	☐
erg bleek.....	☐
blauw/paars.....	☐

VI. Poliep(en)

geen.....	☐	
kleine (geen belemmering doorgang).	☐	L / R
matig grote (belemmering doorgang).	☐	L / R
grote (afsluiting doorgang).....	☐	L / R

VII. Overige bevindingen:.....

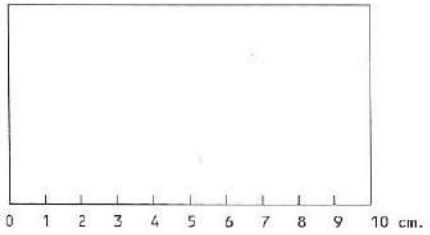
.....

PALPATIE sinus maxillaris:

niet pijnlijk..	☐	
matig pijnlijk.	☐	L / R
erg pijnlijk...	☐	L / R

ECHO sinus maxillaris:

passend bij: normale sinus.....	☐	(alleen voorwand echo < 2 cm. en event. herhalingsecho's)
gezwollen slijmvlies	☐	L / R (echo op 2 à 3 cm.)
sinusitis.....	☐	L / R (back wall echo op 4 à 6 cm.)
cyste of grote poliep	☐	L / R (dubbele echo op 4 à 6 cm.)
onduidelijk beeld....	☐	L / R (alleen dan) schets:



PERCENTAGE EOSINOFIELEN IN EEN UITSTRIJKJE VAN HET NEUSSECREET

patiëntcode:

Uitslag:

	% eo's	
geen eosinofilie.....	< 5%	☐
geringe eosinofilie...	5 à 10%	☐
matige eosinofilie....	10 à 50%	☐
sterke eosinofilie....	> 50%	☐

Afname, kleuring en beoordeling vonden plaats volgens Mygind[1]. Hij beschouwt **≥10% als pathologisch**.

N.B.: Het betreft een éénmalige bepaling.
Factoren die de bepaling kunnen beïnvloeden zijn o.a.:
- afname buiten periode van expositie aan allergeen,
- gebruik van (locale) corticosteroïden,
- infectie van het neusslijmvlies.

Zie voor gegevens hierover de bevindingen bij de anamnese.

Literatuur:
1. Mygind N. Essental Allergy. Oxford, Blackwell Scientific Publications; 1986: 302-7.

TOTAAL IGE, PHADIATOP EN RASTS

Patiëntcode:

Totaal IgE: kU/l (normaal: <100 kU/l)

Phadiatop: - / +

RASTs	RASTcode	Klasse (0-4)*
mengsel van boompollen	Tx9	
mengsel van graspollen	Gx1	
mengsel van kruidpollen	Wx3	
mengsel van schimmels	Mx1	
huisstofmijt (Derm.pteron.)	D1	
kat	E1	
hond	E5	
paard**	E3	
cavia**	E6	
konijn**	E82	

* Klasse Conc. allergeen spec. IgE
0 <0,35 kU/l (niet aantoonbaar)
1 0,35 tot 0,70 kU/l (laag)
2 0,70 tot 3,50 kU/l (matig)
3 3,50 tot 17,50 kU/l (hoog)
4 >17,50 kU/l (zeer hoog)

** Alleen op indicatie, n.a.v. de anamnese.

HUIDTESTS (PHAZET) Patiëntcode:

Om de interpretatie niet te beïnvloeden wordt alleen de grootte van de kwaddels weergegeven (d.m.v. tape overgenomen): zie volgende bladzijde. Hieronder kunt u desgewenst uw eigen interpretatie noteren. Aanwezigheid van erytheem wordt aangegeven d.m.v. + of -.

positieve controle			
negatieve controle			
BOMEN			
els	T2		
berk	T3		
GRASSEN			
kropaar	G3		
timothee	G6		
KRUIDEN			
bijvoet	W6		
weegbree	W9		
SCHIMMEL			
alternaria	M6		
HUISSTOFMIJTEN			
Derm.pteron.	D1		
Derm.farinae	D2		
DIEREN			
kat	E1		
hond	E5		
paard	E3		
cavia	E6		
konijn	E82		

Geen weergave=geen kwaddel. E +/--erytheem aan- of afwezig.

positieve controle E +/-	negatieve controle E +/-
els E +/-	Derm. pteron. E +/-
berk E +/-	Derm. farinae E +/-
kropaar E +/-	kat E +/-
timothee E +/-	hond E +/-
bijvoet E +/-	paard E +/-
weegbree E +/-	cavia E +/-
alternaria E +/-	konijn E +/-

Appendix 3

List of diagnoses

LIST OF DIAGNOSES

Please indicate the presence or absence of the diagnoses as follows:
(1) (almost certainly) absent
(2) probably absent
(3) questionable
(4) probably present
(5) (almost certainly) present.

1. allergic rhinitis:
   - pollinosis:
     - trees
     - grasses
     - weeds
   - house dust mite
   - mould
   - animals:
     - cat
     - dog
     - horse
     - rabbit
     - guinea pig
     - other: .....
   - occupational allergy: .....

2. vasomotor rhinitis (whith or without nasal hyperreactivity)

3. infectious rhinitis (whith or without sinusitis)

4. nasal polyp(s)

5. rhinitis medicamentosa

6. anatomical obstruction

7. other nasal disorder: .....

8. no nasal pathology

9. non-specific nasal hyperreactivity (not a distinct disorder but a concomitant clinical manifestation):
   absent
   moderate
   strong.

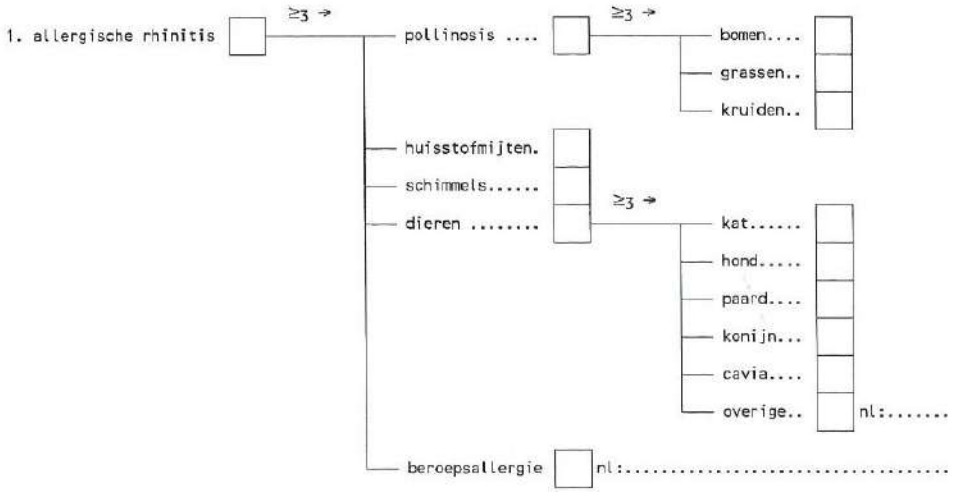
LIJST MET DIAGNOSEN

Patiëntcode:

Lees eerst de "Toelichting bij de lijst met diagnosen".

U kunt achter onderstaande diagnosen de aanwezigheid als volgt aangeven:

1 = (zo goed als zeker) niet aanwezig
2 = waarschijnlijk niet aanwezig
3 = dubieus
4 = waarschijnlijk wel aanwezig
5 = (zo goed als zeker) wel aanwezig



2. vasomotore rhinitis.. ☐ (al of niet met hyperreactiviteit)

3. infectieuze rhinitis. ☐ (al of niet met sinusitis)

4. neuspoliep(en)..... ☐

5. medicamenteuze rhin.. ☐

6. anatomische afwijking ☐

7. overige afwijkingen.. ☐ nl:.....

8. geen afwijkingen..... ☐

9. aspecifieke hyperreactiviteit (geen diagnose maar eventueel bijkomend verschijnsel; zie de toelichting)
(kruis één keuze aan): O afwezig
O matig
O sterk

Appendix 4

Additional tables

Comment

In this Appendix, additional data are presented. For each table, the connection with the text of the thesis is indicated.

Tables 1 and 2 illustrate the text on the methods of the consensus procedure, Chapter 5, page 69.

Table 1. Assessment of the consensus of three experts on the presence of nasal disorders

combinations of judgments of three experts*	consensus: diagnosis
1, 1, 1	absent
1, 1, 2	absent
1, 1, 3	absent
1, 2, 2	absent
1, 2, 3	absent
2, 2, 2	absent
2, 2, 3	absent
3, 3, 1	questionable
3, 3, 2	questionable
3, 3, 3	questionable
3, 3, 4	questionable
3, 3, 5	questionable
3, 4, 4	present
3, 4, 5	present
4, 4, 4	present
4, 4, 5	present
3, 5, 5	present
4, 5, 5	present
5, 5, 5	present
all other combinations**	no consensus

* 1 = (almost certainly) absent; 2 = probably absent; 3 = questionable; 4 = probably present; 5 = (almost certainly) present.
** These combinations consist of contrary judgments (i.e. 1 or 2 combined with 4 or 5).

Table 2. Assessment of the consensus of three experts on the degree of non-specific nasal hyperreactivity

combinations of judgments of three experts*	consensus: non-specific nasal hyperreactivity
1, 1, 1	absent
1, 1, 2	absent
2, 2, 1	mild
2, 2, 2	mild
2, 2, 3	mild
3, 3, 2	severe
3, 3, 3	severe
all other combinations**	no consensus

* 1 = absent; 2 = mild; 3 = severe.
** these combinations consist of contrary judgments (1 combined with 3).

Comment on Tables 3 to 7
Tables 3 to 7 present more detailed results of the consensus procedure, Chapter 5, page 71.

Table 3. Judgments of three experts on the presence of nasal pathology in 365 patients with chronic or recurrent nasal symptoms; judgments on a five-point scale; changes during three consensus procedure rounds

combinations of judgments of three experts*	consensus: diagnosis	allergic rhinitis			vasomotor rhinitis**	infectious rhinitis**	nasal polyps			rhinitis medicamentosa**	anatomical obstruction**
		1st round	2nd round	3rd round			1st round	2nd round	3rd round		
1, 1, 1	absent	159	+1		122	171	347	+1		301	121
1, 1, 2	absent	4	+1		4	21	2			14	48
1, 1, 3	absent	12	+1		15	34	0			12	38
1, 2, 2	absent	0			0	4	0			1	0
1, 2, 3	absent	2			0	7	0			0	2
2, 2, 2	absent	0			0	0	0			0	0
2, 2, 3	absent	0		+1	0	2	0			0	0
3, 3, 1	questionable	3	+1		2	3	0	+1		1	1
3, 3, 2	questionable	3		+2	0	0	0			0	0
3, 3, 3	questionable	0			0	0	0			0	0
3, 3, 4	questionable	1	+1		0	1	0			0	3
3, 3, 5	questionable	0			1	0	0			0	0
3, 4, 4	present	0			1	2	0			0	3
3, 4, 5	present	1	+2		7	3	0			0	11
4, 4, 4	present	2		+2	3	0	0			0	0
4, 4, 5	present	7	+1	+1	3	4	0	+1		0	5
3, 5, 5	present	13	+1		4	2	0	+1		0	13
4, 5, 5	present	18	+3		33	2	0			1	33
5, 5, 5	present	119			24	2	6	+5	+1	0	7
all other combinations	no consensus	21	-12	-6	146	107	10	-9	-1	35	80

* 1 = (almost certainly) absent; 2 = probably absent; 3 = questionable; 4 = probably present; 5 = (almost certainly) present.
** Judgments were given only during the first round.

Table 4. Judgments of three experts on the presence of specified diagnoses of allergic rhinitis in 365 patients with chronic nasal symptoms; judgments on a five-point scale; changes during three consensus procedure rounds

combinations of judgments of three experts*	consensus: diagnosis	tree pollen			grass pollen			weed pollen			house dust mite			moulds			cat		
		1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round
1, 1, 1	absent	304	+3		271	+2		325	+2		230	+2	+1	348	+1		317	+1	+1
1, 1, 2	absent	2			1			1			2			3			1		
1, 1, 3	absent	1			0			8			5	+1	+1	0			1		
1, 2, 2	absent	0			0			0			1			1			0		
1, 2, 3	absent	0			0			0			0	+1		2			0		
2, 2, 2	absent	0			0			0		+1	0			0			0		
2, 2, 3	absent	1			0		+1	0			0		+2	0			0	+1	
3, 3, 1	questionable	3			1			0			5	+1	+1	0			1		
3, 3, 2	questionable	0		+1	0		+1	0			1	+1	+2	0			0		+1
3, 3, 3	questionable	0			0		+1	0			0		+1	0		+1	0		
3, 3, 4	questionable	0	+1	+1	1	+1		0			0			1			0		
3, 3, 5	questionable	0			0			1	+1		1			0			0		
3, 4, 4	present	0	+1		1	+1		0			0	+1	+1	0			0	+2	
3, 4, 5	present	1	+1		3	+1		2			1	+3		3			2		
4, 4, 4	present	0	+2		0	+1		0	+2		0	+1	+2	0		+1	0	+1	+2
4, 4, 5	present	3	+1		2	+2		1			6	+1	+1	1			1		
3, 5, 5	present	0			8	+1		3	+1		8			0			3	+1	
4, 5, 5	present	4	+1		5	+2		10	+1		11	+1		1	+1		5		
5, 5, 5	present	33	+1		58			6			66			1			24		
all other combinations	no consensus	13	-11	-2	14	-11	-3	8	-7	-1	28	-13	-12	4	-2	-2	10	-6	-4

* 1 = (almost certainly) absent; 2 = probably absent; 3 = questionable; 4 = probably present; 5 = (almost certainly) present.

Table 4 (continued). Judgments of three experts on the presence of specified diagnoses of allergic rhinitis in 365 patients with chronic nasal symptoms; judgments on a five-point scale; changes during three consensus procedure rounds

combinations of judgments of three experts*	consensus: diagnosis	dog			horse			rabbit			guinea pig			other animals			occupational		
		1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round	1st round	2nd round	3rd round
1, 1, 1	absent	320		+1	350			355		+1	356			358			360		
1, 1, 2	absent	0	+1		1			2			1			1			0		+1
1, 1, 3	absent	3			3			2			1			1			2	+1	
1, 2, 2	absent	1			1			1	+1		0			0			0		
1, 2, 3	absent	0	+1		0			0			0			0			0		
2, 2, 2	absent	0			0			0			0			0		+3	0		
2, 2, 3	absent	0			0			0			0			0			0		
3, 3, 1	questionable	3			1			1			0			0			0		
3, 3, 2	questionable	0	+2	+2	1			0			0			0		+1	0		
3, 3, 3	questionable	0			0			0			0			0			0		
3, 3, 4	questionable	0	+1		0	+2		0			0			0			0		
3, 3, 5	questionable	1			1			0			0			0			0		
3, 4, 4	present	0	+1	+1	0			0			1	+1		0		+1	0		
3, 4, 5	present	3			0			0			1			0			0		
4, 4, 4	present	0		+1	0			0			0			0			0		
4, 4, 5	present	1			2			0			0			0			0		
3, 5, 5	present	2			0			0			0			0			0		
4, 5, 5	present	2			0			0			1			0			0		
5, 5, 5	present	16			3			2			3			0			0		
all other combinations	no consensus	13	-6	-5	2	-2		2	-1	-1	1	-1		5		-5	3	-1	-1

* 1 = (almost certainly) absent; 2 = probably absent; 3 = questionable; 4 = probably present; 5 = (almost certainly) present.

Table 5. Judgments of three experts on the degree of non-specific nasal hyperreactivity in 365 patients with chronic nasal symptoms; judgments on a three-point scale; changes during three consensus procedure rounds

combinations of judgments of three experts*	consensus: diagnosis	1st round	2nd round	3rd round
1, 1, 1	absent	190		
1, 1, 2	absent	46		
1, 2, 2	mild	42	+1	+1
2, 2, 2	mild	41	+1	
2, 2, 3	mild	13	+1	
2, 3, 3	severe	13		
3, 3, 3	severe	16		
1, 1, 3	no consensus	0		
1, 2, 3	no consensus	3	-2	-1
1, 3, 3	no consensus	1	-1	

* 1 = absent; 2 = mild; 3 = severe.

Table 6. Combinations of nasal allergies in the same patient; data from 365 patients with chronic or recurrent nasal symptoms (number of mono-allergies)

nasal allergy	tree pollen	grass pollen	weed pollen	house dust mites	molds	cat	dog	horse	rabbit	guinea pig
tree pollen	**48 (4)**									
grass pollen	42	**85 (27)**								
weed pollen	22	25	**26 (1)**							
house dust mite	21	33	13	**103 (53)**						
molds	3	5	2	4	**8 (1)**					
cat	18	20	6	30	2	**41 (0)**				
dog	16	18	4	16	1	24	**27 (2)**			
horse	3	4	0	3	1	4	4	**5 (0)**		
rabbit	0	1	0	1	0	1	1	0	**2 (1)**	
guinea pig	3	4	1	5	1	6	3	3	0	**7 (0)**

Table 7. Number of nasal allergies per patient in 365 patients with chronic or recurrent nasal symptoms

number of nasal allergies	number of patients (%)
0	182 (50)
1	89 (24)
2	34 (9)
3	14 (4)
4	19 (5)
5	6 (2)
6	4 (1)
7	3 (1)
total	351 (96)*

* in 14 patients (4%) the presence of allergic rhinitis was questionable.

Comment on Table 8

Table 8 presents detailed information about the medical history of those patients who were diagnosed by the experts as having allergic rhinitis; this table is meant to give an impression of the number of patients who were diagnosed as having a certain nasal allergy, without presenting themselves with symptoms that were indicative of the specific allergy. For each nasal allergy, a list of symptoms is presented, and the number of patients with that symptom is indicated. Patients who had a certain symptom, are not presented in the subsequent line. The items from the medical history are listed in order of their presumed degree of being indicative of the specific allergy; this presumption was based on clinical relevance, as indicated in the literature, and the results from multivariate and bivariate analyses. This Table is discussed in the General Discussion on page 168.

Table 8. Medical history of patients diagnosed as having a nasal allergy (See comment on page 248)

nasal allergy	symptom	number of patients with the symptom
tree pollen (n=48)	symptoms in the spring only/worse	40 out of 48
	symptoms on dry, sunny days	4 out of the remaining 8
	symptoms outdoors	1 out of the remaining 4
	fewer symptoms in the mountains	1 out of the remaining 3
	symptoms in the summer	1 out of the remaining 2
	blocked-up nose all year round	1 out of the remaining 1
grass pollen (n=85)	symptoms in the spring or summer only/worse	68 out of 85
	symptoms on contact with grass	2 out of the remaining 17
	symptoms on dry, sunny days	2 out of the remaining 15
	symptoms outdoors	4 out of the remaining 13
	fewer symptoms by the sea	3 out of the remaining 9
	sneezing all year round	5 out of the remaining 6
	blocked-up nose	1 out of the remaining 1
weed pollen (n=26)	symptoms in the summer only/worse	18 out of 26
	symptoms on dry, sunny days	6 out of the remaining 8
	symptoms outdoors	1 out of the remaining 2
	fewer symptoms on rainy days	1 out of the remaining 1
house dust mite (n=103)	symptoms on contact with house dust or when making beds	71 out of 103
	symptoms in the bedroom	5 out of the remaining 32
	symptoms indoors	10 out of the remaining 27
	fewer symptoms in the mountains	2 out of the remaining 17
	symptoms at night or at rising	11 out of the remaining 15
	sneezing all year round	1 out of the remaining 4
	periods of sneezing	1 out of the remaining 3
	blocked-up nose and itchy eyes	1 out of the remaining 2
	blocked-up nose all year round	1 out of the remaining 1

Table 8 (continued). Medical history of patients diagnosed as having a nasal allergy (See comment on page 248)

nasal allergy	symptom	number of patients with the symptom		
mould (n=8)	symptoms on contact with clothes of husband who works in cheese industry	1	out of	8
	sneezing all year round	4	out of the remaining	7
	periods of sneezing	3	out of the remaining	3
cat (n=41)	symptoms on contact with cats	27	out of	41
	contact with cats	8	out of the remaining	14
	symptoms on contact with house dust	3	out of the remaining	6
	symptoms indoors	1	out of the remaining	3
	sneezing and itchy eyes	2	out of the remaining	2
dog (n=27)	symptoms on contact with dogs	15	out of	27
	contact with dogs	6	out of the remaining	12
	symptoms on contact with house dust	5	out of the remaining	6
	sneezing indoors all year round	1	out of the remaining	1
horse (n=5)	symptoms on contact with horses	3	out of	5
	periods of sneezing and itchy eyes	2	out of the remaining	2
rabbit (n=2)	symptoms on contact with rabbits	2	out of	2
guinea pig (n=7)	symptoms on contact with guinea pigs	6	out of	7
	periods of sneezing and itchy eyes	1	out of the remaining	1

Comment on Tables 9 to 11

Table 9 represents results additional to Table 7.1, page 105.
Table 10 represents the more detailed results of Table 7.2, page 106; Table 11 represents the same data as Table 10, but expressed as histamine equivalent weal diameters instead of mean weal diameters.
The results presented here, are discussed in Chapter 7.

Table 9. Comparison of radioallergosorbent tests (RASTs) with expert consensus diagnoses of nasal allergies in 361 patients with chronic or recurrent nasal symptoms*

	expert consensus diagnoses of nasal allergy					
	horse dander		rabbit dander		guinea pig dander	
RAST class	-	+	-	+	-	+
0	15		48		23	
1						1
2				1		2
3		3		1		2
4						1
total	15	3	48	2	23	6

RASTs against horse dander, rabbit dander, and guinea pig dander were performed only if the patient reported contact with, or symptoms on contact with, the animal.

Table 10. Comparison of skin prick tests, presented as mean weal diameters, with expert consensus diagnoses of nasal allergies in 365 patients with chronic or recurrent nasal symptoms*

mean weal diameter (mm)	expert consensus diagnoses of nasal allergy																	
	tree pollen						grass pollen						weed pollen					
	birch		alder		maximum		cocksfoot		timothy		maximum		plantain		mugwort		maximum	
	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	293	6	299	21	284	5	259	2	264	3	254	1	326	17	336	22	325	13
1	7	1	5	3	11	1	4		2	1	5		2		1		3	
2	8	2	6	8	12	2	7	4	7	6	11	3	6	1		1	6	2
3	2	3		9	2	4	3	7	1	6	3	6	3	1		2	3	3
4	1	3	1	3	2	3	2	10	1	8	2	4		4				4
5-9		25		4		25		45		38		41		3		1		4
10-14		7				7		16		20		26						
15-19		1				1		1		1		2						
20-24										2		2						
total	311	48	311	48	311	48	275	85	275	85	275	85	337	26	337	26	337	26
excl.**	6		6		6		5		5		5		2		2		2	

* mean weal diameter (MWD): the mean of the largest diameter and the perpendicular diameter through the midpoint of the largest diameter; in case of an MWD of the negative control that was equal to or larger than the reaction to the allergen, the outcome '0' was noted; when two allergens were tested for the same diagnosis, the maximum outcome is given in the third column.

** patients were excluded from analysis if the experts reached no consensus on the presence or absence of the nasal allergy.

Table 10 (continued). Comparison of skin prick tests, presented as mean weal diameters, with expert consensus diagnoses of nasal allergies in 365 patients with chronic or recurrent nasal symptoms*

mean weal diameter (mm)	expert consensus diagnoses of nasal allergy																			
	housedust mite						mould (Altern.)		cat dander		dog dander		horse dander		rabbit dander		guinea pig dander	
	Derm.pt.		Derm.far.		maximum													
	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	213	2	231	15	210	2	343	2	307	5	299	3	353		359		355	2
1	15		7	2	15		4		3	3	11	1			2		1	
2	13	3	7	15	16	1	7		10	2	12	3	2				1	1
3	3	10		19	2	11	1	1	2	5	5	5		1	1		1	1
4		17	1	20	1	16		1		9		8		1				2
5-9	2	53		32	2	55		3		15		7		3		2		1
10-14		18				18		1		2								
total	246	103	246	103	246	103	355	8	322	41	327	27	355	5	362	2	358	7
missing***	16		16		16		2		2		11		5		1		0	

* mean weal diameter (MWD): the mean of the largest diameter and the perpendicular diameter through the midpoint of the largest diameter; in case of an MWD of the negative control that was equal to or larger than the reaction to the allergen, the outcome '0' was noted; when two allergens were tested for the same diagnosis, the maximum outcome is given in the third column.

** patients were excluded from analysis if the experts reached no consensus on the presence or absence of the nasal allergy.

Table 11. Comparison of skin prick tests, presented as histamine equivalent weal diameters, with expert consensus diagnoses of nasal allergies in 365 patients with chronic or recurrent nasal symptoms*

histamine equivalent weal diameter	expert consensus diagnoses of nasal allergy																	
	tree pollen						grass pollen						weed pollen					
	birch		alder		maximum		cocksfoot		timothy		maximum		plantain		mugwort		maximum	
	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	289	6	295	21	280	5	257	2	262	3	252	1	322	17	332	21	321	13
0.01-0.19	2	1	4		5	1	3		1		4		1				1	
0.20-0.39	6	2	4	7	9	2	3	4	2	3	4	3	6		1	2	7	2
0.40-0.49	4	1	1	3	5	1	1	3	3	4	3	2		1				1
0.50-0.59	3	2		4	3	3	4	5	2	3	5	2	3	3			3	3
0.60-0.69	1	2	2	5	2	2	4	2	3	2	4	1	1	1		1	1	2
0.70-0.99		6		2		6		12		11		8		2				2
1.00-1.19	2	8	1	5	3	8	1	22		13	1	15		1				1
1.20-1.49		7		1		7		10		14		16						
1.50-1.99		4				4		14		15		20		1		1		2
≥2.00		9				9		11		17		17						
total missing***	307	48	307	48	307	48	273	85	273	85	273	85	333	26	333	25	333	26
	10		10		10		7		7		7		6		7		6	

* histamine equivalent weal diameter (HEWD): the ratio of the mean weal diameter (MWD) of the allergen test to the MWD of the positive control; if both the histamine MWD and the allergen MWD were 0, the outcome was noted as 'missing'; if the histamine MWD was 0 but the allergen MWD was higher, the outcome was noted as '1.0'; in case of a MWD of the negative control that was equal to or larger than the allergen MWD, the outcome '0' was noted; when two allergens were tested for the same diagnosis, the maximum outcome is given in the third column.

** patients were excluded from analyis because the experts reached no consensus on the presence or absence of the nasal allergy, or because both a histamine MWD and an allergen MWD of 0 were recorded.

Table 11 (continued). Comparison of skin prick tests, presented as histamine equivalent weal diameters, with expert consensus diagnoses of nasal allergies in 365 patients with chronic or recurrent nasal symptoms*

histamine equivalent weal diameter	expert consensus diagnoses of nasal allergy																			
	housedust mite						mould (Altern.)		cat dander		dog dander		horse dander		rabbit dander		guinea pig dander	
	Derm.pt.		Derm.far.		maximum													
	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
0	212	2	229	14	209	2	339	2	304	4	295	3	349		354		350	2
0.01-0.19	11		2		11		1		3	1	4	1			2		1	
0.20-0.39	9	1	9	11	11		6		5	5	13	3		1				1
0.40-0.49	5	1	2	7	6	1	2		2	1	4	1			1		2	
0.50-0.59	4	4	1	12	4	3	2		2	4	4	4	1					
0.60-0.69	1	10		16		11			2	3	2	4	1					1
0.70-0.99		18	1	14	1	18		1		4		1		1				
1.00-1.19	1	24		15	1	22		2	1	7	1	5		2				3
1.20-1.49	2	15		4	2	15		2		3		2				1		
1.50-1.99		14		8		17	1	1		3		1		1		1		
≥2.00		14		1		14				5		2						
total missing***	245	103	244	102	245	103	351	8	319	40	323	27	351	5	357	2	353	7
	17		19		17		6		6		15		9		6		5	

* histamine equivalent weal diameter (HEWD): the ratio of the mean weal diameter (MWD) of the allergen test to the MWD of the positive control; if both the histamine MWD and the allergen MWD were 0, the outcome was noted as 'missing'; if the histamine MWD was 0 but the allergen MWD was higher, the outcome was noted as '1.0'; in case of a MWD of the negative control that was equal to or larger than the allergen MWD, the outcome '0' was noted; when two allergens were tested for the same diagnosis, the maximum outcome is given in the third column.

** patients were excluded from analyis because the experts reached no consensus on the presence or absence of the nasal allergy, or because both a histamine MWD and an allergen MWD of 0 were recorded.

Nawoord

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Tot slot wil ik hen noemen die van begin tot eind het meest hebben bijgedragen en daar ook het meest van gemerkt hebben. Ik ben blij dat we dit proefschrift samen letterlijk en figuurlijk kunnen afsluiten, Paola, Yara, Cecile en Lucas.

Curriculum vitae

Marcel J.J.S. Crobach werd geboren op 1 april 1958 te Heerlen. In 1976 behaalde hij het diploma Atheneum-B aan het Romboutscollege te Brunssum. Na te zijn uitgeloot voor de studie geneeskunde studeerde hij een jaar farmacie aan de Rijksuniversiteit te Leiden. In 1977 kon hij met de studie geneeskunde aan dezelfde universiteit beginnen. Tijdens die studie was hij als student-assistent werkzaam bij het Laboratorium voor Fysiologie en de Afdeling Longziekten van het Academisch Ziekenhuis Leiden. In 1984 werd de studie afgerond met het behalen van het artsexamen.

In 1985-1986 vervulde hij de militaire diensplicht als arts-assistent op de afdeling interne geneeskunde van het Militair Hospitaal 'Dr. A. Mathijsen' te Utrecht. Vervolgens kon hij de huisartsopleiding volgen aan de Rijksuniversiteit Leiden; huisartsopleider was Y. Groeneveld in het Gezondheidscentrum Merenwijk te Leiden. In 1987 werd hij geregistreerd als huisarts. Na diverse waarnemingen ging hij in 1989 in parttime dienstverband werken in het Gezondheidscentrum Merenwijk te Leiden, waar hij sindsdien de praktijk deelt met Y. Groeneveld.

Daarnaast was hij sinds 1987 parttime aangesteld aan de Vakgroep Huisartsgeneeskunde van de Rijksuniversiteit Leiden, aanvankelijk voor het schrijven van onderwijsprogramma's voor de beroepsopleiding, sinds 1989 als onderzoeker in het kader van het Stimuleringsprogramma Huisartsgeneeskunde van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO). Dit resulteerde in het onderhavige proefschrift.

Per 1 juni 1995 zal hij als huisarts gaan werken in het Medisch Centrum Groenveld te Venlo.

Stellingen

1. De vaak geuite stelling dat de anamnese de hoeksteen van de diagnostiek van allergieën is, kan als juist worden gezien mits men zich realiseert dat van een hoeksteen alleen geen gebouw kan worden gemaakt. *(Dit proefschrift)*

2. Anamnestische aanwijzingen voor aspecifieke nasale hyperreactiviteit leveren geen bijdrage aan de diagnostiek van allergische, noch van niet-allergische neus-aandoeningen. *(Dit proefschrift)*

3. Bij patiënten met chronische of recidiverende neusklachten is de Phadiatop test geschikt om patiënten met allergische rhinitis te onderscheiden van patiënten zonder allergische rhinitis. *(Dit proefschrift)*

4. Het diagnostiseren van allergische rhinitis en identificeren van de oorzakelijke allergenen kan slechts met voldoende zekerheid gebeuren indien de anamnese gecombineerd wordt met de resultaten van radioallergosorbent tests (RASTs) of huid tests. *(Dit proefschrift)*

5. Voor de diagnostiek van allergische rhinitis leveren radioallergosorbent tests (RASTs) en huidtests gelijkwaardige informatie. *(Dit proefschrift)*

6. Het maken van een uitstrijkje van het neusslijmvlies ter beoordeling van het percentage eosinofielen dient te worden ontraden, enerzijds omdat de bijdrage aan de diagnostiek klinisch niet-relevant is, anderzijds omdat de patiënt het als een kwelling ondervindt. *(Dit proefschrift)*

7. Omdat patiënten vaak meer onder de indruk zijn van huidtests dan van uitslagen van serologisch onderzoek, zullen huidtests meer bijdragen aan een gedegen uitvoering van saneringsmaatregelen.

8. Personen met een allergie voor katten zijn gebaat bij het wekelijks baden van de kat. *(R. Glinert, et al, J Allergy Clin Immunol 1990)*

9. Omdat het chronisch gebruik van nasale corticosteroïden minder schadelijk is dan het chronisch gebruik van locale decongestiva, is het onlogisch dat de eerste alleen op recept en de laatste vrij verkrijgbaar zijn.

10. Het aannemen van een gouden standaard bij diagnostisch onderzoek impliceert vaak het nemen van een gulden middenweg.

11. Personen die een anafylactische reactie na een insektesteek kregen, dienen niet te volstaan met het meenemen van een corticosteroïd in de golftas. *(M.J.J.S. Crobach en J.D. Mulder, Lancet 1989)*

12. In het verlengde van verwondering over en berusting in het onvermogen van het menselijk brein tot begrip van oneindigheid van tijd en ruimte, ligt besef van de beperktheid van een zuiver natuurwetenschappelijke levensbeschouwing.

13. Aan de tekst op pakjes sigaretten waarin wordt gewaarschuwd dat roken de gezondheid schaadt, dient te worden toegevoegd dat "meerokende" kinderen een grotere kans hebben op ontwikkeling van allergieën. *(S. Arshad, et al, Lancet 1992)*

14. Hoe meer er in de patiënt wordt gekeken, des te minder wordt er naar de patiënt gekeken. *(L.H.J.Th. Crobach, 1995)*

15. In periodes waarin rivieren buiten hun oever dreigen te treden, zouden lege mijnen als noodbassin kunnen dienen.

Leiden, 11 mei 1995

M.J.J.S. Crobach

Stellingen behorend bij het proefschrift:
Crobach MJJS. Chronic and recurrent nasal symptoms: a diagnostic study in general practice with special reference to allergic rhinitis. Leiden: Rijksuniversiteit Leiden, 1995.