

Beneficial effects of propylene and polyethylene glycol and saline in the treatment of perennial rhinitis

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Summary

Although propylene-and-polyethylene-glycol and saline have been used in clinical studies as placebos, their possible therapeutic role as wetting agents in the treatment of perennial rhinitis was investigated. Clinical and laboratory response to these agents was measured in eighteen patients during a 2-week baseline period and with 4 weeks of active treatment in a double blind randomized study. After 2 and 4 weeks there was a significant improvement compared to baseline in nasal function ($P < 0.05$) and blockage index ($P < 0.01$) combining both groups, with no difference between treatments. Patients had less sneezing at 2 and 4 weeks ($P < 0.01$), and less stuffiness at 4 weeks ($P < 0.01$). There was a significant correlation between improvement in blockage index and nasal biopsies when both were judged independently of the other. This study has demonstrated that wetting agents offer both subjective and objective improvement in the treatment of perennial rhinitis and merit consideration prior to (or along with) other agents with known systemic side effects.

Introduction

Standard allergy and otolaryngology textbooks recommend antihistamines and decongestants as the mainstay of treatment for perennial rhinitis (Spector *et al.*, 1976; Tennenbaum, 1972; Seeborn, 1978). Rarely, a comment is made regarding the beneficial effect of the installation of a moisturizing agent into the nose (DeWeese & Saunders, 1973). Recent studies comparing active steroid aerosols with placebo suggest that in some circumstances the placebo might significantly affect objective parameters such as nasal blockage and secretions or even inflammatory oedema and nasal eosinophils (Jones *et al.*, 1979). Propylene and polyethylene glycol (P and P glycol) and saline, two agents used as placebos in studying perennial rhinitis were employed to test the hypothesis that wetting agents might ameliorate nasal signs and symptoms of obstruction and inflammation. The clinical response to these wetting agents was also correlated with biopsy findings.

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Materials and methods

Patient selection

Patients aged 21 or over were selected from the outpatient population of Hadassah Medical Centre in Jerusalem. They fulfilled the following criteria: (1) a history of perennial non-allergic rhinitis for at least two years duration; (2) severe enough symptoms to require the use of medication more than 50% of the time; (3) undesirable side effects from the usual medications; (4) no systemic or topical steroids in use for at least six months prior to the study.

Patients with nasal polyps who gave symptoms of nasal obstruction were excluded as were patients on immunotherapy. Patients were instructed not to change their basic medication programme which included a decongestant and/or antihistamine. Informed consent was obtained from all patients prior to the study.

Nasal spray

Propylene and polyethylene glycol a solution containing 20% propylene glycol and 15% polyethylene glycol, buffered to pH 6.0 was dispensed in plastic atomizer bottles. Physiological saline 0.65% with benzyl alcohol as a preservative buffered and made isotonic with sodium bicarbonate (supplied as Ocean spray, Fenton, Missouri) was dispensed in atomizer bottles with exactly the same appearance.

The investigator, his technician, and the patients were unaware of the contents of the randomly dispensed solutions.

Method of study

The study was divided into two periods: a 2-week baseline period and a 4-week period of treatment with either the P and P glycol or saline. During these periods, the patients kept a daily symptom diary recording the number of hours per day each symptom (sneezing, stuffiness, runny nose, nose blowing and post nasal drip) was present. The patient was instructed to take two sprays in each nostril four times daily. During each visit, the clinical status of each patient was assessed.

Adverse side effects were recorded as to the date of onset, severity, duration and whether in the opinion of the investigators the reaction was or was not due to the study drug.

A complete physical examination was performed at the beginning of the baseline period and at the end of the 4-week treatment period. Physical examination of the nose was carried out at 2-week intervals throughout the study. The appearance of the nasal mucosa was recorded and graded as normal, edematous, atrophic or polypoid. The colour was described as normal, pink, red or purplish. Nasal secretions were graded as: none, clear, watery opalescent or grossly purulent.

Laboratory examinations

Skin tests. A screening battery of skin tests was applied to each subject to rule out reagin-mediated problems. These included selected moulds, weeds, grasses and trees.

Total IgE determinations. Total serum IgE measurements were obtained in subjects utilizing a radioimmunoassay test kit (Phadebas IgE test, Pharmacia Diagnostics).

Nasal smear. Nasal smears for eosinophils were obtained posteriorly from the floor of the nose and beneath the middle turbinate. These were stained with Wright's polychromatophilic stain.

Nasal biopsies. Nasal biopsies on study patients were performed at baseline and at the end of the 4-week treatment. After a solution of Pantocaine (amethocaine HCL 10%) and 0.25% ephedrine was sprayed into the nasal chamber, a small punch biopsy forceps was used to remove a piece of tissue measuring approximately 2×2 mm from the anterior end of the inferior turbinate. The tissue was immediately placed in buffered formalin. A minimal amount of bleeding was produced by this procedure. In a few patients, the bleeding was controlled by pressure, but in most the bleeding did not require any specific treatment. Slides were stained with Giemsa, haematoxyline and eosin, and periodic-acid-Schiff reagent. Nasal biopsies from control patients without perennial rhinitis were obtained using the same method as described above. Informed consent was obtained from all patients.

A pathologist without prior knowledge of the nature of the biopsies classified the oedema as: 0 = absent, 1+ = mild, 2+ = moderate, and 3-4+ = marked. The number of eosinophils, mast cells, and plasma cells refer to the count made per high powered field. A second pathologist also read the same slides. Any discrepant readings were averaged.

Nasal airflow measurements. A Wright Peak Flow Meter (Airmed Limited, Harlow, England) was adapted to measure nasal air flow by attachment to a tight fitting nasal mask (Forregger Co., Inc. Smithtown, N.Y.). The patient was instructed to hold the mask firmly to his face and with his mouth closed tightly to exhale as rapidly as possible ($PEFR_n$) for three nasal measurements. Three mouth exhalations ($PEFR_m$) were measured without the face mask. Peak flow measurements were performed immediately before installation of the q.i.d. study medication excluding the night-time measurements.

Blockage index (BI) was calculated by using the average of the three nose and mouth measurements according to the formula of Taylor *et al.* (1973).

$$\frac{PEFR_m - PEFR_n}{PEFR_m} = BI$$

Statistical evaluations. Repeated measure analyses of variance using the BMDP2V program were used to analyze mouth functions, nose functions, blockage index, eosinophil smears, and rating scales. Mean comparisons were made using the methods in Winer (1971). The Wilcoxon match-pairs sign-ranks tests, the Mann-Whitney U-Test and *t*-tests were used to test the biopsy data (Siegel, 1956).

Results

Demographic

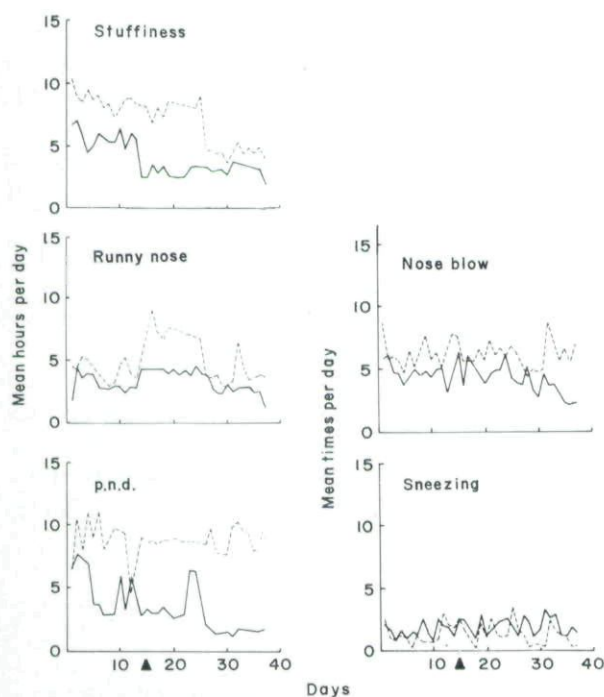
Table 1 lists the demographic data of the eighteen patients who finished the perennial rhinitis study. A nineteenth patient dropped out early in the study. There was no statistically significant difference between the two groups regarding number of patients, age at the time of the study, sex or duration of illness. All patients had symptoms for more than 2 years. Although isolated positive skin tests were present, there was no significant differences between the two groups.

Symptoms scores from the patient diary

The average number of times (or hours per day) that a symptom was recorded in the diary during the 2 weeks of baseline and the 4-week study period is presented in Fig. 1.

Table 1. Demographic information of patients using two wetting agents with treatment of perennial rhinitis

	P and P glycol	Saline	Significance
Number of patients	9	9	
Age (yrs) { Mean	40	37	NS
Range	21-65	22-55	NS
(Overall mean age = 35 yrs)			
Sex { Male	3	6	NS
female	6	3	
Duration of disease { 2 yr	0	0	
2-5 yr	2	6	
5-10 yr	3	1	
10+ yr	4	2	

**Fig. 1.** Number of hours per day (stiffness, runny nose, post nasal drip) or number of times (nose blowing, sneezing) symptoms were present during the baseline and treatment periods with propylene and polyethylene glycol (—) or saline (---).

Comparing the first week of baseline with the last week of the treatment, there was a significant decrease in post-nasal drip and nose blowing after P and P glycol. There was less stiffness after both treatments ($P < 0.001$) but no changes in sneezing or runny nose symptoms.

Doctor's 2-week ratings

Doctors also rated patient symptoms at 2-week intervals (not shown) for the above symptoms during the clinical visit with somewhat different results. No difference in sneezing symptoms was found between those patients receiving either propylene glycol or saline yet, by combining the groups there was a statistically significant decrease in sneezing at both 2 and 4 weeks compared to baseline ($P < 0.01$). There also was significantly less stuffiness at 4 weeks but not at 2 weeks compared to baseline ($P < 0.01$). There was a decrease in runny nose symptoms at 2 weeks ($P < 0.05$) but not 4 weeks. There was no significant difference between groups over time for nose blowing. Interestingly, for post nasal drip, patients on saline continued to improve but those on P and P glycol actually worsened at 4 weeks compared to 2 weeks ($P < 0.05$). There also was a significant improvement in overall symptoms at two weeks ($P < 0.05$) and 4 weeks ($P < 0.01$) compared to baseline but there was no difference between the two groups.

Serum IgE determinations

IgE values on the patients were all within normal limits (200–400 $\mu\text{g/ml}$) with the exception of one patient who had 660 $\mu\text{g/ml}$.

Nasal examinations

Tabulation of a score for appearance of nasal mucosa and secretion based on a grading system of severity showed great variation from patient to patient and no significant change in secretions over time.

Nasal smear for eosinophils

There were no differences in the eosinophil counts on nasal smear between groups comparing baseline with 2 and 4 weeks. Although there was a trend toward a decreased count at 2 weeks, this was only maintained with P and P glycol.

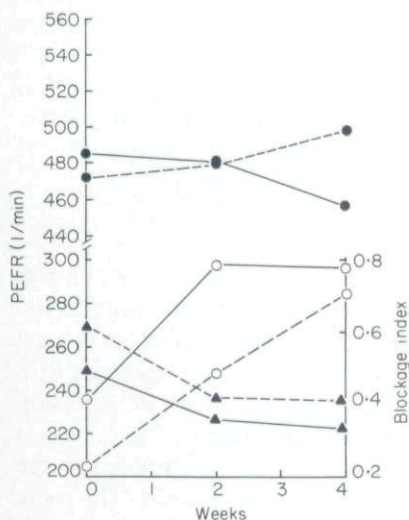


Fig. 2. Nasal and mouth peak expiratory flow measurements and blockage index (PEFR mouth—PEFR nose/PEFR mouth) obtained throughout the study comparing propylene and polyethylene glycol with saline. ●, Mouth PEFR; ○, nose PEFR; ▲, blockage index; —, P and P glycol; ---, saline.

Table 2. Nasal and mouth functions (PEFR), serum IgE and biopsy data on twelve patients with perennial rhinitis who received saline or propylene and polyethylene glycol

Patient number	Age (yr)	Sex	Treatment category*	Serum IgE ($\mu\text{g/ml}$)	(PEFR) Functions Nose/Mouth			Change in BI† baseline VRS 4 wk
					Baseline	2 wk	4 wk	
1	22	M	S	12	280/680	388/633	362/649	↓0.15
2	26	M	P	NA	378/NA	383/NA	NA/NA	Same (?)
3	26	M	S	NA	263/520	291/521	275/560	↑0.02
4	29	M	S	660	237/577	195/280	393/600	↓0.25
5	24	F	S	140	125/387	190/390	135/360	↓0.06
6	41	M	S	57	180/415	216/417	290/417	↓0.27
7	19	F	P	5.2	347/387	340/419	308/390	↑0.09
8	54	F	S	120	137/288	153/	130/240	↓0.06
9	24	F	P	11	220/400	253/380	275/377	↓0.18
10	63	F	P	68.5	NA/NA	110/NA	120/245	?
11	51	F	S	31.5	125/NA	157/NA	191/NA	↓0.23
12	24	F	P	7.4	83/365	252/432	NA/NA	↓0.35

* Treatment category: S=saline; P=propylene & polyethylene glycol.

† BI=blockage index. BI was estimated from available data or 2-week data when necessary.

Nasal airflow studies

In combining the two groups, there was a significant improvement in nasal functions after 2 weeks and 4 weeks as compared with baseline, but no difference between 2 and 4 weeks. Mouth functions did not differ statistically over time or between treatment groups. There was a significant decrease in the blockage index over time (Fig. 2 and Table 2). The difference was found between baseline and 2 weeks and baseline and 4 weeks ($P < 0.01$).

Side effects

Side effects were almost non-existent in both the P and P glycol and saline groups. Occasionally patients thought their nasal discharge increased perhaps from the administered solution itself.

Biopsy data

Two patients served as controls at the time of the study. An additional nine controls processed and read by one of the two pathologists are also included (see Jones *et al.*, 1979) in Table 3. A certain amount of inflammation was present in many of the normal biopsies. Table 3 also shows the biopsy data at baseline of the twelve patients with perennial rhinitis who had adequate baseline and 4-week specimens for analysis. Biopsy findings at baseline varied considerably among individuals. There was a significant difference between the baseline biopsies of the normals compared to the rhinitics only regarding the nasal mucosa; columnar epithelium was statistically more common in the normals. When the biopsies were compared to those after 4 weeks of treatment certain patterns were notable. Some individuals had normal appearing biopsies which would not be expected to change. Others had improvement in the

Table 3. Comparison of the baseline biopsies of normals with the baseline biopsy of rhinitic patients

Baseline biopsy of normals						Baseline biopsy of rhinitics					
Mucosa	BM*	Oedema†	Eosinophils per hpf	Mast cells per hpf	Plasma cells per hpf	Mucosa	BM*	Oedema†	EOS	Mast cells	Plasma cells
1 Col	I	0-1	0	0	1-2 Sq	1-2 Sq	A & I	0	0-2	1-2	0-2
Sq						Sq	I	0	0	0-1	0
2 Col	I	0-1	0	3-5	0-1 Sq	0-1 Sq	I	0	0	0-4	0-4
3 Col	I	0-1	10-15	0-1	3-5 Col	3-5 Col	A & Th	2	20	7	0-2
						& Sq					
4 Col	I	2	0-3	2-3	1-2 Sq	1-2 Sq	I & Th	1	0-2	0	2-3
						& Col					
5 Col	I	0-1	1-2								
6 Col	I	1	0-1	1-2	1-2 Sq	1-2 Sq	I & A	0	0	0	0
7 Col	I	1-2	2-4	3-5	2-5 Col	2-5 Col	I & Th	2	0	0	0
Sq						Col	I & Th	0	0	3-4	0
8 Col	sI A	0	0-1	3-6	8-12 Sq	8-12 Sq	I, A & Th	2	0-1	0-1	0-1
						& Col					
9 Col	I	0	0	3-5	0 Sq	0 Sq	I, Ab, Th	0	0	10-20	0
						& Col					
10 Col	I	1	0	0-1	2-4 Sq	2-4 Sq	Th	2	10	0-1	0-1
						& Col					
11 Col	I	0	4-6	0	0 Sq	0 Sq	Th & I	1	0	4-6	0
						& Col					

* Basement membrane: I = intact; A = attenuated; Th = thickened; Ab = absent.

† Oedema: 0 = none; 1 = mild; 2 = moderate; 3-4 = marked.

Table 4. Four week biopsy data and pathologists' evaluation of change in the perennial rhinitic patients

Mucosa	BM*	Oedema†	EOS	Mast cells	Plasma cells†	Pathologists evaluation of change
Col	I and A	0-1	0-1	1-3	0-1	Better
Sq & Col	I	1	0-1	0	0-1	Same
Col	I	0	0	0	0-4	Same
Col	A and I	2	2-4	0-4	0	Better
Sq & Col	I, A, Th	0	0	1-2	0	Same
Sq	I and A	0	0	0	0	Same
Sq & Col	I and A	1	0-1	2-3	1	Same
Sq & Col	I, A, Ab	2	10	0-2	1	Worse
Sq & Col	A	1	0	0-1	0	Better
Sq & Col	Ab, Th	1	0	4-7	0	Better
Sq & Col	Th	1	0-1	4-5	0	Better
Sq	I	0	0	1-2	0	Same

* † Key as in Table 3.

biopsy findings after 4 weeks of treatment (Table 4). One of the pathologists was asked to grade the paired biopsies as to 'better', 'same' or 'worse' and was blinded as to which was obtained at baseline versus 4 weeks. His results (Table 4) were compared to the percentage change in blockage index after 4 weeks. By the method of linear regression, there was a good correlation ($r=0.68$) and significant relationship between these two parameters ($P<0.01$). In all specimens examined, mucous glands appeared normal so no special comments about them are included.

Discussion

To our knowledge, this is the first double-blind randomized study that systematically examines the effect of two wetting agents in the treatment of perennial rhinitis. Although it is not uncommon for a placebo group to show some benefit as part of a 'placebo effect' (Benson & Epstein, 1975). Jones and co-authors (1979) reported that placebo could significantly improve certain objective parameters such as nasal blockage, nasal secretions and even the percentage of nasal eosinophils on smear. Spector *et al.* (1980) also showed that post-treatment nasal biopsies usually showed improvement over the baseline nasal biopsies. Although many popular textbooks in allergy and immunology do not mention moisturizing agents as part of the treatment of perennial rhinitis (Spector *et al.*, 1976; Tennebaum, 1972; Seebohm, 1978). One textbook, however, specifically mentions the beneficial value of instilling moisturizing agents alone into the nose (De Weese & Saunders, 1973). In a previous study, we were surprised at the objective changes that occurred after P and P glycol and wondered if there was something special about it or if a more common wetting agent such as saline could prove to be beneficial. The first study was done in Denver with a dry climate, the second in Jerusalem with a slightly higher humidity. Our study revealed no obvious difference between the two wetting agents, both being most useful in decreasing nasal stuffiness. The effect of long term use is still not known. Interestingly, Turkeltaub *et al.*

(1976) described three patients with allergic rhinitis who noted transient irritation following inhalation of P and P glycol. One additional patient developed irritation during the last two weeks of treatment.

Biopsies on normal individuals were necessary to put the findings of these patients in proper perspective. Thus, eosinophils, mast cells, and other inflammatory cells often are a component of a so-called normal biopsy and these inflammatory cells probably have the function of combating foreign substances that come in contact with the nose. One of the characteristic findings of a normal biopsy in this biopsy location was the presence of columnar epithelium. The change of epithelium from squamous to columnar in some of the patients corresponded to clinical worsening. However, the pathologist graded the total biopsy including oedema and number of inflammatory cells when assessing possible improvement.

From the results of the study, wetting agents offer another therapy that can be tried in certain individuals with perennial rhinitis. A substance such as saline is associated with none of the side effects commonly present with other well known agents used in the treatment of rhinitis such as sleepiness with antihistamines, and hypertension with decongestants. Another possibility is to utilize wetting agents concomitant with these other agents but in smaller doses. As one would predict from the biopsy findings, perennial rhinitis is really a heterogeneous group of illnesses that affect the nose. Biopsies have potential in predicting those patients who might respond to wetting agents or even other commonly used agents. They correlated in this study with improvement in the blockage index.

Other investigators have reported on results of nasal biopsies, but detailed description of a placebo group is lacking. Knight *et al.* (1979) concluded that beclomethasone did not significantly change the histological picture seen in successive biopsies although eosinophilic infiltrates appeared to decline. On the other hand, Mygind *et al.* (1978) also biopsied the nose after beclomethasone steroid aerosol and found a significant decrease in oedema, eosinophils and goblet cells. Almost an equal number of his patients demonstrated a change in their biopsy towards pseudostratified epithelium as towards squamous epithelium. However, his biopsies were not taken from the same location as ours. Any investigators who have studied perennial rhinitis have pointed out the heterogeneity of the patients represented in this condition. Connell (1976) has reported on the different histological pictures in patients with perennial rhinitis. Mygind (1976) suggested at least three subgroups (Mygind, 1979): perennial allergic rhinitis, perennial intrinsic rhinitis, and perennial cholinergic rhinitis. The patients in our study most appropriately would fit into the latter category. Such differences in populations might easily lead to differences in results. Malm *et al.* (1976) found that the nasal blockage and secretions were significantly less during placebo treatments than during the week without treatment. His patients were skin-test negative (as ours) and had vasomotor rhinitis. The subpopulation of skin test negative patients of Schulz *et al.* (1978) also did not show a statistically different response comparing placebo with flunisolide. In fact, these investigators were impressed enough by the 'higher placebo effect' to make special comment that the viscous solution used as a vehicle for flunisolide was 'in itself therapeutic for the nasal mucosa'. It's hard to assess appropriately the real incidence of improvement with placebo for two obvious reasons: (1) those studies which might show no difference between placebo and active aerosols probably would not readily get published and (2) individual patient responses are usually not shown and therefore, responders in a subgroup of a population are not discussed.

In summary, solutions of both saline and P and P glycol were associated with subjective and objective improvement in patients with perennial rhinitis. Such wetting agents merit a trial before (or probably along with) other therapeutic agents which are associated with more unpleasant side effects.

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References

- BENSON, H. & EPSTEIN, M.D. (1975) The placebo effect; a neglected asset in the care of patients. *Journal of the American Medical Association*, **232**, 1225.
- CONNELL, J.T. (1976) Bronchial asthma-mechanisms and therapeutics. In: *Allergic Rhinitis* (eds E. B. Weiss and M. S. Segal), p. 481. Little, Brown & Co., Boston.
- DE WEESE, D.E. & SAUNDERS, W.H. (1973) The nasal septum; rhinoplasty; maxillary and nasal fractures. In: *Textbook of Otolaryngology*, p. 214. C. V. Mosby Co., St. Louis.
- JONES, L.M., SPECTOR, S.L., ENGLISH, G.M. & TAYLOR-DAWSON, K.T. (1979) Treatment of perennial rhinitis with flunisolide corticosteroid spray. *Annals of Allergy*, **42**, 139.
- KNIGHT, A., UNDERDOWN, B.J., CONNELL, J.T., NEDZELSKI, J. & ELIE, R. (1979) Immunological parameters in perennial rhinitis. *Clinical Allergy*, **9**, 159.
- MALM, L. & WIHL, J.O. (1976) Intranasal beclomethasone dipropionate in vasomotor rhinitis. *Acta Allergologica*, **31**, 245.
- MYGIND, N. (1979) Clinical investigation of allergic rhinitis and allied conditions. *Allergy*, **34**, 195.
- MYGIND, N., SORENSEN, H. & PEDERSEN, C.B. (1978) The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol. *Acta Otolaryngologica*, **85**, 437.
- SCHULZ, J.I., JOHNSON, J.D. & FREEDMAN, S.O. (1978) Double-blind trial comparing flunisolide and placebo for the treatment of perennial rhinitis. *Clinical Allergy*, **8**, 313.
- SEEBORN, P.M. (1978) Allergic and nonallergic rhinitis. In: *Allergy and Principles and Practice*. Vol. 2 (eds E. Middleton Jr, C. E. Reed & E. F. Ellis), pp. 868-876. C. V. Mosby Co., Saint Louis.
- SIEGEL, S. (1956) *Nonparametric Statistics*, p. 75-83, p. 116-127. McGraw Hill, New York.
- SPECTOR, S.L., FARR, R.S. & HARNETT, J.C. (1976) The interface between allergy and otolaryngology. In: *A Textbook of Otolaryngology* (ed. G. E. Emglish), pp. 291-312. Harper & Row Publishers, Inc., Maryland.
- SPECTOR, S.L., ENGLISH, G.M. & JONES, L. (1980) Clinical and nasal biopsy responses to treatment of perennial rhinitis. *Journal of Allergy Clinical Immunology*, **66**, 129.
- TAYLOR, G., MACNEIL, A.R. & FREED, D.L. (1973) Assessing degree of nasal potency by measuring peak expiratory flow rate through the nose. *Journal of Allergy and Clinical Immunology*, **52**, 193.
- TENNENBAUM, J.I. (1972) Allergic rhinitis. In: *Allergic Diseases Diagnosis and Management* (ed. R. Patterson), pp. 161-196. J. B. Lippincott Co., Philadelphia, PA.
- TURKELTAUB, P.C., NORMAL, P.S. & CREPEA, S. (1976) Treatment of ragweed hay fever with an intranasal spray containing flunisolide, a new synthetic corticosteroid. *Journal of Allergy and Clinical Immunology*, **58**, 597.
- WINER, B.J. (1971) *Statistical Principles in Experimental Design*, 2nd edn, pp. 196-201. McGraw Hill, New York.

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