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Treatment of perennial allergic rhinitis by local hyperthermia

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ABSTRACT **Ninety-five patients with documented perennial allergic rhinitis have been treated with local hyperthermia of the nasal passages in a randomized double-blind trial. The treatment consisted of one series of three 30-min insufflations of humidified air at 43°C at a 2-hr interval. In the active treatment group, 75% ($P < 0.00003$) and 68% ($P < 0.00001$) of the patients were free of symptoms 1 week and 1 month, respectively, after treatment, compared with a 28% and 17% response in the placebo group. We conclude that local hyperthermia is effective in the treatment of perennial allergic rhinitis.**

One of the factors controlling viral virulence is the sensitivity of viral development to temperature. The more thermoresistant the vegetative phase, the more virulent the virus. The capacity to replicate at pyrexial temperature is one of the factors of virulence. Experiments performed on various animal species infected with a number of viruses have shown that hyperthermy decreases the severity of viral infections whereas hypothermy increases the severity (1–9). It has been postulated (10) that fever and local hyperthermy are among the defense mechanisms against viral diseases—a viewpoint now widely accepted. Moreover, we know how hyperthermy works (11). Man is expected to react to hyperthermy as experimental animals do. However, no link has yet been established between the ability of man to develop fever and the ability to better withstand or overcome a viral infection.

Due to the cooling produced by air flow, the temperature of nasal turbinates varies between 31°C and 35°C (12, 13), thus allowing the development of rhinoviruses, the main agents of common cold. Patients suffering from this disease have been treated, in double-blind tests, by three 30-min insufflations (at 2-hr intervals) of humidified air at 43°C. This suppressed the symptoms in 78% of the patients—that is, cured the coryza (14).

No theoretical concept allowed one to foresee that hyperthermia would be efficient against perennial allergic rhinitis; surprisingly, it proved to be effective (14). In order to strengthen our conclusions, we have carried out a further clinical test with such patients. This report summarizes the results of double-blind randomized clinical trials.

MATERIALS AND METHODS

The Rhinotherm (patent pending) was developed on the basis of experience gained with local tumor hyperthermia in experimental animals (15, 16), and in human patients (17). It was designed and built by one of us (A.Y.) and G. Ben-Moshe at the Radiation Unit of the Weizmann Institute of Science and will be described in detail elsewhere. Hot air (43°C) humidified (water particles 4–8 μm in diameter) emerging through two exhaust nozzles is insufflated into the nasal passages. The exhaust nozzles are 1.5 cm from the nostrils. Temperature reversal by inhalation and exhalation must be avoided: the air inflow and the kinetic energy are regulated in such a way that air penetrates the nasal passages while exhalation through the nose is avoided. Each device was checked and calibrated before the start of treatment which causes neither increased pressure in the nasal passages nor discomfort to the patient.

Temperature Measurements. The ideal mode of temperature measurement would be a direct reading of the temperature of the nasal epithelium during treatment. However, it is difficult to maintain a good surface-sensor contact; suturing is unethical and would result in inflammation. The problems of nasal tract temperature measurement are well known and the temperature recorded in the nasal tract of normal healthy humans varies from 31°C to 36.6°C (12, 18). We have placed a thermocouple on the nasal tract but could not completely control its position on the nasal surface for the whole treatment period (30 min). In our tests, the readings for the heated nasal passages (at 2.5 cm inside the nostrils) were around 43°C, a temperature that represents a combination of the inflowing hot air temperature and of the tissue temperature during treatment. Temperatures at 1-min intervals are shown in Fig. 1.

Patients. The study population consisted of 95 patients (53 males and 42 females) with an average age of 30.5 years (range, 5–72). Patients were selected on the basis of a history of perennial allergic rhinitis characterized by typical symptomatic manifestations. A full medical history of all patients was taken, including duration of disease, age at onset, family history of atopy with specific reference to any other disease, tests against common allergens, nasal provocation test, and severity of present symptoms of rhinitis. Additionally, onset of persistent symptoms must have been at least 1 year prior to admission into the study, and symptoms had to have been severe enough to require treatment.

Physical examination included anterior rhinoscopy with special attention to the color of the mucous membranes, type of nasal discharge, and degree of obstruction of the nose. Sinus x-rays were interpreted independently by a radiologist. Leukocyte counts were performed on all patients. Nasal smears were examined for eosinophils and bacterial flora. Skin tests were performed with the prick technique using disposable hypodermic needles on normal skin, according to accepted methods, and nasal provocation tests were carried out. Allergens were grouped into three main classes: pollens, molds, and inhalants. The pollen group included grass mixture (Bermuda grass, Johnson grass, Orchard grass, redtop grass, rye perennial grass), mugwort, sagebrush, timothy, sunflower, cultivated oats, cultivated wheat, acacia, orange, olive, tree of heaven, and eucalyptus. The molds group included actinomycetes, *Alternaria*, *Candida albicans*, *Hormodendrum*, *Mucor*, *Penicillium* mixture, *Aspergillus fumigatus*, *Aspergillus* mixture, and yeast

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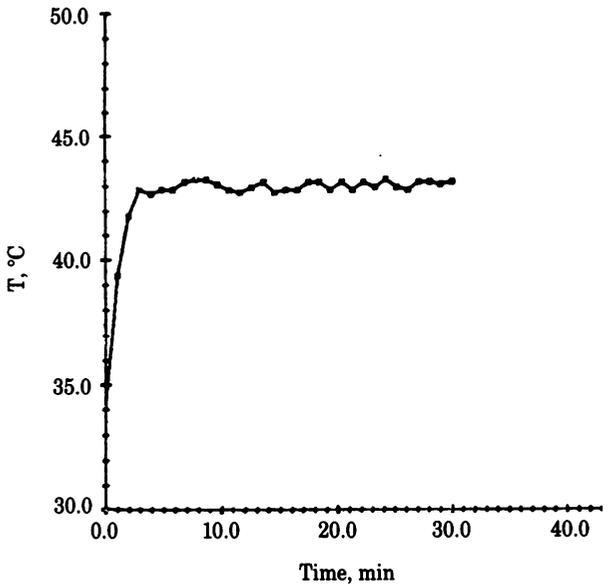

FIG. 1. Intranasal temperature readings during treatment, measured 2.5 cm inside the nostrils, at 1-min intervals.

mixture. The inhalant group included house dust mite, house dust, dust-endo, dust fortified mixture, feather mixture, human hair, and animal hair. Patients were also tested for allergic reactions to insects (honey bee, wasp mixture, mosquito mixture, stinging insect mixture, and nonstinging insects) and foods (whole cow's milk, cheese, egg yolk, egg white, whole egg, beef, chicken, lamb, pork, turkey, veal, anchovy, herring, codfish, sardine, tuna mixture, chocolate, and coffee).

No patient had taken corticosteroid medication in the month before admission. The patients had been in a desensitization program within the previous 2–3 years but had not received an allergen extract within the 4 weeks before admission. All patients were allergic at least to one of the factors as confirmed by skin test and history and displayed nasal congestion, itching, sneezing, blockage of the nose, and nasal discharge (Table 1). For two weeks before the trial, the patients avoided the use of vasoconstrictors, antihistaminics, antibiotics, corticosteroids, anti-inflammatory drugs, or any drug that could affect the results. Asthmatic patients were instructed to continue with their routine therapy without corticosteroids.

Patients with acute sinusitis, severe respiratory infections, severe bronchial asthma, or severe obstruction due to anatomic variation and patients suffering from medication abuse (rhinitis medicamentosa) or who were dependent on corticosteroids were excluded from the study.

Treatment and Follow-Up. Devices were identical in external appearance; the placebo device emitted 5% of the air ejected by the active device and this air was at room temperature. A code system was used so that neither patient nor physician knew who received active treatment and who received placebo. After informed consent was obtained, patients were treated with either the active or placebo device on a double-blind randomized basis. The patients were told that treatment was to be at different temperatures, without preference for any fixed temperature. Each patient was subjected to three 30-min sessions within the same day, at 2-hr intervals. Assessment of results was based on nasal examination and on the severity of symptoms (sneezing, blockage, running, and itching) as observed by the clinician before and 1, 7, and 30 days after treatment and as recorded in the patient's diary. Disappearance of symptoms was taken as a positive response to treatment.

Table 1. Clinical characteristics of patients before treatment

	Active treatment (67 patients)	Placebo (28 patients)
Symptoms:		
Itching	49	17
Sneezing	62	26
Blockage of nose	64	26
Itching + sneezing	45	16
Itching + sneezing + blockage of nose	43	15
Sinusitis	11	4
Nasal discharge:		
Purulent	9	4
Mucoid	29	8
Watery	65	28
Allergic sensitivity		
Pollens	25	7
Molds	11	7
Inhalants	31	8
Pollen + mold	9	5
Pollen + inhalant	21	4
Mold + inhalant	10	5
Pollen + mold + inhalant	8	4
Blood eosinophils:		
1–5%	36	18
6–10%	16	7
>10%	15	5
Full family history	28	12
Age range, years	5–72	9–59

RESULTS

All the patients who entered the trial had documented perennial allergic rhinitis and previous hyposensitization. They previously had been subjected to conventional treatments—e.g., antihistaminics, desensitization, steroid sprays, Lomudal spray, and Rynacrom. These treatments had been either temporarily effective or not effective at all.

Sixty-seven patients underwent active treatment, and 28 patients were in the placebo group; 31 patients in the active treatment group and 10 patients in the placebo group had exacerbated symptoms prior to treatment.

Anterior rhinoscopy prior to treatment revealed that 42 patients in the active treatment group and 20 in the placebo group had pale-blue to gray mucous edema; 8 patients of the active treatment group and 3 of the placebo group had red inflamed mucosa. Hypertrophy of the turbinates was found in 16 patients of the active group and 6 patients of the placebo group. Septal defects were found in 8 patients of the active and 4 patients of the placebo group. Nasal polyps were found in 11 patients of

Table 2. Pooled follow-up data on all patients in study

	Patients, no.	Patients free of symptoms			
		At 1 week		At 1 month	
		No.	%	No.	%
Active treatment	67	50	75*	46	69†
Placebo	28	8	29	5	18
Mean age, yr:	32				
Range	12–72				
Disease duration, yr:					
Mean	11				
Range	1–40				

* For difference from placebo, $P < 0.00003$.
† For difference from placebo, $P < 0.00001$.

Table 3. Detailed follow-up data on patients according to their sensitivity to allergens

Patient status	Active treatment					Placebo				
		Free of symptoms					Free of symptoms			
		1 week		1 month			1 week		1 month	
	n*	No.	%	No.	%	n*	No.	%	No.	%
Pollens	25	18	72	16	64	7	2	28	0	—
Molds	11	8	73	8	73	7	2	28	0	—
Inhalants	31	23	74	20	65	8	2	25	2	25
Pollen + mold	9	6	67	7	78	5	1	20	0	—
Pollen + inhalant	21	15	71	14	67	4	1	25	0	—
Mold + inhalant	10	7	70	7	70	5	1	20	0	—
Pollen + mold + inhalant	8	6	75	6	75	4	1	25	0	—
With exacerbation	31	23	74	20	64	10	2	20	1	10
Without exacerbation	36	26	72	26	72	18	3	16	3	16
Blood eosinophils:										
1–5%	36	26	72	23	64	18	4	22	3	16
6–10%	16	10	63	11	69	7	2	28	1	14
>10%	15	14	93	10	67	5	1	20	0	—

For difference between active treatment and placebo: $P < 0.00001$ by χ^2; $P < 0.05$ by analysis of variance.
* n = Total number in group.

the active and in 6 patients of the placebo group.

Table 2 summarizes the overall results obtained in this study. In the active treatment group, 75% ($P < 0.00003$) and 69% ($P < 0.00001$) of the treated patients were free of symptoms 1 week and 1 month, respectively, after treatment, compared with 28% and 17% in the placebo group. Table 3 summarizes the results of treatment in patients with different allergic characteristics. In patients allergic to pollens, molds, or inhalants alone or to all three allergens, the response was around 75% positive at 1 week and about 70% at 1 month after treatment ($P < 0.00001$ by χ^2 test). By analysis of variance (19), the null hypothesis is rejected at the 0.05 level; hence we take a small risk of being wrong. The table shows also that the response was fairly uniform in patients with different amounts of eosinophils. It is noteworthy that, in the active treatment group, the results obtained 1 week and 1 month after treatment were close to each other. In contrast, the response in the placebo group dropped to 0 at 1 month after treatment in 7 of the 12 subgroups presented in Table 3.

Table 5. Results of active treatment after placebo

Treatment	Patients, no.	Free of symptoms, no.			
		At 1 week		At 1 month	
		No.	%	No.	%
Placebo	19	5	26	1	5
Active treatment	19	12	63	12	63

After the 1-month follow-up, 19 of the 28 patients in the placebo group agreed to undergo active treatment and another 1 month of follow-up.

Table 4 summarizes the results according to symptoms. Response was analyzed in relation to each symptom and to the three main symptoms taken together. Nasal discharge was subdivided according to whether it was purulent, mucoid, or watery. The results demonstrate a significant difference between the active treatment and the placebo group responses. In patients with each symptom alone or with all three major symptoms, active treatment resulted in a response of around 70% at 1 week and around 65% at 1 month versus 14–15% in the placebo group ($P < 0.00001$ by χ^2 test and $P < 0.0035$ by analysis of variance).

At the end of the 1-month follow-up period, 19 patients of the placebo group agreed to undergo active treatment and another month of follow-up. This group served as a positive crossover test. Table 5 presents the results of the tests in this group 1 month after treatment. They are close to those achieved in the main study (Table 2).

All the patients found that the method of delivery of treatment was acceptable.

Side Effects. After treatment, nonsignificant short-duration side effects were noted in the active treatment group as follows: nasal irritation, 2 patients; cough, 1 patient (who had bronchial asthma); headache, 2 patients. In the placebo group, the results were: nasal irritation, 1 patient; headache, 2 patients. No treated patient had adverse changes in the nasal mucosa.

Table 4. Detailed follow-up data on patients according to symptoms

	Active treatment					Placebo				
		Free of symptoms					Free of symptoms			
		1 week		1 month			1 week		1 month	
	n*	No.	%	No.	%	n*	No.	%	No.	%
Itching	49	36	73	33	67	17	4	24	3	18
Sneezing	62	45	73	42	68	26	6	23	4	15
Blockage of nose	64	48	75	43	67	26	5	19	4	15
Itching + sneezing	45	33	73	30	68	16	4	25	3	19
Itching + sneezing + blockage	43	31	73	28	65	15	3	20	2	13
Discharge:										
Purulent	9	6	68	6	68	4	0	—	0	—
Mucoid	29	19	66	19	66	8	1	13	1	13
Watery	65	48	74	42	65	28	5	18	5	18

For difference between active treatment and placebo: $P < 0.0000$ by χ^2; $P < 0.0035$ by analysis of variance.
* n = Total number in group.

DISCUSSION

Perennial allergic rhinitis is a condition characterized by chronic symptoms including nasal obstruction, sneezing attacks, itching, and continuous watery nasal discharge due to an allergic reaction, without significant seasonal variation. Nonspecific irritants and infection may influence the course of the disease, and there are rhinitis patients who present symptoms not primarily associated with the nose and in whom skin tests and case histories indicate allergy. Allergic rhinitis accounts for the largest number of patients with respiratory allergy, and some of these patients develop asthma as a late sequela (20). Also patients suffering from this disease may develop complications due to chronic nasal inflammation.

The purpose of this study was to assess the efficacy of the Rhinotherm device, developed for applying local hyperthermia to the upper respiratory tract, in the treatment of perennial allergic rhinitis. All the treated patients had a well-documented medical history of allergic rhinitis, and their symptoms, as well as their sensitivity to allergens and past medication, were recorded for up to 40 years. The results obtained in this double-blind study were based upon physician assessment—i.e., examination of the patient before and 1 week and 1 month after treatment—and on the patient's diary. This assessment leads to the conclusion that local hyperthermia is effective in the treatment of perennial allergic rhinitis.

The febrile response with its associated symptoms is a specific reaction of the delayed hypersensitive type (21). It was suggested that the source of endogenous pyrogen in hypersensitivity fever is the hypersensitive cell itself (22). It has been shown that the anaphylactic release of histamine from guinea pig lung (23), rat mesentery (24), and human leukocytes (25) is abolished by preheating the tissue or cells at 45°C. Thus, there may be an optimal febrile response assisting the host's defense, as has been shown in the case of viral infection in the upper respiratory tract (14). It appears that absolute temperature itself is not as important as is the increase to a certain temperature above the temperature that is normal for the species—i.e., establishing a temperature gradient. Observations in humans and animals indicate that, at the beginning of infection, the nasal mucosal tissue might be 1–5°C below core temperature (13). Local hyperthermia applied to the nasal passages may enhance elements of the host's defense arsenal, increasing the host's defense against the conjugate factors leading to the symptoms of perennial allergic rhinitis. Indeed, the results show that during the first week after active treatment the symptoms disappeared in 75% of the treated patients and only in 28% of the placebo patients.

One month after treatment the positive responses were 68% and 17%, respectively. It should be emphasized that these results were achieved in the absence of medicine or drug taken by the patients 2 weeks before treatment and during the follow-up period.

Because perennial allergic rhinitis is a disease state that continues for a number of years, it is to be expected that chronic inflammatory changes will occur and that a psychic factor is involved, which poses the constant question raised in any double-blind trial: Is the placebo totally devoid of therapeutic activity? Undoubtedly in a disease such as perennial allergic rhinitis, particularly of many years' duration, there would be some placebo response, as can be seen from the results. Nevertheless, we have been able to demonstrate a clear-cut significant difference between the active treatment and the placebo as judged by both patient and clinician and a significant statistical difference between the two groups of patients with regard to nasal patency with almost no side-effects. The results obtained with active treatment in patients previously treated by the placebo are in line with the results obtained in this study. Of particular interest is the positive response in patients suffering from all the major symptoms and sensitive to all three groups of allergens tested.

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