Allergic and non-allergic rhinitis:

by

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Academic dissertation

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List of original publications

This thesis is based on the following original articles, which are referred to by the Roman numerals I–IV in the text.

I. Simola M, Böss I, Holopainen E and Malmberg H. Long-term clinical course of hypersensitive rhinitis. Rhinology 29:301–306, 1991

II. Simola M, Holopainen E, Malmberg H. Changes in skin and nasal sensitivity to allergens and the course of rhinitis; a long-term follow-up study. Annals of Allergy, Asthma, & Immunology 1999;82:152–156

III. Simola M and Malmberg H. Sense of smell in allergic and nonallergic rhinitis. Allergy 1998;53:190–194

IV. Simola M and Malmberg H. Nasal histamine reactivity; relationships to skin-test responses, allergen provocation and symptom severity in patients with long-continuing allergic rhinitis. Acta Oto-laryngologica 2000;120:67–71

Some unpublished data have also been included. The publishers of the original articles have kindly granted their permission to reprint the papers in this thesis.

ABBREVIATIONS

ALU	Arbitrary logarithmic unit
CI	Confidence interval
dS	Decismel
NAR	Nasal airway resistance
PC_{25}	Provocative concentration inducing a change of 25%
PC_{50}	Provocative concentration inducing a change of 50%
PC_{100}	Provocative concentration inducing a change of 100%
PD_{25}	Provocative dose inducing a change of 25%
PD_{50}	Provocative dose inducing a change of 50%
PD_{100}	Provocative dose inducing a change of 100%
TNR	Total nasal resistance

INTRODUCTION

Allergic or non-allergic non-infectious rhinitis is a common disease with a prevalence of 10–40 per cent (Malmberg 1979, Jones *et al.* 1998, Jessen and Janzon 1989, Sibbald and Rink 1991). The upward trend in prevalence figures reported during the last few decades (Åberg 1989, Åberg *et al.* 1995, Rimpelä *et al.* 1995) has been an incentive to extensive research on nasal allergy and hyperreactivity. The natural course of rhinitis has not been given much attention, however, and only a few reports have been published. In these studies, individual symptom severity has shown a downward trend with advancing age (Smith 1971, Broder *et al.* 1974, Lehtonen and Haahtela 1988, Linna *et al.* 1992).

Skin testing is the basic method of investigating patients with suspected nasal allergy. In selected cases, e.g. in suspected occupational rhinitis and in research set-ups, nasal allergen provocation for verification of the skin test results may still be indicated. Barbee and co-workers (1987) have shown that skin-test results vary in the course of time, but it is unclear whether the variations occur concomitantly with changes in nasal symptom severity and nasal sensitivity to allergens.

Extensive research work has been carried out on the physiology of olfaction and several methods have been utilized in assessing the sense of smell. Olfactory thresholds are known to be related to age. They are markedly higher among elderly people (Deems and Doty 1987), but in studies of rhinitis patients, the influence of age has usually been neglected. There are also a few studies in which quantitative assessment has shown deterioration in the sense of smell in patients with rhinitis (Cowart *et al.* 1993, Apter *et al.* 1995).

The term nasal hyperreactivity is currently defined in two ways. According to Gerth van Wijk (1991), hyperreactivity in the airways refers only to an increased sensitivity to non-specific stimuli or irritants which do not act as allergens. In contrast, the German consensus statement (Bachert and Ganzer 1996) recognizes two categories of nasal hyperreactivity: specific, i.e. caused by allergens, and non-specific, associated with non-specific stimuli. Nasal histamine provocation is one of many methods which have been used to assess the degree of nasal hyperreactivity. Attempts have been made to use this method as a test for differentiating a nose with non-specific hyperreactivity from a healthy nose in the same way as bronchial histamine provocation is used in the diagnostics of bronchial hyperreactivity (Sovijärvi *et al.* 1993). These efforts have produced contradictory results. Some investigators (Clement *et al.* 1985, Gerth van Wijk and Dieges 1987) have been able to discriminate allergic rhinitis patients from control subjects on the basis of histamine provocation, but often differences have not been demonstrable between various types of rhinitis patients or between rhinitis patients and control subjects (McLean *et al.* 1977, Guercio *et al.* 1979). Unlike bronchial challenge, nasal histamine provocation has appeared to be unsuitable for routine clinical practice because of considerable overlapping between patients and controls, but it has been used with some success as a research tool in selected set-ups.

This study was carried out in order to investigate various aspects of the course of allergic and non-allergic hypersensitive rhinitis over a follow-up period of more than 20 years.

REVIEW OF THE LITERATURE

Classification and definition of rhinitis

The terms denoting various types of rhinitis have changed in the course of time. Earlier virtually all non-infectious types of rhinitis were called ”allergic”. In his authoritative textbook on nasal allergy in the late 70’s, Mygind (1979) divided rhinitis into three main classes, viz., hay fever, perennial rhinitis and nasal polyposis. Perennial rhinitis was further classified into allergic, non-allergic eosinophilic (intrinsic) and non-allergic non-eosinophilic (autonomic) groups. In 1994, an international working group defined rhinitis as an ”inflammation of the lining of the nose, characterised by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and itching”. Their consensus report classified rhinitis into three main types: allergic (seasonal or perennial), infectious (acute or chronic) and ”other”, which includes idiopathic rhinitis, non-allergic rhinitis with eosinophilia syndrome, nasal polyps, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, primary atrophic rhinitis and rhinitis produced by food or emotional factors (International Rhinitis Management Working Group 1994). This classification was also mainly followed by Mygind and co-workers (1996b) in their latest textbook. In a recent German consensus statement on allergic rhinitis and its differential diagnosis (Bachert and Ganzer 1996), the term hyperreactivity (”Hyperreaktivität”) was used instead of rhinitis. Nasal hyperreactivity was divided into allergic (seasonal, perennial, occupational or nutritional), drug-induced, neurogenic, toxic, postinfectious or idiopathic. In addition, hyperreactivity of unknown origin was recognized as a separate entity.

Natural course of rhinitis

Few data are available on the natural course of non-infectious rhinitis.

Some reports from the 60’s and 70’s describe the results of questionnaire studies in children or young adults. In a study of 638 high school students (Freeman and Johnson 1964), improvement or regression of seasonal rhinitis had occurred after the age of 10 years in 40% of the students with onset of hay fever in early childhood and in 29% of those who had their first symptoms in adolescence. Of the adolescent-onset group, one fourth reported that symptoms had increased since onset but this seldom occurred in the early-onset group. Yet, hay fever disappeared in only 7% and perennial rhinitis in 4% of students with these symptoms. Smith (1971) found that 8.9% of 112 farm children had been completely cured and 28.6% had become better over a period of five years. Hagy and Settipane (1976) followed 903 college freshmen for seven years after entering college and found hay fever as a new disease in 12.6%, perennial rhinitis in 4.8% and asthma in 2.5% of the students, the annual incidences being 1.8%, 0.7% and 0.35%, respectively.

A whole community (Tecumseh, USA) was studied by Broder and co-workers (1974) in two surveys four years apart. Their diagnostic criterion of probable allergic rhinitis was report of hay fever, sinus trouble or persistent nasal symptoms together with two of the following: (1) itching of eyes, nose or throat, or burning, watering or

redness of eyes; (2) association of symptoms with exposure to allergen(s); or (3) diagnosis of hay fever or allergic rhinitis by physician. The incidence in the residents of Tecumseh during this time was 2% and the prevalence 8.7%. Remission had occurred, i.e. allergic rhinitis had been absent for two or more years, in 5% of female and in 10% of male subjects.

Rawle and co-workers (1983) followed patients with asthma or hay fever for 10 to 40 years and reported a decrease in severe asthmatic symptoms and a progressive loss in serum antibodies to *Dermatophagoides pteronyssinus* but found no apparent tendency for skin test reactivity to decline with time. In a Finnish study of rhinitis patients without asthma, Lehtonen and Haahtela (1988) noted that hypersensitive rhinitis showed complete remission in 2%, was less severe in 54%, equally severe in 26% and more severe in 18% of subjects at follow-up after seven years. The prognosis of allergic rhinitis in patients with at least two positive skin tests was better than the prognosis of non-allergic rhinitis. Symptoms had disappeared or become less severe in 62% of allergic patients, but only in 46% of patients with non-allergic eosinophilic rhinitis and in 42% of those with non-allergic non-eosinophilic rhinitis. Another Finnish study (Linna *et al.* 1992) showed that symptoms had disappeared completely over a period of 9.5 years in 10% of 154 children with allergic rhinitis, diagnosed with skin tests and in questionable cases with conjunctival or nasal provocation.

A comprehensive questionnaire study of 9,946 households with a total of 22,285 persons was recently published by Nathan and co-workers (1997). In this study, the frequency of self-diagnosed rhinitis (”seasonal allergy” or ”allergy all the time”) was 14.2% (seasonal 8.8%, perennial 5.4%), being highest (18%) between the ages of 18–49 years and decreasing gradually after the age of 50 years to 8% in subjects over 65 years.

Sense of smell in rhinitis

The sense of smell is essential to our appreciation of the flavour and tastiness of food and, more importantly, to detection of the smell of burning, dangerous vapours and spoiled food. The proportion of subjects with smell disorders is not well defined. An American questionnaire study revealed that 66% of over 1200 respondents were aware of a period in their life when smell acuity was decreased and seven per cent reported that their sense of smell was impaired at the time the survey was taken (Henkin 1995). The olfactory threshold is known to be markedly higher among elderly people (Deems and Doty 1987). Besides age, more than 200 diseases and other conditions (Leopold 1993) have been associated with changes in the chemical senses. The most frequent causes of olfactory loss are obstructive nasal and sinus diseases, which comprise 15–33% of cases, upper respiratory infections (15–32%) and head trauma (9–18%) (Deems *et al.* 1991, Leopold 1993). Evidence of a direct relationship between nasal resistance to airflow and olfactory threshold has not been presented (Eccles *et al.* 1989, Cowart *et al.* 1993).

Apter and co-workers (1995) examined 227 patients with a history of olfactory loss, 116 (51%) of whom suffered from chronic rhinitis. In addition, skin tests were performed on 62 patients with chronic rhinitis and olfactory loss without any neurological aetiology. At least one positive test was recorded in 44 (71%) subjects.

There are comparatively few studies in which the sense of smell of rhinitis patients has been measured. Seiden and co-workers (1989) evaluated 34 patients with allergic rhinitis. Twenty of them (59%) reported that they had experienced some taste or smell problem and 12 patients (35%) had a measurable smell loss, as measured by the smell identification test. Cowart and co-workers (1993) measured the olfactory thresholds of 91 patients with symptoms of allergic rhinitis and 80 non-atopic control subjects and found that the thresholds were significantly higher in allergic patients than in control subjects, with 23.1% of the patients demonstrating a clinically significant loss of smell.

In studies of rhinitis patients, the influence of age has usually been neglected.

Skin tests in rhinitis patients

Skin-test reactivity to allergens is the classic method to verify a diagnosis of allergic rhinitis and other allergic diseases (Mygind *et al.* 1996a). Allergy skin testing may be performed as a prick test, which consists of placing a drop of test solution on the skin and pricking through the drop with a sharp instrument, or as an intracutaneous (intradermal) test, in which a small amount of test solution is injected into the skin (Malling 1993). According to the position statement of the American Academy of Allergy and Immunology, prick testing is preferred for initial testing, because it is less expensive, quicker, causes less discomfort and correlates better with clinical sensitivity than does intracutaneous testing (Position statement 1993). Also scratch tests were used in the past, but, according to the position paper of the European Academy of Allergology and Clinical Immunology, they are no longer recommended because of low specificity (Malling 1993).

The epidemiology of skin-test results as compared with clinical disease has been thoroughly studied by Hagy and Settipane (1969). They interviewed a cohort of college freshmen on history of allergy among the subjects, their siblings, parents and grandparents. The frequency of hay fever was 21.1% and of non-seasonal rhinitis 5.2%. Skin scratch tests were performed with 15 allergens, including pollens, danders and moulds. The frequency of at least one positive skin-test reaction was 63.8% in the group with asthma, hay fever or non-seasonal rhinitis. In their follow-up study seven years later (1976), they found a significant association between onset of allergic rhinitis as a new disease and a positive prior skin-test reaction. Of asymptomatic students with a positive pollen scratch test, 31.9% developed clinical hay fever during the follow-up period, whereas the corresponding percentage was only 7.7 for those with negative skin tests. For non-seasonal rhinitis, the proportions were 8.6% and 3.2%, respectively. Since the skin tests were not repeated at the end of the follow-up period, it was not possible to determine, how many individuals with negative skin tests as freshmen may have developed positive reactions to allergens during the subsequent seven years.

It is well known that ageing is associated with a decrease in the occurrence and intensity of skin reactions to common allergens. In a cohort study with repeated evaluations, Barbee and co-workers (1976, 1987) found an overall increase in skin-test reactivity during the eight-year period between two tests, the peak prevalence

occurring between ages 25 and 34, but at both evaluations there was a downward reactivity trend from this age group towards older age. The decrease in reactivity is thought to be caused by a reduction of IgE synthesis and a decrease in the skin capacity to respond to an immunological challenge (Delespesse *et al.* 1977). This phenomenon can be accounted for by relating the allergen test to the histamine control test (Mygind *et al.* 1996a).

Nasal provocation

In a nasal provocation test (nasal challenge) the nasal mucosa is exposed to allergens or irritant agents and the subsequent reaction monitored. Provocation is a useful tool in research work and in cases where a verified allergy diagnosis is needed (Albegger 1991). In clinical work, the majority of provocation tests are done with allergens. Nasal challenge is also used to assess non-specific nasal reactivity and reactions have been induced with a variety of chemical substances and also with physical stimuli.

Application methods

There are several techniques of introducing the test substance into the nose. Soluble agents can be dropped (Bachert and Keilmann 1988, Mullins *et al.* 1989), sprayed (Pipkorn 1982, Yaniv *et al.* 1991, Hallen and Juto 1992, Majchel *et al.* 1992) or nebulized into the nose (McLean *et al.* 1977, Van de Heyning *et al.* 1989, Braunstein *et al.* 1992) or the nasal cavity washed with the test solution (Greiff *et al.* 1990). Challenge by topical application can be done with paper disks (Okuda 1977, Svensson *et al.* 1981, Ogino *et al.* 1992) or small swabs of cotton wool (Grobler *et al.* 1966, Holopainen *et al.* 1976), impregnated with the challenge substance (Naclerio and Baroody 1992), or whole pollen grains delivered in the form of dry powder (Naclerio *et al.* 1983). Gaseous agents can be delivered into the nose with any system that conveys gases into the airways (Andersson *et al.* 1995). For topical application, inferior turbinate and agger nasi are more sensitive locations than nasal septum or middle turbinate (Okuda 1977). Allergens in liquid form are often preferred to powder because of the lower risk of complications (such as asthmatic reaction or anaphylactic shock). Topical application limits the antigen contact to a very small area of the mucosa, which should lower the risk of complications (Holopainen *et al.* 1976). However, it is possible that paper disks themselves induce mucosal exudative inflammation (Andersson *et al.* 1995). None of the above methods can be regarded as absolutely superior, though theoretically the technique with minimum non-specific effects should be the method of choice.

Many investigators prefer unilateral provocation (Pipkorn 1982, Corrado *et al.* 1986, Doyle *et al.* 1990) while others use bilateral challenge (Okuda 1977, Clement *et al.* 1985, Gerth van Wijk and Dieges 1991). Van de Heyning and co-workers (1989) recommend that both nasal cavities be challenged and the most reactive side considered, while Bachert and co-workers (1990) and Albegger (1991) favour unilateral challenge on the wider side.

Registration of the nasal response

The provocation response has traditionally been assessed by observation of sneezing, nasal discharge and mucosal swelling by rhinoscopy (Pipkorn 1982, Albegger 1991). Mygind and co-workers (1986) recommend recording

the subject's sensation of nasal secretion, itching and congestion on a semiquantitative categorical score or a visual analogue scale. Counting the sneezes is a simple method to assess the irritative response (Pipkorn 1982, Gerth van Wijk and Dieges 1987). Another simple method is to measure the volume of elicited secretion, collected by letting it drip into a funnel (Corrado *et al.* 1986, Gerth van Wijk and Dieges 1987) or by suction (Pirilä and Nuutinen 1998). Doyle and coworkers (1990) weighed the subject's handkerchiefs before challenge and after nose blowings after challenge. Naclerio and Baroody (1992) absorbed secretion into preweighed paper disks and reweighed them after a preset period of time. The difference in weights reflected the amount of secretion collected in a fixed period of time.

Rhinomanometry is widely accepted as an accurate objective method to register the challenge response by measuring changes in nasal airway resistance (NAR) (Corrado *et al.* 1986, Doyle *et al.* 1990). The most physiological and currently most commonly used rhinomanometric technique is active anterior rhinomanometry (Clement 1984), where, simultaneously with measuring the air flow through one nostril with a pneumotachometer, the nasopharyngeal pressure is recorded contralaterally with a manometer which is connected to the other nostril. In posterior rhinomanometry, the nasal flow is measured through a mask placed over the nose and nasopharyngeal pressure determined with a tube held between the lips and over the tongue (Goode 1986). A major disadvantage of the method is that only 50–80% of people tolerate the tube in the mouth and can relax the soft palate to maintain an open connection between the oral cavity and the nose while a nasal mask is applied (Kortekangas 1972, Masing 1979, Gleeson *et al.* 1986, Schumacher 1989).

In the Broms system for numerical description, the increase in nasal resistance is expressed as degrees of angle (Broms *et al.* 1982, Pipkorn 1982). More often, the resistance is calculated at a fixed pressure gradient, usually at 150 Pascal, which is the recommendation of the International Standardization Committee for Rhinomanometry (Clement 1984). The increase in nasal resistance is registered as the difference between values at various steps of the provocation (McLean *et al.* 1977, Clement *et al.* 1985, Gerth van Wijk and Dieges 1987, Mullins *et al.* 1989, Van de Heyning *et al.* 1989). Stable conditions during the course of the provocation are a *sine qua non* for successful use of rhinomanometry. Especially critical are a correct fitting of the face mask without any distortion of the nose, tightness of all seams between the different parts of the rhinomanometer and between the equipment and the patient (Pinkpank 1986).

Nasal peak expiratory and inspiratory flow measurements have also been used to register changes in nasal patency to measure nasal obstruction following challenge (Haahtela 1978, Schumacher and Pain 1979, Wihl and Malm 1988, Holmström *et al.* 1990, Hellgren *et al.* 1997, Phagoo *et al.* 1997). In the last 20 years, acoustic rhinometry (Hellgren *et al.* 1997, Zweiman *et al.* 1997) and rhinostereometry (Juto and Lundberg 1982) have been introduced as sophisticated novel methods for measuring mucosal swelling.

Nasal histamine provocation

Application of histamine into the nose induces a sneezing reflex, a secretory response and mucosal

swelling, resulting in an increase in NAR (Grobler *et al.* 1966, Gerth van Wijk and Dieges 1987). Both histamine phosphate (Grobler *et al.* 1966) and histamine chloride (Okuda 1977) have been used as the challenge agent. Often, however, only ”histamine” is mentioned in a report.

A simple classification of the challenge result as either negative or positive is seldom meaningful for histamine reactions, though sufficient for allergen challenge. It is more sensible to assess the intensity of the reaction at various steps. If rhinomanometry is chosen as the method of assessment, the dose or concentration required to induce an increase of 25% (PD_{25} or PC_{25}), 50% (PD_{50} or PC_{50}) or 100% (PD_{100} or PC_{100}) in NAR can be determined (McLean *et al.* 1977, Clement *et al.* 1985, Gerth van Wijk and Dieges 1987, Mullins *et al.* 1989, Van de Heyning *et al.* 1989).

At present there is no standard procedure for nasal histamine provocation but a certain method is used in one or a few centres only and the results of different studies are poorly comparable.

Numerous attempts have been made to prove the hypothesis that rhinitis patients are more sensitive to histamine than healthy subjects and to develop a method which would identify rhinitis subjects. One of the first attempts was made in 1966 by Grobler and co-workers, who showed that responsiveness to nasal histamine was related to the degree of nasal complaints in patients with chronic bronchitis. Okuda and co-workers (1983) used only sneezing as a criterion and defined the end point as the minimum concentration of histamine which produced sneezes within one minute. They recorded a difference in the sensitivity between the normal and the allergic nose and also between an allergic nose with positive provocation and a nose with negative provocation. Clement and co-workers (1985) found a ”slightly significant” difference in nasal histamine thresholds between patients with non-allergic rhinitis and controls, as assessed by changes in NAR at a flow of 0.25 l/s. Corrado and co-workers (1986) reported that subjects with perennial allergic rhinitis showed significantly greater histamine-induced changes in NAR, rhinorrhoea and also methacholine-induced rhinorrhoea than subjects without rhinitis. Using a doubling of nasal resistance as a criterion, Mullins and co-workers (1989) found that the histamine doses required to induce this response were lower among patients with perennial or seasonal allergic rhinitis than among control subjects. Van de Heyning and co-workers (1989) were able to differentiate between patients with non-allergic rhinitis and healthy control subjects by determining PD_{25}, PD_{50} and PD_{100}. In their opinion, determination of PD_{25} was the most valuable clinical test in unilateral provocation, but, according to Gerth van Wijk and Dieges (1987) on the other hand, measurement of NAR proved insensitive, while assessment of nasal secretion and sneezing was a sensitive method for discrimination between rhinitis patients and controls.

Often, however, considerable overlapping has been demonstrated in reactivity between rhinitis patients and healthy controls, which clearly thwarts the discriminating potency of the method (McLean *et al.* 1977, Guercio *et al.* 1979, Gerth van Wijk and Dieges 1991).

Thus, results are contradictory and nasal histamine provocation is not recommended for routine diagnostics. As a research tool, histamine provocation has been successfully used in

the evaluation of drug therapy (Pipkorn 1982, Baroody *et al.* 1992, Ogino *et al.* 1992) as well as rhinitis group comparisons, as described above.

The causes underlying nasal hyperreactivity are not fully understood. Earlier, many researchers supported the assumption that mucosal permeability is enhanced in allergic rhinitis (Salvaggio *et al.* 1964, Inagaki *et al.* 1985, Gerth van Wijk and Dieges 1987) but later studies have demonstrated decreased mucosal absorption in patients with rhinitis (Greiff *et al.* 1993, Greiff *et al.* 1997). Other potential explanations for nasal hyperresponsiveness have also been suggested, including changes in responsiveness at receptor level, neural hyperfunction and effector end-organ hyperresponsiveness (Andersson and Mygind 1995).

Nasal allergen provocation

Skin testing does not necessarily give relevant information on the sensitivity of the airways to allergen. Earlier when the quality of allergen extracts was poorer than it is today, irritants frequently caused false positive skin reactions (Mygind *et al.* 1996a). Nasal allergen provocation was, therefore, used to obtain more reliable information on the specificity of nasal allergy. Modern preparations are better in this respect. Petersson and co-workers (1986) reported good agreement between the results of skin prick tests and nasal or conjunctival provocation tests for birch and timothy allergens. For skin prick tests and clinical history, the agreement was somewhat poorer. The positive predictive value of the skin prick test as compared with the provocation test was 95% and the negative predictive value 97% for birch allergen, with a frequency of 55%. For timothy allergen, the predictive values were 78% and 96% and the frequency 52%. The frequencies of positive findings in their patient groups were higher than the prevalence of allergic rhinitis in the population (Malmberg 1979, Varjonen *et al.* 1992, Norrman *et al.* 1994), which implies that in representative samples of the population the positive predictive values would be smaller (Altman 1994a).

Standardized extracts are not always available, especially in the case of rare allergens. In these situations and also when definite causality between allergen exposure and nasal disease must be verified, nasal allergen provocation is still necessary in rhinological diagnostics (Melillo *et al.* 1997). The most important indications are discrepancy between patient history and allergy tests, verification of nasal allergy prior to starting immunotherapy, and diagnosis of occupational rhinitis. The fact that the test is time-consuming also makes it less suitable for routine diagnostics.

In allergen provocation, the nasal mucosa is exposed to allergen in controlled conditions which try to mimic natural exposure. If allergic symptoms appear, a causal relation is very likely.

There are several criteria for positivity of the challenge. Holopainen and co-workers (1976) considered the reaction positive when two of the following responses were observed: sneezing, itching, secretion or subjectively noted obstruction of the nose, a change in the colour of the mucous membrane, swelling of the turbinates noted by rhinoscopy, or an increase of 25% or more in total nasal resistance (TNR) measured by posterior rhinomanometry. Okuda (1977) regarded sneezing, definitive nasal secretion or swelling of the nasal mucous membrane as a positive response and used a 3-grade scale, according to the number

of symptoms and the number of sneezes, for further assessment of the reaction. Central European recommendations (Bachert *et al.* 1990, Albegger 1991) suggest either an increase of 60% in nasal resistance or a decrease of 40% in nasal airflow, measured by rhinomanometry, or more than three points on a combined score of nasal discharge (0–2 points), sneezing (0–2 points) and remote symptoms, i.e. tearing, pharyngeal swelling, ear blocking, conjunctival redness, urticaria, cough, and dyspnoea, (0–2 points) as alternative criteria of positivity. In patients with suspected occupational rhinitis, Hytönen and Sala (1996) used four-point scales of rhinoscopically evaluated nasal blockage and rhinorrhoea and regarded the provocation as positive, if the change in the total score was four points or more.

Sipilä and co-workers (1990) compared the changes in unilateral nasal resistance caused by the nasal cycle with those elicited by allergen challenge and recommended that if results of nasal provocation are expressed by rhinomanometry, at least a doubling or an even higher increase in the resistance must occur before the result is considered positive. Pirilä and co-workers (1997) monitored the nasal patency of 12 subjects with suspected occupational allergic rhinitis at 15-minute intervals for 3 hours before and for 30 minutes after nasal challenge with diluent. They found a high degree of spontaneous variation in NAR, which increased with longer observation time. According to their results, a unilateral increase of 100 per cent could be used as a cut-off value at the risk level of 5–10 per cent, when the observation period after the provocation was 30–60 minutes. They further recommended that resistance changes should be interpreted with caution and that other objective means should be used in addition.

Acoustic rhinometry has only recently been introduced in the evaluation of allergen provocation. Lane and co-workers (1996) monitored the minimum cross-sectional area and the nasal cavity volume of the first 7.5 cm from the nasal vestibule. Nasal allergen challenge induced a mean reduction of 70% in minimum cross-sectional area and of 58% in nasal volume. Hytönen and co-workers (1996) registered changes in nasal mucosal swelling during allergen challenge with acoustic rhinometry and concluded that changes in the volume or minimum cross-sectional area of the nasal cavity, measured separately in the anterior and middle parts, were less usable in the diagnostics of occupational rhinitis than a combined variable, calculated as the mean of the percentages expressing the changes in the volume and area variables. Their recommendation for the limit of an essential change was a decrease of 15% or more in the combined variable.

Other agents used for nasal provocation

Methacholine is a cholinergically acting compound, which induces a secretory response in nasal mucosal glands. Both methacholine bromide (Borum and Mygind 1979) and methacholine chloride (Malmberg *et al.* 1983) have been used as provocation agents to measure nasal hyperreactivity. In comparison with histamine phosphate, methacholine and also phentolamine seem to be less sensitive agents for discriminating between healthy subjects and rhinitis patients (Gerth van Wijk and Dieges 1987).

Other substances that have been employed in challenge measurements of nasal hyperreactivity are polymyxin B, ammonia (McLean *et al.* 1978),

platelet activating factor (PAF) (Klementsson and Andersson 1992) and substance P (Devillier *et al.* 1988). Nasal reactions to physical stimuli, especially to cold dry air, have also been studied (Togias *et al.* 1988).

Measurement of olfaction

The simplest form of testing the sense of smell is to determine whether the subject can detect any odorant at all. This type of testing is not very precise and is unsatisfying in diagnostics. Good clinical practice requires quantitative, repeatable tests for objective documentation of olfactory ability. The two aspects that are most commonly tested are olfactory threshold and identification ability.

The measurement of the detection threshold attempts to quantify the most diluted concentration of an odorant that a subject can detect. Earlier, this was done by diluting odorous gas with air, or liquid odorant with alcohol or odourless diluent, and measuring the weakest dilution the subject could detect. The modern general format of this test is to use a series of bottles containing a range of concentrations in predetermined steps. The odorant is presented from lowest to highest concentration until the subject correctly identifies it. In order to avoid the tendency of the subject to say ”yes” to undetectable stimuli, a similar bottle containing only the diluent is presented simultaneously and the subject is forced to choose between a stimulus and a blank (Amoore and Ollman 1983, Amoore and O'Neill 1986, Cain 1989). Pyridine and *n*-butyl alcohol are two of the most widely used test chemicals, but phenyl ethyl alcohol (Doty *et al.* 1978) and phenylethyl methyl ethyl carbinol (Rosen *et al.* 1979) have been recommended because they have less trigeminal activity. Machine-assisted measurements of olfactory function are not usually practised in clinical work. Investigative work has been done on olfactory-evoked potentials using electroencephalographic techniques or on positron emission tomography scanning of the olfactory cortex (Henkin 1995).

Odour quality identification is the basis of the most commonly used procedures for clinical assessment of ability to smell. The subject can be asked to name each of a set of odours (odour naming test), to indicate whether or not an odour smells like a certain fragrance (yes–no odour identification test) or to recognize the odour from a list (multiple-choice odour identification test) (Doty 1991). In clinical work, the most popular type is the multiple-choice test (Wright 1987, Cain *et al.* 1988). The UPSIT test (University of Pennsylvania Smell Identification Test) designed by Doty and co-workers (1984) is particularly compact and widely used. The test comprises booklets, each page of which has an area with the smell encapsulated in small crystals. The smell is released by scratching the odorous area. The disadvantage of this test is that it contains some odours that are not universally familiar. To solve this problem, Doty and co-workers (1996) developed a 12-item cross-cultural smell identification test.

Both threshold and identification tests are useful in clinical diagnostics of disorders of the sense of smell. Some authors prefer using either one of the methods, while others recommend that both types of measurements be used (Moore-Gillon 1989). Some centres use a composite score of the two methods (Cain 1989). Both techniques are considered good

indicators of the sensitivity of the sense of smell, and the correlation between the tests is good (Cain *et al.* 1988).

PURPOSE OF THE STUDY

The aims of this study were

1. to describe the changes in symptom severity that had occurred in a series of patients with allergic or non-allergic rhinitis over a period of nearly 20 years;
2. to analyse skin-test sensitivity some 20 years after primary testing and to relate possible changes in reactivity to ageing, duration of rhinitis, and changes in severity of rhinitis symptoms;
3. to measure and compare olfactory thresholds in rhinitis patients and healthy control subjects and to analyse possible relationships between the sense of smell and rhinitis, age, gender, smoking, prick-test results, nasal resistance, and history of nasal or paranasal surgery; and
4. to measure nasal reactivity to histamine in patients with long-continuing allergic rhinitis and to assess whether the degree of nasal hyperreactivity corresponded with changes in allergy test results and in rhinitis symptom severity.

SUBJECTS AND METHODS

Definitions

The terms used for rhinitis forms discussed in this thesis were defined as follows:

Allergic or *atopic rhinitis* refers to the form of rhinitis that occurs as a consequence of the IgE-dependent activation of mast cells in the nasal mucosa, i.e. represents the type I reaction of the classification by Coombs and Gell (Mygind 1979).

The term *non-allergic rhinitis* denotes a chronic disease of the nasal mucosa which by current investigation methods cannot be related to allergy, infection, structural lesions or other known aetiology (Mygind *et al.* 1996b).

The term *hypersensitive rhinitis* or *nasal hyperreactivity* is used as a comprehensive concept for both allergic and non-allergic rhinitis (Bachert and Ganzer 1996).

Patients

This follow-up study was carried out in patients with allergic or non-allergic rhinitis at the Department of Otorhinolaryngology, Helsinki University Central Hospital, and covers a period of 18 to 25 years. The patients were initially examined in 1969-72 when patients remitted to the Department with a clinical diagnosis of allergic rhinitis were enrolled in a study and underwent a fixed set of investigations including clinical examination of the nose by anterior and posterior rhinoscopy, exfoliative nasal cytology, bacteriological culture of the nasal secretion, allergy tests, X-ray examination of sinuses and teeth, and blood tests for haemoglobin, eosinophil count, antistaphylolysin and antistreptolysin titres. A diagnosis of allergic or non-allergic (intrinsic) rhinitis was then established in 770 patients (Binder *et al.* 1982, Binder *et al.* 1984). If needed, operations for structural deformities of the nose and chronic sinusitis were performed.

Four follow-up studies were performed in a group of patients from the original series in 1989–94. The group was the same in all studies, but the size of the group varied from 180 patients in study I to 73 patients in study IV.

Study I was a questionnaire study in all patients of the original series who could be located in 1989. Of 261 contacted subjects, 186 filled out the questionnaire and 180 were accepted for the study. Two forms were rejected because of missing identification and four because of conflicting and inadequate information. There were 108 women and 72 men. Their mean age at the time of the initial study was 29 years (range 3.6–69 years) and the time period between the initial study and the questionnaire was on average 18 years (range 17–20 years).

Study II was an analysis of changes in rhinitis symptoms in relation to skin test reactivity and nasal sensitivity to allergens in 108 of the 180 patients in study I (61 women and 47 men, ages 27–78 years, mean 51 years). The mean duration of follow-up was 23 years (range 20–25 years). One patient withdrew at an early stage before allergy tests were performed and one patient was excluded because of no recordable reaction to any substance including the histamine control.

Study III was an evaluation of the sense of smell in 105 of the 108 patients, 61 women and 44 men, aged 27 to 78 years, mean 51 years. In addition to the patient who withdrew

early, two patients who did not have time for further testing did not participate in the study.

Study IV was performed in a subgroup of the 108 patients in studies II and III. The subgroup included all 75 patients in whom the diagnosis of allergic rhinitis had been confirmed in 1969–72. Apart from the patient who was not tested because of early withdrawal, one patient could not be provoked because of upper respiratory infection. The analyses were done in 73 patients, 46 women and 27 men, aged 28 to 74 years, mean age 48 years.

Control subjects (study III)

In order to compare the olfactory thresholds in rhinitis patients and subjects without nasal diseases, a control group was collected among patients with no acute or chronic nasal complaints, admitted to hospital for elective ear, palatine tonsil or neck surgery. The group consisted of 104 subjects (56 women and 48 men, aged 17–71 years, mean 39 years).

Collection of anamnestic data

Questionnaires were compiled for collecting data on the course of rhinitis and changes in symptom severity in studies I–III.

The items on the questionnaire filled out by all 180 patients in study I are listed in Table 1.

Prior to the first follow-up visit (II), all 108 patients completed a second questionnaire for more detailed information on past and present history (Table 2).

In study III, a questionnaire was also used to collect information on possible past and present rhinitis symptoms, smoking habits and asthma-like symptoms in the group of control subjects (Table 3).

Table 1. Anamnestic data collected with the help of a questionnaire (I) in 1989

Age at onset of rhinitis	Occurrence of asthma (if yes, when and how diagnosed?)
The first symptom of allergy (rhinitis, eczema or asthma)	Occurrence of nasal polyps (if yes, when?)
Occurrence of rhinitis symptoms (still/no longer occur)	Operations performed because of nasal disorders (polypectomy, ethmoidectomy, septoplasty, sinus operation)
In case of remission:	Effect of the operation on symptoms of rhinitis and/or asthma
Age at the remission of rhinitis	Influence of analgetics on rhinitis symptoms
Factor(s) that caused the remission	Influence of smoking on rhinitis symptoms
In case of continuing symptoms:	Influence of alcohol (beer, wine, liquor) on rhinitis symptoms
Annual occurrence (seasonal, perennial)	Medication used for rhinitis
Factors associated with the symptoms (pollen of the trees, hay or mugwort; dust; animals, other)	
Changes in the annual period of the symptoms (shorter, unchanged, longer)	
Changes in severity of symptoms (milder, equally severe, worse)	

Table 2. Anamnestic data collected prior to the follow-up visit (II, III and IV) in 1993–94. The items that were not included in the earlier questionnaire are shown in italics.

Occurrence of rhinitis symptoms (still/no longer occur)	Occurrence of nasal polyps
Changes in rhinitis symptoms (total remission, milder, unchanged, worse) a) after the first questionnaire study in 1989 and b) altogether after the first investigation in 1969–72	If yes, when for the first time
In case of continuing symptoms:	Operations for polyposis
Annual occurrence (seasonal, perennial, *combined*)	*Medication for polyposis*
Months, when symptoms occur	Medication for rhinitis
Occurrence of asthma	*Other medication*
Age at onset of asthmatic symptoms	*Occurrence of occupational rhinitis*
Diagnosis established: a) by physician, b) at hospital	*Loss of the sense of smell*
Entitled to special drug reimbursement	*Hoarseness (never, occasionally, in conjunction with rhinitis symptoms, constantly)*
Current symptoms of asthma	*Snoring (unknown, never, occasionally, often, constantly)*
	Smoking (never, ex-smoker, 1–5, 6–10, 11–20, more than 20 cigarettes/day or equivalent amount of pipe tobacco)
	Nasal surgery

Table 3. Anamnestic data collected with the help of a questionnaire from control subjects (study III)

Occurrence of atopic eczema in childhood	Current rhinitis symptoms
History of allergic symptoms (nasal obstruction or discharge, sneezing, cough, dyspnea, rash, eye symptoms)	Current symptoms of respiratory infection
Age at onset of possible rhinitis	Smoking (never, ex-smoker, 1–5, 6–10, 11–20, more than 20 cigarettes/day or equivalent amount of pipe tobacco)

Ethics

The study protocol was approved by the ethics committee of the Department of Otorhinolaryngology of Helsinki University Central Hospital. All subjects gave their informed consent with regard to participation in the study.

Allergy tests in the initial study

All patients had initially in 1969–1972 undergone a fixed set of investigations including history taking, allergy testing with scratch or intracutaneous tests, nasal provocation, and otorhinolaryngological examinations (Binder *et al.* 1982, Binder *et al.* 1984). The number of patients in the initial series was 770.

The following allergens were included in the initial skin tests and the results were available for the follow-up analysis: birch (95 patients included in studies II and III), grass species (timothy or meadow foxtail, 95 patients), *Compositae* species (dandelion, *Chrysanthemum* species, mugwort, 90 patients), house dust or house dust mite (95 patients), animal dander (horse, cow, dog, and cat, 83 patients), chicken feather (78 patients), wool (78 patients), mould mix (76 patients), and food allergens (hazelnut, egg, fish,

cow's milk, 45 patients). In grading the test results, a scale from "-" to "++++" was used, "+" indicating a weal whose diameter was at least 25% of the diameter elicited by the positive histamine control, and "++" indicating a weal with a diameter at least 50% of the positive control. The criterion for a positive skin test was a reaction greater than "+". Seventy-eight per cent of the patients showed at least one positive skin test result.

The nasal provocation was considered positive when at least two of the following criteria were met after challenging the nose with allergen: itching, sneezing, discharge, subjectively noted obstruction of the nose or a rhinoscopic finding of changes in the nasal mucosa (swelling or colour change) or an increase of 25 per cent or more in TNR as measured by active posterior rhinomanometry (Holopainen *et al.* 1976, Malmberg *et al.* 1978). The patient was considered allergic, if he or she had at least one positive skin test confirmed by positive nasal provocation. Sixty-nine per cent of the patients fulfilled this criterion.

Skin tests in the follow-up study (II, III, IV)

Skin prick tests were performed with Soluprick® allergen solutions (ALK, Denmark). All patients were tested with 22–26 common allergens, including birch, alder, meadow foxtail, orchard grass, meadow fescue, ryegrass, timothy, Kentucky bluegrass, mugwort, dandelion, horse, dog, cat, and cow dander, wool, chicken feather, *Dermatophagoides farinae* and *pteronyssinus*, *Alternaria alternata*, *Candida albicans*, *Cladosporium herbarum*, guinea pig, latex, egg, fish and cow's milk. During the period of the follow-up visits, the standard test series of the clinic was extended to include latex, egg, fish and milk allergen, which were, therefore, tested only on 52 patients. The patient was considered prick-test positive, if at least one allergen elicited a weal whose diameter was at least 3 mm larger than that of the negative control.

Nasal allergen provocation (studies II, IV)

Nasal allergen provocation was performed on patients who had been diagnosed as allergic in the initial study or were prick-test positive or had a positive history of allergic symptoms possibly caused by some specific allergen. At the beginning of the session, anterior rhinoscopy was performed and the amount of mucus and degree of conchal swelling were recorded. The nose was first challenged with the diluent of the allergen extract (ALK-Diluent®, ALK, Denmark) and assessment was made after 15 minutes. After challenging with Aquagen® SQ (ALK, Denmark) aqueous allergen solution, the response was assessed after 15 and 30 minutes (and 45 minutes for house dust mite allergen) unless a positive reaction had been recorded earlier. The provocation was done bilaterally with a spray dose of 0.1 ml. In most cases, a concentration of 100,000 SQ units per ml (SQ-U/ml) was used. In seven cases in which an exceptionally strong reaction was anticipated, 1000 SQ-U/ml was used first and, if needed (in four patients), a stronger solution later. Rhinorrhoea and conchal swelling were graded in each nasal cavity on a three-point scale (none – mild – considerable). The number of sneezes between the provocation and recording was counted. Other possible symptoms

or signs, i.e. tearing, pharyngeal swelling, ear blocking, conjunctival redness, urticaria, cough, and dyspnoea, were registered.

In conjunction with all assessments, nasal resistance was measured on each side at 150 Pa pressure and TNR calculated using a RhinoComp® computerized active anterior rhinomanometer. The technique complied with the recommendations of the International Committee on Standardization of Rhinomanometry.

The recorded changes were converted into a provocation result score as described in Table 4 (slightly modified after Albegger (1991)). The provocation was considered positive, if a score of at least 3 points was achieved or if the patient got 2 points, but TNR increased at least 50% compared with the measurement after the diluent challenge.

Table 4. The score of nasal allergen provocation (II, IV)

1. Average increase in nasal discharge	
none	0 points
change from none to mild or mild to considerable on at least one side	1 point
bilateral reaction, change from none to considerable on at least one side	2 points
2. Average increase in swelling of the inferior turbinates	
none	0 points
change from none to mild or mild to considerable on at least one side	1 point
bilateral reaction, change from none to considerable on at least one side	2 points
3. Irritation	
0–2 sneezes	0 points
3–5 sneezes	1 point
6 sneezes or more	2 points
4. Remote symptoms	
tearing, pharyngeal swelling or ear blocking	1 point
conjunctival redness, urticaria, cough or dyspnoea	2 points

Nasal histamine provocation (study IV)

Nasal hyperreactivity was measured by histamine provocation. Prior to histamine challenge, a control challenge was performed bilaterally by spraying a 0.1 ml dose of phosphate buffer into the nostril. The nose was then washed with phosphate buffered saline and a nasal smear sample taken with a cotton swab. Histamine challenge was carried out stepwise with bilateral 0.1 ml doses of 0.025%, 0.1%, 0.4% and 1.6% histamine diphosphate solutions, diluted with phosphate buffer. As in allergen provocation, the degree of rhinorrhoea and conchal swelling was assessed and the number of sneezes counted after each provocation step, and NAR measured with active anterior rhinomanometry at the beginning of the session and after each of the challenge steps. The recordings before spraying the first histamine dose were used as baseline values. If rhinomanometric data could not be obtained because of total obstruction in the course of the histamine challenge, the last measured value multiplied by the ratio of the means of these two values for the whole series was used in the analyses.

Nasal responsiveness to histamine was compared between the following subgroups of patients:

1. prick-test positive versus prick-test negative patients
2. patients with positive nasal allergen provocation versus patients with negative provocation
3. patients with or without changes in rhinitis symptom severity, i.e. patients whose rhinitis symptoms had disappeared, become milder, remained equally severe or worsened during follow-up for 23 years.

The following variables were used in the analysis:

1. The concentration which induced an average increase of at least one point in nasal secretion or at least five sneezes (slightly modified after Gerth van Wijk and Dieges (1987)).
2. The sum of the irritation score, as defined in Table 4, and average discharge (scored none = 0, mild = 1, considerable = 2 on each side) at each step.
3. The sum of variable 2 and average swelling of the turbinates (scored none = 0, mild = 1, considerable = 2 on each side) at each step.
4. TNR at baseline and after each histamine dose.

Olfactory threshold (study III)

The olfactory threshold was measured with a commercially available smell test kit (Olfacto-Labs, Berkeley, California) (Amoore and Ollman 1983, Amoore and O'Neill 1986). Sensitivity to odour was tested stepwise with phenylethyl methyl ethyl carbinol at 3.2 concentrations in nine pairs of polypropylene squeeze bottles, the control bottle in each pair containing the plain diluent. The subject was asked to choose the bottle he or she thought contained the odorant and the test was repeated three times at each step. The weakest concentration at which the subject picked the correct bottle all three times was accepted as the olfactory threshold. Numerically, the threshold was expressed as arbitrary logarithmic units (ALU), designated as ”decismels” (dS) by the manufacturer, analogically with the audiological decibel scale. The concentrations in use were -25, -15, -5, 5, 15, 25, 35, 45, and 55 ALU. In the statistical analyses, the value of 65 ALU was used for those who could not identify the strongest concentration. To avoid the possible effect of recent smoking on the result, an interval of at least 15 minutes was required between smoking and testing.

Statistics

McNemar’s test was used to analyse paired dichotomous data. Differences between groups were tested using Student’s *t* test, the Mann–Whitney *U* test, Fisher’s exact test, Pearson’s Chi squared test, and the Chi squared test for trend. For analysis of variance, the non-parametric Kruskal–Wallis analysis of variance, the parametric analysis of variance and analysis of variance for repeated measurements were used. Multiple comparisons were performed using the Scheffé test. Correlations were tested by calculating Pearson’s product moment correlation coefficients or Spearman’s rank order correlation coefficients. Agreement between the results of the prick test and nasal allergen provocation was tested with kappa statistics (Altman 1994b).

In study III, stepwise multiple linear regression analysis was used to examine the associations between olfactory threshold and age, presence of rhinitis, gender, and smoking in all

subjects and between olfactory threshold and age, diagnosed asthma, gender, ethmoidal and maxillary operations, prick-test positivity, nasal resistance, duration of rhinitis, actual rhinitis symptoms, and smoking in the patient group. The age-related 95% reference interval for the olfactory threshold was calculated using the method described by Isaacs and co-workers (1983). A linear regression model was first fitted to the data of the control group. Another linear regression model was fitted to the standard deviations of the residuals about the first regression. For this purpose, the age range was divided into five 10-year brackets: 15–25, 25–35, 35–45, 45–55, and 55–65 years. In addition, the two persons aged over 65 years were consolidated in the 55–65 age group. The reference interval was calculated as

$$f_1(\text{age}) \pm 1.96 \times f_2(\text{age})$$

where f_1 and f_2 are the functions of age fitted to the threshold data and the residuals, respectively.

RESULTS

Patient history (studies I, II)

According to the questionnaires (I) completed after a follow-up period of 18 years, 131 of 180 subjects still had symptoms of rhinitis. Favourable changes were reported by 116 subjects (64%, 95% confidence interval (CI) 57%–71%), i.e. symptoms had either disappeared or become milder. The details are shown in Table 5. Remission had occurred in 24 of 111 (22%) in the group with initially confirmed nasal allergy and in 25 of 69 (36%) in the non-allergic rhinitis group. The difference between the proportions was 0.15 (95% CI 0.01–0.28, χ^2 = 4.58, P = 0.032). The number of patients with no or milder symptoms was 73 of 111 (66%) in the allergic group and 43 of 67 (64%) in the non-allergic group (difference between the proportions 0.02, 95% CI -0.13 to 0.16, χ^2 = 0.05, P = 0.83).

The series of 108 patients studied in 1993–94 included 24 (49%) of the subjects who reported no symptoms and 84 (64%) of the subjects who stated that they still had symptoms. The difference between the proportions was 0.15 (95% CI -0.01 to 0.31, χ^2 = 3.41, P = 0.065).

The overall change in symptom severity was assessed also in connection with the clinical follow-up visit (II, IV). In this evaluation, the proportion of symptom-free patients was 8 in the whole series of 108 (7%). Grouped together, the patients whose rhinitis was in remission or had become milder were as many as 73 (68%, 95% CI 58%–76%). Table 5 shows the distribution of patients by changes in symptom severity. Assessed on the basis of the prick-test results in 1993–94, remission had occurred in 6 of 72 (8%) in the prick-test positive and in 2 of 34 (6%) in the prick-test negative group. The number of patients with no or milder symptoms was 47 of 72 (65%) in the prick-test positive and 25 of 34 (74%) in the prick-test negative group (difference between the proportions 0.08, 95% CI -0.10 to 0.27, χ^2 = 0.72, P = 0.40). Grouped according to the results of allergen provocation, 39 patients of 60 (65%) in the challenge-positive group and 28 patients of 39 (72%) in the challenge-negative group had no or milder symptoms of rhinitis (difference between the proportions 0.07, 95% CI -0.12 to 0.25, χ^2 = 0.50, P = 0.48).

Age and gender showed no association with the change in rhinitis symptom severity. The mean age was 50.7 (SD 11.7) years in the group with favourable changes and 50.6 (SD 11.8)

Table 5. Changes in rhinitis symptoms in 180 patients participating in a questionnaire study (I) 18 years after initial examinations and diagnosis and in 108 patients participating in a clinical study after a follow-up period of 23 years

Change in symptom severity	No. of patients, 18 years' follow-up (N=180)	No. of patients, 23 years' follow-up (N=108)
Disappeared or less severe	116 (64%)	73 (68%)
Equally severe	42 (23%)	19 (18%)
More severe	20 (11%)	16 (15%)
Symptomatic, but change not reported	2 (1%)	

years in the group with equally or more severe symptoms (difference between the means 0.2 years, 95% CI –4.7 to 5.0 years, t = 0.062, P = 0.95). Forty-three of 61 (70%) female and 30 of 47 (64%) male patients reported that their rhinitis symptoms had ceased or become milder (difference between the proportions 0.07, 95% CI -0.11 to 0.25, χ^2 = 0.54, P = 0.46) (Simola M *et al.*, unpublished data).

Smoking was significantly associated with the development of rhinitis symptoms. Only 9 of 21 (43%) smokers reported that symptoms had disappeared or become milder, while their number was 64 (74%) in the group of 87 non-smokers or ex-smokers (difference between the proportions 0.31, 95% CI 0.08 to 0.54, χ^2 = 7.28, P = 0.0070). When history of smoking was used as a criterion, the difference was smaller. Symptoms had disappeared or become milder in 34 of 54 (63%) subjects with a history of smoking and in 39 of 54 (72%) subjects who had never smoked (difference between the proportions 0.09, 95% CI -0.08 to 0.27, χ^2 = 1.06, P = 0.30) (Simola M *et al.*, unpublished data).

Table 6. Changes in skin-test positivity of 106 rhinitis patients during the follow-up period of 23 years.

Allergen group	Positive, initial study	Positive, Study II	Difference in proportions	95% CI
Pollen	59/100 (59%)	63/100 (63%)	0.04	-0.05 to 0.11
House dust*	56/94 (60%)	15/94 (16%)	-0.44	-0.35 to -0.46
House dust mite	6/69 (9%)	12/69 (17%)	0.09	-0.02 to 0.14
Animal dander	23/82 (28%)	34/82 (41%)	0.13	-0.01 to 0.25

* House dust mite tested instead of house dust in the follow-up study

Allergy tests (studies II, III and IV)

Seventy-two (68%, 95% CI 58%–77%) of 106 analysed patients showed at least one positive reaction in skin prick tests (study II). The number of positive tests per patient ranged from 1 to 17 (median 8, quartiles 3 and 11, mode 11). The proportion of skin-test positive patients had decreased significantly, as compared with the initial study, where the percentage was 78. The difference between the proportions was 0.10 (95% CI 0.02–0.16, χ^2 = 5.26, P = 0.022, McNemar's test). Different allergen groups are analysed for proportions of skin-test positive patients in Table 6. Though the proportions of positive reactions to pollen, house dust mite and other animal allergens remained relatively stable, there were several individual patients in whom the reactions had converted from negative to positive or reverted from positive to negative: ten conversions and six reversions in pollen allergen tests, eight conversions and two reversions in house dust mite allergen tests, 21 conversions and ten reversions in animal allergen tests. All prick-test positive patients in the follow-up study had a positive reaction to pollens, house dust mite or animal dander, i.e. no patient had positive reactions exclusively to the four allergens that were added to the test series during the study.

There was a significant downward trend in prick-test positivity with advancing age both in the whole series and in the patient group with initially confirmed allergy. In the whole series,

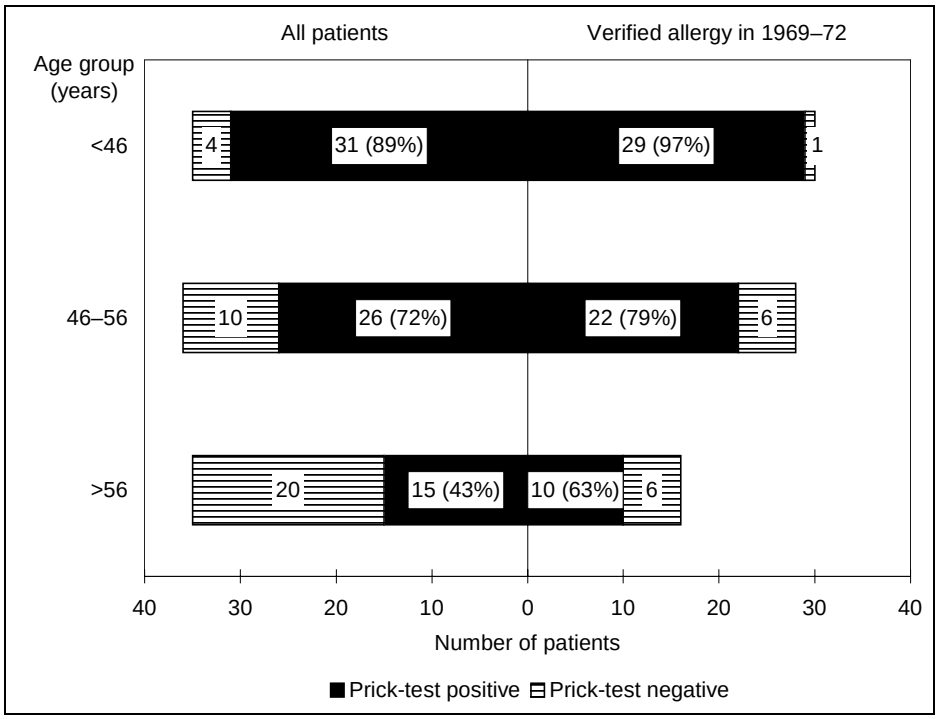

Figure 1. Age-related prick test reactivity in the follow-up study. Numbers and percentages of prick-test positive and negative subjects distributed by age in the whole series (χ^2_{trend} = 16.79, P *< 0.0001) and in the group of patients with initially verified allergy (χ^2_{trend} = 8.86,* P *= 0.0029).*

the patients with at least one positive prick-test reaction in the present study were significantly younger (mean age 47.1, SD 10.8 years) than the prick-test negative patients (mean age 58.0, SD 9.9 years, difference between the means 10.9, 95% CI 6.6–15.2 years, t = 4.98, P < 0.0001). In the group of patients with initially confirmed nasal allergy, the mean ages were 46.3 (SD 10.6) years in the prick-test positive and 55.5 (SD 9.8) years in the prick-test negative group (the difference between the means 9.2, 95% CI 2.8–15.5 years, t = 2.88, P = 0.0053). The numbers of prick-test positive and prick-test negative patients are presented by age group in Figure 1.

No association could be seen between skin-test reactivity and duration of rhinitis symptoms. The average duration was 30.7 (SD 6.7) years in the prick-test positive and 32.5 (SD 11.4) years in the prick-test negative group. The difference was not significant (U = 1066.5, P = 0.97, Mann–Whitney test). Ninety-eight patients (93%) reported that they still had symptoms of rhinitis, and eight (8%) that symptoms no longer occurred. Of those who still had symptoms, 64 now reported milder, 18 equally severe, and 16 more severe symptoms. There was no difference in the proportions of prick-test positive patients between the groups with different symptom changes, the percentages varying between 64 and 75 (χ^2_{trend} = 0.38, P = 0.54) in the whole series and between 77 and 100 (χ^2_{trend} = 2.24, P = 0.13) in the patient group with initially verified allergy.

A similar significant downward trend was apparent in the evaluation of the results of nasal allergen challenge in relation to age. In the whole series,

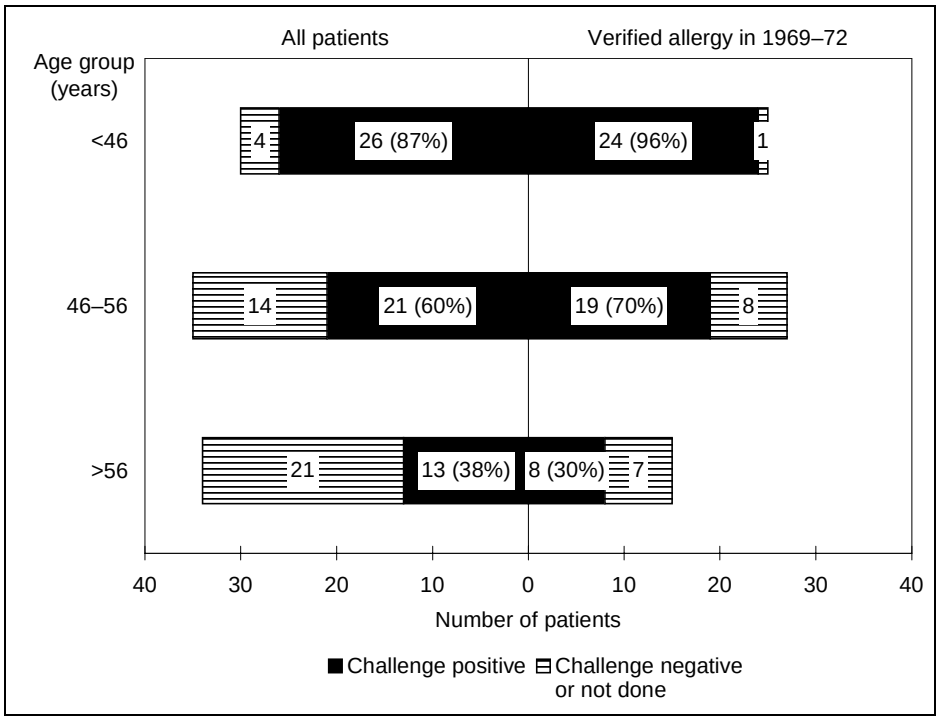

Figure 2. Nasal allergen provocation results in relation to age in the follow-up study. Numbers and percentages of challenge positive and negative subjects distributed by age in the whole series (χ^2_{trend} = 15.61, P *= 0.0001) and in the group of patients with initially verified allergy (χ^2_{trend} = 10.05,* P *= 0.0015).*

the mean ages of the challenge-positive and challenge-negative patients were 46.1 (SD 10.8) and 58.0 (SD 9.6) years, respectively, (difference between the means 11.9, 95% CI 7.6–16.1 years, $t = 5.57$, $P < 0.0001$), while the mean ages of these patients were 45.2 (SD 10.3) and 57.0 (SD 9.6) years in the group with initially confirmed allergy (difference between the means 11.9, 95% CI 6.0–17.7 years, $t = 4.07$, $P = 0.0001$). The proportions of challenge-positive patients are depicted by age group in Figure 2.

Forty-two of 75 patients with initially confirmed allergy had received allergen immunotherapy. Thirty-eight (90%) of them were still prick-test positive, whereas 22 of 30 (73%) tested in the group without immunotherapy showed a positive prick-test result. The difference between the proportions was 0.17 (95% CI -0.01 to 0.35, $P = 0.11$, Fisher's exact test). One patient was not tested because of early withdrawal and two patients could not give reliable information on immunotherapy. A similar result was obtained for nasal challenge: the challenge was positive in 32 of 39 (82%) challenged patients who had received immunotherapy and in 18 of 26 (69%) who had not (difference between the proportions 0.13, 95% CI -0.09 to 0.34, $P = 0.25$, Fisher's exact test).

Altogether 78 patients were both prick-tested and challenged with allergen in the follow-up study. In 58, both tests indicated allergy and in 10, both tests were negative. Two prick-test negative patients showed a positive challenge reaction and eight prick-test positive patients a negative reaction in

the challenge. The value of kappa was 0.59 (95% CI 0.35–0.83), which, according to Altman (1994b), reflects moderate agreement.

Nasal histamine provocation (study IV)

To compare histamine reactivity in different groups, the 73 patients were grouped according to the results of prick tests and nasal allergen provocation in conjunction with study II. Allergic rhinitis had been confirmed in all patients in the initial study. Sixty of 73 patients (82%) now showed at least one positive prick-test reaction and 50 of 66 (76%) had a positive response to allergen provocation.

Seven patients with initially verified allergy were excluded from the allergen challenge analysis: three refused and for four the appropriate allergens for provocation were not available.

Prick-test negative and prick-test positive groups had nearly identical responses to histamine challenge, as assessed with the concentration which induced an average increase of at least one point in nasal secretion or at least five sneezes (variable 1). The median end point concentration was 0.1% in both groups (U = 375.5, P = 0.83). In the comparison of the challenge-negative and the challenge-positive groups, the median end point concentration was 0.05% in the former and 0.025% in the latter group. This difference was not significant (U = 309, P = 0.16).

The analysis of variance for repeated measurements indicated that prick-test positive patients reacted more strongly to increasing histamine concentrations than those whose skin-test reactivity had ceased during the follow-up period. This type of interaction was seen both with regard to sneezing and discharge (variable 2) ($F_{4,280}$ = 3.38, P = 0.01) and with regard to sneezing, discharge and swelling (variable 3) ($F_{4,280}$ = 3.28, P = 0.012) but not to TNR (variable 4), which gradually became 3.7-fold in the prick-test negative and 4.1-fold in the prick-test positive group ($F_{4,268}$ = 0.07, P = 1). Also when the series of variable 2 were analysed in the groups with positive and negative nasal provocation results, histamine elicited stronger reactions in the patients with verified nasal allergy than in the challenge-negative group ($F_{4,256}$ = 2.67, P = 0.033). This was also true for the series of variable 3 ($F_{4,256}$ = 2.76, P = 0.028) but not for TNR, which progressively became 3.4-fold in the challenge-negative and 4.3-fold in the challenge-positive group ($F_{4,248}$ = 0.47, P = 0.76).

The sizes of weals elicited by the histamine control in the skin-prick test correlated poorly with the nasal response to histamine. Spearman's rank order coefficients between the histamine control weal and variables 1–4 were -0.11 to 0.07.

Sixty-seven patients (92%) reported that they still had symptoms of rhinitis and six (8%) that symptoms no longer occurred. Of those who still had symptoms, 44 (60% of the whole series) now reported milder, 13 (18%) equally severe and 10 (14%) more severe symptoms. The groups with different symptom severity changes did not differ significantly by any analysed variable in histamine provocation.

Nasal polyposis

Thirty-five of 106 analysed prick-tested patients (33%, 95% CI 24%–42%) reported that nasal polyps had been diagnosed. Seventeen of 35

(49%) were prick-test positive at the follow-up examination, while the proportion of prick-test positive patients was 55 (77%) among 71 patients without polyposis. Thus, the cumulative prevalence of nasal polyposis was 24% in the prick-test positive and 53% in the prick-test negative group. The difference between the proportions was 0.29, 95% CI 0.10–0.49, $\chi^2 = 8.98$, $P = 0.0027$ (Simola M *et al.*, unpublished data).

The occurrence of polyposis was not linked with changes in the severity of rhinitis symptoms. In the whole series, favourable rhinitis changes had occurred in 24 (67%) of 36 with a history of polyps and in 49 (68%) of 72 without polyposis (difference between the proportions 0.01, 95% CI -0.17 to 0.20, $\chi^2 = 0.02$, $P = 0.88$) (Simola M *et al.*, unpublished data).

Olfactory threshold (study III)

The olfactory thresholds of 105 rhinitis patients and 104 healthy control subjects were analysed with forward stepwise multiple regression analysis with age in years as a continuous independent variable, level of smoking history as a six-category independent variable and history of rhinitis, current smoking, gender and history of smoking as binary independent variables. Only age ($P < 0.0001$) and history of rhinitis ($P = 0.024$) showed significant association with olfactory threshold in this model with an adjusted coefficient of determination (R^2_{adj}) of 0.202. In the patient data, history of polyp operations ($P = 0.0032$) and age ($P = 0.0015$) were associated with poorer smell test results, whereas prick-test positivity ($P = 0.017$) was associated with better smell-test results.

In the linear regression analysis of the control group, the equation of olfactory threshold f_1(age) as a function of age (in years) was

$$f_1(\text{age}) = 2.4 + 0.29 \times (\text{age}),$$

with a residual standard deviation of 10.5 and standard error of the coefficient of 0.073 ($P = 0.0001$).

The equation of the olfactory threshold as a function of age fitted to the patient data f_3(age) was

$$f_3(\text{age}) = -7.6 + 0.62 \times (\text{age}).$$

The residual standard deviation was 17.4 and the standard error of the coefficient 0.147 ($P = 0.0001$).

The difference between the regression coefficients was 0.33 (95% CI 0.02–0.64, $t = 2.08$, $P = 0.039$), indicating that the sense of smell deteriorated more rapidly in rhinitis patients than in the control group.

There were two (2%) hyposmic subjects, i.e. persons whose olfactory threshold was higher than the upper 95% reference limit, in the control group and 16 (15%) in the group of rhinitis patients. The 0.13 difference in the proportions was significant (95% CI 0.06–0.21, $\chi^2 = 11.77$, $P = 0.0006$).

The natural logarithms of TNR and olfactory threshold showed no significant association (Pearson's correlation coefficient -0.15, 95% CI -0.34 to 0.04, $P = 0.13$).

Olfactory thresholds were lower in the group of prick-test positive patients than in the prick-test negative group. In the analysis of variance with age as a covariate, the means were 18.9 and 33.9 and the adjusted means 21.2 and 31.5 logarithmic units, respectively. The difference between the groups was significant ($P = 0.0096$). There was a significant intergroup difference ($P = 0.0097$) also between different types of rhinitis (seasonal allergic, n=28, perennial allergic, n=36, non-allergic, n=33, according to skin-test results). The

average olfactory thresholds were 17.5, 18.6, and 35.0, and the age-adjusted means 20.4, 18.7 and 32.0 units, respectively. Non-allergic patients demonstrated significantly higher thresholds than seasonal (P = 0.0006) and perennial (P = 0.0006) allergic patients but no difference could be found between the types of allergic rhinitis (P = 0.97) (Scheffé test).

Nasal polyposis severe enough to require polypectomy or ethmoidectomy was associated with impaired sense of smell. Thirty patients (29%) reported that they had undergone surgery for nasal polyps. Ten (33%) of them were hyposmic, whereas only 6 (8%) of the 75 patients with no polyp operations had olfactory thresholds above the reference interval (difference between the proportions 0.25, 95% CI 0.07–0.43, Yates-corrected χ^2_c = 8.78, P = 0.0031). Among the patients with and without prior maxillary sinus operations, the proportions of hyposmic subjects were 3 (27%) of 11 and 12 of 87 (14%), respectively (difference between the proportions 0.13, 95% CI -0.14 to 0.41, P = 0.37, Fisher's exact test).

The patients' subjective view of their olfactory perception was in accordance with the results of the measurements. The mean olfactory threshold was 35.3 (SD 21.9) units in the group of 38 who reported deterioration of the sense of smell and 17.2 (SD 13.0) units in the 64 who thought they had normal sense of smell (difference between the means 18.1, 95% CI 11.2–24.9 units, t = 5.24, P < 0.0001 (Simola M *et al.*, unpublished data).

DISCUSSION

Subjects

The patients in this study represent a small proportion of the rhinitis patients included in the initial study at our clinic two decades earlier. While a long observation period is likely to give a more accurate picture of changes, certain disadvantages become apparent. The number of patients in the first survey was 770, but only 23% of them took part in the questionnaire study (I) 18 years later, and 14% in the clinical follow-up studies (II, III and IV). Many patients had died or been disabled due to ageing or diseases, but presumably the main reason for lack of compliance was moving to another area or unwillingness to be re-investigated. It is plausible that patients who have no or very mild symptoms are more reluctant to participate. If this is the case, remission or improvement is in fact more frequent than our results suggest. This assumption is also supported by the difference in compliance between symptomfree and symptomatic subjects who had participated in our first questionnaire study; refusal to take part in the clinical follow-up investigations was more frequent among symptomfree subjects than among those who still had symptoms of rhinitis.

Patient history

Two questionnaires were used to collect information on the development of rhinitis symptoms and other relevant data in the patient history. As many as 66–68% of the patients stated that their rhinitis symptoms had either ceased or become milder. The percentage is somewhat higher than the 56% reported by Lehtonen and Haahtela (1988) after seven years' follow-up of adult patients, and clearly higher than the 38% reported by Smith (1971) in a group of children followed for five years. It is understandable that many subjects have difficulties in remembering details of their symptoms over a period of 20 years and there are obvious sources of error in using a questionnaire to collect information. This was particularly evident in the answers concerning appearance of asthmatic symptoms. To avoid errors due to the patients' misunderstanding of their asthma-like symptoms, we used a rather strict "official" criterion of asthma in the analysis of the smell-test results (III), i.e. entitlement to special drug reimbursement for treatment of asthma. The criterion of polyposis in study III, i.e. history of operations for nasal polyps, was also intentionally strict. Anamnestic data revealed history of polyps in a few more patients and it is possible that nasal endoscopy or computed tomography would have revealed even more polypoid changes. These methods were not available at the time of the initial study in 1969–1972 and were, therefore, not included in the follow-up study.

We tried to keep the main questions about rhinitis symptoms as simple as possible and asked the patient, if symptoms still occurred and if so, whether symptoms were now milder, equally or more severe, as compared with the symptoms 20 years ago. Even this seemed to be difficult for some patients, especially if a patient with purely seasonal rhinitis answered the question out of the season. The difference between the proportions of symptomfree subjects in the two successive questionnaires probably

reflects this difficulty. However, when symptomfree patients and patients whose symptoms had become milder were grouped together, the difference between the data was smaller. There was an unexpectedly weak association between changes in symptom severity and other variables such as age, gender, prick-test result, allergen provocation result, history of nasal polyps, history of sinusitis and history of asthma. A probable explanation for this is that the answer to the question about the symptoms only expressed the relative change as compared with the initial state and not the absolute severity of rhinitis. This means that the same answer was received from a patient in whom a very severe form of rhinitis had changed to moderately severe and from a patient whose mild symptoms had almost disappeared. It is also possible that patients with a long-continuing disease adapt to their symptoms, which impairs the sensitivity of a questionnaire study. It is, indeed, difficult to obtain reliable information on the development of symptoms with a questionnaire alone. Diary keeping or some other prospective form of collecting information regularly would be a better alternative. Clearly, this is not feasible in a 20-year follow-up study.

Allergy tests

At the time of the initial study between 1969 and 1972, the skin prick test was not a common method in allergy diagnostics, but the more sensitive and less specific intracutaneous and scratch tests were usually used. Today, skin prick testing is recommended for screening of allergy because of its simplicity, rapidity of performance, low cost and high specificity (Mygind *et al.* 1996a). In the present follow-up study, the standard prick-test series of the clinic was used and the selection of test allergens was wider than in the initial study, especially with regard to animal allergens.

Nasal allergen provocation no longer plays a major role in clinical management of rhinitis (Mygind *et al.* 1996a). In this follow-up study, the patients were challenged in order to verify present nasal allergy status. The bilateral method was chosen to minimize the effects of the nasal cycle. To include information on all aspects of the allergic reaction of the nose in the criteria of positivity, a combined score of sneezes, changes in nasal discharge and mucosal swelling and presence of non-nasal symptoms and signs was compiled. Nasal resistance was measured, but it was used as a criterion of positivity only in borderline cases to distinguish between a weak reaction and a negative one. This can be seen as an intermediate criterion between two extremes, viz. the view that rhinomanometry alone can be used to determine whether a reaction is positive or not (Grobler *et al.* 1966, Bachert *et al.* 1990, Albegger 1991) and the view that the test result can be reliably assessed with rhinoscopy alone and rhinomanometry need not be used at all (Hytönen and Sala 1996). In principle, an objective method of assessment like rhinomanometry is a useful supplement, which can enhance the reliability of the interpretation of the provocation result. However, a satisfactory level of repeatability can be reached, only if particular attention is directed to the tightness of the parts of the equipment and the proper, distortion-free position of the mask in every mesurement. It is possible that the posterior method of measurement has less possible sources of error in this respect. Unfortunately, it is impossible to perform on many subjects, which was the main reason, why

anterior rhinomanometry was used in this study.

The criteria of positivity were intentionally lax. This can be justified in this type of setting, where the main purpose was to identify the individuals who still had the property to react to allergens, even though the clinical disease might have disappeared or the patient had very mild symptoms. The criteria should be more stringent, if the purpose was to confirm the diagnosis of a present clinical disease, as is the case e.g. in the diagnostics of occupational rhinitis, which is currently the principal indication for nasal provocation in clinical practice.

When the patients were first classified as allergic or non-allergic in 1969–72, rather strict criteria were used. For the diagnosis of nasal allergy, a positive skin test had to be confirmed by positive nasal provocation because of the high sensitivity but low specificity of the intracutaneous and scratch tests. The initial results and those obtained in the present study may thus be considered comparable. However, it must be borne in mind that the composition and quality of the old house dust extract does not correspond with the modern concept of a standardized allergen extract and cannot be compared to the house dust mite allergen extract which was used in the follow-up study. Therefore, the comparison of the old and new house dust and house dust mite provocations revealed some differences that probably do not reflect a true change in the allergy status of the patients.

Allergic reactivity showed a clear downward trend in the older subjects. This is consistent with earlier results (Barbee *et al.* 1987). In the skin-test responses, significantly more changes had occurred from positive to negative than vice versa. The main reason for the difference seemed to be the large number of probably non-specific house dust reactions. When these reactions were excluded from the comparison, the difference essentially disappeared. In the majority of patients the condition was unchanged. A more detailed comparison of different allergen groups revealed more changes, however, indicating that while reactivity to some allergens decreased, the patients developed new reactions. New allergies were found especially for animal danders.

Barbee and co-workers (1987) have reported a higher frequency of skin-test reactivity among ex-smokers than among smokers or non-smokers. In our series, no significant differences could be seen between these groups. It is possible that the long follow-up period in itself had such a strong impact on skin-test reactivity that a minor difference between various smoking groups was not revealed.

At the time of the initial study, immunotherapy was a fairly common form of allergy treatment. Our data did not show any benefit of allergen immunotherapy in the long-term results. However, no definite conclusions can be drawn from this, because our patients were not included in a randomized trial, but were selected for immunotherapy, when there were adequate indications. Moreover, the extracts which were used at the time cannot be compared with today's specific immunotherapy preparations.

Nasal histamine provocation

There are no accepted standards for the procedure of nasal allergen provocation, only some loose recommendations. As regards nasal histamine provocation, there is hardly any uniformity at all but a variety of

methods are used. In study IV, we used a modification of the procedure described by Gerth van Wijk and Dieges (1987). Histamine phosphate was chosen as the test substance, because it induces changes in nasal mucosal thickness and glandular function and it is also an irritative agent. Histamine phosphate is widely used as a test substance in bronchial challenge, from which the fourfold increase in the concentration of the successive solutions was adopted.

A combined score for changes in nasal discharge and irritation was used as a variable, because it has proved useful in discriminating between rhinitis patients and control subjects in nasal histamine challenge (Gerth van Wijk and Dieges 1987). This variable did not show differences in our study, where fourfold histamine concentration steps were used instead of the double concentrations of the original report. More variables were created to make the analysis more sensitive. Thus, assessment of variables 2 (sneezing and discharge) and 3 (sneezing, discharge and swelling) with analysis of variance for repeated measurements showed significant differences both between the groups of prick-test positive and prick-test negative patients and between the groups of challenge-positive and challenge-negative patients. In the majority of our patients, severity of allergic symptoms and allergy test reactivity had changed considerably in the 20 years since the verification of allergic rhinitis (II). The results of the histamine provocations suggest that there is a link between nasal histamine sensitivity and the development of sensitivity to allergens as revealed by skin tests and nasal provocation. The differences became apparent only at the strongest concentrations, and even then the test was only capable of differentiating between the groups, not to predict the status of a single patient. As described in an earlier study (Gerth van Wijk and Dieges 1987), TNR was less sensitive than the other variables in detecting differences between the groups of subjects.

Several factors may account for the association between changes in allergy test reactivity and nasal histamine sensitivity in patients with long-standing verified allergic rhinitis. A decrease in nasal histamine sensitivity could be conveniently explained by a concomitant decrease in histamine sensitivity of the skin, but the poor correlation between histamine-induced changes in nasal status and skin weal suggests that this explanation is not valid. In their study, Gerth van Wijk and Dieges (1987) compared nasal reactivity of healthy subjects and patients with allergic rhinitis and suggested that the difference in reactivity might be explained by increased permeability of the diseased mucosa, which made possible a greater penetration of the test agents. They also presented two other hypotheses, viz., an elevated reflex-mediated activity in allergic patients and hyper-reactivity to changes in glands and vessels, which both might, in fact, also reflect the altered permeability of the mucosa. The assumption that mucosal permeability is enhanced in allergic rhinitis patients has also been made by earlier investigators (Salvaggio *et al.* 1964, Inagaki *et al.* 1985). If this were true, recovery of normal permeability would lead to a simultaneous decrease in nasal histamine and allergen sensitivity. Decline in skin reactivity would then reflect a weakening of allergen-induced reactions in the course of time. Symptom severity should decrease accordingly, but in our series this did not always occur. Moreover, later studies have shown

contradictory results suggesting that mucosal absorption is in fact reduced in patients with allergic rhinitis (Greiff *et al.* 1993, Greiff *et al.* 1997). Thus, other explanations must exist, e.g. a functional disturbance of the nasal epithelial lining, which may result in increased exposure of the tissue, especially the sensory nerves, to exogenous stimuli and agents (Andersson and Mygind 1995).

Many studies have been done in the hope of developing nasal histamine provocation into a routine diagnostic procedure for evaluating rhinitis patients. Ours was not an exception but we did not succeed in defining useful simple variables for mapping nasal hyperreactivity. At present, nasal histamine provocation remains a research tool for comparisons between patient groups or between findings at different points of time but of minor importance in daily clinical work.

Olfactory threshold

Though disorders of olfaction are common clinical problems, they are usually poorly identified and there is no specific medical specialty to promote their evaluation or treatment (Henkin 1995). Hyposmia is often reported as a common feature in association with long-standing rhinitis, but there are few reports in which the sense of smell has been quantitatively assessed in rhinitis patients. Moreover, the influence of age has, as a rule, been neglected in this context. Study III describes the age-adjusted reference interval of olfactory threshold, as measured with a commercially available method. Also when age-related changes are allowed for, the results of the study confirm that rhinitis impairs the sense of smell.

The proportion of hyposmic subjects was larger in the rhinitis group than in the control group, also when the impact of age was taken into consideration. Furthermore, the regression analysis results indicated that the sense of smell deteriorated more rapidly in rhinitis patients than in persons with healthy noses. One would expect that the longer the patient suffers from rhinitis, the poorer the sense of smell. However, we could not find any significant direct association between the duration of rhinitis and the olfactory threshold. This might be explained by the fact that the series of patients in this study was highly selected and all had had nasal disease for more than 20 years, i.e. such a long time that minor differences in the duration may not have had a demonstrable influence on olfaction. In a non-selected sample of rhinitis patients the result could be quite different. Olfactory threshold and nasal patency could be expected to be closely associated with one another. Many studies, including the present one, have shown that this is not the case (Eccles *et al.* 1989, Cowart *et al.* 1993, Lane *et al.* 1996). Nasal resistance, as measured by rhinomanometry, reflects the air flow through the nose, but, except for the cases with total obstruction, not the air flow to the locus of the olfactory epithelium. Probably, olfactory threshold is related to circumstances in the upper parts of the nasal cavities rather than the size of the lower turbinates, which mostly regulates the degree of nasal obstruction.

The olfactory thresholds of prick-test positive patients were lower than those of patients with non-allergic rhinitis. This result suggests that non-allergic disease could be more damaging to the sense of smell than allergic rhinitis. Nasal polyposis usually indicates severe chronic rhinitis, and it is not surprising that a

disease requiring polyp operations had led to higher olfactory thresholds than other types of rhinitis. A history of maxillary sinus operations had less impact on olfaction. There may be several reasons for this difference. Firstly, chronic maxillary sinusitis is usually not as persistent a disease as polyposis and, secondly, the diseased mucosa lies farther from the olfactory epithelium than the affected mucosa in ethmoidal polyposis and surgery involves less manipulation of the region of the olfactory epithelium.

CONCLUSION AND SUMMARY

The main purpose of this study was to obtain information about changes in rhinitis symptoms and allergy test results over a long period of time and to relate the changes to the results of smell tests and nasal histamine provocation.

The downward trend in the present results indicates that symptoms of rhinitis tend to disappear or become less severe with the passage of time. The proportion of patients whose symptoms had either disappeared or become milder was 64% after 18 years' and 68% after 23 years' follow-up. The change in symptom severity was not associated with age or gender.

During the follow-up period, the proportion of patients with positive skin tests decreased from 78% to 68%. However, if the patients with a positive reaction to only house dust in the initial study were excluded, the decrease essentially disappeared. The detailed records of reactions to different allergens, on the other hand, showed that individual reactivity to allergens had changed either from negative to positive or vice versa in several patients. Prick-test positivity tended to decrease with advancing age, but there was no association between skin-test reactivity and duration of rhinitis symptoms or between skin-test reactivity and changes in rhinitis symptom severity.

According to the smell test results, ageing is the most important factor that determines the changes in the sense of smell but even when age-related changes are taken into account, also chronic rhinitis impairs the sense of smell. This was seen both in the result of the regression analysis, indicating that the sense of smell deteriorated more rapidly in rhinitis patients than in subjects without rhinitis, and in the comparison of the proportions of hyposmic subjects, the proportion being greater in the group of rhinitis patients than in the group of healthy persons. Prick-test positive patients had lower olfactory thresholds than patients with non-allergic rhinitis. Nasal polyposis requiring polyp operations was associated with higher olfactory thresholds than other types of rhinitis, whereas a history of maxillary sinus operations had less impact on olfaction. In this study, duration of rhinitis, gender, smoking status and NAR showed no association with the olfactory threshold.

Long-term development of skin reactivity to allergens was linked with nasal sensitivity to histamine, but neither skin reactivity to allergens nor nasal sensitivity to histamine was associated with a change in nasal symptom severity. Thus, an association between the results of allergy tests and nasal histamine provocation can be apparent in a comparison of skin-test positive and negative patients, but overlapping between the patient groups is considerable and histamine provocation is not suitable as a diagnostic method to examine individual patients.

In clinical work, the physician often sees a patient who wants to know, how his or her rhinitis is going to develop in the long run. The conclusion which can be drawn from this study is that we can encourage our patients with the knowledge that their rhinitis symptoms are likely to get milder and the allergic reactivity will probably decrease, but the changes may need years or decades to emerge.

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