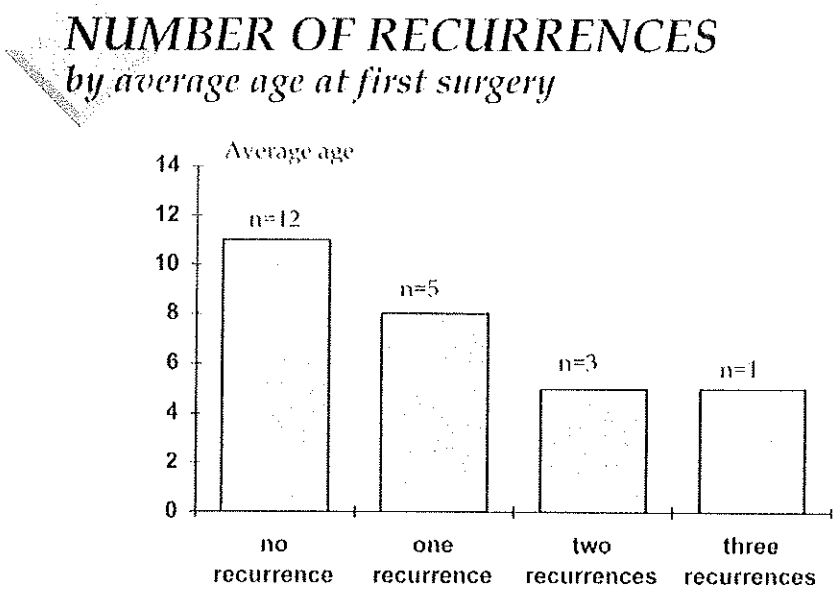

Fig. 19. Graph showing the number of children (n=21) and the number of recurrences (n=35) depending of the age at first surgery.

deviation had not been corrected, it would have continued to impair nasal breathing and would have made postoperative care on that side impossible), and three partial medial conchotomies were performed because of severe polypous degeneration of the middle turbinate.

Three to six months after surgery there was a 100% decrease of nasal obstruction (main preoperative complaint). The quality of sleep and the day-time somnolence was also improved in 100%. The complaints of headache had disappeared for the most part in 80%, but some patients still complained of partial or total anosmia (20%), rhinorrhea (40%) and recurrent spells of rhinosinusitis (65%). Rhinoscopy showed persistent purulent secretions in practically all children. Two patients showed no recurrence of polyps during that period, and 12 experienced limited recurrences. In 3 cases a massive recurrence was seen at 6 months after surgery, again resulting in severe nasal obstruction.

Long-term follow up averaged 7 years (9 months to 10 years). During that period, surgery was performed 35 times in 21 children (Fig. 19). Massive recurrence justifying repeated surgery was seen in 42% of the cases. Therefore, the number of operations for each child averaged 1.6 (1 to 4 operations). Twelve patients (58%) were completely free of recurrence and needed no further surgery. Seven children (33%) all younger than 10 years at the time of the first surgery showed recurrent massive polyposis. Three of these (14%) had more than one recurrence and one child had more than two recurrences. The duration between the first and the second surgery (average 1.5 years, 6 months to 4 years) was always shorter than between the second and third surgery (average 4 years, in three cases only), or between the third and the fourth surgery (4 years, in one case). Two older patients (9%) aged 12 and 15 years respectively at the time of the first surgery showed localized recurrence in the frontal recess as previously mentioned 3 and 7 years after the initial surgery.

Decision in favor of surgery

Stern et al. (1982) claimed that spontaneous and permanent disappearance of polyps occurs in 31% of the patients with massive polyposis in cystic fibrosis [10]. Such a statement makes any surgical intervention in cystic fibrosis children doubtful. Careful study of the natural history of massive polyposis in cystic fibrosis can refute such a statement. The authors of the current study had previously studied a population of 84 cystic fibrosis patients using endoscopy. They found medial bulging of the lateral nasal wall in 10 children (12%; 6 males and 4 females, mean age 5 years, range: 3 months to 8 years), and inflammatory polyps coming out of the middle meatus in 30 patients (45%; 28 males and 10 females, mean age 15 years; range 5-34

years) [93]. Such observations made of the prevalence of the disease in relation to age reveal something about the disease's natural history. It seems that the disease starts at an early age (0-10 years) with a medialization of the lateral nasal wall due to a mucopyosinusitis of the maxillary sinus, followed by nasal polyposis at a later age (5-20 years) and protruding from the middle meatus (mean age 15 years). Clement and Brihaye had seen CT evidence that at a later age some patients show a kind of spontaneous ethmoidectomy with limited polyposis. This observation supports Stern's statement, although Stern and colleagues never recorded a case of spontaneous and permanent disappearance of polyps. Therefore, as remarked, asymptomatic and minimally symptomatic patients with CF should not undergo sinus surgery, and extreme caution should be used before electing to operate on symptomatic patients with cystic fibrosis [115 117]. When facial deformation occurs in children with complete nasal obstruction (broadening of the nasal dorsum and development of a high arched palate due to mouth-breathing) resulting in a poor quality of life, surgery is the only option. The argument favoring simple polypectomy as a sufficient surgical option [86] in the context of an expected spontaneous improvement is opposed by a very high recurrence rate in the series of patients treated only with polypectomy (61% [91], 72% [86], and 87% [107]). When combining intranasal ethmoidectomy with Caldwell Luc, the recurrence rate dropped dramatically (12% [91] and 35% [108]).

The youngest patient ever operated upon in the literature was a 13 month-old girl [113]. She underwent surgery because of nasal obstruction caused by medial displacement of the lateral nasal wall. The same condition was seen in the current study in a 3 month-old boy, resulting in total nasal obstruction and stridor. Tunkel et al. (1994) called this condition "maxillary sinus mucocoeles." This condition, however, is not caused by mucocoeles, but by mucopyosinusitis. The mucosa of the maxillary sinus already shows polypous degeneration (not found in mucocoeles), and the lumen is filled with the typical putty-like purulent secretions. Because of ostial dysfunction the pressure in the maxillary sinus increases and the nasal lateral wall is displaced medially.

Parson (1992) stated that the extent of intranasal surgery of polyposis was found to be inversely proportional to the recurrence rate [115]. Even with a total sphenoidectomy, the recurrence rate will still be high if the follow-up time is long enough. Those articles that deal with long-term results (average of 2-3 years) showed recurrence rates of ±50 % [115 116 118]. The current study confirmed that the longer the follow-up, the higher the recurrence rate.

The average age of the 12 patients with no recurrence was 11 years, with 1 recurrence 8 years, with 2 recurrences 5 years, and the one with 3 recurrences was also 5 years of age at the time of the first surgery. Thus, the younger the child is at initial surgery, the higher the odds are to have a recurrence. Two factors may be responsible for this observation. First, an early nasal manifestation of cystic fibrosis may represent a more aggressive type of the disease, and/or second, it may also be that the aftercare in these young children (average 5 years of age) is very difficult and not adequate for preventing early recurrence (several sittings under general anesthesia are required for an adequate cleansing of the nasal cavity after surgery). The exception, however, confirms the rule. From Table IV it is clear that some children were operated on at a very young age for nasal polyposis and remained free of recurrence during a long follow-up time (one child underwent surgery for the first time at age 4 and was followed-up for 10 years).

Acetylsalicylic acid intolerance (Widal-Abrami Triad)

The first complete description of the "aspirin idiosyncrasy-asthma-nasal polyposis" syndrome (with a note on aspirin desensitization) was published in 1922 by F. Widal, P. Abrami and J. Lermoyez [119 120]. Since then, many clinicians and researchers have attempted to elucidate both the underlying mechanisms of the "triad". The prevalence of analgesic intolerance (AI) is less than 1% in the general population and much more common in certain risk groups of patients who have bronchial asthma, chronic urticaria and nasal polyps, where it is 10% in asthmatic patients. The condition where AI and asthma are seen together is classically known as "aspirin-induced asthma" or "Samter's Syndrome" [121], and recently called "analgesic-induced asthma" (AIA). In the classical description of this syndrome, rhinitis starts first and is later accompanied by nasal polyps, asthma and AI. In some cases, AI may be the first disorder to appear [122-124].

Arachidonic acid metabolism differences

In vitro leukotriene (LTC4/D4/E4) release from blood leukocytes is very different in normal individuals, nasal polyp patients, and Widal-Abrami triad subjects after pre-incubation with IL-3, and incubation with C5a and aspirin (10 or 100 µg/ml). With 10 µg/ml of aspirin, the concentration of leukotrienes was ~751 pg/ml in normal individuals, ~343 pg/ml in nasal polyp patients, and ~2196 pg/ml in Widal-Abrami patients (p=0.0006); with 100 µg/ml, the numbers were ~268, 412, 1701 pg/ml (p=0.005) respectively [125].

When studying the generation of eicosanoids by epithelial cells in patients with nasal polyposis and rhinosinusitis (aspirin-tolerant, ASA-TRS) and in Widal-Abrami triad subjects (aspirin-intolerant, ASA-IRS), Marek Kowalski et al. found that unstimulated epithe-

Table IV. Flow chart of 20 children with cystic fibrosis and nasal polyposis showing at what age each ethmoidectomy and recurrence surgery was performed. The last column shows the duration of the follow-up in years for each individual child.

Age at 1st operation	Age at 2nd operation	Age at 3rd operation	Age at 4th operation	Average follow up time (in years)
0	3			6
2				4
4				4
4				10
4	4			7
4	4	10		10
4	5	10		8
5	8	10	14	12
6	7	11		10
6	10			8
6				5
7				2
10				2
10				6
11				5
13				3
14				12
15				5
15				8
27				5
			Mean	6.6

lial cells from ASA-IRS generated significantly less prostaglandin E2 (PGE-2) compared with ASA-TRS: ~0.8 ng/µg dsDNA vs. ~2.4 ng/µg dsDNA respectively. Basal levels of 15-hydroxyeicosatetraenoic acid (15-HETE) were very different after cell incubation with aspirin for 60 minutes, with a significant increase (~ +359%) in 15-HETE generation only in ASA-IRS patients, and no effect on ASA-TRS [126].

Exogenous PGE-2 given by inhalation almost completely abrogates aspirin-induced asthma and the accompanying increase in leukotriene production. A Catalan group studied the cyclooxygenase-2 (COX-2) mRNA expression in ASA-IRS and ASA-TRS patients. COX-2 mRNA expression in ASA-IRS group was seven-fold ($p<0.0001$) lower in nasal polyps, and six-fold lower ($p<0.01$) in nasal mucosa when compared to ASA-TRS, suggesting an inadequate COX-2 regulation in Widal-Abrami triad patients [127].

Önerci and Kalyoncu studied the clinical features of analgesic induced asthmatic patients and determined the rate of polyp surgery in a series of 247 patients during the period between January 1991 and June 2000. Demographics, clinical and laboratory data collected are displayed in Table V. Routine skin prick tests (unless contraindicated) and serum total IgE levels were performed in all patients. Bronchial asthma was diagnosed by anamnesis according to international guidelines. The diagnoses of analgesic intolerance and analgesic-induced asthma were made according to history. A sufficient and reliable clinical history of at least 2 events was required for AI. The reaction should have occurred within 3 hours after the ingestion of the analgesic. In the case of only one event, confirmation by oral provocation test was required. Oral provocation tests were performed in the selected patients with the purpose of determining the analgesics that they could use safely. Data on analgesic intolerance are shown in Table VI. Surgery was performed in 61 patients. 56 patients had prior surgeries at other institutions; these operations included sinonasal polypectomy, Caldwell-luc, intranasal ethmoidectomy, sphenoidotomy, external ethmoidectomy, frontal sinus trephination, frontal sinus obliteration with osteoplastic flap. Thirty-two patients underwent conservative surgery and 29 patients underwent extended surgery. During the early postoperative period, sinonasal symptoms improved in all patients. Asthma improved in all but one patient. The worsening of asthma in this patient after surgery despite patent nasal airways might be explained by inspiration of unhumidified, unfiltrated, unwarmed air into the lungs, or postnasal discharge, or sinopulmonary reflex. Twenty-seven patients required revision surgery. The indications for revision surgery were: nasal ob-

Table V. Demographic, clinical and laboratory characteristics of the analgesic-induced asthma patients.

	N = 247
• Age	41.2 ± 12.4
• Gender (Females)	179 (72.5%)
• Beginning ages for (mean ± SD)	
Rhinosinusitis	27.5 ± 11.2
Bronchial asthma	31.5 ± 12.3
Nasal polyp	33.3 ± 12.0
Analgesic intolerance	35.8 ± 12.2
• Asthma severity	
Mild	79 (32%)
Moderate	126 (51%)
Severe	34 (17%)
• Accompanying disorders	
Rhinosinusitis	193 (78.1%)
Nasal polyps	85 (34.4%)
Food allergy/intolerance	57 (23.1%)
Antibiotic allergy/intolerance	39 (15.8%)
Metal allergy	27 (10.9%)
Dermographism	26 (10%)
Chronic urticaria	16 (6.5%)
• Familial history of atopy	148 (59.9%)
• Familial history of analgesic intolerance	21 (8.5%)
• Skin prick test performed	205 (83%)
• Positive reaction among the patients tested	61 (24.7%)
Mite sensitivity	36 (14.6%)
Pollen sensitivity	25 (10.1%)
Animal dander sensitivity	7 (2.8%)
Fungus sensitivity	4 (1.6%)
• Log$_{10}$ of total serum IgE	1.82 ± 0.59
• Keeping pets	24 (12.6%)
• Smoking status (ever smoked)	59 (23.9%)

struction, increased complaints of asthma, posterior nasal discharge, recurrence of diffuse polyposis and recurrence of complaints after cessation of systemic corticosteroids. Despite postoperative marked reduction of asthma, 82% of this group required asthma treatment during postoperative follow-up. Twenty-nine patients underwent extended surgery. In this group, five patients required revision surgery due to disease in the maxillary sinus or in the frontal recess. No worsening of asthma occurred. Only two patients required asthma treatment during follow-up care. Failure in revision cases was explained by factors summarized in Table VII.

Önerci and Kalyoncu's study concluded that analgesic-induced asthma is more common in middle-aged females. Also, some diseases accompany this condition such as rhinosinusitis, nasal polyps, food allergy/intolerance, metal allergy and chronic urticaria as reported previously, and with which our current results are in accordance. The beginning ages for rhinosinusitis, asthma, nasal polyps, and analgesic intolerance were 27.5±11.2, 31.5±12.3, 33.3±12.0 and 35.8±12.2, respectively, in which the order of appearance is also in accordance with the literature. Intolerance to aspirin, metamizole and acetaminophen are most common which may be due to their common use. It is important to suggest alternative analgesics to the analgesic intolerant asthmatics, most of whom are frightened to use any analgesic even when they have severe pain. Oral provocation tests should be performed before recommending an analgesic to these patients. At least one alternative analgesic was found for the tested patients, and the safety profiles of nimesulide, meloxicam, and rofecoxib are similar to that of codeine and acetaminophen.

Surgery on the sinuses and nasal airways reduces asthmatic medication requirements and the frequency of hospitalization for asthma following surgery. Ther-

Table VI. Data on analgesic intolerance

• Patients oral provocation tests performed	135 (34.7%)
No. of tests with aspirin and no. of positive ones	5-4
No. of tests with acetaminophen and no. of positive ones	50-14
No. of tests with metamizole and no. of positive ones	3-2
No. of tests with naproxen and no. of positive ones	0-0
No. of tests with codeine and no. of positive ones	86-7
No. of tests with sodium salicylate and no. of positive ones	14-4
No. of tests with nimesulide and no. of positive ones	43-9
No. of tests with meloxicam and no. of positive ones	35-4
No. of tests with rofecoxib and no. of positive ones	13-1
• Intolerance with history	
Aspirin	168 (68%)
Metamizole	126 (51%)
Acetaminophen	50 (20.2%)
Naproxen	49 (19.8%)
Other	26 (10.5%)
• Refractory period (from ingestion of the drug to the	38.5 ± 42.8
• emergence of the reaction in minutes)	
• Emergency room referrals in the last year due to analgesic intolerance	127 (51.4%)
• Type of reaction (with clinical history)	
Bronchospasm	166 (67.2%)
Urticaria	73 (29.6%)
Angioedema	65 (26.3%)
Anaphylaxis	21 (8.5%)
Rhinitis	15 (6.1%)
Gastrointestinal symptoms	4 (1.6%)

Table VII.

- Insufficient ethmoidectomy
- Insufficient opening of anterior wall of sphenoid sinus
  - Decreased ventilation
  - Decreased drainage
  - Insufficient drug concentration
  - Insufficient cleaning
- Insufficient surgery of the frontal sinus
  - Polyps at the frontal recess and frontal ostium area
  - Polyps and mucoceles in the frontal sinus
  - Stenosis of frontal ostium
- Insufficient surgery of the maxillary sinus
  - Insufficient maxillary sinus ostium
  - Reclosure of the ostium
  - Decreased ventilation and drainage
  - Insufficient drainage due to thick secretions .
  - Insufficient cleaning
- Insufficient removal of septa
  - Insufficient drug concentration behind the septa
  - Insufficient cleaning of the polypoid mucosa behind the septa
  - Pool for collection of secretions
  - May be the focus for polyp regeneration
- Free bony spicles, granulation tissue and polyp recurrence

apeutic intervention of sinonasal disease has an impact on the lower airways. An extended approach appears to offer a significant advantage over conservative treatment for those ASAI patients requiring surgical management for severe diffuse nasal polyposis.

Quality of life

To assess the quality of life in patients with nasal polyposis, Radenne et al. [128] used the SF-36 questionnaire. The study clearly demonstrated that nasal polyposis impairs quality of life, supporting the claims of patients with nasal polyposis when they express their difficulties with daily activities. Comparison of quality of life profile between perennial allergic rhinitis and nasal polyposis showed that the impact of nasal polyposis on life is globally more important than the impact of rhinitis. Limitations of physical and mental activities were insignificant when comparing both conditions. Nasal polyposis did not seem to cause more waste of working time nor did it alter daily physical activities more significantly than perennial rhinitis. Both conditions involve the same nasal symptoms, but anosmia and nasal obstruction are greater in nasal polyposis. The consequences of greater degrees of anosmia and nasal obstruction in nasal polyposis could explain the differences in the quality of life scores between the two nasal inflammatory diseases. Indeed, headaches, snoring, and sleep disorders are caused by nasal obstruction [129] and could explain the higher score of body pains and the poorer scores of vitality and social functioning in patients with nasal polyposis compared to patients with perennial allergic rhinitis.

Interestingly, the treatment of nasal polyposis (e.g., nasal topical corticosteroids, endonasal surgery) improved both symptoms (anosmia and obstruction) even without objective changes in pulmonary function tests [128].

Another study by Dunlop et al. enrolled 50 asthmatic patients with a history of either chronic rhinosinusitis or nasal polyposis. 12 months after endoscopic sinus surgery, 20 patients felt that their asthma control had improved postoperatively, 20% used less steroid inhaler, and 28% less bronchodilator inhaler. Significant reductions in oral steroid requirements ($p<0.001$) and hospitalization for asthma ($p<0.025$) were also recorded postoperatively. There was no evidence for a worsening of asthma after nasal polypectomy [130].

Senior BA et al. performed a study to assess the long-term impact of functional endoscopic sinus surgery (FESS) in patients with chronic rhinosinusitis and asthma at an average follow-up of 6.5 years. 30 patients who responded reported a history of asthma. Of these, 27 (90%) reported that their asthma was better than it had been before FESS, 6.5 years ago. Average reported improvement increased from 49% at 1.1 year after surgery to 65% at 6.5 years after FESS. Asthma attacks declined in 20 of 27 (74.1%). Half reported less inhaler usage, and 2/3 less oral steroid use. A combination of FESS, careful postoperative care, and appropriate medical therapy for rhinosinusitis has a favorable long-term effect on asthma in patients with symptomatic chronic sinusitis. In this study asthma severity, frequency of attacks, and need for medication were all improved [131].

Bousquet and colleagues showed that the quality of life in subjects with nasal polyposis associated with asthma was worse than that found in subjects with nasal polyposis alone. Quality of life scores in asthmatic patients without nasal polyposis are better than those of our patients with isolated nasal polyposis, suggesting that nasal polyposis impairs quality of life to a higher degree than asthma. However, nasal polyposis and asthma seem to have a cumulative negative effect on the quality of life [132, 133].

Diagnosis of nasal polyposis

Nasal polyposis remains a significant challenge to the treating physician. Nasal endoscopy provides a tool by which the clinician can accurately diagnose, meticulously and atraumatically perform surgery, and provide precise postoperative care and follow-up for patients with nasal polyp disease. There are two main problems regarding the diagnosis and sequelae of nasal polyposis. The first problem is a large number of undetected, i.e., overlooked, polypous diseases of the ostiomeatal complex itself due to the fact that nasal endoscopy has not yet become a routine procedure in all ENT departments in different countries, and particularly because in a certain number of patients it is not always easy to insert the endoscope into the ostiomeatal complex to perform a precise examination. The second problem lies in declaring the etiology of the findings of nasal polyposis, whether obvious or hidden polyposis.

Although many nasal polyposis patients are asymptomatic, nasal obstruction is the main symptom that surfaces. Nasal blockage in nasal polyposis is multifactorial: mechanical bulk of the polyp tissue, pathological state of nasal mucosa with mucosal swelling and edema, associated with or underlying a chronic rhinosinusitis, and lastly the possibility of septal deviation. By evaluating the obstructive symptoms of nasal polyposis, the pathological cause of the disease can be determined and treated accordingly.

Extent of nasal polyposis

With respect to the mechanical bulk of the polyp tissue itself, there are various classifications of the extent of nasal polyposis within the nasal cavity.

In 1995 the International Committee on Sinus Disease, Terminology, Staging and Therapy [134] recommended a ternary system of staging depending on whether the polyps are within or outside of the middle meatus. Thus, Stage 0 is no polyps; Stage 1 confines them to middle meatus; and Stage 2 describes them as extending beyond the middle meatus. This classification suffers from a lack of accuracy once the polyps prolapse beyond the middle meatus. Lildholdt [135] used the inferior turbinate as a reference point, thus differentiating between polyps lying between the middle turbinate and upper edge of the inferior turbinate and those (Stage 4) which extend below the root of the inferior turbinate towards the floor of the nose.

In patients with gross intranasal polyposis, the diagnosis is self-evident. Some unfortunate patients will have an external expansible deformity of their nose or the polyps may prolapse externally from their nostrils. A CT scan will almost certainly show sinus opacification or "whiteout" (Stage 4). Here, nasal endoscopy and rhinomanometry will have little role to play.

However, such cases are unusual and the majority of patients will present with Grade 1 polyps or polyps lying just outside the middle meatus. Nasal endoscopy and rhinomanometry have a very important role in determining the management of these patients.

Rhinomanometry

Rhinomanometry has had a long and controversial history in rhinology. Its usefulness, accuracy, and advantages have been utilized and championed by many clinicians [136-142], whereas others have found it of little or no use [143-148]. The test has been used extensively in both clinical and research activities. Clinically, it provides an objective measurement of nasal function, giving the clinician an indication of the degree and cause of nasal obstruction. It measures nasal reactivity in challenge in the field of allergic rhinitis and also has been utilized to assess pre- and postoperative surgical results in outcome studies. It is also important in providing an objective measurement of nasal function in medico-legal controversies.

Kane evaluated the role of rhinomanometry in nasal polyposis. A study was created in which 40 consecutive patients who were referred with Grade 1 nasal polyps (confined to middle meatus) were enrolled. Rhinomanometric evaluation was performed both pre-operatively and six months post-operatively. An outcome tool was also utilized, which in this case was Jay Piccirillo's Sino-Nasal Outcome Test 20 (SNOT 20) [149-151]. This form was filled out in the pre-op period and then six months postoperatively. Active anterior rhinomanometry was performed in all patients using an Atmos 300 Rhinomanometer. The test was performed in a warm room with the patient in an upright sitting position after an appropriate period of rest as recommended by the International Standardisation Committee [152]. Measurements of nasal resistance were taken in base-line condition and 10 minutes after topical vasoconstriction with phenylephedrine (0.5%). No patients had used any decongestant medications orally or topically 24 hours prior to measurement. Only patients in whom active anterior rhinomanometry could be utilized were included in the study. Patients with a septal perforation or complete obstruction on one side due to a severe deviated nasal septum were excluded. The nasal resistance was measured at 150 Pascals as recommended by the Standardisation Committee. The demographic details of the patients are depicted in Table VIII. Three primary comparisons in this study were pre-operative and post-operative pre-sprays for left and right flow (Fig. 20); pre-operative and post-operative pre-sprays for total resistance (Fig. 21) and SNOT 20 pre- and post-operative scores (Fig. 22). Scores for individual pre-operative right and left nasal resistance compared to post-operative right and left resistance were also made (Figs. 23a and 23b). The most important measurement of this study is the one between the resting pre-operative pre-spray total air-flow and nasal resistance values and the post-operative pre-spray total airflow and nasal resistance values; these have been demonstrated to have been statistically improved ($p<0.0005$ and 0.003 respectively). Unilateral nasal resistance on both sides of the nose also showed statistically significant improvement. If the rhinomanometry assessment was lacking clinically relevant septal deflections, particularly in the valvular area, this would have become manifest as unsatisfactory unilateral nasal resistance improvement values (Table IX). Kane concluded that rhinomanometry offers great assistance in the assessment of patients with nasal polyposis, particularly in allowing clinicians to decide whether a septoplasty is necessary or not in patients who require functional endoscopic sinus surgery.

Tab. VIII. The demographic details of the patients in the study by Kane.

Demographics	
• N.	40
• Male	26
• Female	14
• Age 26 years - 75 years Avg. 51 years	
• Hayfever	14
Asthma	14
• Smokers	4
• ASA sen.	2
• Previous surgery	18
(Septoplasties	14)

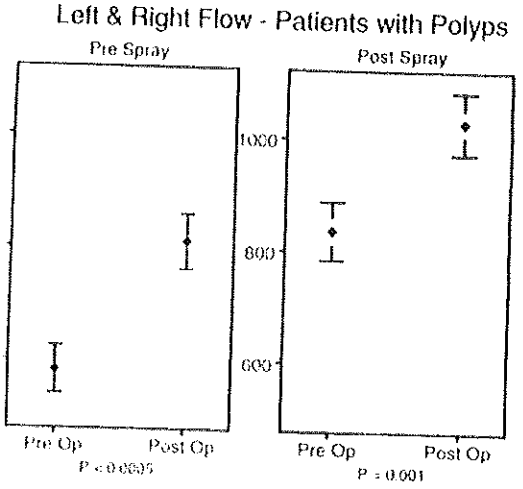

Fig. 20. Preoperative and postoperative pre-sprays for left and right flow.

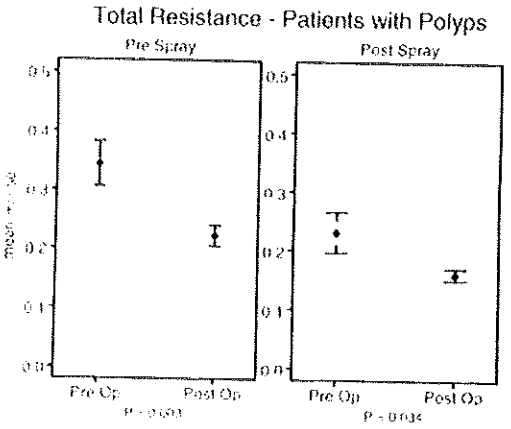

Fig. 21. Preoperative and postoperative pre-sprays for total resistance.

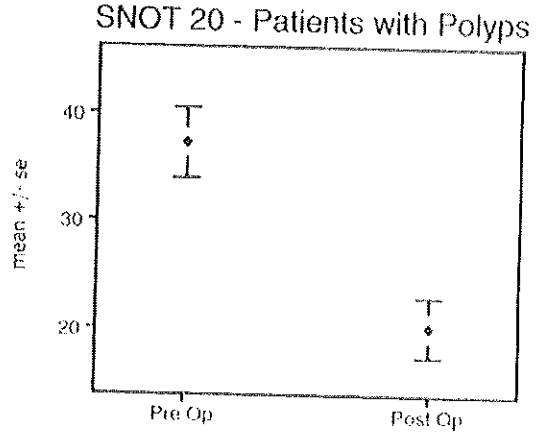

Fig. 22. SNOT 20 pre- and postoperative scores.

Pulmonary function tests

In most of the cases of so-called hidden polyposis, the patient suffers from impaired nasal breathing despite apparently normal endonasal findings and no visible morphological obstruction inside the nose. This is due to the lack of the respiratory receptors in the ostiomeatal mucosa, which is damaged by polypous degeneration both at the lateral surface of the middle turbinate and at the lateral nasal wall. The receptors in healthy mucosa seem to be responsible mostly for the normal subjective feeling of good nasal breathing and objective depth of pulmonary breathing (nasopulmonary reflexes) [53]. The receptors are usually replaced by degenerated, polypous or polypoid mucosa. Ogura found evidence of a relationship between nasal obstruction and pulmonary function. It appeared that there was an increase in pulmonary resistance that was directly related to the degree of nasal obstruction [54,55]. It was postulated that a nasopulmonary reflex with the vidian nerve as the afferent limb and the vagus nerve as the efferent limb would account for the observed physiological changes. The clinical corollary of the increased pulmonary resistance and the decreased compliance was a reduction in the PO_2 of the arterial blood, a reduction of FEV_1 (forced expiratory volume in one second), and an alteration of the flow-volume loop study. However, the theoretical model for these changes resulting from nasal obstruction began to unravel with the report by Whicker [55-59].

In a later clinical work the pulmonary function test results were carefully studied in ten healthy subjects with posterior nasal pack. No significant changes were recorded in lung volumes, flow rates or alveolar gas exchange. Aspiration, sedation, and pulmonary reserve were hypothesized to account for previous observation of hypoxemia in patients with nasal obstruction [60,61].

Other proposed mechanisms for explaining how nasal obstruction and polyposis aggravate pulmonary function are:

1) aspiration of the infected nasal secretions during sleep;
2) drying of the mucosa of the lower respiratory system during prolonged periods of oral respiration due to nasal obstruction;
3) production of bacterial toxins, which induce partial inhibition of the β2-receptors;
4) production of cytokines and other inflammatory

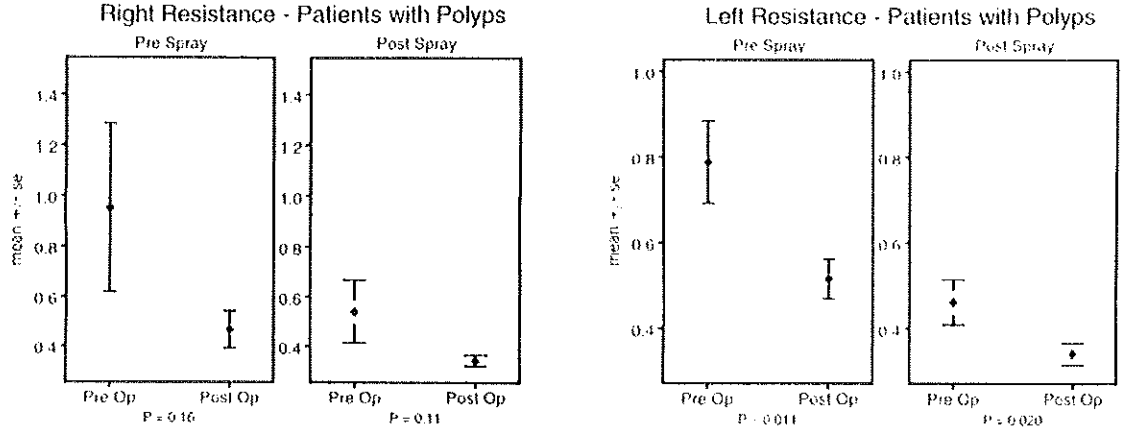

Fig. 23. Scores for individual preoperative right and left nasal resistance compared to postoperative right and left resistance.

Table IX.

Variant to compare pre and post surgery	P Value	Estimated difference
Total leftc and right flow	< 0.0005	230
Total resistance	< 0.003	0.13
SNOT 20	< 0.0005	17

All P-values reported are based on two-sided tests and are not formally adjusted for multiple comparisons. 95% confidence intervals have been reported. All analyses were performed using the SPSS statistical software. Graphs were plotted using the S-PLUS statistical package.

mediators (derived from monocytes, eosinophils and other cells implicated in the inflammation) in the nasal polyps and the paranasal sinuses.

Simaskos and colleagues studied a series of 14 asthmatic patients who underwent surgery for nasal polyposis with the FESS procedure and were followed for an average of 6 months before the operation and 12 months postoperatively. The following parameters were estimated: (1) the functional spirometric tests, i.e., FEV_1, FVC (Forced Vital Capacity), FEF25%-75% (mid-expiratory phase of the Forced Expiratory Flow); (2) the frequency of asthma exacerbations and the number of days of hospitalization required for their cure; (3) the frequency of systemic use of corticosteroids; (4) the daily frequency of the "as required" use of bronchodilators (β2-agonists, ipratropium bromide etc.); and (5) the overall condition of the upper respiratory way: nasal obstruction, rhinorrhea, posterior nasal discharge, coughing, sneezing, and olfaction.

Among the 14 patients, an improvement in the functional pulmonary tests was measured in seven, four showed a slight aggravation, and only three demonstrated an obvious improvement (FEV_1 20.78%-28.51%, FVC 18.89%-26.43%, FEF25%-75% 13.35%-18.54%) (nine of the 14 patients needed to be hospitalized postoperatively because of asthma exacerbations, but the average number of days required for hospital treatment was lower than preoperatively (3.5 versus 4.16) (Tables X, XI and XII). The frequency of inhaled steroid use was significantly decreased in three patients, and control of asthma without steroids was achieved in one patient 5 months after the operation. The frequency of asthma crises and the "as required" use of bronchodilators per month was decreased in three out of the 14 patients. Concerning the symptoms of the upper respiratory pathways, improvement of the nasal obstruction as well as the sense of olfaction and cough was attained in all 14 patients. In ten of these, a decrease of anterior rhinorrhea was reported. Reduction of the posterior nasal discharge and/or sneezing was noticed in 12 out of 14 patients.

Among the 14 patients who underwent surgery in that study, a high percentage showed amelioration of the

Table X. Differences in FEV_1 before and after FESS.

Patient no.	FEV_1 before	FEV_1 after	DIF	%
1	2.15	2.2	0.05	2.32%
2	2.83	2.98	0.15	5.3%
3	2.57	2.63	0.06	2.33%
4	3.1	2.98	-0.12	-3.87%
5	2.8	2.87	0.07	2.5%
6	2.74	2.68	-0.06	-2.18%
7	2.79	3.37	0.58	20.78%
8	3.67	4.5	0.83	22.61%
9	2.22	2.18	-0.04	-1.8%
10	2.59	2.5	-0.09	-3.47%
11	2.42	3.11	0.69	28.51%
12	3.29	3.34	0.05	1.54%
13	2.65	2.77	0.12	4.52%
14	2.79	2.98	0.19	6.81%

Table XI. Differences in FVC before and after FESS.

Patient no.	FVC before	FVC after	DIF	%
1	3.97	4.29	0.32	8.06%
2	4.05	4.23	0.25	6.17%
3	3.49	3.65	0.16	4.58%
4	4.59	4.37	0.22	4.79%
5	3.37	3.52	0.15	4.45%
6	3.28	3.12	0.16	4.87%
7	3.87	4.68	0.81	20.93%
8	3.97	4.72	0.75	18.89%
9	2.95	2.73	0.22	7.45%
10	3.11	3.02	0.09	2.89%
11	3.25	4.11	0.86	26.43%
12	4.28	4.32	0.04	0.93%
13	3.32	3.48	0.16	4.81%
14	2.89	2.96	0.07	242%

Table XII. Differences in FEF25%-75% before and after FESS.

Patient no.	FEF25%-75% before	FEF25%-75% after	DIF	%
1	1.25	1.28	0.03	2.40%
2	3.17	3.25	0.08	2.52%
3	2.95	3.02	0.07	2.37%
4	2.88	2.76	-0.12	-4.16%
5	2.25	2.36	0.11	4.88%
6	2.97	2.79	0.18	-6.06%
7	3.02	3.58	0.56	18.54%
8	3.52	3.99	0.47	13.35%
9	2.67	2.51	-0.16	-5.99%
10	2.83	2.72	-0.11	-3.88%
11	2.69	3.14	0.45	16.72%
12	2.65	2.81	0.16	6.03%
13	2.58	2.62	0.04	1.55%
14	2.76	2.87	0.11	3.98%

subjective parameters concerning the function of the upper respiratory airways. On the other hand, only a low percentage demonstrated significant improvement of the objective parameters concerning asthma (FEV_1, FVC, FEF25%-75%, number of days of hospitalization for asthma crises, frequency of systemic use of corticosteroids, frequency of asthma exacerbations, and use of bronchodilators per month). These outcomes can not support the statement that surgery definitively improves pulmonary function in patients suffering from nasal obstruction and chronic obstructive pulmonary disease, whereas a positive result can be anticipated postoperatively.

Accordingly, by removing polyps from nasal and paranasal cavities, we would expect an improvement of the coexisting asthma and/or lower airway disease. Nevertheless, in several cases, the results from the surgical treatment of patients suffering from nasal obstruction and asthma are not the ones anticipated. For example, concerning the postoperative aggravation of asthma in the above patients, it was proposed that inflammatory mediators were liberated during the polypectomy.

In the bibliography, the surgical treatment of nasal obstruction due to nasal polyposis shows controversial results when there is a history of coexisting asthma [130,162,169].

It is also known that humidification of the inhaled air produces only moderate symptomatic relief in patients suffering from lung disease. Thus, nasal obstruction inducing drying of the respiratory mucosa and inhalation of improperly warmed air can, to some extent, influence the symptoms of the bronchial dysfunction, but the drying of the mucosa itself does not constitute an adequate explanation of the relation between lung disease and nasal polyposis. The hypothesis of partial b-blockade was proposed by Szentivanyi [170], but no likely causative bacterial toxins have been demonstrated in the upper and lower airways of patients with asthma.

Furthermore, sinonasal levels of nitric oxide in rhinitis patients are several times higher than those in the lungs of the asthmatics. It has recently been found that nitric oxide output reflects the clinical severity of asthma; thus, it could be a relevant inflammatory mediator which can easily pass from the nose to the lungs.

Drug therapy of nasal polyposis

The treatment of nasal polyps is controversial. Surgical removal of nasal polyps is associated with discomfort and risks for the patient but is still the treatment of choice for most otorhinolaryngologists. Medical management alone has been little investigated. The objectives of management are to: 1) eliminate rhinitis symptoms, 2) reduce the size of polyps, 3) re-establish nasal airway and nasal breathing, 4) improve or restore the sense of smell, and 5) prevent recurrence of nasal polyps.

Corticosteroid treatment

Corticosteroids are the only type of drug intervention with a proven effect in nasal polyposis. At a cellular level, corticosteroids cause a reduction in the number of antigen-presenting cells, in the number and activation of T cells, in the number of epithelial mast cells, and in the number and activation of eosinophils [124]. Corticosteroids probably relieve symptoms by down-regulating the expression and production of cytokines, such as IL-5, which effectively reduce the inflammation and the number of eosinophils [132].

Intranasal corticosteroid treatment

Intranasal corticosteroids are, by far, the best documented type of treatment for nasal polyposis. There are at least 16 placebo-controlled studies, all of which have shown a significant clinical effect. However, intranasal corticosteroids do not solve all problems for a number of patients with nasal polyposis. This is understandable considering the limited intranasal distribution of a spray [173] as compared to the involvement of the entire nasal and paranasal mucous membranes in this disease.

Betamethasone and dexamethasone are not mentioned in this review, as they, in contrast to modern corticosteroid molecules, exert a significant systemic effect and may work both by a local and a systemic mode of action.

Responsiveness to intranasal corticosteroids

Some patients with nasal polyps apparently do not respond to intranasal corticosteroids, which can have two reasons. First, the disease may be genuinely unresponsive to corticosteroids. This may apply to cystic fibrosis, primary ciliary dyskinesia and other diseases, characterized by noneosinophil-dominated inflammation [174]. Second, the disease can be temporarily unresponsive to intranasal corticosteroids due to inadequate intranasal distribution of the spray in a very blocked nose. An initial negative result with topical therapy, therefore, does not preclude a beneficial effect of systemic corticosteroid treatment and subsequent intranasal therapy [175].

Effect on rhinitis symptoms

While all studies of intranasal corticosteroids have shown an effect on nasal blockage, the effect on sneezing and secretion has varied, probably because many patients predominantly suffer from blockage with little sneezing and rhinorrhea. The overall symptom reduction is about 50% [176, 177]. Two open studies of one-year intranasal treatment have shown that the anti-rhinitis effect is maintained during treatment and that symptoms only slowly recur when the treatment is discontinued [178]. Although corticosteroids do not cure the disease, long-term therapy may break a vicious circle and have a long-lasting efficacy, especially in mild cases.

While intranasal corticosteroids can usually completely control the symptoms of allergic rhinitis, nasal polyposis, involving the entire nasal and paranasal mucosa, is more difficult to control exclusively by local medication.

Reduction in polyp size

Disappearance of nasal polyps is an obvious goal for therapy. A considerable reduction of polyp size may be sufficient to render some patients symptom-free, but even small polyps in the upper part of the nose may reduce the sense of smell and compromise ostiomeatal function, leading to pathology of the paranasal sinuses. It is doubtful whether such polyps are hit by a spray, which probably cannot reach the origin of most polyps in the middle meatus [179]. A rhinoscopic judgement of polyp size, made by different investigators and at different time points, is not reliable as a semiquantitative parameter unless well-defined criteria of polyp size are used. Johansen et al. defined three degrees of nasal polyposis dependent upon whether the largest polyp is above the upper edge of the inferior turbinate, between the upper and lower, or beneath the lower edge [177]. Using these criteria, Johansen et al. found a clear reduction in polyp score during intranasal treatment with budesonide, while Lildholdt et al. found a decrease in the mean polyp size in 52% of budesonide-treated patients compared with 21% in the placebo group [176]. Drettner et al. who gave beclomethasone dipropionate aerosol after polypectomy, stated that "polyps never disappeared completely" [180].

Open nasal airway and nasal breathing

Nasal breathing is a minimum demand on therapy, but a patent nasal airway is not necessarily a normal airway. Pressure from long-standing nasal polyps may have changed the normal slit-like cavity to a wide tube in the lower part of the nose and the same may require surgical treatment. The patient's evaluation of the symptom, nasal blockage, is subjective. In one study, the symptom score for blockage decreased 25% in the placebo group and 65% in the corticos-

teroid group [83]. It is important to add an objective and quantitative measure of nasal patency. A series of placebo-controlled studies have shown increased nasal patency during active therapy, measured by nasal peak flow [17,19,80,82,84], rhinomanometry [85], and acoustic rhinometry [86].

Sense of smell

Loss of the sense of smell, and with that "taste," caused by polyp obstruction of the upper part of the nasal cavity, is a very annoying symptom for most polyp patients. Clinical experience indicates that the effect of intranasal corticosteroids, in contrast to systemic administration, is poor, but unfortunately controlled studies have paid little attention to this symptom. Naggar et al. measured the olfactory function before polypectomy and after a six-week course of beclomethasone dipropionate [87]. The authors conclude that the corticosteroid spray had no effect on the sense of smell. A study of budesonide has shown a significant but modest effect on the sense of smell [88]. Also Jankowski et al. have found a significant, although moderate, effect of budesonide spray on the sense of smell [89].

Recurrence of polyps

Although small polyps may become invisible during intranasal therapy, they may not be completely eliminated from the upper part of the nasal cavity and the middle meatus, not hit by a nasal spray. Three controlled studies of intranasal corticosteroid treatment following surgery have all shown delayed recurrence of symptomatic polyps and reduced need for repolypectomy [19,90,91]. While the reappearance of nasal polyps can be prevented in some cases, the frequency of relapses is merely reduced in other cases, which probably are characterized by a more active inflammation in the nasal and paranasal mucosa.

It is definitely proven that intranasal corticosteroid treatment can reduce polyp size and associated nasal symptoms. Treatment after polypectomy significantly reduces the number of recurrences, which is especially valuable in patients who have previously been subjected to frequent polypectomies.

While intranasal corticosteroids can usually completely control the symptoms of allergic rhinitis, nasal polyposis, involving the entire nasal and paranasal mucosa, is more difficult to control exclusively by local medication. When polyps are large, polypectomy or short-term systemic corticosteroids will improve the intranasal distribution of a corticosteroid spray. Such therapy can be necessary in order to open a blocked nose, for example, when the patient catches a cold or contracts a bacterial sinusitis resulting in a temporary failure of intranasal therapy. There is good reason to use intranasal corticosteroids in many patients with nasal polyposis, with the possible exception of patients without rhinitis symptoms who have had a few polyps removed for the first time [89]. A number of such patients will not experience more symptoms and, consequently, they will not need further treatment [84].

The following speaks in favor of starting intranasal corticosteroid treatment: 1) daily rhinitis symptoms, 2) repeated polypectomies, 3) severe disease with massive involvement of the mucous membranes in the nose and paranasal sinuses, 4) blood eosinophilia, 5) asthma, 6) intolerance to acetylsalicylic acid and other NSAIDs [92], and/or 7) patient's preference for medical therapy. In moderately severe disease, intranasal corticosteroids may be used for 3- to 6- month periods, while patients with severe disease may benefit from constant daily treatment for as long as the disease persists.

With regard to safety, intranasal corticosteroids are the best studied form of rhinitis treatment, having been used for 25 years with no reports of any serious adverse events [93–96].

Systemic corticosteroid treatment

Investigation of systemic corticosteroids in rhinitis in general, and in polyposis in particular, has been remarkably insufficient, probably because of lack of interest and support from the pharmaceutical industry.

There are only two randomized but not double-blind studies describing the effect of systemic corticosteroids in nasal polyposis. In their first study, Lildholdt et al. randomized 53 patients to either surgical removal of visible polyps with a snare or a depot injection of corticosteroid (betamethasone 14 mg). All patients continued with intranasal corticosteroid (beclomethasone aerosol 400 mg/day) for 12 months. Both regimens caused substantial and equal increase in nasal expiratory peak flow [97]. The sense of smell improved significantly in the systemic steroid group at 2 weeks but was not maintained at 2-12 months during intranasal therapy.

In a second study of 124 patients, Lildholdt et al. randomized 33 patients who failed to respond to the initial treatment with intranasal corticosteroid (budesonide powder 400 or 800 mg/day) to treatment with systemic steroid (depot injection of 14 mg betamethasone) or polypectomy with a snare. After one year of continuous intranasal therapy, there was no difference between the two groups with regard to any effect parameter [89]. The authors found that only 15% of all patients did not respond satisfactorily to the treatment given and needed surgery. They conclude: "The primary treatment of nasal polyps should be intranasal and systemic corticosteroids".

In an open study, van Camp and Clement gave 25 patients with massive nasal polyposis a large dosage of oral prednisolone (60 mg/day for 4 days and then tapered off with 5 mg daily, giving a total dose of 570 mg) [98]. There was a considerable reduction in the fre-

quency of all symptoms, in particular nasal obstruction, and also the sense of smell improved. Nasal polyps became invisible at rhinoscopy in 10 of 25 patients. Half of the patients showed improvement judged by a CT scan of the sinuses. Although these 13 patients, called responders, continued on intranasal corticosteroids, "there was a strong tendency of recurrence, which made surgical intervention inevitable." Only one of the initial 25 patients succeeded in avoiding endoscopic sinus surgery. The authors conclude, "systemic steroid treatment should be reserved for those cases that require surgery." They emphasize, however, that surgery can be considerably facilitated by preoperative systemic corticosteroid therapy [199].

Although there is no placebo-controlled study on the effect of systemic corticosteroid treatment alone in nasal polyposis, there is no doubt that it is highly effective. Rhinitis symptoms and polyp size are reduced, and, in contrast to intranasal corticosteroids, there is a clear effect on the sense of smell and on pathology of the paranasal sinuses [198]. A short course of systemic corticosteroids is equally effective to polypectomy with a snare [176, 193]. In severe disease requiring endoscopic ethmoidectomy, preoperative use of systemic corticosteroids facilitates surgery [197].

Only a single course of systemic corticosteroids has been given in published studies. However, there is reason to believe that some patients with severe recurrent polyposis may benefit from repeated courses of short-term systemic corticosteroids but there are, at present, no analysis of the pro's and con's of this type of management. If, for example, a depot injection (methylprednisolone 80 mg or betamethasone 14 mg) is given no more frequently than every 3 months, it corresponds to continuous treatment with 1-2 mg prednisolone a day. Adverse effects from this therapy cannot be expected to be severe and, in some patients with severe disease and abolished olfaction, may be outweighed by increased quality of life.

Combined use of intranasal and systemic corticosteroids

Lildholt et al. have recently performed a placebo-controlled study of the effect of intranasal budesonide and intramuscular methyl prednisolone, alone and as a combination. The results showed that a full effect on rhinitis symptoms, including nasal blockage, can be obtained by intranasal medication alone, while systemic treatment is needed in order to obtain a significant effect on the sense of smell and on sinus pathology, evaluated by a CT scan.

Bonfils evaluated the efficacy of a combined steroid therapy in 181 patients suffering nasal polyposis. Patients were given a regimen combining short-term oral corticosteroids (prednisolone) and steroid nasal spray (beclometasone). Treatment was successful in 68% of the patients. Mean symptom intensity declined by 35 to 80% at 6 months, then remained unchanged to the end of the study (2 years follow-up) [197].

Antihistamine treatment of recurrent polyposis

In histological and immunological preparation of polyps, degranulated mast cells could be found and cellular as well as physiologically active extracellular histamine. The tissue of polyps releases histamine on contact with allergens, especially bacterial allergens [200, 201].

The leukotriene level is elevated in patients with asthma, sinonasal polyposis, and sinusitis. The leukotrienes increase nasal mucosal edema as well as mucus production, and they are responsible for bronchoconstriction in asthma patients. Therefore, antileukotrienes have been shown to be an alternative in controlling polyposis and symptoms after primary polypectomy [202].

Antileukotrienic effects among antihistamines are found in azelastine and mizolastine.

In studies on isolated polyps and dispersed nasal polyp cells, the inhibitory effects of antihistamines and antileukotrienes on mediator and cytokine release could be shown [203, 204].

Mosges and colleagues reported an open survey of 16 patients followed for 25 weeks after polypectomy in 1995 [205]. All patients were treated with topical antihistamine azelastine after surgery. Inclusion criteria were polyposis nasi and allergic rhinitis proven by intracutaneous prick test and nasal provocation. Further study criteria followed the usual demands of the legal restrictions for open surveys. Patients were examined by the investigators, and examinations included computed tomography, active anterior rhinomanometry, acoustic rhinometry, and sniffing tests. Patients and investigators were asked to assess secretion, edema, inflammation and obstruction in a symptom score. A patient diary reported the daily symptom score and quality of life over the period of 25 weeks.

Azelastine seemed to increase the symptom-free period. Symptom score and the individual quality of life ameliorated under antihistamine therapy. Because of the small number of patients included in this survey, a statistically significant result can not be shown. The data collected from these patients showed a tendency toward antiobstructive and antiprogressive effects of azelastine in nasal polyposis. Only four of the patients seemed to be non-responders to conservative treatment and underwent further surgery after 25 weeks because of progradient polyposis. Some symptom scores could be reduced from 70% to 30% of the baseline scores during the period of treatment. The results of the rhinomanometry and the acoustic rhinometry did not correlate with any of the other scores. Further studies on this subject must be done to obtain more valid data proving the tendencies seen in this survey.

The prophylactic effect of azelastine on recurrent polyposis has been shown in the survey. Furthermore, azelastine has the advantage of topical nasal treatment, having an inhibitory effect on eosinophil and neutrophil activation, whereas mizolastine has to be taken systemically at comparatively higher dosage [208, 209]. Cetirizine and its next generation product levocetirizine, the active r-enantiomere of the two enantiomeres of cetirizine, have also proven their benefit in patients with polyposis regarding postoperative quality of life. But they have no influence on polyps and their progression. Rapid time of onset of symptomatic relief is the advantage of these products in allergic rhinitis with nasal polyposis [210, 212].

Surgical treatment of nasal polyposis

The aim of surgery in nasal polyposis is to restore the physiological properties of the nose by making the nose as free from polyps as possible, and to allow drainage of infected sinuses. Complementary medical treatment of polyposis is always necessary, as surgery cannot treat the inflammatory component of the mucosal disease.

The extraordinary recurrence of polyps after simple polypectomy is well known. The rationale for surgery of the ostiomeatal complex was first advocated by Messerklinger [30]. In the last decade, a number of studies have reported good results after endoscopic sinus surgery (e.g., marked improvement of nasal blockage) in nasal polyposis [20].

The extent of the surgery performed is a matter of debate. The choice of surgical method depends upon the surgeon's philosophy and experience, the conventional surgical options starting from the simple snare polypectomy to radical ethmo-fronto-sphenoidectomy with fenestration of the maxillary sinus. In the last decades, the endoscopic polypectomy has been confirmed in the literature to offer better results than the conventional intranasal ethmoidectomy. Recently, with the new development of surgical instrumentation, the powered endoscopic polypectomy surgery is considered to be the best option with the advantage of a bloodless operation.

The extent of the surgery should be determined by the disease but always include uncinectomy, anterior ethmoidectomy, and exploration of the posterior ethmoids. If the posterior cells are involved, surgery should be continued posteriorly with posterior ethmoidectomy and even in some cases with sphenoidotomy. The ostium to the maxillary sinus is to be enlarged, and diseased mucosa from the frontonasal recess is to be removed. A pneumatized concha bullosa association should be dealt with and the lateral mucosa and bone usually removed to decompress the ostiomeatal complex [71].

Clinical studies claiming superior or equal results of medical therapy compared to surgical treatment are always criticized regarding the technique and the surgical approach used to treat nasal polyposis. Are the aims of surgery to remove polyps and to restore ventilation and drainage of the sinuses, or should surgery be more complete to remove a diseased organ, i.e. the ethmoids? Both procedures can be performed under endoscopic control, and the choice between these two surgical approaches currently depends very much upon the individual surgeon's experience and concept.

Jankowski and colleagues compared long-term outcomes of two endoscopic surgical approaches in diffuse and severe nasal polyposis [213]. A retrospective study was conducted with 76 patients operated upon between March 1991 and November 1992 with severe and diffuse nasal polyposis. The first 39 patients underwent surgery by one more experienced surgeons between March 1991 and September 1991, the following 37 by another surgeon between October 1991 and November 1992. The first surgeon was a proponent of radical ethmoidectomy using a systematic procedure that he named "nasalization". The other junior surgeon decided in favor of a less radical ethmoidectomy that he named "functional ethmoidectomy". The results of surgery in these two groups of patients were obtained by a third independent author using: 1) a study questionnaire mailed in January 1996 to all patients for evaluation of functional results, 2) a systematic endoscopic follow-up a few weeks later (between February and May 1996), and 3) a CT scan following the endoscopic examination.

Nasalization was described by Jankowski as a radical ethmoidectomy systematically removing all the bony lamellae and mucosa within the labyrinth, with a large antrostomy, sphenoidotomy, frontotomy, and middle turbinectomy. Functional ethmoidectomy was described as a procedure tailored to the extent of the pathology, leaving in place apparently non-diseased ethmoidal cells and mucosa, proceeding to antrostomy, sphenoidotomy, frontotomy or middle turbinectomy only if deemed necessary. Surgical procedures were always bilateral in both groups.

Questionnaire

Patients were asked to evaluate the overall functional benefit of surgery, nasal obstruction, rhinorrhea, and sense of smell in a visual analogue score. Patients were also asked regarding change of their asthmatic condition and if they developed asthma after surgery. Also documented were the duration of topical steroid use and whether the patients needed systemic steroids.

Endoscopy

The presence of crusts or secretions was noted first. The nose was cleared if necessary. The patency of the middle antrostomy, frontotomy, and sphenoidotomy

Table XIII. Scoring scale for endoscopic evaluation of the ethmoid cavity mucosa (see paragraph "endoscopic evaluation" for explanation).

	Right		Left	
No oedema/Diffuse red cavity	0	+10		0
Localized oedema				
- Ethmoidal roof	0 anterior	-1	anterior	0
	0 middle	-1	middle	0
	0 posterior	-1	posterior	0
- Orbital wall	0 anterior	-1	anterior	0
	0 middle	-1	middle	0
	0 posterior	-1	posterior	0
- Nasal septum	0 anterior	-1	anterior	0
	0 middle	-1	middle	0
	0 posterior	-1	posterior	0
	Middle tubinate	0 present 0 absent		
Diffuse oedema	0	ZERO		0
Recurrence of polyps				
Stage 1 (Polyps lie above the orbital floor)	0 1/3 ethmo	-1	1/3 ethmo	0
	0 2/3 ethmo	- 2	2/3 ethmo	0
	0 3/3 ethmo	- 3	3/3 ethmo	0
Stage 2 (Upper limit of inferior turbinate)	0 1/3 ethmo	-4	1/3ethmo	0
	0 2/3 ethmo	- 5	2/3 ethmo	0
	0 3/3 ethmo	- 6	3/3 ethmo	0
Stage 3 (Floor of the nasal cavity)	0 1/3 ethmo	-7	1/3 ethmo	0
	0 2/3 ethmo	- 8	2/3 ethmo	0
	0 3/3 ethmo	-9	3/3 ethmo	0
Stage 4 (Polyps protrude to the nasal vestibule)	0	10		0
Final score	Right:		Left:	

was classified as open, stenotic or invisible. The appearance of the olfactory region was noted as normal, fibrotic, edematous, or polypoid. The endoscopic appearance of the ethmoid cavity mucosa was methodically scored according to the scale presented in Table XIII.

CT scan evaluation

The soft tissue shadows into the sinuses were measured using the application NIH Image (version 1.6 PPC) for Power Macintosh 62oon5. The CT scan images were first digitalized on a Silicon Graphics station (application IRIS-Capture; resolution 384 x 286 pixels; format TIFF; gray scale (n=256) using a high resolution macrocamera (focal 60 cm). All images were digitalized using the same settings to avoid variability in the luminosity, contrast or distance. The surface (S) of each sinus could then easily be measured by drawing its bony limits on the computer screen. A second drawing was added marking the limits of the soft tissues contained in the sinus. The surface (s) of the lumen was then determined. The percentage of soft tissue opacity (STO) contained in a sinus was then easily calculated with the formula: STO = (1-s/S) x 100.

Results of patients subjected to analysis is displayed in Table XIV. The overall functional result of surgery is displayed in Figure 24. The benefits of surgery on nasal obstruction and anterior rhinorrhea were significantly higher in the nasalization group than in the ethmoidectomy group, while posterior rhinorrhea and sense of smell were not statistically significant (Fig. 25). Asthma condition following surgery is shown in Figure 26. Approximately half of the patients in each group reported that they continued to spray topical steroids into their nose on a regular daily basis. Only a few patients with nasal polyposis without asthma (two in the junior's ethmoidectomy group and one in

Table XIV. Follow-up summary

Surgical period	SENIOR'S NASALISATION GROUP March-Sept. 1991	JUNIOR'S ETHMOIDECTOMY GROUP Oct. 1991-Nov. 1992
Number of consecutive patients	39	37
Number of reponses to the questionnaire	35	25
Lost to follow-up	6	12
Number of reoperated patients	3	7
(reoperated asthmatics)	(2)	(3)
Number of functional assessments	30	18
(for asthma)	(16)	(4)
Number of endoscopic assessments	19	11
Number of CT-scan assessments	18	11

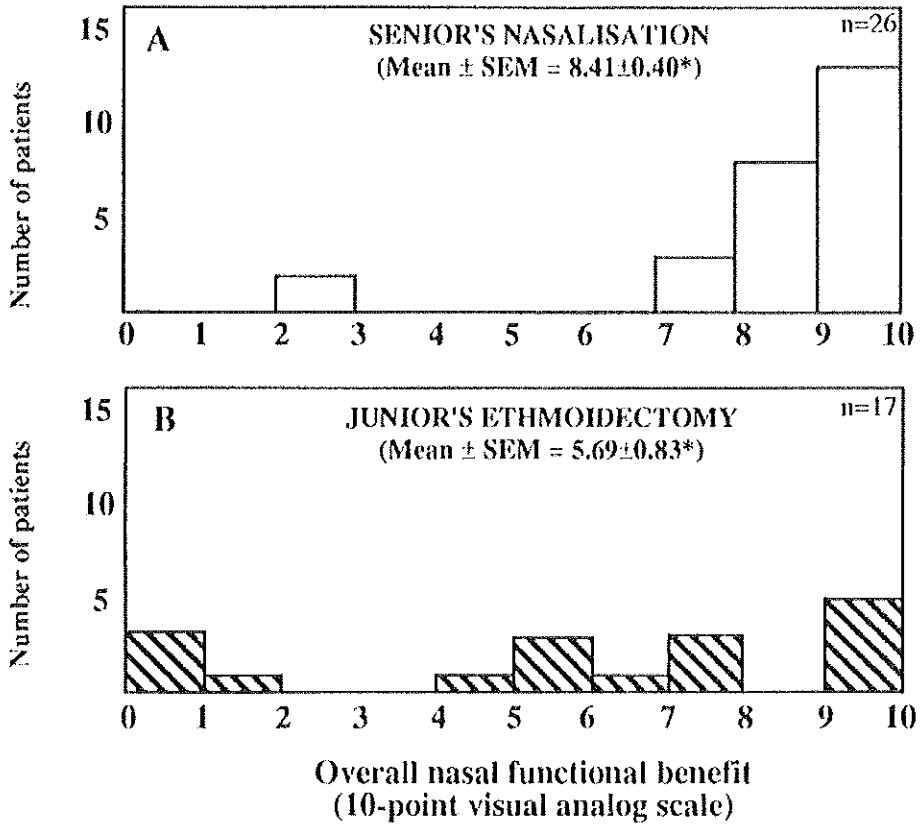

Fig. 24. Overall nasal functional benefit since surgery (A) 56 months (range 54-60 months) after the senior's nasalization, (B) 46 months (range 40-52 months) after the junior's ethmoidectomy. 0 = same discomfort as before surgery, 10 = normal functioning nose. (*p=0.002). (Note: four patients of the senior's nasalization group and one of the junior's ethmoidectomy group did not answer this question).

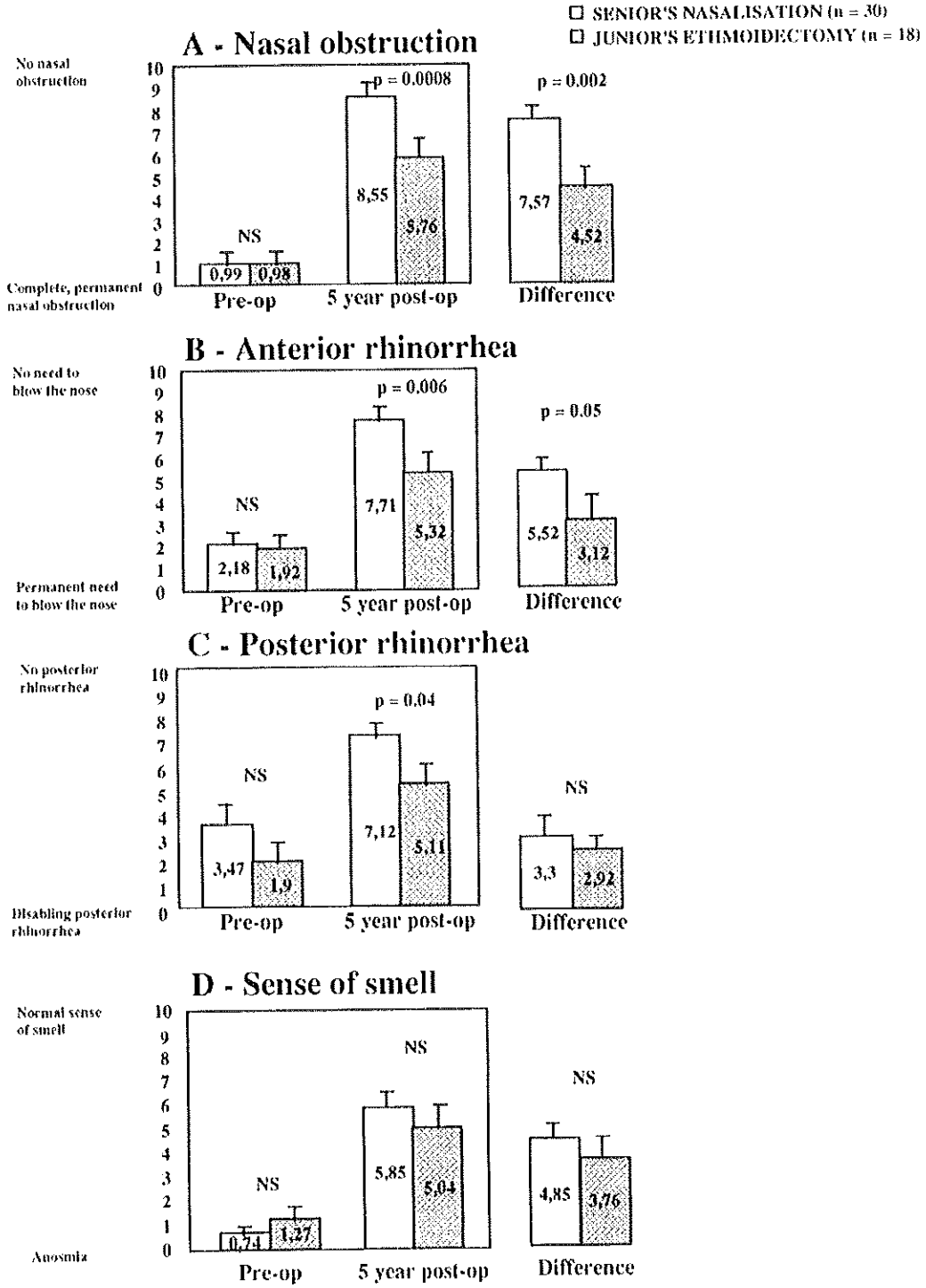

Fig. 25. Comparison of pre and 5 year postop nasal symptoms between the senior's nasalization and the junior's ethmoidectomy (mean ± SEM). (A) Nasal obstruction; (B) Anterior rhinorrhea; (C) Posterior rhinorrhea; (D) Sense of smell.

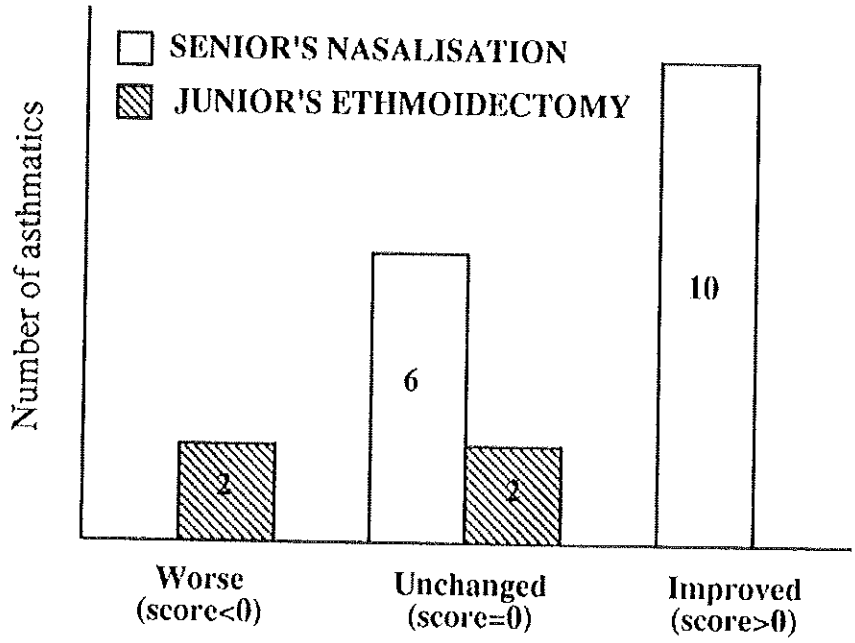

Fig. 26. Comparison of asthma status 5 years after the senior's nasalization (16 asthmatics, 130 patients) and the junior's ethmoidectomy (4 asthmatics, 118 patients).

the senior's nasalization group) reported the use of systemic steroids. Among asthmatics, however, the number who had needed at least one systemic steroid treatment during the year prior to receiving the questionnaire was significantly higher in the junior's ethmoidectomy group.

Endoscopic results were based on a total of 30 patients. The endoscopic score was significantly better in the senior's nasalization group than in the junior's ethmoidectomy group (Fig. 27). Middle antrostomy was found to be open in 37/38 and stenotic in 1/38 nasalization cavities; open in 14/22, stenotic in 7/22, and invisible in 1/22 ethmoidectomy cavities (operative reports showed that middle antrostomy had been performed in all patients).

Frontotomy was found to be open in 6/38, stenotic in 16/38 and invisible in 16/38 nasalization cavities; open in 4/22, stenotic in 4/22, and invisible in 14/22 ethmoidectomy cavities.

Sphenoidotomy was found to be open in 20/38, stenotic in 11/38, and invisible in 6/38 nasalization cavities; open in 2/22 ethmoidectomy cavities (operative reports showed that sphenoidotomy had not been performed in one nasalization procedure and had been performed in only two ethmoidectomy procedures).

Recurrence rate of polyps was 10/44 (22.7%) in the first group and 21/36 (58.3%) in the ethmoidectomy group. Recurrences were observed with the same frequency in the anterior, middle or posterior ethmoid cavity in the senior's nasalization group, whereas they were more frequently found in the anterior or middle than in the posterior ethmoid cavity in the junior's ethmoidectomy group. Areas of localized edema were found much more frequently in the anterior ethmoid cavity in both groups. The topography of polyp recurrence is demonstrated in (Fig. 28).

The mucosa of the olfactory region was found to be normal in 25/38, fibrotic in 9/38, edematous in 4/38, and polypoid in 0/38 nasalization cavities; normal in 14/22, fibrotic in 2/22, edematous in 5/22, and polypoid in 1/22 ethmoidectomy cavities. There was no relationship between the endoscopic appearance of the olfactory region and the sense of smell as measured by a visual analogue scale ($r = 0.15$, $p = 0.54$ in the senior's nasalization group; $r=-0.18$, $p=0.63$ in the junior's ethmoidectomy group).

Soft tissue opacity of CT scan studies was very similar in both groups in the anterior and middle ethmoid cavity areas. There was, however, significantly less soft tissue opacity in the posterior ethmoid cavities of the seniors nasalization group (Fig. 29). A good correlation was found in both groups between the endoscopic score and the CT scan score (Fig. 30). The CT

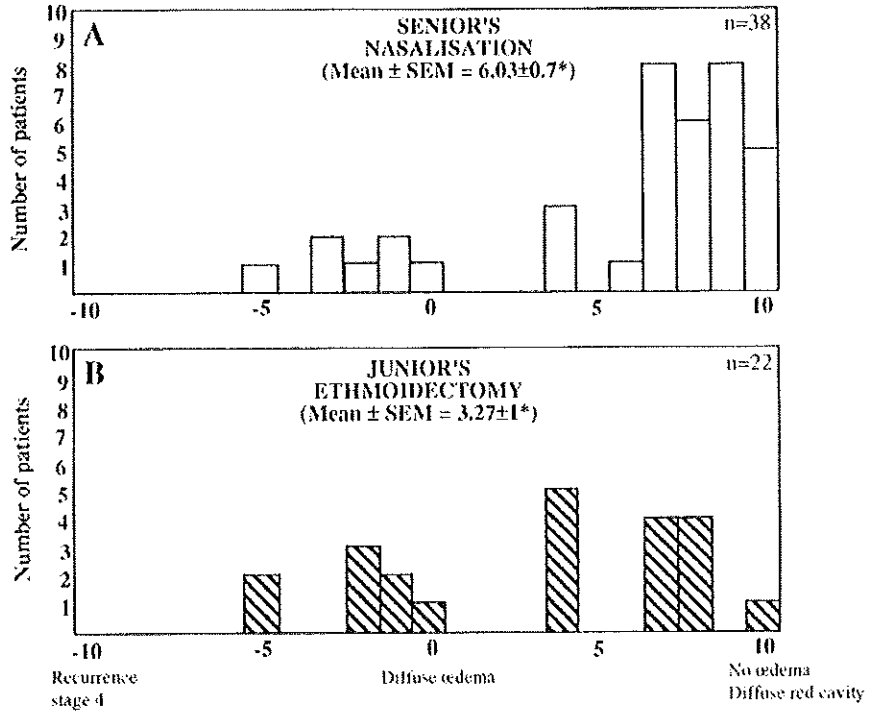

Fig. 27. Endoscopic scores of the ethmoid cavity mucosa after nasalization (A) and ethmoidectomy (B); (*p=0.02).

scan score was calculated as the mean of soft tissue opacity found on both the 3 axial and 3 coronal planes.

The mean percentage of soft tissue opacity in the maxillary, frontal, and sphenoid sinuses was very similar in both groups (Fig. 31).

No correlation was found between the patency of the middle antrostomy and the score of soft tissue opacity in the maxillary sinus. The score was calculated as the mean of soft tissue opacity found in both the axial and coronal planes. A good correlation was found in the senior's nasalization group between the patency of the sphenoidotomy and the score of soft tissue opacity in the sphenoid sinus (no calculation of correlation was made in the junior's ethmoidectomy group as only two sphenoidotomies had been performed) (Fig. 32).

Previous results clearly show better results five years after the senior's nasalization approach. Significantly fewer patients needed to be reoperated, and the recurrence rate of nasal polyps was significantly lower. In the non-reoperated patients, functional results were significantly better.

Despite cases of patients lost to follow-up, the absence of randomization and obvious bias against the nasalization group, the senior's nasalization group was significantly better.

Postoperative care after polyposis surgery

Polyps continue to recur after surgery causing a stressful condition for the patient and the surgeon. The answer to this condition is that we should regard the postoperative care to be of great importance. A very attentive postoperative care should be performed that will be able to diagnose and treat early recurrence of small polyps. Unfortunately, there is no link between the choice of surgical methods and the recurrence of polyps. Even with the recent surgical options, polyps may recur that require re-operation, and in some patients the repetitive operations may reach to quite a number such as twenty. Since the growth of the polyp is influenced by so many unknown conditions, the answer to inhibiting the regrowth of the polyps and thus preventing re-operation is a long-term, meticulous postoperative care.

The growth of polyps can be controlled by frequent meticulous post-operative care using the endoscope with which early minimal recurrence can be identified and treated promptly. Long-term medication may also be necessary. In this way the repeated complicated surgeries that are very common in polyposis patients can be prevented. It can be concluded that the long-term successful outcome of the surgery is strongly dependent upon the careful and meticulous postoperative care and management [211-215].

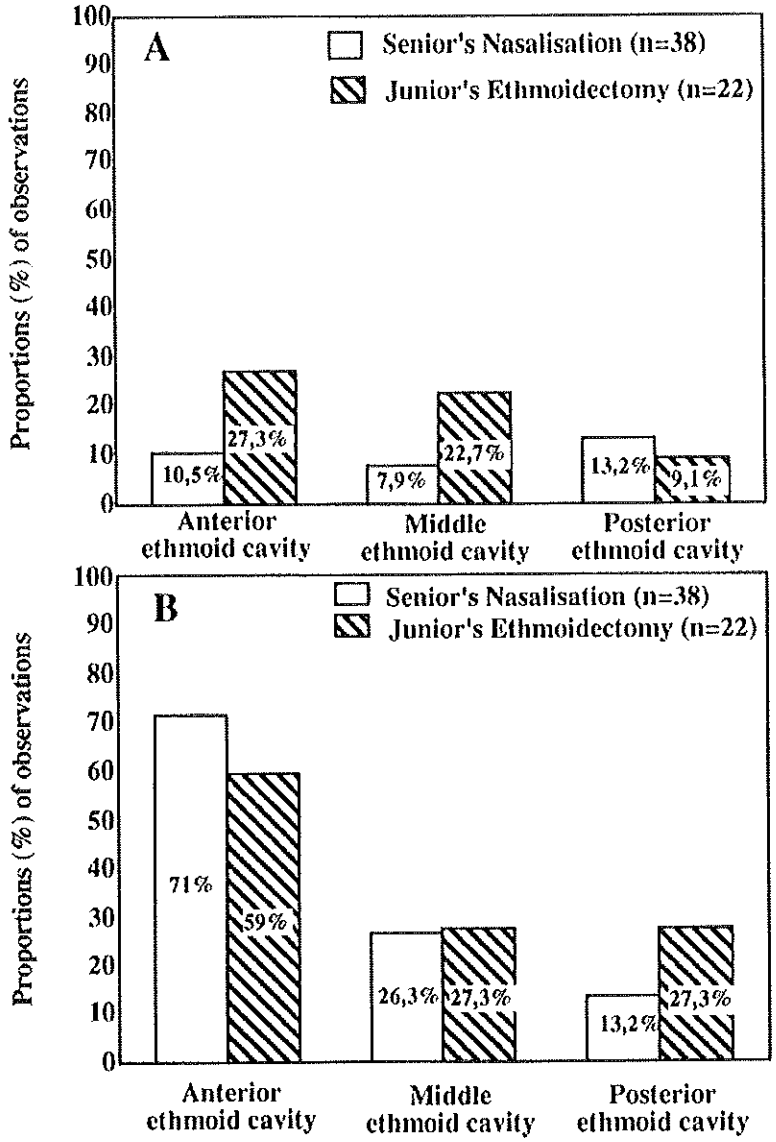

Fig. 28. Location of nasal polyp recurrences (A) and of oedematous areas of mucosa (B) seen on endoscopy

Wound-healing after general endoscopic surgery may take from a few weeks to several months, depending on the extent of the surgery and the individual mucosal reaction [26, 27]. The usual postoperative follow-up lasts about 4-6 weeks. The patient undergoes nasal cleaning twice a week for 2 or 3 weeks and then once a week for another 2 or 3 weeks. But in polyposis patients where polyps are likely to recur, follow-up lasts longer and is continued once a month for a year or more [28].

Soetjipto presented the importance of the long-term postoperative care [29]. Seventy-three postoperative polyp surgery patients were included in this study with the follow-up period of 2-4 years. All patients underwent a postoperative care that consisted of the following:

1) Naso-endoscopy examination to perform a nasal cleaning and to diagnose early polyp growth. Nasal cleaning was performed twice weekly for 2 or 3 weeks, once weekly for another 2 or 3 weeks, and then once monthly for 1 year or more or whenever the patient experienced any problems.

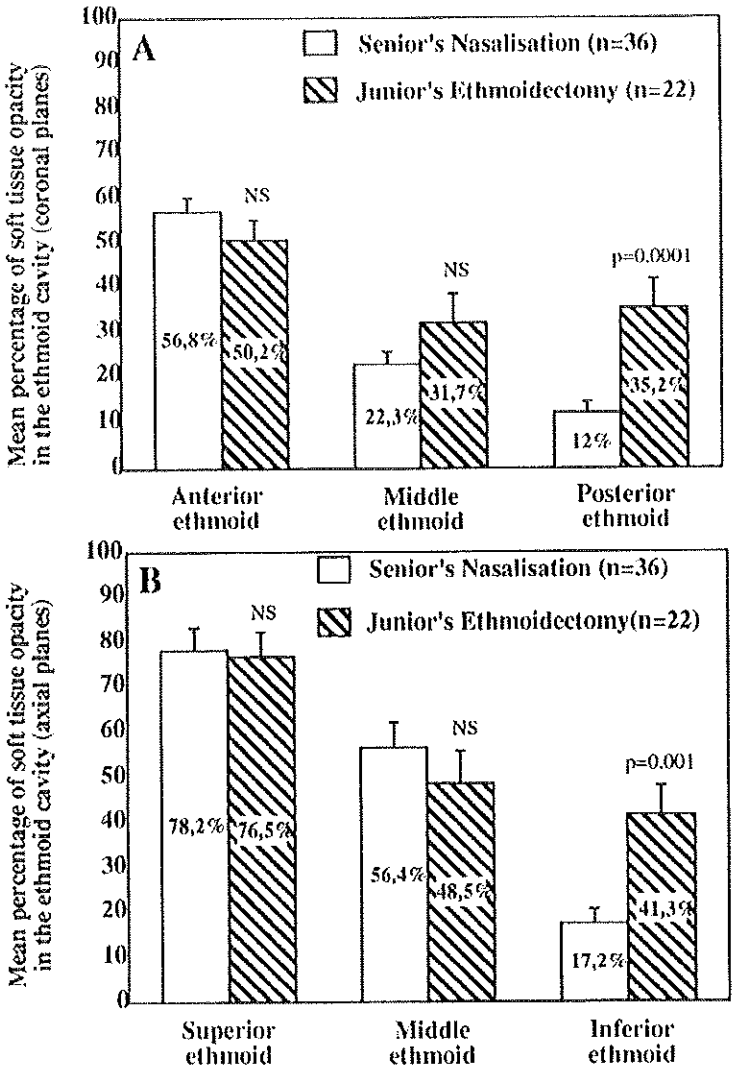

Fig. 29. Correlation between the endoscopic score of the ethmoid cavity mucosa and the CT scan score of soft tissue opacity

2) Any early polyp growth found upon naso-endoscopy was treated with either each or a combination of the following: a) chemical or electrical coagulation; b) nasal steroid and c) oral steroid given as usual dose or high pulsed dose.

Coagulation of polyps was performed by using a cotton applicator dipped in AgNO3 or an electric cautery. Coagulation was performed in a small localized polyp or polyps.

A pulsed oral steroid was given using a dexamethasone tablet 0.5 mg at the dose of 12 mg/day for 3 days, 8 mg/day for another 3 days, and 4 mg/day for another 3 days. Oral steroids were usually given to patients with massive polyp recurrence or polyps with a broad base. A pulsed oral steroid was allowed to be given only 2 or 3 times per year.

All patients were given nasal steroids. Antibiotics and antihistamines were given when necessary.

The ages of the patients ranged from 12 to 65 with predominant groups of 20-29 and 40-49. Preoperative naso-endoscopic staging of the polyp according to the Lund and Mackay classification was as follows: grade II polyp was found in 46 patients (63%) and grade III in 27 patients (37%). No grade I polyps were found in this series.

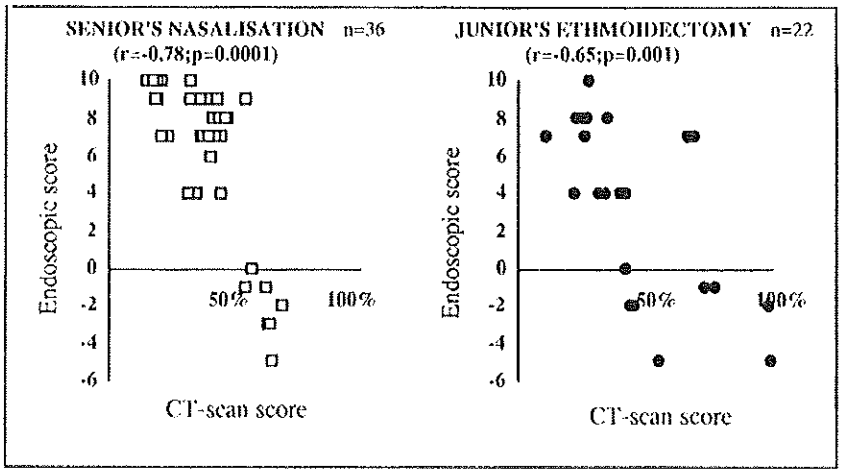

Fig. 30. Correlation between the endoscopic score of the ethmoid cavity mucosa and the CT scan score of soft tissue opacity

All patients underwent endoscopic polyp surgery; two patients also underwent an additional Caldwell-Luc operation (one bilateral and the other unilateral) due to massive polyps in the maxillary sinus. Oral antibiotics and decongestants were given to all patients postoperatively for 1-2 weeks. Topical decongestants were also given for 5-7 days followed by nasal steroids. Antihistamines were given to atopic patients if necessary.

Polyps recurred in 13 patients or 17.8%, the time to recurrence ranged from 2 weeks to 21 months post-surgery. Coagulation of polyp recurrence was performed in all 13 patients and ranged from 2 to 6 times in a single patient, while nasal steroids were given in all patients. This kind of post-operative care resulted in only 2 out of 73 polyp (2.74%) patients requiring reoperation.

Postoperative care must be performed routinely over an extended period of time. Prompt treatment must be carried out to avoid worsening of the disease which could necessitate subsequent, complicated surgery. Post-operative care in post-surgical treatment of nasal polyps is important in preventing polyps to form and grow, thereby avoiding re-operation, and thus supporting the ultimate result of surgery.

Complications of polyp surgery

Although the removal of all nasal polyps does not prevent recurrence, the temptation to remove the whole pathology increases the risk of complications. Distorted anatomy by massive polyposis, poor information in whitened out CT films, scarring from previous surgery, and intraoperative bleeding are common findings in cases in which complications have occurred.

A variety of tools (from simple cutting forceps to a sophisticated computer-assisted navigation system) have been developed and are aimed at the same target of reducing complications; however, lack of experience with such modern tools can lead to serious complications which are otherwise difficult to cause in simple polypectomy surgery.

Intraoperative complications are best avoided by meticulous technique and good preoperative planning. If bleeding persists during surgery such that it interferes with visualization, it is safer to stop the procedure and, if necessary, return at a later time using an alternative approach. Poor visualization attributable to bleeding appears to be a primary cause of major complications.

Orbital injury can be avoided by good preoperative study of CT scans. The eyes should be routinely checked during the procedure for signs of lid edema, ecchymosis or proptosis. Should an orbital dehiscence be suspected during surgery, palpation of the anterior globe while examining through the endoscope can highlight this problem. Prolapse of orbital fat through an injured lamina papyracea can be mistaken for nasal polyps specially under the use of shaver systems. The lamina papyracea should be positively identified and skeletonized in the region of suspected dehiscence. If a piece of orbital fat obscures an area of the dissection, bipolar cautery can be applied to reduce the fat. The patient should be monitored for signs of an orbital hematoma such as lid edema, ecchymosis and proptosis.

Intraoperative identification of CSF leak should be immediately explored and immediate closure by a free tissue graft attempted.

Immediate postoperative complications such as epis-

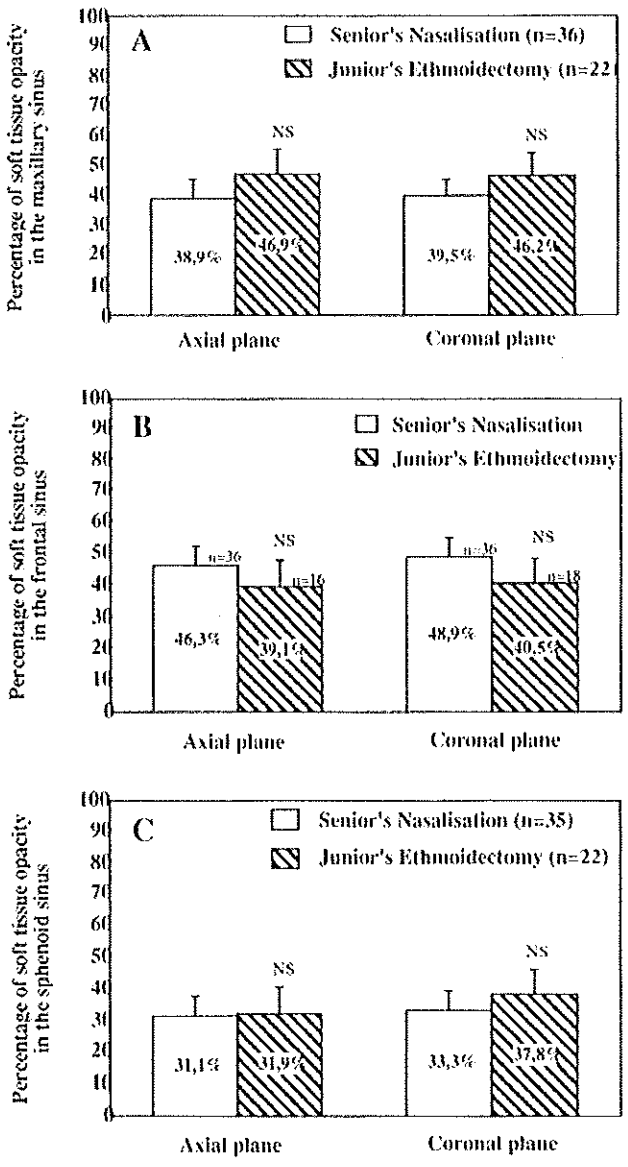

Fig. 31. Mean percentage of soft tissue opacity (± SEM) in the maxillary (A), frontal (B) and sphenoid (C) sinus on axial and coronal CT scan planes.

taxis is usually controlled by topical hemostatic agents, vasoconstriction or packing. Endoscopic localization of the bleeding site with treatment via electrocautery or direct packing of the bleeding site can be highly effective in most cases [219].

Postoperative CSF rhinorrhea due to unrecognized skull base injury should be investigated to define the site of leak. Nasal endoscopy and coronal CT scan provides adjunctive information. Further procedures for defining the leak site may be required (intrathecal water soluble contrast in an active rapid leak or radioactive serum albumin). Specific protocol MRI that highlights CSF and suppresses fat can be useful [220].

Long-term complications of disease recurrence such as fibrosis or stenosis are best avoided as mentioned through good postoperative care. Disease recurrence can be asymptomatic and discovered only on routine follow-up.

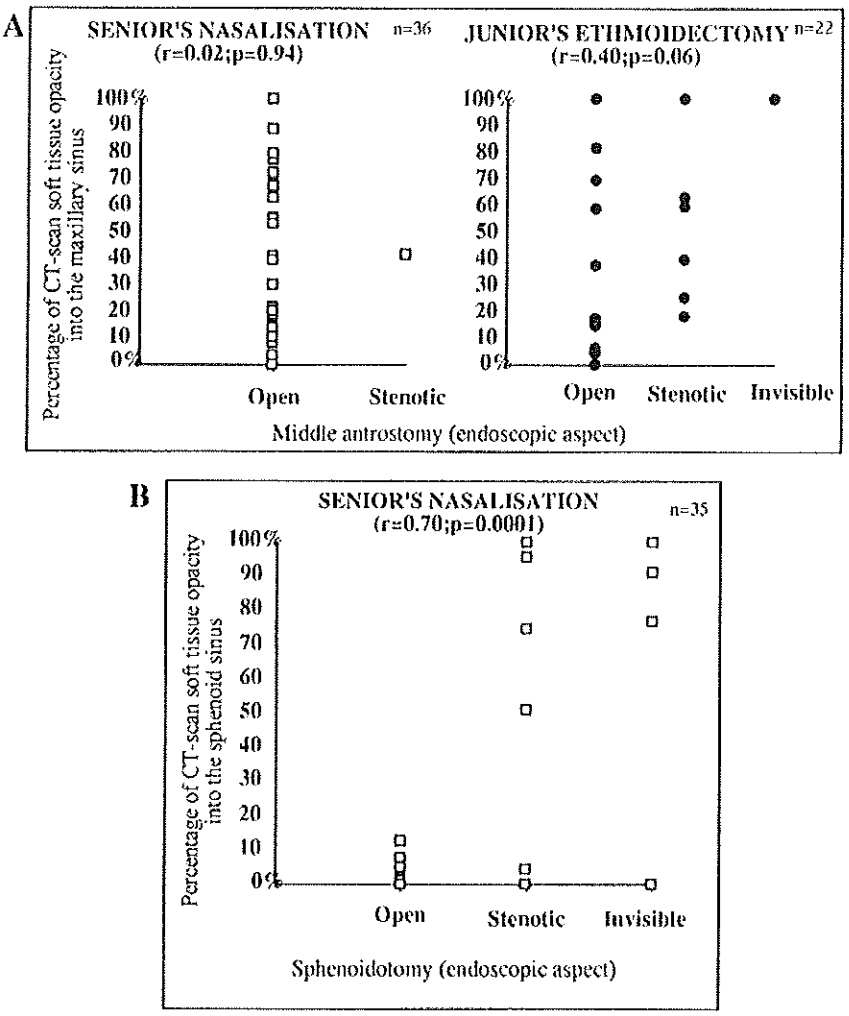

Fig. 32. Correlation between the endoscopic appearance of the middle antrostomy (A), the sphenoidotomy (B), and the percentage of CT scan soft tissue opacity in the sinus.

Medical versus surgical therapy

The treatment of nasal polyposis is a subject of debate. Surgical or medical treatment or both have been recommended as the treatment of choice [23]. In clinical rhinological research there is a need for randomized, controlled prospective studies to compare the effects of various types of treatment. One obstacle in performing such studies is the difficulty of finding a well-matched control group. Regarding nasal polyposis, the two major problems are the many different factors contributing to the cause on the one hand and problems with staging of the disease on the other. A control group should preferably be matched for age, sex, social habits, associated diseases, and heredity. Many clinical trials support medical treatment as the primary sole treatment [87,176,222,224]. Lildholdt 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 found to be similar in the medically and surgically treated groups [198]. Blomqvist's study recommended that the selection of those who will most likely benefit from surgery should be based on the patient's symptoms and not on the examiner's polyp score. Medical treatment seems to be sufficient for treating most symptoms of nasal polyposis. When hyposmia is the primary symptom, no additional benefit seems to

be gained from surgical treatment. If nasal obstruction is the main problem after steroid treatment, surgical treatment is indicated [225]. According to the "Position Statement on Nasal Polyps" [226], medical treatment should be used for at least one month before surgery is contemplated in patients with typical nasal polyposis because some studies have indicated that no additional treatment is necessary in those patients who respond to medical treatment.

Prevention of recurrence

Removal of the entire pathology in nasal polyposis can not guarantee a recurrence-free prognosis. Therefore, recurrences do not appear to be linked to the type of surgery, but rather the onset seems to be linked to intrinsic, partially recognizable factors responsible for the primary and secondary polypogenesis.

In 180 patients studied prospectively for one to eight years after their first nasal polypectomy, Larsen and Tos found that one third of patients underwent one or more additional polypectomies [193]. Regrowth rates of nasal polyps have been reported to be as high as 87% in one year [193].

A variety of medications has been tested as a postoperative measure to prevent recurrence. Topical steroids of different preparations have primarily been tested [181 191-194 227] followed by other topical applications of many preparations of various compounds with marginal differences in the control rates, e.g. antihistamines (azelastine) [228], antileukotrienes [229], lysine acetylsalicylate [230 231], capsaicin [232], and furosemide [233 235].

Predicting disease recurrence is an even more difficult task. Analyzing unfavorable factors prognosticating recurrence (age, sex, severe deviation of the septum causing restriction, severe turbinate hypertrophy, surgery or repeated surgery for recurrence, type of macro-micro endoscopic surgery, allergy to seasonal inhalants, allergy to perennial inhalants, mixed allergies) did not prove to have any significant influence on recurrences. Bilateral involvement of the sinus system represented a negative trend with regard to recurrences, like the involvement of more than one subsite (anterior ethmoid, posterior ethmoid, maxillary sinus, sphenoid), ASA and NSAID intolerance and abundant eosinophilic infiltration [29].

Better knowledge of the etiopathogenesis and pathophysiology of nasal polyposis modifies our procedures for preventing polyposis recurrence. As described previously, an important element in the genesis of nasal polyps and their relapses is the development of edema secondary to increased plasma and water absorption into the lamina propria of the nasal polyp tissue [33]. The increase of the net flux of sodium and chloride leads to an increased absorption of water across the apical surface of the respiratory epithelium leading to edema and therefore to the growth of the nasal polyp. Furthermore, the imbalance of sodium and chloride transmembranal net flux probably leads to a dysregulation of calcium homeostasis with its concomitant effect on interstitial and intracellular second membrane messengers. The depletion of calcium results in a destabilization of the cells populating the nasal mucosa of polyp-prone patients. In addition, the release of major basic protein from the eosinophils has an effect on the epithelial architecture and on the sodium and chloride flux into and out of the apical epithelial cells of the tissue.

Considering these data, the use of furosemide, a diuretic of ansa, for the treatment of naso-sinusal polyps acquires a strong rationale. This drug, by acting in nasal-epithelial cells at the level of Na/Cl membrane co-clearance, is able to create a chemical gradient between the interstice and the surface of the epithelium, that leads to an ionic flow of sodium, chlorine, and water [35]. This is the anti-edemagenic effect of furosemide.

Bellussi and associates demonstrated the long-term efficacy of intranasal furosemide and compared this topical diuretic with an intranasal steroid, mometasone furoate, in preventing postoperative relapses of sinonasal polyposis. Between 1991 to 2000, 170 patients were selected (95 males and 75 females) aged 19 to 63 years (mean age 37.3). All the enrolled patients were affected by bilateral complete or partially obstructive sinonasal polyposis, indicated for surgical treatment after failure of medical treatment. Patients suitable for surgery were only considered when medical management failed to reduce the nasal volume greater than 50% of the normal values in each nasal fossa (normal total nasal volumes: 24.5±1.5 cm³). All patients were surgically treated in the Department of Otorhinolaryngology at the University of Sienna, Italy. Patients did not differ regarding the type and extent/severity of pathology of the nose and sinuses. Surgical procedures are summarized in Table XV.

In the immediate postoperative period, all patients received standard medical treatment consisting of nasal lavage with physiological solution and emollient oil. One month after surgery all patients underwent the following examinations:

- ENT examination;
- nasal endoscopy;
- active anterior rhinomanometry (AAR);
- acoustic rhinometry (AR).

All of these above-mentioned parameters were found to be within normal values in all the patients; moreover, residual polyposis was not present in any patient postoperatively. At the time of recruitment, the 170 patients were randomly divided into three groups. Specifically from 1991 to 1997, patients were assigned to the furosemide treatment (group I) or to the lack of post-surgical treatment (group II). After that period, considering the positive results obtained with furosemide treatment [236], it was decided to compare

Table XV. Surgical procedures.

	Group I (97 Pt)	Group II (40 Pt)	Group III (33 Pt)
Endoscopic polypectomy plus anterior ethmoidectomy	53	25	17
Endoscopic polypectomy plus antero-posterior ethmoidectomy	18	15	16
Endoscopicpolypectomy	26	1	1

Pt: Patients

the efficacy of this drug versus topical steroids (rationally most accepted treatment for the prevention of postsurgical relapses of polyposis). No further patients were enrolled in group II (no treatment after surgery), while enrollment was begun for the mometasone group (group III).

At the end of follow-up, group I consisted of 97 patients (54 males and 43 females), group II consisted of 40 patients (18 males and 22 females), and group III included 33 patients (23 males and 10 females). Each patient assigned to group I started treatment with furosemide diluted in physiological solution (2 ml of furosemide and 2 ml of saline) administered as nasal puffs (2 puffs per nostril a day, each puff corresponding to 500 µg) for 30 days.

This therapy was administered for 1 month and then interrupted for 1 month and so on for the first 2 years (6 months of treatment/year); patients followed this treatment for 1 month and interrupted for 2 months during the third, forth and fifth years of treatment (4 months of treatment/year). After 5 years of treatment, furosemide was administered for 1 month twice a year. Group II received no specific treatment. Finally, patients assigned to group III started a treatment with mometasone furoate, a topical corticosteroid, administered as nasal puffs (2 puffs per nostril a day, corresponding to 200 µg/day) for 30 days. As suggested [230], mometasone furoate was given according to a therapeutic protocol requiring the administration of the drug for 1 month and then its interruption for 1 month for the first 2 years (6 months of treatment/year); then 1 month of treatment and 2 months of washout during the third, fourth, and fifth years of follow-up (4 months of treatment/year); and after the fifth year for 1 month twice a year. During the follow-up, no other treatments were administered to the patients enrolled in the study. In order to exclude systemic effects of furosemide, blood pressure was controlled every day during the 5 months of the first year of treatment, and blood parameters and renal functionality were checked every 6 months following surgery.

All 170 patients were examined every 6 months for a maximum of 9 years to a minimum of 1 year. Specifically, the group I follow-up ranged between 1 to 9 years, whereas the follow-up of group II and III ranged between 1 to 6 years and 1 to 3 years, respec-

Table XVI. Nasal volumes during follow-up.

Years	Furosemide	No treatment	Mometasone furoate
1	24.6 ± 1.4	24.2 ± 1.6	24.5 ± 1.6
2	24.6 ± 1.5	23.5 ± 1.4	24.2 ± 1.5
3	24.2 ± 1.5	22.0 ± 1.6	24.0 ± 1.3
4	23.8 ± 1.4	19.8 ± 1.4	
5	23.4 ± 1.6	18.5 ± 1.4	
6	22.5 ± 1.4	16.6 ± 1.7	
7	21.3 ± 1.4		
8	20.7 ± 1.6		
9	20.1 ± 1.8		

Data were measured by acoustic rhinometry and expressed as mean value ± SD in cm^3.

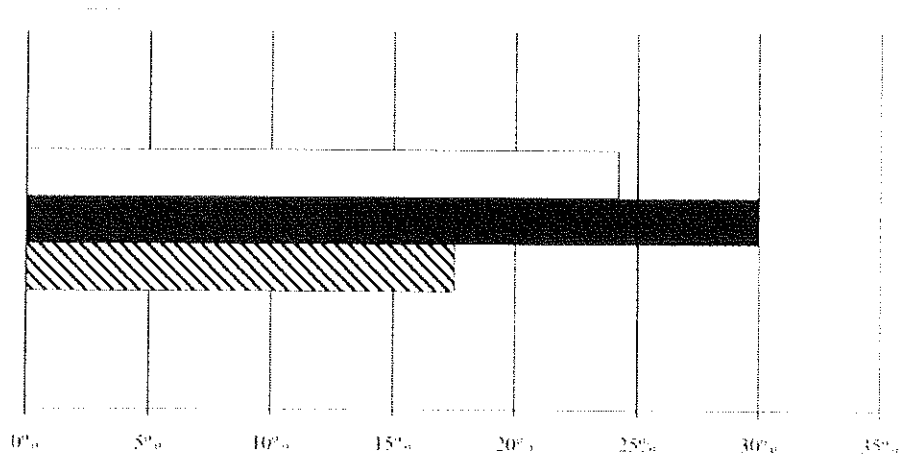

Fig. 33. Nasal polyposis relapses.

tively. Every check-up included the same set of examinations performed 1 month after surgery.

Relapsing nasal polyposis was classified as:

- Stage 0: no visible polyps;
- Stage 1: polyp or polyps confined to middle meatus and acoustic rhinometry values within the normal range (normal total nasal volumes: 24.5±1.5 cm^3);
- Stage 2: polyps prolapsing beyond the middle turbinate with a reduction of nasal volumes <50% measured through AR;
- Stage 3: sub-obstructive forms that require further surgery (reduction of nasal volumes >50%).

Results

Group I and group III patients tolerated the therapy with furosemide or mometasone well and no patient abandoned therapeutic protocols; moreover, in these two groups, no side effects were noticed, either cutaneous, pancreatic or hematic related, with furosemide or mometasone furoate treatment.

The modifications of nasal volumes, measured by acoustic rhinometry, in the three groups during the follow up are summarized in Table XVI. Specifically, surgery restored a valid nasal patency which remained in the normal range in all the three groups of patients

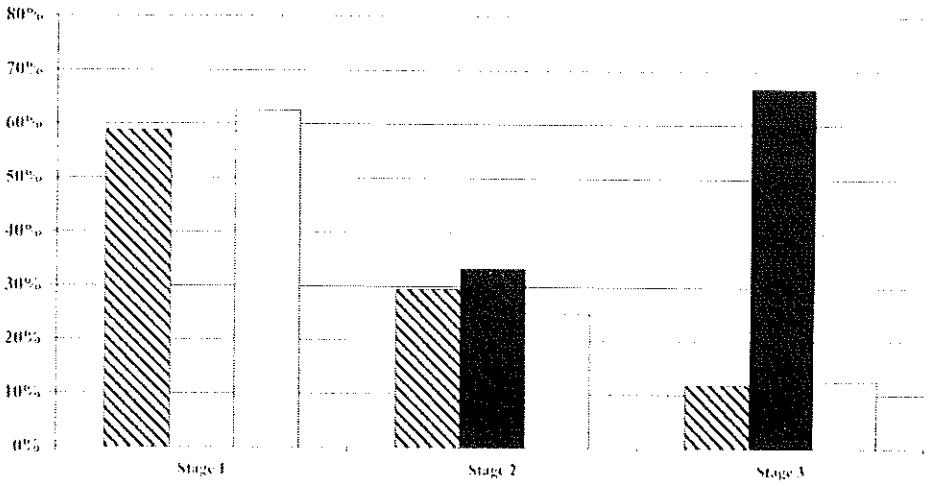

Fig. 34. Severity of nasal polyposis relapse.

for the first year of follow-up. Then, in the nontreated group we noted a significant worsening of this parameter, falling to a mean value of 16.6±1.3 cm^3 at the end of the follow-up period for that group ($p<0.05$). On the contrary, during the first 3 years of follow-up, both furosemide and mometasone furoate treatments maintained patients' nasal patency in the physiological range. Moreover, in the furosemide group the normality of this parameter was also noted after 9 years of follow-up. Twelve out of 40 patients (30%) and 8 out of 33 patients (24.2%) belonging respectively to group II and III and experienced nasal polyposis relapses, whereas relapses developed in only 17.5% of the group I population (17 out of 97 patients) (Fig. 33).
Focusing on the distribution of these relapses according to severity stages, the prevalence of early stage relapses was noted in patients treated with furosemide or mometasone furoate (58.8 % and 62.5 % stage I polyps, respectively), whereas patients who did not receive any treatment experienced more severe grades of relapsing nasal polyposis, with 66.7 % of stage III polyps in this group ($p<0.005$) (Fig. 34).

In that present study, patients treated with furosemide had relapses in only 17.5% of cases compared to the group treated with both mometasone furoate and in the non-treated group, which had recurrences of 25.2% and 30% respectively.
It is also important to highlight that data collected from the group treated with furosemide were obtained after a follow-up of 9 years, which is a significantly longer follow-up period when compared with the ones of the group treated with mometasone furoate or non-treated, which were followed up for 3 and 6 years respectively. Considering the severity of relapsing polyposis, it was found that only 11.8% and 12.5% of relapsing polyps in the groups treated with furosemide or mometasone furoate could be classified as stage III polyps, whereas, in group II there was a 66.6% recurrence for this stage ($p<0.005$).
In conclusion, according to the long-term follow-up data, furosemide represents an efficacious therapeutic aid in the prevention of relapses of sinonasal polyposis and undoubtedly a valid alternative to corticosteroids.

List of abbreviations

AAR	active anterior rhinomanometry
AI	analgesic intolerance
AIA	aspirin-induced asthma, analgesic-induced asthma
AR	acoustic rhinometry
ASA	acetylsalicylic acid
ASAI	acetylsalicylic acid intolerance
ASA-IRS	aspirin-intolerant rhinosinusitis
ASA-TRS	aspirin-tolerant rhinosinusitis
ATP	adenosine triphosphate
cAMP	cyclic adenosine monophosphate
CI	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
COX	cycloxygenase
CT	computed or computerized tomography
DAB	diaminobenzidine
ECM	extracellular matrix
ENT	ear, nose and throat
ESS	endoscopic sinus surgery
FEF	forced expiratory flow
FESS	functional endoscopic sinus surgery
FEV	forced expiratory volume in one second
FVC	forced vital capacity
GM-CSF	granulocyte-macrophage colony-stimulating factor
HETE	hydroxyeicosatetraenoic acid
HLA	human leukocyte antigen
HSPG	heparan sulfate proteoglycan
ICAM	intercellular adhesion molecule
Ig	immunoglobulin
IL	interleukin
LFA	leukocyte function antigen
MBP	major basic protein
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
PAS	para-aminosalicylic acid
PBS	phosphate-buffered saline
PCNA	proliferating cell nuclear antigen
RANTES	regulated on activation normal T cell expressed and secreted
RCB	rat monoclonal antibody
Rt	transepithelial resistance
SCF	stem-cell factor
SNOT	Sino-Nasal Outcome Test
STO	soft tissue opacity
Th	T-helper
TIMP	tissue inhibitors of matrix metalloproteinase
TNF	tumor necrosis factor
VCAM	vascular cell adhesion molecule
VLA	very late antigen

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