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# EVALUATION OF MEDICAL AND /OR SURGICAL TREATMENT OF ANOSMIA / HYPOSMIA IN ASSOCIATION WITH INFLAMMATORY DISEASE OF THE UPPER AIRWAY

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*To my wonderful family*

**ABSTRACT**

**Background:** There is a lack of evidence-based, prospective studies in treatment of nasal polyposis. The correlations between symptoms, polyp scores and computed tomography (CT) scans have not been studied sufficiently. Little, if any, sense of smell is common in nasal inflammatory disease. It is clinically well-known that the quality of life deteriorates when one starts to lose the sense of smell.

**Aims**: *I & III.* To compare the effects of medical treatment and combined surgical / medical treatment on olfaction, polyp scores and symptoms in patients with nasal polyposis and evaluate CT scans as a method for comparing these effects. *II.* To compare the effects on olfaction of topical glucocorticoid treatment and placebo given for six months in addition to oral glucocorticoids for 10 days, in patients with anosmia / hyposmia. *IV.* To study the effects of loss of smell on the patient's quality of life and the coping strategies used.

**Methods:** *I & III.* Thirty-two patients with nasal polyposis were randomized to unilateral endoscopic sinus surgery after pretreatment with oral prednisolone for 10 days and nasal budesonide bilaterally for one month. Postoperatively, they were given nasal steroids (budesonide) bilaterally for one year. During this period, they were assessed with nasal endoscopy, symptom scores and olfactory thresholds. CT-scans of the sinuses, performed before and one year after operation, were evaluated using the Lund staging system. *II.* The study was randomized, double-blind and placebo-controlled. The criterion for inclusion in the blinded phase was an improvement of at least two steps in the butanol odour threshold test, after open treatment for 10 days with oral and nasal corticosteroids. Forty patients were included. Twenty of them were randomized to treatment with fluticasone propionate, 10 to placebo and 10 others served as controls. The topical treatment was continued for 6 months. *IV.* Seventy-two patients with anosmia (46%) or hyposmia (54%) filled in the validated Multi-clinic Smell and Taste Questionnaire, the validated General Well-being Schedule (GWBS) and answered other questions shown to be of good validity.

**Results:** *I.* The combination of local and oral steroids, improved the sense of smell, but surgery had no additional effect. Symptom scores became significantly better with medical treatment alone and surgery had additional beneficial effects on nasal obstruction and secretions as well as polyp scores. *III.* From before to one year after surgery, we found a significant improvement in the CT total scores, osteomeatal complex (OMC) and the maxillary sinus scores, on the operated side, but not on the unoperated side. *II.* The three groups showed a similar improvement in their sense of smell after the initial 10-day treatment with combined oral and nasal corticosteroids. Patients who continued the local treatment maintained their improvement at the same level during the study whether or not they had been given nasal corticosteroids or placebo. We found no significant differences between the treatment groups. *IV.* Several negative effects were common, i.e., risks associated with the loss of smell, interference with daily routines and deterioration in well being. Physical health, financial security, profession, partnership, friendships, emotional stability and leisure also seemed to be negatively affected and GWBS scores showed a reduction in psychological well being. The patients became more aware of the importance of olfaction after its loss, and adopted several types of problem- and emotion-focused coping strategies.

**Conclusions:** *I.* Medical treatment seems to be sufficient for the treatment of most symptoms of nasal polyposis. When hyposmia is the main symptom no additional benefit seems to be gained from surgical treatment. If nasal obstruction is the chief problem after steroid treatment, surgical treatment is indicated. Selection of those who will benefit from surgery should be based on the patient's symptoms and not on the physician's polyp score. *III.* CT of the sinuses shows long-lasting improvement in the total and CT scores of the OMC after combined surgical and corticosteroid treatment, as compared to medical treatment alone. *II.* In patients with anosmia/hyposmia partly caused by local inflammation, no further improvement in the olfactory threshold is achieved by continuing to use a topical intranasal glucocorticoid after an initial combined topical and systemic glucocorticoid treatment. *IV.* We found that the loss of smell had substantial adverse effects on the quality of life and that high priority should be given to its diagnosis and treatment. Moreover, a combination of problem- and emotion-focused coping strategies may be suggested to patients who have recently lost their sense of smell.

*Key words: Nasal polyposis, olfaction, medical/surgical treatment, corticosteroids, scoring, staging, endoscopy, symptoms, anosmia, hyposmia, olfactory threshold test (butanol), computed tomography, sinuses, well-being, clinical, evaluation*

# LIST OF PUBLICATIONS

I. **A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis**
Ebba Hedén Blomqvist, MD, Lars Lundblad, MD, PhD, Anders Änggård, MD, PhD, Per-Olle Haraldsson, MD, PhD, Pär Stjärne, MD, PhD.
*J Allergy Clinical Immunol 2001;107:224-8*

II. **Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia / anosmia**
Ebba Hedén Blomqvist, MD, Lars Lundblad, MD, PhD, Hans Bergstedt DDS, PhD, Pär Stjärne, MD, PhD. *Acta Otolaryngol 2003; 123: 862-868*

III. **A randomized prospective study comparing computed tomography of medical and medical-surgical treatment of nasal polyposis**
Ebba Hedén Blomqvist, MD, Lars Lundblad, MD, PhD, Hans Bergstedt, DDS, PhD, Pär Stjärne, MD, PhD. *submitted for publication*

IV. **Consequences of olfactory loss and adopted coping strategies.**
Ebba Hedén Blomqvist, MD, Annika Brämerson, MD, Pär Stjärne, MD, PhD, Steven Nordin, PhD. *Rhinology, accepted for publication*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| 1-butanol | n-butyl alcohol |
| AML | Ascend Method of Limits |
| ASA | Acetyl Salicyl Acid |
| CCCRC | Connecticut Chemosensory Clinical Research Centre |
| $CO_2$ | Carbon Dioxide |
| CT | Computed Tomography |
| CWBS | General Well-Being Schedule |
| EOG | Electro-Olfactogram |
| ERPS | Olfactory Event-Related Potential |
| ESS | Endoscopic Sinus Surgery |
| GM-CSF | Granulocyte Colony-Stimulating Factor |
| HRQoL | Health-related Quality of Life |
| ITT | Intention to Treat |
| LVCF | Last Value Carried Forward |
| MCSTQ | Multi-Clinic Smell and Taste Questionnaire |
| NMDA | N-Methyl-D-Aspartate |
| NSAID | Non-Steroid Anti-Inflammatoric Drug |
| OMC | Osteomeatal Complex |
| PP | Per Protocol |
| QoL | Quality of Life |
| SOIT | The Scandinavian Odour Identification Test |
| SS | Single Staircase |
| UPSIT | The University of Pennsylvania Smell Identification Test |
| URI | Upper Respiratory Infection |
| VAS | Visual Analog Scale |

| | |
|---|---|
| Definitions: | Anosmia (total) = inability to detect any qualitative olfactory sensation. |
| | Hyposmia (general) = reduced sensitivity to all odours |
| | Parosmia = perception of an atypical odour in response to a particular stimulus |
| | Phantosmia = perception of an unpleasant odour when there is no odour present |

# 1 BACKGROUND

## 1.1 INTRODUCTION

We are almost always exposed to pleasant, delightful aromas and disgusting, repellent, bad smells. Many of these smells are almost perceptible and we are frequently unaware of them. However, imagine the day you lose your sense of smell. The only sensations you will then have from a nice-smelling meal with various spices and aromas will be salty, bitter, sweet or sour. You will not feel like inviting your friends for dinner, since you cannot smell the aromas that help us taste food. The nice expensive wine you serve now tastes like sour water and you cannot distinguish between the smell of fresh and rotten fish. You will probably feel socially insecure because you do not know how your home smells or even how you smell at a given time.

For patients with anosmia, these are common problems which greatly impair their quality of life. It is not merely a question of not being able to enjoy food and drink, feeling socially uncertain or being worried about not being able to smell warning odours. It can also impair relationships and some patients become depressed by this handicap.



*Fig. 1. The sense of smell plays an important role in our relationships.*

In humans, the sense of smell has several functions. Perhaps most importantly, olfaction directs our attention, enhanced by positive or negative emotions, towards environmental hazards (e.g., smoke and poisonous fumes) or to sensations that, in a general sense, have positive connotations, such as nutritious food. It is also well-documented that this sense regulates food intake (Mattes and Cowart, 1994, Friedman and Mattes, 1991). Indeed, some anosmic patients have gained weight, which they have usually ascribed to a "gustatory" reward in the form of a sweet desert after a dull meal (Mattes et al., 1990). The role of olfaction in interpersonal relations has been shown by the communication between women who live together because they synchronize their menstrual cycles (McClintock, 1971) and between a mother and her newborn child (Porter et al., 1983). Some data also suggest that women may select a spouse partly on the basis of his body odour (Ober et al., 1997, Wedekind et al., 1995).

These findings indicate that patients suffering from a loss of smell can be expected to have a poorer quality of life in several respects, which implies that the diagnosis and treatment of this symptom should be given high priority. Negative effects on mood, enjoyment of food, matters of safety, personal hygiene, social interaction and sexual life have been found in such patients (Varga et al., 2000; Hufnagl et al., 2003). Signs of depression have been detected in 17% (Temmel et al., 2002) to 29% (Deems et al., 1991) of patients with olfactory dysfunction. Temmel and co-workers also reported that 73% of patients with olfactory dysfunction complained of difficulties with cooking, 68% of mood changes, 56% of loss of appetite, 50% of eating spoiled food, 41% of poor perception of their own body odour, 30% of spoiling/burning foods and 8% of problems at work. Finally (Miwa et al., 2001) found that overall satisfaction with life had been reduced to only 50%.

## 1.2   OLFACTION

### 1.2.1  Anatomy

The olfactory mucosa is located at the top of the nasal cavities, on the superior and medial nasal conchas on the upper part of the nasal septum, where it extends up towards the lamina cribrosa on both sides. The olfactory cells are therefore found at the end of a pair of narrow "odour pockets", and even moderate swelling can reduce air flow and conduction in olfaction. However, in a state of the art review on olfaction and its alteration by nasal obstruction, rhinitis and rhinosinusitis (Doty and Mishra, 2001), the authors concludes that air flow access is not the only factor that causes the loss of smell in such patients.
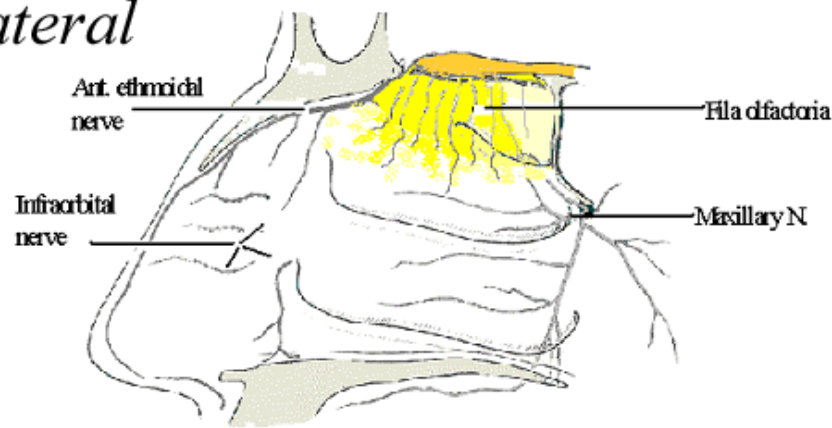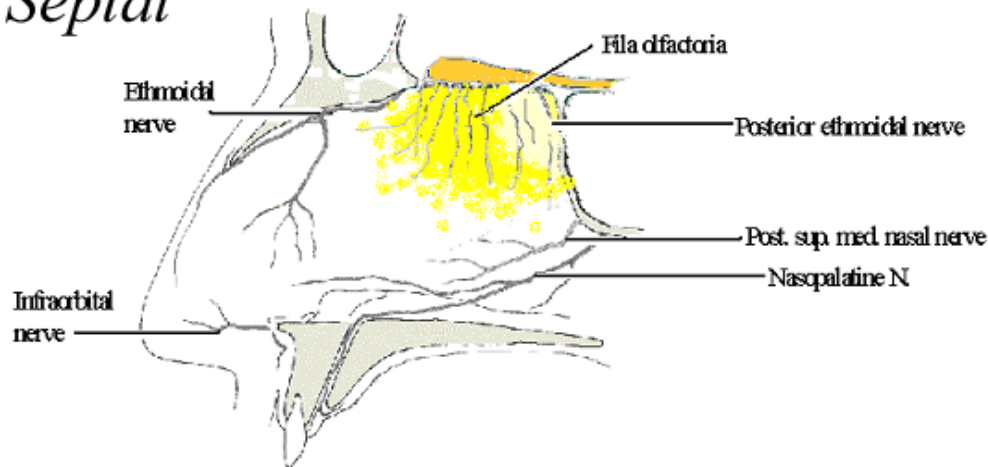
*Fig. 2. Schematic drawing of olfactory and trigeminal innervations of the nasal cavity of the lateral (top) the septal walls (bottom). The respiratory epithelium is innervated by branches of the ophthalmic and maxillary trigeminal nerves.*

A part from the special sensory function associated with cranial nerve I (CN I) – the olfactory nerve - the nasal cavity contains general sensory and autonomic fibres. The former is derived from the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve (CN V). The autonomic input originates from the cervical sympathetic chain and parasympathetic efferent fibres from the sphenopalatine ganglion.

The qualitative sensations of smell are mediated by CN I; however, many, if not all, odorous chemicals can stimulate the free nerve endings of CN V, and produce such sensations as irritation, tickling, burning, warming, cooling and stinging. These sensations, most of which protect the person from harmful sources of stimulation, are classified by various authors as a component of the "common chemical sense" (Cain 1974). Some data also show that the trigeminal and olfactory systems interact centrally. For example, olfactory and trigeminal pathways converge on the same neural elements in the mediodorsal nucleus of the thalamus of the rat, which block the trigeminal pathway that enhances odour-induced activity in the nucleus (Inokuchi et al., 1993). It should also be noted that CN V may also modulate the activity of olfactory receptor cells in the neuroepithelium via a local axon reflex associated with the release of substance P (Bouvet et al., 1987).

## 1.2.2 Epidemiology and Pathophysiology

In the USA, several hundred thousand patients who complain of smell and taste disorders, especially of the former, are seen by physicians each year (Gent et al., 1987). A population-based study of persons aged 53-97 years shows that as many as 24% have an impairment of olfactory function (Murphy et al., 2002), while another study of persons aged 20 years or more suggests a prevalence of 19% (13% with hyposmia and 6% with anosmia) (Brämerson et al., 2004). They also found a significant relation between impaired olfaction and ageing. Other data indicate that the prevalence of olfactory problems in the general population may be less (Hoffman et al., 1998), but that it increases exponentially with age.

Although more than 200 conditions and 40 medications have been linked to taste and smell disorders, in most patients the cause will be classified as nasal/sinus disease, idiopathic, postviral URI or head trauma (Scott, 1989b). The findings in 441 patients examined in the Taste and Smell Clinic of the Connecticut Chemosensory Clinical Research Centre (Goodspeed et al., 1987) showed that the commonest cause of reduced olfaction was nasal and/or sinus disease (30% of patients), followed by idiopathic conditions (26%) and previous upper respiratory infections (19%). In a study (Temmel et al., 2002) of 278 consecutive patients with hyposmia or anosmia, the following causes were found: trauma (17%), upper respiratory tract infection (URI) (39%), sinonasal disease (21%), congenital anosmia (3%), idiopathic (18%) or other causes (3%). In another study (Seiden and Duncan, 2001), 428 patients were examined in a university-based taste and smell clinic from July 1987 through December 1998. The commonest aetiologies of olfactory loss were head injury (18%), upper respiratory infection (18%) and nasal or sinus disease (14%).

**Non-conductive disorders**

Most of these cases are probably of sensorineural origin. They are caused by head trauma, neurodegenerative diseases, exposure to toxic substances, medical treatment, endocrine / metabolic disturbances, congenital disorders and idiopathic conditions. In rare cases of tumours, the aetiology may be conductive and sensorineural, depending on the location of the tumour. Advancing age is also associated with a gradual impairment of smell. Medication-related disorders sometimes can be corrected by discontinuing the medicine.

**Conductive disorders**

These conditions are usually regarded as treatable and they are often caused by various inflammatory disorders in the nose and sinuses - e.g. nasal polyposis, chronic sinusitis, persistent non-allergic rhinitis, allergic inflammation and in some cases a preceding upper respiratory infection. Some data show (Scott, 1989c) that only dysfunctions of smell caused by disorders of the nose and/or sinuses are amenable to therapy.

In one study, patients with olfactory dysfunction and nasal and sinus diseases (i.e., sinusitis, rhinitis and/or polyposis) was evaluated (Mott et al., 1997) and it was found that three fourths (74%) had complete loss of olfactory function (anosmia) and one fourth (26%) partial loss (hyposmia). It is reported (Cowart et al., 1993) that olfactory thresholds were significantly higher in allergic patients than in controls, and that 23% of the patients had a clinically significant loss of smell.

In the study (Seiden and Duncan, 2001) mentioned above, only 30% of the patients with a conductive loss complained of nasal obstruction, but 58% had a history of chronic sinusitis. In 45%, the olfactory loss fluctuated in severity at times. Since systemic steroids temporarily reversed the conductive olfactory loss in 83% of patients, this could be a useful diagnostic test. In contrast, topical steroids did so in only 25% of cases. Anterior rhinoscopy was of diagnostic value in only 51% of cases, but nasal endoscopy missed the diagnosis in 9%, which emphasises the importance of including nasal endoscopy in the physical examination.

### 1.2.3   Treatment of olfactory dysfunction

#### 1.2.3.1   Surgery

Several potentially curable causes of chemosensory dysfunction using surgery including nasal polyposis, have been identified (Jafek and Hill, 1989). For example, various authors have reported improvement in olfaction after sinus surgery ranging from 52% (Downey et al., 1996) to 68% (Shin et al., 1999) and 78% of cases (Hosemann et al., 1993). However, in these studies, the importance of simultaneous medical treatment is not clear. In patients with anosmia caused by chronic rhinosinusitis / nasal polyposis, the effect of endoscopic sinus surgery on the sense of smell was studied (Rowe-Jones and Mackay, 1997). The authors collected data prospectively on 115 patients, before and six weeks after surgery. All patients had bilateral chronic rhinosinusitis. Symptom scores (VAS) and paired phenylethyl methyl ethyl carbinol olfactory detection thresholds showed a statistically significant improvement. The improvement in all olfactory symptom scores was found to correlate with the increase in nasal volume, as measured by acoustic rhinometry. Recently, long-lasting subjective improvement of the reduced sense of smell was achieved by combining nasalisation (extensive sinus surgery) and low doses of nasal steroids (Jankowski and Bodino, 2003) in patients with nasal polyposis.

#### 1.2.3.2   Medical treatment

##### 1.2.3.2.1   Corticosteroid Treatment

**Systemic corticosteroids**
Many patients with hyposmia/anosmia report an improvement in their sense of smell after short-term treatment with oral glucocorticoids and several studies have shown that steroids alone can improve olfaction in nasal and sinus disease (Goodspeed et al., 1986, Jafek et al., 1987, Mott, 1991 and Scott, 1989a). Stevens studied the response to steroids in 12/24 patients who remained anosmic after endoscopic nasal and sinus polypectomy (Stevens, 2001). Although they were unresponsive to nasal steroids, oral steroids normalised the sense of smell in most of the patients. The mechanism for improvement in olfaction after treatment with systemic glucocorticoids is not entirely understood. The effect of glucocorticoids may be due to a reduction in the inflammatory swelling of the nasal mucosa, which increases the penetration of odours to the olfactory region. It also seems possible that the improvement in olfaction is due to the effects on the olfactory cells themselves.

**Intranasal corticosteroids**

Hyposmia is a neglected symptom in patients with rhinitis. In a study of 25 patients with perennial rhinitis (Golding-Wood et al., 1996), patients with initial symptoms of hyposmia significantly improved their UPSIT scores on olfactory testing and their symptom scores (VAS) for hyposmia, after six weeks of treatment with nasal corticosteroids (betamethasone sodium phosphate drops).

1.2.3.2.2   <u>Non Steroid Medical Treatment</u>

**Zinc / Caroverine**

The treatment of non-conductive olfactory disorders is largely an unsolved problem. Recently (Quint et al., 2002), the effects of the N-methyl-D-aspartate (NMDA) antagonist, caroverine were studied. Some possible mechanisms for such effects included reduced feedback inhibition in the olfactory bulb due to NMDA antagonistic actions and antagonism of an excitotoxic action of glutamate. When compared to baseline, treatment with caroverine improved odour thresholds and odour identification in anosmic patients. In hyposmic patients, it significantly improved odour identification ability. In contrast, zinc sulphate had no significant effect on olfactory function. These findings indicate that caroverine may be effective in the treatment of non-conductive disorders of smell. However, more research is needed in this field.

## 1.2.4  Tests of olfaction

Numerous tests have been devised to assess the ability to smell, although many are too unreliable or time-consuming to be practical in clinical work (Doty and Kobal, 1995). Remarkable progress has been made during the last decade in the development of reliable, valid and clinically applicable psychophysical and electrophysiological methods for testing olfactory function.

**Psychophysical tests**

A procedure that provides a quantitative measurement of sensory function and requires a verbal or conscious overt response on the part of the examinee is considered to be a psychophysical procedure. The most widely used psychophysical tests of olfactory function are those in which:

A. The sensitivity of the sensory system to low concentrations of odorants is measured - e.g., detection threshold tests.

B. The ability to identify odorants is determined when cued responses are made available - e.g., forced-choice odour identification tests.

Other types of olfactory tests - e.g., tests of remembering odours, differential thresholds, odour discrimination, intensity scaling - have not yet proved to be useful in clinical work (Doty, 1997) and are therefore not described.

*A. Threshold tests*

Two types of threshold procedures are frequently used clinically: the ascending method of limits (AML) and the single staircase (SS) procedures. In the AML procedure, odorants are presented sequentially from low to high concentrations and the point of

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transition between detection and no detection is estimated. In the SS method, the concentration of the stimulus is increased after trials in which a subject fails to detect the stimulus and reduced after trials in which correct detection occurs. In both these procedures, the direction of the initial stimulus presentation is made from weak to strong in an effort to reduce the adaptation effects of prior stimulation (Pangborn, 1964). Two of the best known and evaluated of these tests are; the single ascending series butanol odour detection threshold test and the phenyl ethyl alcohol single staircase odour detection threshold test.

   *a)  Single ascending series butanol odour detection threshold test*
This test employs n-butyl alcohol (1-butanol) as the odorant. Desirable attributes of butyl alcohol include its water solubility, low toxicity, ready availability in high purity and neutral odour quality. It has attained wide acceptance as a reference odorant in various applied settings because of these same attributes (Cain et al, 1988). The lowest concentration at which a subject correctly indicates which of two plastic squeeze bottles, one containing the odorant and the other the diluent, produces the strongest odour on five consecutive trials serves as a measure of the threshold (Cain and Rabin, 1989). *For further details, see under Methods and Discussion. We  used this test  in our studies.*

   *b)  Phenyl ethyl alcohol single staircase odour detection threshold test*
This test employs the rose-smelling odorant phenyl ethyl alcohol by using a modified single staircase procedure, with several staircase reversals. The geometric mean of the last four of seven staircase reversal points is taken as the estimate of the threshold (Doty, 1997).


*B. Quality identification tests*
These tests require stimulus quality identification and include odour-naming tests, yes/no identification tests and multiple-choice identification tests. The commonest of the latter tests is the University of Pennsylvania Smell Identification Test (UPSIT). For Scandinavians, however, it has some disadvantages because we are not familiar with all of the odours included in the test. The Scandinavian Odour-Identification Test (SOIT) was developed to address the needs of the Scandinavian population (Nordin et al., 1998).


**Neurophysiological tests**
Several methods have been used to measure reliably the effects of odorants on human electrophysiological responses. Although these techniques are now available for assessment, they are still largely experimental and appear to be less sensitive than psychophysical methods for evaluating many olfactory deficits (Doty, 1997). Therefore, they are only mentioned very briefly here.


   *A.  The Human Electro-olfactogram (EOG)*
The EOG is generally considered to consist of summated generator potentials from olfactory receptor cells. This potential is recorded with macroelectrodes from the surface of the olfactory mucosa.
   *B.  The Olfactory Event-related Potential (ERPs)*
 This method shows EEG-related responses generated in the cortex. In an olfactometric set-up the stimulants are presented intranasally. The trigeminal nerve is possible to stimulate with gaseous carbon dioxide ($CO_2$) and the olfactory nerve can be activated

by various odorants, such as phenyl ethyl alcohol. One of the main problems with this technique is to distinguish between responses elicited by activation of the chemoreceptors of the olfactory nerve and those of the trigeminal nerve (Smith et al. 1971).

## 1.3 NASAL POLYPOSIS

The condition seems to result from an underlying mucosal pathology and histological analysis has shown evidence of the exudation and retention of albumin and tissue fluid, together with localized eosinophilic inflammation in the polyps. Common symptoms include a reduced sense of smell, nasal obstruction, secretion, occasional headache and a feeling of pressure over the sinuses. Nasal polyps may obliterate the sinus ostia and predispose to infections in the sinuses. Its aetiology is not yet fully understood (Stammberger, 1999, Tos, 1997, Bernstein, 1997). However, it is usually associated with intrinsic asthma and ASA/NSAID intolerance. This condition may seriously affect the patient's quality of life (Radenne et al., 1999).

### 1.3.1 Epidemiology

Nasal polyposis, a common inflammatory condition, occurs in 1-2% of the adult population in Europe (Hosemann et al., 1994) and, in a recent prevalence study from Sweden (Johansson et al., 2003) its overall prevalence in the examined population was 2.7%. The presence of nasal polyposis correlates with other parameters, such as the presence of asthma, especially non-allergic asthma, which is associated with a higher prevalence of nasal polyposis (13%) and an even higher prevalence in those with aspirin intolerance and asthma (36%) (Holmstrom et al., 2002).

### 1.3.2 Pathophysiology

According to a multivariate theory about the pathogenesis of nasal polyps, irritation or viral-bacterial-host interactions can cause an inflammatory change in the nasal mucosa, which may lead to the formation of polyps (Bernstein, 2001). Cells in a nasal polyp, such as epithelial cells and fibroblasts, may produce granulocyte colony-stimulating factor (GM-CSF) and other cytokines, which are a possible pathway of the inflammatory response in nasal polyps. Allergy may be involved in the development of this cascade of events. The resultant oedema can lead to growth and enlargement of the nasal polyp.

The formation of polyps and their enlargement are therefore activated by processes involving the mucosal epithelium, matrix and inflammatory cells, which may, in turn, be initiated by both non-infectious eosinophilic inflammation and viral infections in the respiratory tract (Bernstein et al., 1995, Norlander et al., 1996).

*1.3.2.1 Allergic inflammation*

As mentioned above, allergy may be one of the mechanisms involved in the development of the cascade of events that cause the formation of nasal polyps. The incidence of sub clinical food intolerance seems to be increased in these patients (Pang et al., 2000). Fungal colonization in the mucus of the nasal mucosa may function as an antigenic trigger, according to the Mayo Clinic concept (Ponikau et al., 1999). Another theory is that colonization of the nasal mucosa by S. aureus, which acts as a superantigen, may be one of the triggering mechanisms that will lead to the formation of nasal polyps (Bachert et al., 2001).

*1.3.2.2 Non-allergic inflammation*

Close to half of the patients with aspirin intolerance and asthma have nasal polyposis, and arachidonic acid metabolism may be involved in the pathophysiological process, irrespective of the aetiology of the polyp. Leukotrienes are inflammatory mediators and the synthesis of these mediators results from the cleavage of arachidonic acid in cell membranes. This occurs in a series of events that cause contraction of the smooth muscle in the human airway, chemotaxis and an increase in vascular permeability. These effects account for their important role in asthma, allergic rhinitis and possibly paranasal sinusitis with the formation of nasal polyps. However, no convincing data are available which show that anti-leukotrienes should be used for the treatment of nasal polyposis (Mygind et al., 2000).

## 1.3.3 Diagnosis and Staging

An estimate of the severity of nasal polyposis must be based on a good scoring system. Several systems are used and it is therefore difficult to compare the results of other studies concerning polyp scores. Such systems determine the location of the polyps, but not always in relation to their size or volume. This may be a problem when scoring is used to evaluate the effects of treatment. With our scoring system, we regarded polyps medial to the middle turbinate as arising from the posterior ethmoidal sinuses. The advantage of this method is that it is a more holistic system for assessing polyps. Involvement of the posterior ethmoids reflects a more serious disease than involvement of the anterior ethmoids alone. On the other hand, this system has a disadvantage. If a patient with large polyps from the posterior ethmoidal sinuses is successfully treated with corticosteroids and the polyps become smaller and the symptoms improve, the score does not change so long as there are remnants of polyps from the posterior ethmoidal sinuses. At the International Conference on Sinus Disease: Terminology, Staging and Therapy, held in July 1993 (Lund and Kennedy, 1995a), an international scoring system for nasal polyposis was proposed. With this system, a polyp score of 0 = absence of polyps, 1 = presence of polyps, confined to the middle meatus and 2 = presence of polyps beyond the middle meatus. This system was not available when we designed our study. However, we prefer our scoring system because it includes involvement of the posterior ethmoidal sinuses as a sign of more extensive disease. In a recent study (Johansson et al., 2000) in which several methods for endoscopic staging of nasal polyposis were evaluated, the score system with three steps only showed a poorer correlation on repeated measurements than a four-step one.

### 1.3.4  Treatment

The treatment of nasal polyposis is disputed. Surgical or medical treatment or both have been recommended as the treatment of choice.

#### 1.3.4.1  Surgery

The functional aim of endoscopic sinus surgery (ESS) is to ensure patency of the osteomeatal complex, the key to a successful surgical outcome. The rationale for surgery of the osteomeatal complex was first recommended by Messerklinger (Stammberger and Posawetz, 1990). Several studies on the results of endoscopic surgery have reported excellent subjective results in all - e.g., marked improvement in nasal blockage and nasal polyposis (Lund and MacKay, 1994). Improvement has occurred in about 90% of short and long-term follow-up studies (Vento et al., 2000, Weber et al., 1997, Senior et al., 1998, Stammberger, 1999). However, the results can be difficult to interpret because most are reported in terms of improvements in various types of nasal symptoms and there is a lack of a definition of cure (Lund and MacKay, 1994).

#### 1.3.4.2  Medical treatment

**Corticosteroid Treatment**
Today corticosteroids are regarded as the most effective drug for treating nasal polyposis. Intranasal corticosteroids form the basis of the non-surgical treatment of nasal polyposis. Their effects are mediated by binding of the drug to the cytoplasmic glucocorticoid receptor of the target tissue. They reduce the number of eosinophils, T cells and cytokine production as well as the amount of microvascular leakage (Mygind and Lildholt, 1997, Lildholt et al., 1997).
According to the Position Statement on Nasal Polyposis (Lildholt, 1994), medical treatment should be given for at least one month before surgery is contemplated in patients with typical nasal polyposis. Some studies suggest that in those patients who respond to medical treatment, no additional treatment is necessary. Thus, Lildholt et al compared a single intramuscular depot injection of betamethasone with that of snare polypectomy, followed by a maintenance dose of topical nasal beclomethasone dipropionate for one year. The improvement was similar in the medically- and surgically- treated groups (Lildholt et al., 1988). However, the severity of nasal polyposis in that study was not entirely satisfactory, since nasal endoscopy was not performed. In a three-phase trial in 126 patients with bilateral nasal polyposis, the same author reported the findings of the first double-blind phase (Lildholt et al., 1995), in which they compared the effects of budesonide nasal Turbuhaler, 400 or 800 micrograms/day and placebo for one month. The treatment was successful in 82% of the patients treated with budesonide powder but in only 43% in the placebo group. The effects on nasal symptoms, like nasal blockage, secretion and sneezing are well-known (Mygind and Lildholdt, 1996, Mygind and Lildholt, 1997, Lildholt et al., 1997), but those on the sense of smell are less clear-cut. However, systemic corticosteroids are effective in reducing the size of the polyps and all nasal symptoms, including the reduced sense of smell. Moreover, when patients with massive nasal polyposis were treated for four days with 60 mg oral prednisolone followed by a gradual reduction of 5

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mg a day, 72% of the patients showed subjective improvement due to the involution of polyps (van Camp and Clement, 1994). On the CT scans of the sinuses, however, only 52% showed definite improvement.

Although systemic corticosteroids are effective in the treatment of nasal polyps, patients with diabetes, glaucoma, gastric ulcer, cardiac decompensation, hypertension or psychosis should be treated only after careful evaluation, because of the risk of adverse side-effects. In those with osteopenia or a high risk of developing osteoporosis (e.g., postmenopausal women), assessment of bone density can be useful as well as dietary supplements of vitamin D and calcium.


**Non-steroid Medical Treatment**

*Antihistamines*
When patients suffer from both seasonal or perennial allergic rhinitis and nasal polyposis, the treatment with antiallergic drugs can be beneficial. IgE-mediated disease does not cause nasal polyps, but when present, it may contribute to episodes of exacerbation of the polyps (Settipane, 1991).

*Antileukotrienes*
The efficacy of the leukotriene synthesis inhibitor, zileuton, and the leukotriene receptor antagonist, zafirlukast, was evaluated in a non-placebo-controlled study. An improvement or at least stabilization of sinonasal polyposis occurred in 50% of the patients (Parnes and Chuma, 2000). However, no really convincing evidence is available which shows that antileukotrienes should be used to treat nasal polyposis (Mygind et al., 2000).

*Antimicrobial therapy*
The finding that specific IgE antibodies to staphylococcal enterotoxins are seen in patients with severe polyposis (Bachert et al., 2001) also points to a possible role of bacterial superantigens, but this does not necessarily mean that antibiotics are indicated. Macrolides may have antiinflammatory effects and shrinkage of nasal polyps with low-dose long-term macrolide treatment has been reported. The efficacy of the macrolide, roxithromycin, was studied (Ichimura et al., 1996) in patients with nasal polyposis and an overall incidence of improvement of 52% was reported. However, more placebo-controlled, double-blind studies must be done before this treatment can be recommended in general.

*Antifungal therapy*
During the last few years, a new concept has been presented suggesting that nasal polyps and rhinosinusitis are caused by an immune reaction to fungus. Fungal colonisation in the mucus of the nasal mucosa would then be an antigenic trigger, according to some authors in the Mayo Clinic (Ponikau et al., 1999). In one study, they sought to establish the safety and clinical efficacy of intranasal antifungal drug therapy with amphotericin B as a medical treatment in 51 randomly-selected patients with chronic rhinosinusitis. They concluded that direct mucoadministration of this antifungal drug seems to be safe and therefore further controlled and blinded trials are indicated

(Ponikau et al., 2002). Thus, prospective controlled studies are needed before this new treatment can be recommended for nasal polyposis.

## 1.4   COMPUTED TOMOGRAPHY

CT scan of the paranasal sinuses is regarded as a prerequisite before surgery because it gives important information about variations in anatomy. Several reports have been published on its value for the preoperative staging of mucosal disease. Various scoring systems have been described for grading the severity of the disease (Kennedy, 1992, Friedman et al., 1990, Metson et al., 1997). In a study of four staging systems by comparing observer agreement and ease of use by 10 independent observers (Oluwole et al., 1996), it was concluded that the Lund and MacKay system (Lund and Mackay, 1993) was the best for clinical work. A few minor modifications of this system were made at the International Conference on Sinus Disease: Terminology, Staging and Therapy, held in July 1993 (Lund and Kennedy, 1995b), when it was proposed that it should be used as an international scoring system for evaluating CT scans. The American Academy of Otolaryngology also regards the Lund system as a better method for preoperative staging (Lund and Kennedy, 1997). It can be used in revision endoscopic sinus surgery as well (Bhattacharyya, 1999a, Katsantonis et al., 1990), which permits postoperative scoring of CT scans and objective quantification of the postoperative findings. The functional aim of endoscopic sinus surgery (ESS) is to ensure patency of the osteomeatal complex, the key to a successful surgical outcome, and it is therefore also scored separately with the Lund scoring system.

Several authors have assessed the value of CT scans for preoperative staging and objective follow-up of the findings (Franzen and Klausen, 1994, Bhattacharyya, 1999b, Sharp et al., 1999). The surgical failure rate increases when more objective measures, such as abnormal findings on postoperative endoscopy or CT scans, are used instead of persistent symptoms alone (Kennedy, 1992).

## 1.5   HEALTH RELATED QUALITY OF LIFE IN NASAL POLYPOSIS AND OLFACTORY DISTURBANCES

Quality of life (QoL) is a broader concept than health-related quality of life (HRQoL) because QoL depends also on factors other than health, such as income, consumption, etc. A person's state of health or HRQoL affects the QoL of that person, but other aspects of life are also important to his/her perceived QoL.

Quality of life is a multidimensional concept, which is difficult to measure. Various methods have been developed to measure HRQoL, and they can be classified as generic or disease-specific measurements of the state of health (McDowell, 1996). One advantage of disease-specific methods is that they consider aspects of importance for a specific disease. Generic methods describe the state of health in dimensions that are more general, in health profiles, which permits comparison of interventions of various diseases regardless of the type of disease. A generic method can also be used to measure the health of a population. In this thesis - *(Paper IV),* we used the Multi-clinic

Smell and Taste Questionnaire (MCSTQ) as a disease-specific method and the General Well-being Schedule (GWBS) as a self-reporting generic method. The latter gives a broad view of psychological well-being and distress on the basis of dimensions of anxiety, depression, general health, positive well-being, self-control and vitality (Dupuy, 1978, McDowell and Newell, 1996).

Nasal polyposis can induce severe symptoms and impairs the quality of life even more than perennial allergic rhinitis (Radenne et al., 1999). In that study, the improvement in the HRQoL after treatment of nasal polyposis, as scored with the SF-36 (36-item Short Form health survey) questionnaire, was related to an improvement in nasal symptoms. The severity of nasal polyp disease has usually been correlated to the degree of nasal obstruction. In our study *(Paper I)* of subjective symptom-scoring, we found that the patients scored a reduced sense of smell as the major complaint *(Fig 6).*

In a recent study (Johansson, Bramerson et al. 2004) the clinical presentations of individuals with nasal polyps detected by endoscopy in a general population sample was compared with those of patients with nasal polyp disease seeking medical attention. HRQoL was measured using the generic SF-36 questionnaire and the findings reflected that both individuals with undetected polyps and polyp patients have impaired HRQoL. The authors concluded that nasal polyps alone, as seen occasionally, are indicative of airway disease involving the upper and lower respiratory tracts. Compared with the individuals with nasal polyps in the population sample, patients actively seeking medical care for nasal polyposis experienced more symptoms of nasal blockage and an impaired sense of smell, and had more extensive polyps. There were equal frequencies of asthma symptoms in these two groups. Compared with the controls, the individuals with nasal polyps in the population sample had a greater frequency of asthma symptoms and aspirin intolerance and also experienced an impaired sense of smell.

Several authors (Leopold, 2002, Temmel et al., 2002, Miwa et al., 2001) have shown that olfactory dysfunction severely affects the quality of life. Negative effects have been found on mood, enjoyment of food, matters of safety, personal hygiene, social interaction and sexual life (Varga et al., 2000, Hufnagl et al., 2003) as well as signs of depression in 29% (Deems et al., 1991) and 17% (Temmel et al., 2002). In another study, overall satisfaction with life was reduced to only 50% (Miwa et al., 2001).

Among many complaints due to olfactory loss, the main ones have been related to food (73% complained of difficulties with cooking, 56% of less appetite and 50% of eating spoiled food) (Temmel et al., 2002). This loss in QoL seemed to be of greater importance in younger than in older people, and in women than in men.

However, it is not only a reduction in the sense of smell (hyposmia, anosmia) that affects the patient's well-being. Qualitative distortions in olfaction seem to be more upsetting to a person's quality of life than a simple loss (Leopold, 2002).

# 2  AIMS OF STUDY

*Paper I*
The aim of this study was to compare the effects of medical treatment with those of combined surgical and medical treatment of nasal polyposis, as regards olfaction, nasal symptoms and polyp scores.

*Paper II*
The aims of this study were to determine whether long-term treatment with a local glucocorticoid (Fluticasone propionate = Flixonase) could maintain or further enhance the improvement in olfaction obtained after 10 days of treatment with systemic glucocorticoids in addition to nasal glucocorticoids and to clarify the relationship between subjective symptoms and clinical observations.

*Paper III*
The aims of this study were to evaluate CT scans as a method for comparing the effects of medical treatment alone and combined surgical and medical treatment of nasal polyposis. We also wished to determine the correlations between symptoms, olfactory thresholds, polyp scores and computed tomography (CT) scans as well as the correlations between those differences.

*Paper IV*
The aims of this study were to investigate the effects of loss of smell as regards the quality of life and coping strategies. Previous studies of the consequences of olfactory loss have almost exclusively used closed questions (predetermined, reply alternatives) which do not permit insight into other possible consequences of the loss of smell. The purpose of the present study was therefore to: (a) determine whether the loss of smell (anosmia and hyposmia) entail consequences other than those previously reported, by also using open-ended questions, (b) study the importance of olfaction and (c) evaluate the problem- and emotion-focused coping strategies (Billings and Moos, 1981) that are used by these patients.

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# 3  MATERIAL AND METHODS

## 3.1  PATIENTS

*Papers I and III*
Thirty-two consecutive patients (17 males) with nasal polyposis, recruited from the Outpatient Clinic of the Department of Otorhinolaryngology, Karolinska Hospital, were included. At the time of surgery, they were 22 - 64 years old, median 48 years. As regards nasal anatomy and the extent of nasal polyposis, they all had symmetrical nasal airways and nasal polyposis on nasal endoscopy and anterior rhinoscopy. On the first visit, the polyp score was not allowed to differ by more than 1 point between the nasal cavities or be less than 1 on either side. All subjects who had a history of nasal surgery, severe systemic disease (diabetes, etc.) or smoking more than 20 cigarettes daily were excluded.

*Paper II*
Forty-eight consecutive patients (29 females), recruited from the Outpatient Clinic of the Department of Otorhinolaryngology, Karolinska Hospital, were included. Our subjects all had a subjective reduction in the sense of smell and an average odour threshold (sum of threshold on the left and right sides divided by two) of 8 or less.
In the blinded phase of the study, 40 patients (24 females), 26-65 years of age (mean 50 years), having a subjectively reduced sense of smell, were included. For inclusion in the blinded phase, we required an improvement of at least two steps in the butanol odour threshold test. Seven subjects failed to fulfill this criterion cocerning improvement in the odour thresholds and one was excluded before any treatment was given, because of a high blood glucose level.

*Paper IV*
Of 135 consecutive patients in the Out-patient Clinics of the Departments of Otorhinolaryngology at Karolinska Hospital, Stockholm and Central Hospital, Skövde, 72 (29 males, 43 females, aged 15-78 years, M = 56.1) with the chief complaint of loss of olfactory sensitivity (self-reported anosmia 44%; hyposmia 56%) agreed to participate. Forty-six per cent of the patients were anosmic and 54% hyposmic, according to the CCCRC threshold test (Cain, 1989). Twenty-six per cent suffered from parosmia (perception of an atypical odour in response to a particular stimulus) 5% phantosmia (perception of an unpleasant odour when there is no odour present) and 3% had both. Many patients complained of chronic or frequent nasal/respiratory symptoms and conditions. Fifteen per cent of the patients had had olfactory loss for less than 1 year, 42% for 1-3 years, 25% for 3-5 years, 15% for 5-10 years and 3% for more than 10 years. On the basis of the medical history and a general ENT examination, including rhinoscopy and nasal endoscopy after application of a local anaesthetic and decongestant, we found various causes of the loss of smell in these patients. The commonest aetiologies were a preceding upper respiratory infection (53%) and an unknown cause (22%).

## 3.2  METHODS

**Olfactory thresholds**

The olfactory threshold test, described by the Connecticut Chemosensory Clinical Research Centre (CCCRC), uses aqueous dilutions of 1-butanol (n-butyl alcohol) as the odorant. The highest concentration (4%) in deionized water is called dilution step 0; then the solution is diluted by successive factors of three to step 13. The test solutions were presented in squeezable polyethylene bottles. Olfactory thresholds were considered normal at dilution threshold 8.0 (Cain et al., 1988). Testing began with a low concentration of butanol dilution and a blank. The subject had to decide which smelled the strongest. If the answer was wrong, the concentration was increased, if the answer was correct, the subject was given a bottle containing a solution with the same concentration and a blank. Five correct answers in a row were regarded as the olfactory threshold. Each nostril was tested separately and the other nostril was occluded.



*Fig. 3. Preparation of the olfactory threshold test with butanol.*

**Surgery** *(Papers I & III)*

Endoscopic sinus surgery was performed under general anaesthesia. Local anaesthesia, with Lidocaine-hydrochloride 10 mg/ml / epinephrine 5 microg/ml, was also used to minimise bleeding and improve visualisation. The extent of the surgery was determined by the disease, but always included uncinectomy, anterior ethmoidectomy and exploration of the posterior ethmoids. If the posterior cells were involved, surgery was continued posteriorly with posterior ethmoidectomy and, in some cases, sphenoidotomy. The ostium to the maxillary sinus was enlarged and diseased mucosa from the fronto-nasal recess was removed. If there was a pneumatised concha bullosa (when the middle turbinate was pneumatised), the lateral mucosa and bone were usually removed to decompress the ostieomeatal complex. Care was taken to preserve an intact mucosa.

**Nasal endoscopy**
The patients were evaluated with nasal endoscopic examinations after local anaesthesia and a decongestant (Nafazolin hydrochloride - lidocaine hydrochloride 0.02% and 3.4% respectively).

**Polyp scoring**
The polyps were scored (0-3) according to their endoscopic appearance
0 - No polyposis
1 - Mild polyposis (small polyps not reaching the upper edge of the inferior turbinate)
2 - Moderate polyposis (medium-sized polyps between the upper and lower edges of the inferior turbinate)
3 - Severe polyposis (large polyps reaching the lower edge of the inferior turbinate and/or polyps from posterior ethmoidal sinuses).

**Symptom scores using VAS**
The patients were given a diary for entries concerning smell and rhinitis, in which they were to note the subjective degree of the sense of smell and other symptoms, before each of the visits. These symptom scores using VAS (visual analogue scale) were graded from 0 mm = no symptoms to 100 mm = maximum severity of symptoms.

**Computed tomography of sinuses, nasal cavities and the frontal cranial fossa**
In *Paper II*, we studied whether any pathological condition was associated with the patient's reduced sense of smell, before inclusion.
CT scans were done with a Toshiba scanner at 100 kV and 100 mA with contiguous 5-mm cuts in the coronal plane. In *Paper III,* the CT scans from 31 of the 32 patients were available for review. They were assessed in blinded fashion by one experienced radiologist, on two different occasions with similar results.

**The Lund staging system**
This system is based on a simple numerical score derived from the CT scan. Each sinus group is given a grade: 0 = no abnormality, 1 = partial opacification and 2 = total opacification. The sinus groups include the maxillary, frontal, sphenoid, anterior and posterior ethmoidal sinuses. Since it is difficult to use this score for the osteomeatal complex, the condition of this complex is scored as 0 = no obstruction and 2=obstruction. A total score of 0 to 24 can be given and each side can be considered separately (0 to 12). However, it was recently shown that the Lund score in the general population is not 0 and a total score of 0 to 5 may be considered within normal limits (Ashraf and Bhattacharyya, 2001).

**Multi-clinic Smell and Taste Questionnaire (MCSTQ)**
We used questions from the Multi-clinic Smell and Taste Questionnaire (Nordin et al., 2003) to assess self-reported parosmia, phantosmia, respiratory symptoms and the duration of olfactory loss, as well as questions pertaining to the consequences of loss of smell, the importance of the sense of smell and coping with a loss of smell. Some of the questions concerning consequences have been evaluated metrically and shown to be comprehensible and to generate reliable answers (Nordin et al., 2003), and most of them were of open-ended character.

The questionnaire also included the questions, *"How important are the following aspects for your quality of life: physical health, financial security, work life, partnership, friendship, emotional stability and leisure?"* (Each aspect was to be rated on a six-point scale ranging from zero, not important at all, to five, very important), and *"To what extent has your loss of smell affected the following aspects of your life: physical health, financial security, work life, partnership, friendship, emotional stability and leisure?"* (Each aspect was to be rated on an 11-point scale ranging from minus five, very severe deterioration, to five, very marked improvement).

**General Well-being Schedule (GWBS)**
The questionnaire included the General Well-being Schedule (GWBS). It is a self-report instrument that provides a broad-ranging indication of psychological well-being and distress based on the dimensions of anxiety, depression, general health, positive well-being, self-control and vitality (Dupuy, 1978, McDowell and Newell, 1996). The GWBS has also been used in various clinical studies (e.g. concerning bone mass (Bravo et al., 1997) and blood pressure (Monk, 1981). The GWBS, ranging between 0 and 110 (a high score indicates positive well-being), has good test-retest reliability and normative data (Bowling, 1997). It generates valid and reliable answers (Fazio, 1977) and some of the questions used to assess the effects of loss of smell in this study have likewise been shown to be comprehensible and generate answers of good reliability (Nordin et al., 2003).

## 3.3  PROCEDURES
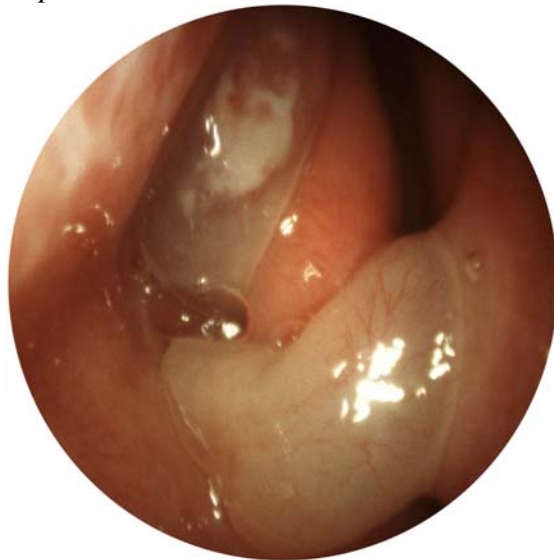
*Papers I & III*       4a                                                    4b



*Fig.4. Endoscopic view of the nasal cavities* on the unoperated right side (a) and operated left side (b), *o*ne year after surgery.

The patients were treated with oral prednisolone for the first 10 days (40 mg daily for three days, followed by a reduction of 5 mg daily), and nasal budesonide bilaterally for one month (Rhinocort Turbuhaler 400 micrograms daily). They were then randomised to surgery on the right or left side. After the operation, the same dose of nasal budesonide was given bilaterally for one year. The patients were evaluated before

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treatment, shortly before surgery and 1, 3, 6 and 12 months after surgery. Following the study, all patients were asked if they wanted to undergo an operation on the unoperated side. CT scans were done before treatment *(Fig. 5a)* and one year after *(Fig. 5b)* the unilateral surgery and bilateral corticosteroid treatment.



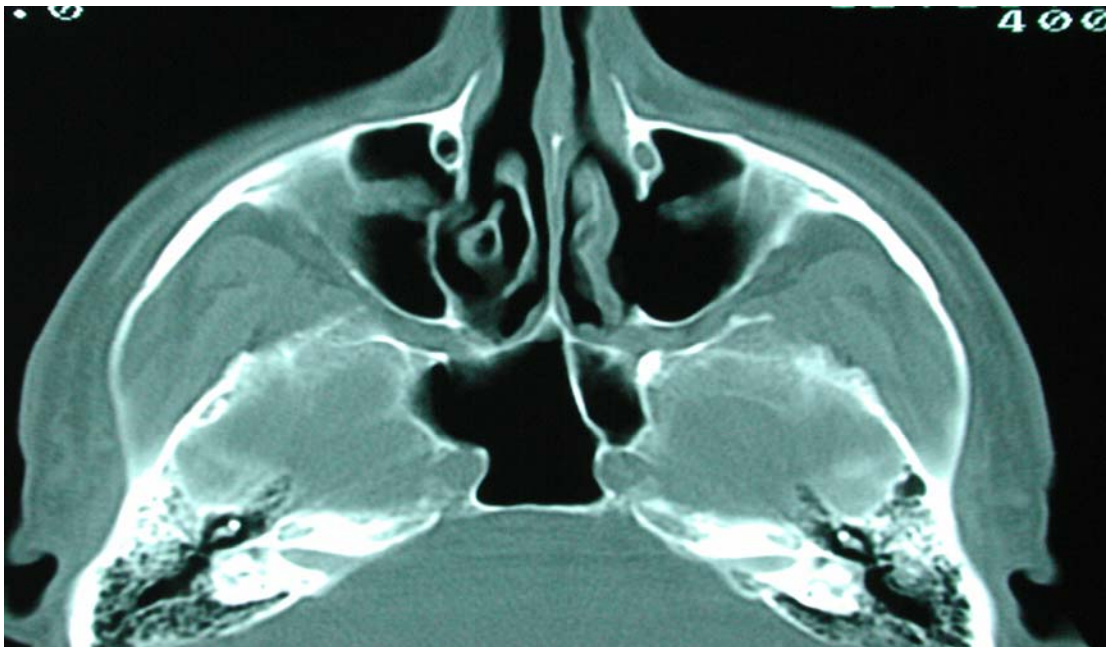*Fig. 5a. CT scan (axial view). The paranasal sinuses before treatment*



*Fig. 5b. CT scan. The paranasal sinuses one year after ESS on the left side and bilateral corticosteroid treatment*

*Paper II*
This study was double-blind, placebo-controlled and randomised. The blinded treatment phase was preceded by an open treatment period for 10 days with oral and nasal corticosteroids. Patients were then treated with oral prednisolone (40 mg daily for three days, followed by a reduction of 5 mg daily). At the same time (from treatment days 1-10), nasal glucocorticoid treatment with fluticasone propionate (Flixonase) was started (50 micrograms / dose, two sprays bilaterally, totalling 200 micrograms) o.d. In the blinded phase 20 patients were randomised to treatment with fluticasone propionate 200 micrograms daily (Flixonase) and 10 to placebo. Ten other patients were randomised as controls and given no further treatment. The treatment was continued for six months and the patients were examined before, immediately after the 10-day combined glucocorticoid treatment and two and six months after inclusion in the double-blind part of the study.

*Paper IV*
The entire questionnaire was mailed to the patients who filled it in at home and returned it by mail.

## 3.4   STATISTICAL METHODS

In all studies, values of P<0.05 were considered significant.

*Paper I.* The Wilcoxon signed rank test was used for the statistical analysis.

*Paper II.* On the basis of a preceding pilot study and an 80% power to detect a statistically significant difference (p < 0.05) between the treatment groups, 40 patients were included in the double-blind, placebo-controlled and randomised part of the study. In the statistical analysis, we used the Kruskal-Wallis and Mann-Whitney tests with Bonferroni´s correction for comparisons of several groups. The Wilcoxon test was used to compare various examinations in a group. *Intention-to-treat (ITT) analysis* was the main test used for the evaluation. All randomised patients in the study were evaluated with this method because it is usually recommended for this purpose. *Per protocol (PP) analysis* was employed solely for drawing conclusions, if we found no statistical differences between the treatment groups as regards the primary efficacy variable (the butanol threshold value). In the PP analysis, all randomised patients were included who had participated in the study without any divergences.

*Paper III.* The CT scan staging data were analysed, using the Sign test. The Wilcoxon matched-pairs signed rank test was not used because we had many ties (rows of similar values) and its significance would therefore have been erroreously high. Although the Sign test may not be as sensitive as the Wilcoxon matched-pairs signed rank test, it was thought to be the best test for our data.
The Spearman Correlation test was used to determine the correlations between the CT scan staging data and the olfactory thresholds, polyp scores and symptom scores, respectively.

*Paper IV.* The data were analysed using the one-sample Sign test, Wilcoxon signed rank test or chi-square analysis.

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# 4 RESULTS

*Paper I*
**Symptom scores** *(fig 6)*
A reduced sense of smell, nasal obstruction and nasal secretions were common symptoms, but only a few patients complained of headache or of pressure over their sinuses. Before treatment, we found no significant differences in the scores for these five symptoms between the operated and unoperated sides. All of these nasal symptoms improved significantly during the first month of treatment with the combination of oral and local steroids. The sense of smell and nasal secretions on both sides continued to improve during the first month after surgery. However, the sensation of nasal obstruction improved from before to one month after operation, on the operated side alone.

One year after surgery, the patients noted no significant difference in the sense of smell between the two sides, but surgery had improved the sensation of nasal obstruction, nasal secretions and pressure over the sinuses.
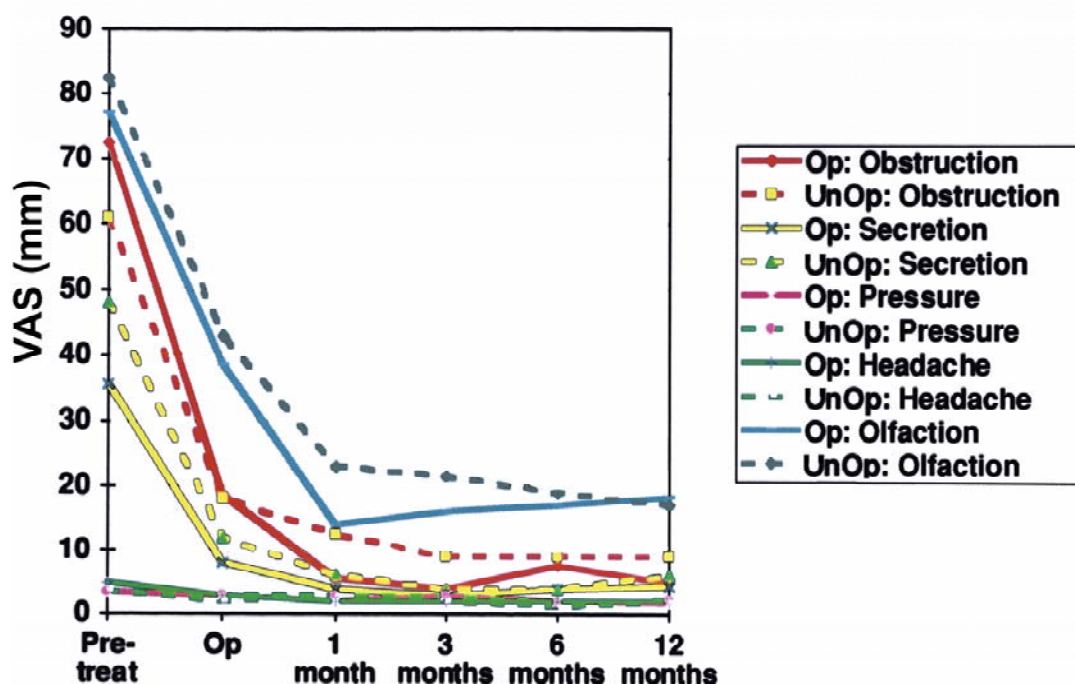


*Fig.6. Symptom score (VAS) n=32.*

All of the patients were offered an operation on the unoperated side at the end of the study, but oly twenty-five per cent of them accepted additional surgery, because of persistent symptoms.

**Polyp scores**
No significant difference was found in the polyp scores between the operated and unoperated sides, before treatment or preoperatively. Preoperative treatment significantly reduced the polyp scores. After surgery, the polyp scores were significantly lower on the operated side than on the unoperated one on all of the follow-up examinations. No significant changes in the polyp scores occured on the unoperated side after surgery.

**Olfactory thresholds (butanol test)**
The olfactory thresholds were similar on the operated and unoperated sides, on every examination. Olfaction improved siginifically after the first month of combined treatment with oral and nasal steroids, but not there after.

*Paper II*
We found no significant differences in the primary efficacy variable (butanol threshold values) between the ITT and PP analyses.

**Computed tomography of sinuses, nasal cavities and frontal cranial fossa**
The air passage below the cribriform plate was seen in 34 patients (79%), the conchae bulosae in 14 patients (33%) and eight (19%) had prominent ethmoidal bullae and/or agger nasi.

**Olfaction**
The olfactory thresholds and scored sense of smell improved significantly in all three groups to about the same extent after the initial 10-day treatment with combined oral and nasal corticosteroids. Patients who continued the local treatment showed no change in the olfactory thresholds until their 6-month visit, regardless of whether they had received nasal corticosteroids or placebo *(fig 7)*. We found a significant deterioration in the olfactory thresholds in the control group from the second to the third visit. However, no statistically significant differences were detected between the three groups on any of the four examinations concerning the olfactory thresholds and the scored sense of smell.
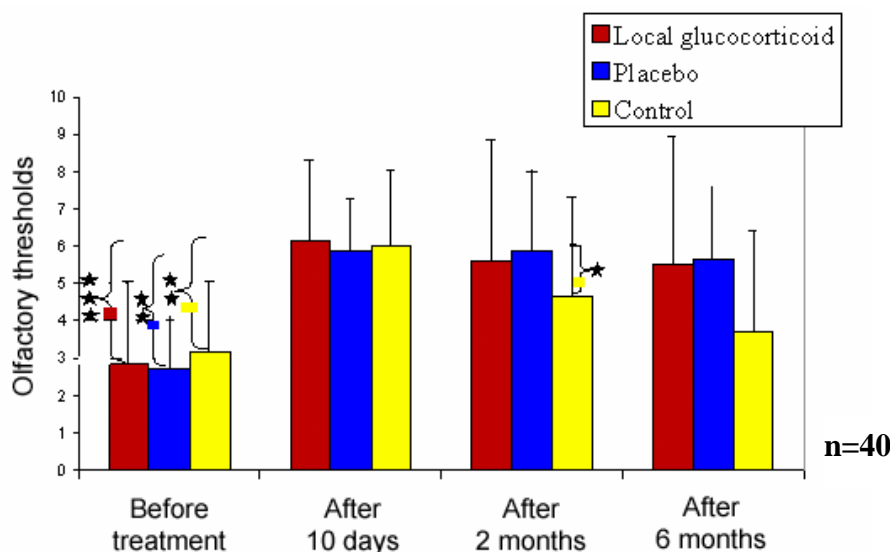


*Fig.7. Olfactory thresholds (Paper II).*

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**Symptom scores**
The VAS scores of the patients´ symptoms for nasal secretions, obstruction, well-being and sneezing showed a few statistically significant differences of no clinical importance in the groups. Apart from sneezing, we found no statistically significant differences between the three groups on the four examinations.

**Endoscopic examination**
Likewise, we found no striking differences between the three groups which correlated with the treatment or the olfactory results.

*Paper III*
**CT scores**
The improvement on the operated side, as compared to the unoperated side, was significant after one year, as judged by the Lund CT total scores, and the osteomeatal scores. Before and after one year, no significant difference was noted on the unoperated side, but there was a significant improvement on the operated side, as judged by the Lund scores of the osteomeatal complex, maxillary sinus and total scores. However, we found no statistically significant differences in the other sinuses.

**Correlations between <u>differences</u> in the CT scores and those in the olfactory thresholds, polyp scores and symptoms;**
We found no statistically significant differences of clinical importance before operation between the two sides. As regards the correlations between differences in the CT scores and those in the olfactory thresholds, polyp scores and symptoms, respectively, *between the operated and the un-operated sides one year after treatment*, the correlations were significant between the differences in olfactory thresholds and those in the CT scores of the frontal sinus and sphenoid sinus, respectively. We also found significant correlations between the differences in olfactory thresholds and those in the CT scores of the posterior ethmoidal sinus and maxillary sinus, respectively, *on the operated side, before and one year after treatment*, but not on the *un-operated side.*

**Correlations between the CT scores and the olfactory thresholds, polyp scores and symptoms, respectively**, before and one year after surgery, on the operated and un-operated sides. Although we found a few significant correlations, no clear-cut pattern was detected (not shown).

*Paper IV*
**Consequences of loss of smell**
About 2/3 of the patients reported a decline in the quality of life. The negative effects mainly concerned personal hygiene, eating and drinking, but not being bothered by unpleasant odours was frequently regarded as a positive effect. The commonest answers to the questions about risks, interference with daily routines and well-being were the inability to detect smoke from a fire, difficulties with cooking and depression. Many felt that their appreciation of food had declined and about 1/3 reported that their appetite was poorer.

On the basis of the GWBS scores, 51.4% of the patients had "positive well-being" (scores 73-110), 20.8% "moderate distress" (scores 61-72), and 27.8% "severe distress" (scores 0-60). These percentages can be compared to population-based normative data (Bowling, 1997) of 71.0%, 15.5%, and 13.5%, respectively. Chi-square analysis shows a significant difference in the distribution of the three categories between these patients and normative data.

**Importance of the sense of smell**
About 90% of the patients stated that they became more aware of the importance of olfaction and its loss, and they rated its importance (in relation to other senses) as higher in the period after than before the loss.

**Coping with the loss of smell**
Patients usually adopted more than one coping strategy. The commonest emotion-focused strategy was trying to accept the situation *(fig. 8a)* and the most frequent problem-focused strategy was letting a family member taste food that might be spoiled *(fig. 8b).* Other common strategies consisted of seeking information, asking a relative to check whether one had used the right amount of perfume/after-shave and comparing their problems with those who had worse symptoms.
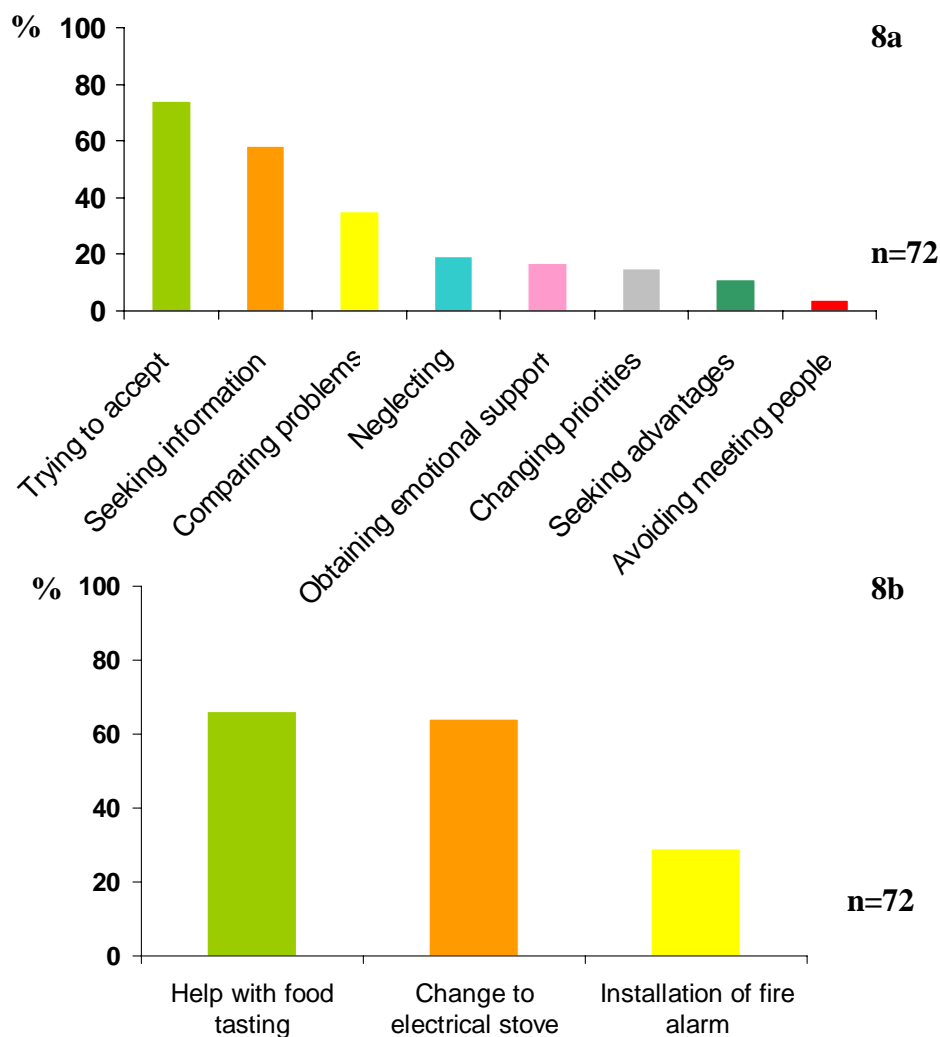




*Fig. 8a. Emotional coping mechanisms. Fig. 8b. Practical coping mechanisms.*

# 5  DISCUSSION

We designed a method for randomised, controlled comparison of medical treatment and surgical treatment in addition to medical treatment of nasal polyposis. We found that surgical treatment does not improve hyposmia further, but it reduces nasal obstruction, even after combined oral and nasal steroid treatment. We found disparity between the objective findings using the polyp score and the symptom score. We also found a significant improvement on the operated side, as compared to the unoperated side, after one year of bilateral medical treatment with nasal corticosteroids, using the Lund CT total and osteomeatal score.

The advantage of our study design in *Papers I and III*, is that we have a control group, well-matched for age, gender, social habits, associated diseases and heredity, etc., because the patients served as their own controls. This design has been used effectively to evaluate the effect of adenoidectomy on otitis media with effusion (Maw and Herod, 1986). The inclusion criteria must be strict and patients who have asymmetrical nasal airways should be excluded. These requirements were also met by using CT scoring, since we found no significant difference between the operated and the unoperated sides, in any patient or in the total CT scores, before inclusion in this study. When medical or surgical treatment is thought to have the same effect, this design can be recommended for evaluation and research.

An estimate of the severity of nasal polyposis must be based on a good scoring system. At the International Conference on Sinus Disease: Terminology, Staging and Therapy held in July 1993 (Lund and Kennedy, 1995a), an international scoring system for nasal polyposis was proposed. This system had not been reported when we designed our study. However, we prefer our scoring system because it includes involvement of the posterior ethmoidal sinuses as a sign of more extensive disease. In a study (Johansson et al., 2000) in which several methods for endoscopic staging of nasal polyposis were evaluated, the score system with three steps only showed poorer correlations in repeated measurements than the four-step one.

Many otolaryngologists take CT scans of the paranasal sinuses to determine the extent of paranasal sinus disease, although both positive and negative correlations between sino-nasal symptoms and CT evidence of rhinosinusitis have been reported (Bhattacharyya et al., 1997, Bolger et al., 1991).In a recent study (Kenny et al., 2001), the severity of various sinus symptoms (fatigue, sleep disturbance, nasal discharge, nasal blockage or a decrease in the sense of smell) correlated with the severity of the CT findings showing rhinosinusitis. However, isolated headache and/or facial pain or pressure were less reliable predictors of the CT scan findings supporting this diagnosis. Paranasal sinus abnormalities on CT scan were common in patients referred for a CT scan of the head, and 27% of patients with no symptoms of rhinosinusitis had opacification of the sinuses (Flinn et al., 1994). Mucosal abnormalities were present in 92.2% of patients (153/166) scanned for chronic sinus complaints and in 41.7% (15/36) scanned for other reasons (Bolger et al., 1991).

Nasal polyposis can induce severe symptoms and impair the quality of life even more than perennial allergic rhinitis (Radenne et al., 1999). The severity of this disease has generally been correlated to the degree of nasal obstruction. In our study *(Paper I)* of subjective symptom-scoring, we found that the patients scored a reduced sense of smell as their major complaint *(Fig 6)*. In *Paper III*, we found that the CT scores of individual sinuses and the total scores were of little prognostic value as regards olfactory thresholds, polyp scores and symptoms, respectively. This accords with our findings in *Paper I*, in which we also found a disparity between the objective findings, using the polyp scores, and the symptom scores. Treatment should therefore be based not on the CT scoring, but on the patients' symptoms. This view is also supported by the clinical impression that there is no clear-cut relation between the patients' symptoms, clinical examination (polyp scores) and CT findings.

The significant correlations between the differences in olfactory thresholds and those in the CT scores of the frontal sinus and of the sphenoid sinus, respectively, between the operated and unoperated sides, one year after surgery may indicate that extensive inflammatory disease of the sinuses may have a detrimental effect on olfaction. This accords with the finding of a significant correlation between the differences in olfactory thresholds and obstruction and those in the CT scores of some sinuses on the operated side before and after operation. No such correlation was found on the unoperated side.

*In Paper I*, we showed that surgical treatment of nasal polyposis induced no additional improvement in hyposmia/anosmia than treatment with combined oral and nasal steroids. This does not contradict our present findings, but presumably shows that a subgroup of patients has both persistent anosmia and pathological changes in several sinuses. Their disease is probably more severe, and additional surgery might be useful. This is also in line with a recent study (Jankowski and Bodino, 2003), showing that the sense of smell of patients with hyposmia/anosmia produced by nasal polyposis can be restored, after failure of medical treatment, by the combination of nasalisation (radical anterior and posterior ethmoidectomy including middle turbinate resection) and long-term nasal steroids. In that study, however, the sense of smell was only evaluated subjectively with symptom scoring (V.A.S.).

However, other data indicate that olfactory impairment in IgE-mediated nasal allergy has a higher correlation to the degree of inflammation, measured by eosinophil cationic protein (ECP), than nasal volume flow, measured by anterior rhinomanometry (Klimek, 1998, Klimek and Eggers, 1997). A reduced sense of smell, measured with the olfactory threshold test, also correlates better with an increase in nasal secretions than a reduced nasal volume, as measured by acoustic rhinometry (Hinriksdottir et al., 1997). Therefore, it seems rational that even in patients with nasal polyposis, inflammation must be treated primarily. However, our findings indicate that if no improvement occurs in olfaction and obstruction with corticosteroid treatment alone and if the patients show extensive pathological changes on the CT scan, additional surgery should be considered.

In our studies, we used the *butanol odour detection threshold test* to assess our patient's ability to smell. This test serves an important function of validation since hyposmia and anosmia are technically defined in terms of sensitivity, rather than in terms of odour

identification. In a comparability study (Cain and Rabin, 1989), the correlation between UPSIT and the butanol odour threshold test (one part of the CCCRC test) was 0.92 while the correlation was 0.89 between the results from the left and right nostrils, which is an excellent test-retest reliability. Detection threshold values are more reliable than recognition threshold values, but the phenyl ethyl alcohol single staircase odour detection threshold test was found to be even more reliable than the butanol odour detection threshold test (Doty et al, 1995). However, in the former test, the threshold estimate (Doty, 1997) is calculated from the geometric mean of the last four of seven staircase reversal points, which is far too time-consuming for clinical work. The advantages of 1-butanol as the odorant also include its water solubility, low toxicity, ready availability in high purity and neutral odour. Another advantage of our studies is that, apart from the tests done in Skövde *(Paper IV),* all of the odour detection threshold tests have been assessed by the same person (i.e., the author).

Although the clinical impression is that oral steroids can improve olfaction in nasal and sinus disease, the reduced sense of smell tends to recur shortly after the treatment is stopped if no additional treatment is given. We have found no studies that focus on effect-duration of oral steroids on nasal inflammation. However, when oral steroid treatment in nasal polyposis was studied (van Camp and Clement, 1994), they found a strong tendency of recurrence within five months after successful oral steroid therapy, which would suggest that the effect-duration of the oral steroids had probably ceased several months earlier.

In the double-blind part of *Paper II*, we included only patients who had improved by at least two steps in the butanol odour threshold test, because we wished to select patients with a reduced sense of smell at least partly caused or aggravated by a local inflammation. We found that in 23 of 40 patients, an upper respiratory infection (URI) had caused their loss of smell. Treatment with corticosteroids is of no value in patients with sensorineural damage to the olfactory epithelium. This could explain why local corticosteroids and placebo had similar effects in most of the patients with a previous URI. The improvement after the initial treatment with combined oral and nasal corticosteroids suggests that although the cause was probably sensorineural, it was often combined with a conductive aetiology caused by nasal inflammation. However, the reduced conduction in these patients was probably quite mild, according to our findings on computed tomography, in which air passage below the cribriform plate was seen in 79%.

The effects of local steroids and placebo might also be due to a placebo effect of being given active treatment. A reduction in nasal symptoms and an improvement in mucociliary clearance have been reported after nasal lavage (Holmström et al., 1997, Lundblad et al., 2001). Nasal irrigation may therefore contribute to the positive effects. Although, it seems unlikely that the small amount of diluents that is given with the normal dosage of a nasal spray can have a beneficial effect on olfaction, a positive effect cannot be ruled out.

In *Paper IV*, we evaluated the known effects of a loss of smell and tried to determine whether there are any others, by using open-ended questions. The aim was also to assess the effects of this symptom in relation to food, the quality of life from a broader

point of view and the psychological well-being. The findings clearly showed that the quality of life in general deteriorated after the onset of this symptom, since it was reported by 67% of the patients. Other studies (Leopold, 2002, Temmel et al., 2002, Miwa et al., 2001) also show that olfactory dysfunction severely affects the quality of life. The negative consequences of an olfactory loss found with the open-ended questions suggest that previous research has been comparatively successful in detecting some of the main effects on the quality of life – e.g., personal hygiene (36%) and eating and drinking (21%), which have also been noted by others (Varga et al., 2000, Hufnagl et al., 2003, Frasnelli et al., 2002) and the risks of failure to perceive fire or smoke (42%), rancid or ill-smelling food (19%) and dangerous chemicals/gases (12%), (Hufnagl et al., 2003, Frasnelli et al., 2002). Similarly, interference with daily routines, such as difficulties in cooking (21%) and eating (8%), have been noted by others (Frasnelli et al., 2002), but washing oneself and cleaning the home more often (10%) have not been observed before. Finally, depression as an aspect of well-being (17%) has also been reported (Deems et al., 1991). The percentages we found are, in general, lower than those in previous studies, probably because we have noted only the main effects.

A second aim of the study was to assess the importance of olfaction. It was evident that olfaction became more important after its loss, as reported by 88% of the patients. This view is also supported by the rating of olfaction in relation to the other senses (hearing, vision, touch and taste), since it was rated as much more important after than before the loss had occurred. However, this finding should be interpreted with caution because of the retroactive nature of both questions. It is noteworthy that when students were asked which of their senses they would choose to lose if they were forced to, 79% of them rated their sense of smell as the least important of their five senses (Van Toller, 1999). These data and those of the present study (also comparisons with other senses) suggest that this phylogenetically old sense is used at a low level of consciousness and that it is not until the sense is lost that the person will detect its value.

A third aim of the present study was to assess which coping strategies are adopted by patients who have lost their sense of smell. We found that they used several typical strategies to cope with their problems. Since the causes of various types of loss of smell cannot be treated successfully (Murphy, 2003), such strategies may be appropriate for many patients. Various emotional coping strategies were reported and are also used by persons with other stressful conditions in general (Stone and Neale, 1984). Problem-focused coping was commonly chosen by the patients - e.g., trying to obtain more information about the condition that also is a very commonly used coping strategy in stressful conditions in general (Billings and Moos, 1981).

It has been suggested that qualitative distortions in olfaction are more upsetting to a person's quality of life than a simple loss (Leopold, 2002). In *Paper IV*, 26% of the patients reported parosmia, 5% phantosmia and 3% both. These qualitative distortions may therefore have added to our patients' decline in the quality of life. Although all patients in our studies were not entirely cured, most of them showed a significant improvement in their sense of smell, which was probably important for their quality of life. It is well-known that olfactory loss commonly occurs in nasal and sinus disease (Mott et al., 1997). Since several of these diseases can be treated successfully (Jafek

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and Hill, 1989) and the patients report substantial adverse effects on their quality of life after olfactory dysfunction, treatment of such conditions should be given high priority.

# 6  CONCLUSIONS

I. No additional improvement in hyposmia/anosmia can usually be expected from surgery after treatment with combined oral and nasal steroids, in patients with diffuse bilateral nasal polyposis. However, our findings indicate that if no improvement occurs in olfaction and obstruction with corticosteroid treatment alone and if the patients show extensive pathological changes on the CT scan, additional surgery should be considered.

II. Selection of those who will benefit from surgery should be based mainly on the patient's symptoms and not on the polyp scores or the degree of polyposis scored on CT.

III. If an objective method is needed to evaluate patients with diffuse bilateral nasal polyposis, olfactory thresholds seem to be better than the polyp scores.

IV. Surgery significantly reduces the polyp scores and its effect is long lasting, but in our study, the polyp scores showed no relation to the symptom scores. Our data suggest that surgical treatment of nasal polyposis reduces nasal obstruction, even after combined oral and nasal steroid treatment.

V. Computed tomography of the sinuses shows long-lasting improvement in the total CT scores and CT scores of the osteomeatal complex after combined surgical and corticosteroid treatment, as compared to medical treatment alone.

VI. Treatment with combined oral and nasal corticosteroids can improve olfaction in patients with a reduced sense of smell, although reduced conduction or an inflammatory disorder may not be obvious.

VII. In patients with anosmia /hyposmia in whom an underlying inflammation cannot be excluded, and if there are no contraindications for treatment, combined oral and nasal corticosteroids for 10 days can be considered. In the presence of an obvious inflammation on endoscopy or a positive allergy test, treatment with local corticosteroids may be continued.

VIII. The quality of life deteriorates after the onset of a loss of smell. Moreover, several types of negative effects on the quality of life, risks associated with the loss, interference with daily routines and deterioration in well-being were found as well as adverse effects on appreciation of food and on appetite.

IX. Physical health, financial security, profession, partnership, friendship, emotional stability and leisure as well as psychological well-being may be negatively affected by a loss of smell.

X. The importance of olfaction becomes more apparent after its loss, and  these patients adopt several characteristic types of problem- and emotion-focused coping strategies.

XI. High priority should be given to the diagnosis and treatment of olfactory loss and to further research in this field. A combination of problem- and emotion-focused coping strategies may be suggested to patients who have recently developed this condition.

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# 8  REFERENCES

Ashraf, N. and N. Bhattacharyya (2001). "Determination of the "incidental" Lund score for the staging of chronic rhinosinusitis." Otolaryngol Head Neck Surg **125**(5): 483-6.

Bachert, C., P. Gevaert, et al. (2001). "Total and specific IgE in nasal polyps is related to local eosinophilic inflammation." J Allergy Clin Immunol **107**(4): 607-14.

Bernstein (1997). The immuno histopathology and pathophysiology of nasal polyps (The differential diagnosis of nasal polyposis). Providence, Rhode Island, OceanSide Publications, Inc.

Bernstein, J. M. (2001). "The molecular biology of nasal polyposis." Curr Allergy Asthma Rep **1**(3): 262-7.

Bernstein, J. M., J. Gorfien, et al. (1995). "Role of allergy in nasal polyposis: a review." Otolaryngol Head Neck Surg **113**(6): 724-32.

Bhattacharyya, N. (1999). "Computed tomographic staging and the fate of the dependent sinuses in revision endoscopic sinus surgery." Arch Otolaryngol Head Neck Surg **125**(9): 994-9.

Bhattacharyya, N. (1999). "Test-retest reliability of computed tomography in the assessment of chronic rhinosinusitis." Laryngoscope **109**(7 Pt 1): 1055-8.

Bhattacharyya, T., J. Piccirillo, et al. (1997). "Relationship between patient-based descriptions of sinusitis and paranasal sinus computed tomographic findings." Arch Otolaryngol Head Neck Surg **123**(11): 1189-92.

Billings, A. G. and R. H. Moos (1981). "The role of coping responses and social resources in attenuating the stress of life events." J Behav Med **4**(2): 139-57.

Bolger, W. E., C. A. Butzin, et al. (1991). "Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery." Laryngoscope **101**(1 Pt 1): 56-64.

Bouvet, J. F., J. C. Delaleu, et al. (1987). "Olfactory receptor cell function is affected by trigeminal nerve activity." Neurosci Lett **77**(2): 181-6.

Bowling, A. (1997). Measuring health: A review of quality of life measurement scales. Philadelphia, Open University press.

Bramerson, A., L. Johansson, et al. (2004). "Prevalence of olfactory dysfunction: the skovde population-based study." Laryngoscope **114**(4): 733-7.

Bravo, G., P. Gauthier, et al. (1997). "A weight-bearing, water-based exercise program for osteopenic women: its impact on bone, functional fitness, and well-being." Arch Phys Med Rehabil **78**(12): 1375-80.

Briner, H. R., D. Simmen, et al. (2003). "Impaired sense of smell in patients with nasal surgery." Clin Otolaryngol **28**(5): 417-9.

Cain, W. S. (1974). "Contribution of the trigeminal nerve to perceived odor magnitude." Ann N Y Acad Sci **237**(0): 28-34.

Cain, W. S. (1989). "Testing olfaction in a clinical setting." Ear Nose Throat J **68**(4): 316, 322-8.

Cain, W. S., J. F. Gent, et al. (1988). "Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center." Laryngoscope **98**(1): 83-8.

Cain, W. S. and M. D. Rabin (1989). "Comparability of two tests of olfactory functioning." Chemical Senses **14**(4): 479-485.

Cowart, B. J., K. Flynn-Rodden, et al. (1993). "Hyposmia in allergic rhinitis." J Allergy Clin Immunol **91**(3): 747-51.

Deems, D. A., R. L. Doty, et al. (1991). "Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center." Arch Otolaryngol Head Neck Surg **117**(5): 519-28.

Doty, R. L. (1997). Practical approaches to clinical olfactory testing. Taste and smell disorders. A. M. Seiden. New York, Stuttgart, Thieme**:** 38-51.

Doty, R. L. and G. Kobal (1995). Current trends in the measurement of olfactory dunction. Handbook of Olfaction and Gustation. R. L. Doty. New York, Marcel Dekker**:** 191-225.

Doty, R. L., D. A. McKeown, et al. (1995). "A study of the test-retest reliability of ten olfactory tests." Chem Senses **20**(6): 645-56.

Doty, R. L. and A. Mishra (2001). "Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis." Laryngoscope **111**(3): 409-23.

Downey, L. L., J. B. Jacobs, et al. (1996). "Anosmia and chronic sinus disease." Otolaryngol Head Neck Surg **115**(1): 24-8.

Dupuy, H. (1978). Self-representations of general psychological well-being of American adults. American Public Health Association Meeting, Los Angeles.

Fazio, A. F. (1977). "A concurrent validational study of the NCHS General Well-Being Schedule." Vital Health Stat 2(73): 1-53.

Flinn, J., M. E. Chapman, et al. (1994). "A prospective analysis of incidental paranasal sinus abnormalities on CT head scans." Clin Otolaryngol **19**(4): 287-9.

Franzen, G. and O. G. Klausen (1994). "Post-operative evaluation of functional endoscopic sinus surgery with computed tomography." Clin Otolaryngol **19**(4): 332-9.

Frasnelli, J. A., A. F. Temmel, et al. (2002). "Olfactory function in chronic renal failure." Am J Rhinol **16**(5): 275-9.

Friedman, M. and R. Mattes (1991). Chemical senses and nutrition. Getchell TV et al., eds., Smell and taste in health and disease. R. Press. New York**:** 391-404.

Friedman, W. H., G. P. Katsantonis, et al. (1990). "Computed tomography staging of the paranasal sinuses in chronic hyperplastic rhinosinusitis." Laryngoscope **100**(11): 1161-5.

Gent, J. F., R. B. Goodspeed, et al. (1987). "Taste and smell problems: validation of questions for the clinical history." Yale J Biol Med **60**(1): 27-35.

Golding-Wood, D. G., M. Holmstrom, et al. (1996). "The treatment of hyposmia with intranasal steroids." J Laryngol Otol **110**(2): 132-5.

Goodspeed, R. B., J. F. Gent, et al. (1987). "Chemosensory dysfunction. Clinical evaluation results from a taste and smell clinic." Postgrad Med **81**(1): 251-7, 260.

Goodspeed, R. B., J. F. Gent, et al. (1986). Corticosteroids in olfactory dysfunction. Clinical measurement of taste and smell. R. S. Rivlin. New York, Macmillan**:** 514-518.

Hinriksdottir, I., C. Murphy, et al. (1997). "Olfactory threshold after nasal allergen challenge." ORL J Otorhinolaryngol Relat Spec **59**(1): 36-8.

Hoffman, H. J., E. K. Ishii, et al. (1998). "Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the

1994 disability supplement to the National Health Interview Survey (NHIS)." Ann N Y Acad Sci **855**: 716-22.

Holmstrom, M., K. Holmberg, et al. (2002). "Current perspectives on the treatment of nasal polyposis: a Swedish opinion report." Acta Otolaryngol **122**(7): 736-44.

Holmstrom, M., G. Rosen, et al. (1997). "Effect of nasal lavage on nasal symptoms and physiology in wood industry workers." Rhinology **35**(3): 108-12.

Hosemann, W., U. Gode, et al. (1994). "Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery." Am J Otolaryngol **15**(2): 85-98.

Hosemann, W., W. Goertzen, et al. (1993). "Olfaction after endoscopic endonasal ethmoidectomy." Am J Rhinology **7**(1): 11-15.

Hufnagl, B., J. Lehrner, et al. (2003). Development of a questionnaire for the assessment of self reported olfactory functioning. ECRO, Chem Senses.

Ichimura, K., Y. Shimazaki, et al. (1996). "Effect of new macrolide roxithromycin upon nasal polyps associated with chronic sinusitis." Auris Nasus Larynx **23**: 48-56.

Inokuchi, A., C. P. Kimmelman, et al. (1993). "Convergence of olfactory and nasotrigeminal inputs and possible trigeminal contributions to olfactory responses in the rat thalamus." Eur Arch Otorhinolaryngol **249**(8): 473-7.

Jafek, B. W. and D. P. Hill (1989). "Surgical management of chemosensory disorders." Ear Nose Throat J **68**(5): 398, 400, 402-4.

Jafek, B. W., D. T. Moran, et al. (1987). "Steroid-dependent anosmia." Arch Otolaryngol Head Neck Surg **113**(5): 547-9.

Jankowski, R. and C. Bodino (2003). "Olfaction in patients with nasal polyposis: effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nasalization)." Rhinology **41**(4): 220-30.

Johansson, L., A. Akerlund, et al. (2003). "Prevalence of nasal polyps in adults: the Skovde population-based study." Ann Otol Rhinol Laryngol **112**(7): 625-9.

Johansson, L., A. Akerlund, et al. (2000). "Evaluation of methods for endoscopic staging of nasal polyposis." Acta Otolaryngol **120**(1): 72-6.

Johansson, L., A. Bramerson, et al. (2004). "Clinical relevance of nasal polyps in individuals recruited from a general population-based study." Acta Otolaryngol **124**(1): 77-81.

Katsantonis, G. P., W. H. Friedman, et al. (1990). "The role of computed tomography in revision sinus surgery." Laryngoscope **100**(8): 811-6.

Kennedy, D. W. (1992). "Prognostic factors, outcomes and staging in ethmoid sinus surgery." Laryngoscope **102**(12 Pt 2 Suppl 57): 1-18.

Kenny, T. J., J. Duncavage, et al. (2001). "Prospective analysis of sinus symptoms and correlation with paranasal computed tomography scan." Otolaryngol Head Neck Surg **125**(1): 40-3.

Klimek, L. (1998). "[Sense of smell in allergic rhinitis]." Pneumologie **52**(4): 196-202.

Klimek, L. and G. Eggers (1997). "Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilic inflammation." J Allergy Clin Immunol **100**(2): 158-64.

Leopold, D. (2002). "Distortion of olfactory perception: diagnosis and treatment." Chem Senses **27**(7): 611-5.

Lildholdt (1994). "Position statement on nasal polyps." Rhinology(32): 126.

Lildholdt, T., J. Fogstrup, et al. (1988). "Surgical versus medical treatment of nasal polyps." Acta Otolaryngol **105**(1-2): 140-3.

Lildholdt, T., H. Rundcrantz, et al. (1995). "Efficacy of topical corticosteroid powder for nasal polyps: a double- blind, placebo-controlled study of budesonide." Clin Otolaryngol **20**(1): 26-30.

Lildholt T, Dahl R, et al. (1997). Effect of corticosteroids on nasal polyps. Evidence from controlled trials. Nasal polyposis. An inflammatory disease and its treatment. Lildholt T. Copenhagen, Munksgaard**:** 160-169.

Lund, V. J. and D. W. Kennedy (1995). "Quantification for staging sinusitis. International conference on sinus disease: Terminology, Staging and Therapy ." Supplement to the Annals of Otology, Rhinology & Laryngology **104**(10, Part 2): 17-21.

Lund, V. J. and D. W. Kennedy (1995). "Quantification for staging sinusitis. The Staging and Therapy Group." Ann Otol Rhinol Laryngol Suppl **167**: 17-21.

Lund, V. J. and D. W. Kennedy (1997). "Staging for rhinosinusitis." Otolaryngol Head Neck Surg **117**(3 Pt 2): S35-40.

Lund, V. J. and I. S. Mackay (1993). "Staging in rhinosinusitus." Rhinology **31**(4): 183-4.

Lund, V. J. and I. S. MacKay (1994). "Outcome assessment of endoscopic sinus surgery." J R Soc Med **87**(2): 70-2.

Lundblad, L., P. Sipila, et al. (2001). "Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a nordic, multicenter, randomized, double-blind, placebo-controlled study." Acta Otolaryngol **121**(4): 505-9.

Mattes, R. D. and B. J. Cowart (1994). "Dietary assessment of patients with chemosensory disorders." J Am Diet Assoc **94**(1): 50-6.

Maw, A. R. and F. Herod (1986). "Otoscopic, impedance, and audiometric findings in glue ear treated by adenoidectomy and tonsillectomy. A prospective randomised study." Lancet **1**(8495): 1399-402.

McClintock, M. K. (1971). "Menstrual synchorony and suppression." Nature **229**(5282): 244-5.

McDowell, I. and C. Newell (1996). Measuring health: A guide to rating scales and questionnaires. New York.

Metson, R., R. E. Gliklich, et al. (1997). "Comparison of sinus computed tomography staging systems." Otolaryngol Head Neck Surg **117**(4): 372-9.

Miwa, T., M. Furukawa, et al. (2001). "Impact of olfactory impairment on quality of life and disability." Arch Otolaryngol Head Neck Surg **127**(5): 497-503.

Monk, M. (1981). "Blood pressure awareness and psychological well-being in the health and nutrition examination survey." Clin Invest Med **4**(3-4): 183-9.

Mott, A. E. (1991). Topical corticosteroid therapy for nasal polyposis. Smell and Taste in health and disease. T. V. Getchell, R. L. Doty, L. M. Bartoshuk and J. B. Snow. New York, Raven press**:** 553-572.

Mott, A. E., W. S. Cain, et al. (1997). "Topical corticosteroid treatment of anosmia associated with nasal and sinus disease." Arch Otolaryngol Head Neck Surg **123**(4): 367-72.

Murphy, C., Doty, R.L., & Duncan, H.J. (2003). Clinical disorders of olfaction. Handbook of olfaction and gustation. R. L. Doty. New York, Marcel Dekker**:** 461-478.

Murphy, C., C. R. Schubert, et al. (2002). "Prevalence of olfactory impairment in older adults." Jama **288**(18): 2307-12.

Mygind N and Lildholt T (1997). Medical Management. Nasal polyps: epidemiology, pathogenesis and treatment. Tos M. Providence, RI: OceanSide Publications: 147-155.

Mygind, N., R. Dahl, et al. (2000). "Leukotrienes, leukotriene receptor antagonists, and rhinitis." Allergy **55**(5): 421-4.

Mygind, N. and T. Lildholdt (1996). "Nasal polyps treatment: medical management." Allergy Asthma Proc **17**(5): 275-82.

Nordin, S., A. Bramerson, et al. (1998). "The Scandinavian Odor-Identification Test: development, reliability, validity and normative data." Acta Otolaryngol **118**(2): 226-34.

Nordin, S., A. Bramerson, et al. (2003). "A Scandinavian adaptation of the Multi-Clinic Smell and Taste Questionnaire: evaluation of questions about olfaction." Acta Otolaryngol **123**(4): 536-42.

Norlander, T., K. M. Westrin, et al. (1996). "Experimentally induced polyps in the sinus mucosa: a structural analysis of the initial stages." Laryngoscope **106**(2 Pt 1): 196-203.

Ober, C., L. R. Weitkamp, et al. (1997). "HLA and mate choice in humans." Am J Hum Genet **61**(3): 497-504.

Oluwole, M., N. Russell, et al. (1996). "A comparison of computerized tomographic staging systems in chronic sinusitis." Clin Otolaryngol **21**(1): 91-5.

Pang, Y. T., O. Eskici, et al. (2000). "Nasal polyposis: role of subclinical delayed food hypersensitivity." Otolaryngol Head Neck Surg **122**(2): 298-301.

Pangborn, R. M., H. W. Berg, et al. (1964). "Influence of Methodology on Olfactory Response." Percept Mot Skills **18**: 91-103.

Parnes, S. M. and A. V. Chuma (2000). "Acute effects of antileukotrienes on sinonasal polyposis and sinusitis." Ear Nose Throat J **79**(1): 18-20, 24-5.

Ponikau, J. U., D. A. Sherris, et al. (1999). "The diagnosis and incidence of allergic fungal sinusitis." Mayo Clin Proc **74**(9): 877-84.

Ponikau, J. U., D. A. Sherris, et al. (2002). "Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis." J Allergy Clin Immunol **110**(6): 862-6.

Porter, R. H., J. M. Cernoch, et al. (1983). "Maternal recognition of neonates through olfactory cues." Physiol Behav **30**(1): 151-4.

Quint, C., A. F. Temmel, et al. (2002). "The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study." Acta Otolaryngol **122**(8): 877-81.

Radenne, F., C. Lamblin, et al. (1999). "Quality of life in nasal polyposis." J Allergy Clin Immunol **104**(1): 79-84.

Rowe-Jones, J. M. and I. S. Mackay (1997). "A prospective study of olfaction following endoscopic sinus surgery with adjuvant medical treatment." Clin Otolaryngol **22**(4): 377-81.

Scott, A. E. (1989). "Caution urged in treating 'steroid-dependent anosmia' [letter]." Arch Otolaryngol Head Neck Surg **115**(1): 109-10.

Scott, A. E. (1989). "Clinical characteristics of taste and smell disorders." Ear Nose Throat J **68**(4): 297-8, 301, 304-10 passim.

Scott, A. E. (1989). "Medical management of taste and smell disorders." Ear Nose Throat J **68**(5): 386, 388-90, 392.

Seiden, A. M. and H. J. Duncan (2001). "The diagnosis of a conductive olfactory loss." Laryngoscope **111**(1): 9-14.

Senior, B. A., D. W. Kennedy, et al. (1998). "Long-term results of functional endoscopic sinus surgery." Laryngoscope **108**(2): 151-7.

Settipane G A (1991). Nasal polyps. Rhinitis. S. G. A. Providence, Rhode Island, OceanSide Publication, Inc**:** 173-183.

Sharp, H. R., J. M. Rowe-Jones, et al. (1999). "The outcome of endoscopic sinus surgery: correlation with computerized tomography score and systemic disease." Clin Otolaryngol **24**(1): 39-42.

Shin, S. H., J. Y. Park, et al. (1999). "Clinical value of olfactory function tests after endoscopic sinus surgery;  A short-term result." Am J Rhinol **13**(1): 63-66.

Smith, D. B., T. Allison, et al. (1971). "Human odorant evoked responses: effects of trigeminal or olfactory deficit." Electroencephalogr Clin Neurophysiol **30**(4): 313-7.

Stammberger, H. (1999). "Surgical treatment of nasal polyps: past, present, and future." Allergy **54**(Suppl 53): 7-11.

Stammberger, H. and W. Posawetz (1990). "Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique." Eur Arch Otorhinolaryngol **247**(2): 63-76.

Stevens, M. H. (2001). "Steroid-dependent anosmia." Laryngoscope **111**(2): 200-3.

Stone, A. A. and J. M. Neale (1984). "New measure of daily coping: Development of preliminary results." Journal of Personality and Social Psychology **46**(4): 892-906.

Temmel, A. F., C. Quint, et al. (2002). "Characteristics of olfactory disorders in relation to major causes of olfactory loss." Arch Otolaryngol Head Neck Surg **128**(6): 635-41.

Temmel, A. F., C. Quint, et al. (2002). "Characteristics of olfactory disorders in relation to major causes of olfactory loss." Arch Otolaryngol Head Neck Surg **128**(6): 635-41.

Tos (1997). Early stages of polyp formation. Providence, Rhode Island, OceanSide Publications, Inc.

van Camp, C. and P. A. Clement (1994). "Results of oral steroid treatment in nasal polyposis." Rhinology **32**(1): 5-9.

Van Toller, S. (1999). "Assessing the impact of anosmia: review of a questionnaire's findings." Chem. Senses **24**: 705-712.

Varga, E., P. Breslin, et al. (2000). The impact of chemosensory dysfunction on quality of life, Chem Senses.

Weber, R., W. Draf, et al. (1997). "Endonasal microendoscopic pansinusoperation in chronic sinusitis. II. Results and complications." Am J Otolaryngol **18**(4): 247-53.

Wedekind, C., T. Seebeck, et al. (1995). "MHC-dependent mate preferences in humans." Proc R Soc Lond B Biol Sci **260**(1359): 245-9.

Vento, S. I., L. O. Ertama, et al. (2000). "Nasal polyposis: clinical course during 20 years." Ann Allergy Asthma Immunol **85**(3): 209-14.