

Study of prolonged hyposensitization with *D. pteronyssinus* extract in allergic rhinitis

SISTER MARY GABRIEL, H. K. Ng, W. G. L. ALLAN, LISA E. HILL and A. J. NUNN

Ruttonjee Sanatorium, Hong Kong, and MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, London

Summary

Sixty-six Chinese patients with rhinitis, with or without asthma, were randomly allocated to a course of injections either with *D. pteronyssinus* extract or placebo. The course consisted of 18-22 weekly injections, followed by monthly maintenance injections with the highest concentration for 1 year.

Progress was evaluated by a patient's daily diary and monthly assessments by the physician, by comparisons of skin and nasal challenge tests and by the specific serum IgE concentration, before treatment, at the end of the weekly course, and once during the maintenance course.

No improvement was detected at the end of the weekly course, but during maintenance there was a consistent benefit to the patients receiving the *D. pteronyssinus* extract both in the diary and the physician's assessment, especially the former. There was no consistent change in the skin or nasal challenge tests and there was a trivial fall in the serum IgE levels in the patients on the extract. Adverse reactions were much more common in the patients on the extract, but most were trivial.

The different methods of assessment used and the role of hyposensitization with *D. pteronyssinus* are discussed.

Introduction

The role of hyposensitization with *D. pteronyssinus* extract in the treatment of house dust allergy remains to be settled. The reported findings vary, but so has the design of the studies (Smith, 1971; D'Souza *et al.*, 1973; Taylor, Sanders & Norman, 1974). On the basis of clinical and laboratory assessments, it has been suggested that only some patients might derive benefit, and that a prolonged course of hyposensitization might be required (McAllen, Assem & Maunsell, 1970; D'Souza *et al.*, 1973; Assem & McAllen, 1973).

All of a group of ninety patients with extrinsic asthma in Hong Kong had a positive skin test to extracts of *D. pteronyssinus* and/or *D. farinae* (Pickering & Gabriel, 1973), as had 18% of a group of 575 patients being treated for bacteriologically confirmed

Correspondence: Dr Lisa Hill, MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, Fulham Road, London SW3 6HP.

pulmonary tuberculosis (Hong Kong Tuberculosis Treatment Services; British Medical Research Council, 1975). The present study was therefore undertaken to assess, in Hong Kong, in patients with allergic rhinitis, with or without asthma, the efficacy as well as the patient acceptability of (a), a conventional course of hyposensitization with a specific house dust mite extract of *D. pteronyssinus*, and (b), a subsequent prolonged maintenance course with the same extract.

Patients

Patients were eligible if they were Chinese, were aged 8 years or more, gave a history of perennial or seasonal rhinitis for at least 3 consecutive years, characterized by sneezing, nasal obstruction and discharge, with or without asthma, had a positive skin test and a positive nasal challenge to *D. pteronyssinus* extract, and were not currently receiving corticosteroids or nasal disodium cromoglycate.

Patients were stratified, by age, into two groups: children below the age of 12, and adults. They were randomly allocated either to desensitization with *D. pteronyssinus* extract (DP) or to placebo (P). The study was conducted double-blind, and with the informed consent of the patients or their parents.

Materials and methods

Skin testing

The DP was made up in four concentrations (0.005%, 0.04%, 0.30% and 1.20%) in a solution of 50% aqueous glycerine containing 0.5% phenol (only the 1.20% concentration is available commercially). The control solution consisted of the diluent only.

Nasal challenge testing

Three concentrations of the DP (0.005%, 0.04% and 0.30%) were made up in a solution of carbol saline (physiological saline with 0.5% phenol), the control consisting of the diluent only.

The vaccine

The vaccine for the desensitization course was prepared by the Bencard Division of the Beecham Laboratories, each patient having an individually labelled set of vials. For adults, and children aged 12 years or more (Table 1), three concentrations (0.003%, 0.025% and 0.20%) were used (the commercially available preparations are half the strength of these), and for children below the age of 12 a special dilute preparation (0.0004%) was used at the start of the course. The placebo consisted of physiological saline only.

Hyposensitization schedules

(1) *Weekly courses.* The schedules for weekly hyposensitization are set out in Table 1; children of 8–11 years could complete the course in 22 weeks, older children in 19 weeks and adults in 18 weeks. If adverse reactions occurred after a dose, the courses were longer because the concentration was reduced until no reaction occurred and was then increased again.

(2) *Monthly maintenance course.* For the maintenance course the highest dose of

Table 1. Hyposensitization schedule*

Strength of vaccine (%)	No. of dose	Dose size (ml) for patients aged:		
		8-11 years	12-15 years	16 or more
0.0004	1	0.2	—	—
	2	0.4	—	—
	3	0.7	—	—
	4	1.0	—	—
0.003	1	0.1	0.05	0.1
	2	0.2	0.1	0.2
	3	0.3	0.2	0.3
	4	0.5	0.3	0.5
	5	0.7	0.5	0.7
	6	1.0	0.7	1.0
	7	—	1.0	—
0.025 and 0.20	1	0.1	0.1	0.1
	2	0.2	0.2	0.2
	3	0.3	0.3	0.3
	4	0.5	0.5	0.5
	5	0.7	0.7	0.7
	6	1.0	1.0	1.0
Total number of doses		22	19	18

* Patients in the P series received corresponding numbers of injections of the placebo.

the strongest concentration was injected at 4-week intervals for 1 year, since, in the event, all the patients reached 1.0 ml of the highest concentration.

Pretreatment examination

Before admission patients were questioned about their history of allergy and of asthma, and were skin (prick) tested with house dust and the four concentrations of DP, and of nineteen other common allergens comprising moulds and yeast, grass, tree and shrub pollens, animal fur and feathers, and food protein. A test was reported as positive if a weal of 1 mm or more had developed by 15 min.

Nasal challenge tests were performed by spraying the nasal mucosa on one side with control solution. If no reaction, that is itching, sneezing or obstruction occurred, the other side was sprayed with the lowest concentration of DP. If no reaction occurred the second concentration was used, and if negative, the third. Total and specific serum IgE concentrations were measured, and a total white cell and an absolute eosinophil count were taken.

Assessments and investigations during the study

Progress during the study was assessed as follows:

The Patient's diary. The patient recorded daily the presence and severity of the symptoms of rhinitis (sneezing, obstruction and discharge) and of asthma, on a four-point scale (nil, mild, moderate, severe).

Monthly assessments. These were made by the physician in charge, who, without

access to the patient's diary, examined and questioned the patient concerning the nasal symptoms and asthma, recording them on the same scale as the patient.

Skin tests. These were repeated with the four concentrations of DP (a), at the end of the initial course of hyposensitization (usually 18–22 weeks), and (b), 12 months after the start of hyposensitization, that is, in the middle of the 12-month maintenance course.

Nasal challenge tests. These were performed on the same two occasions as the skin tests.

Other investigations. Specific serum IgE, IgG antibodies, total white cell count and eosinophil count were taken on the same two occasions as the skin tests.

Estimation of specific IgE and of IgG

The radioallergosorbent test or RAST using paper discs (Ceska, Eriksson & Varga, 1972) was used to determine specific IgE to *D. pteronyssinus*. The presence of IgG to *D. pteronyssinus* was determined by radioimmuno-electrophoresis in agar gel. The electrophoresed serum was precipitated with an anti-whole-human serum before the addition of the ^{125}I -labelled antigen (McConahey & Dixon, 1966), and X-ray films were developed to make visible specific antigen uptake by serum IgG.

Results

Seventy-two patients were admitted to the study between May, 1973 and March, 1974, thirty-seven being allocated to hyposensitization with *D. pteronyssinus* antigen (DP series) and thirty-five to the placebo (P series).

Status during and at end of the weekly course (18–22 weeks)

Population in the weekly course. Three patients (two DP, one P) were excluded because they had virtually no symptoms on admission, and three patients (two DP, one P) defaulted during the weekly course, leaving sixty-six patients: thirty-three in each group, for analysis of this phase. The two groups had a similar sex distribution, fourteen DP and eighteen P patients being male. Five DP and six P patients were under 12 years of age. There were twenty-two DP and twenty-two P patients who were subject to attacks of asthma. However in nearly all, the attacks were either so infrequent and/or so mild that it was not possible to assess whether hyposensitization led to any improvement. Only six patients had positive skin tests to DP alone. Nine had positive skin tests to one more allergen, eighteen to two more, eleven to three more, and twenty-two to at least four more. All the latter twenty-two had positive tests to fur, and seventeen of them to feathers. Fifty-six (85%) of the total of sixty-six patients had positive skin tests to fur, thirty-five (53%) to feathers, fifteen (23%) to pollen, eleven (17%) to food protein, and seven (11%) to moulds.

Weal size. The weal size elicited by the highest concentration of DP (the concentration which is commercially available) in the sixty patients with positive skin tests to one or more other allergens was larger than that due to any other allergen in forty-seven patients; it was the same size as the largest reaction in nine; and in the remaining four patients, one of the other allergens produced a larger weal.

The findings of the two series were very similar, and are not tabulated separately here.

Symptomatic improvement. No definite benefit to the DP patients was evident for any of the three symptoms during (data not tabulated here), or at the end of, the course

of weekly hyposensitization (Table 2), either on the patient's or the physician's assessment.

Skin and nasal challenge testing. Improvement in the skin and nasal challenge tests was considered to have occurred when, to evoke a response on re-testing, a higher concentration of the extract than at the pre-treatment test was required. Of twenty patients in each group who had positive skin tests before treatment to the lowest concentration of DP, ten DP and seven P patients reacted to a higher concentration on retesting. In all, fifteen DP (45%) and eleven P (33%) patients had reduced skin sensitivity, a non-significant difference (Table 3). Nasal challenge testing gave closely similar results, 30% of the DP and 36% of the P patients showing improvement (Table 3).

Table 2. Comparisons of improvement at the end of weekly course as assessed* by the patient's diary card and physician

Symptom	Series	Patient's diary card			Physician's assessment		
		No. of patients assessed	Improved		No. of patients assessed	Improved	
			No.	(%)		No.	(%)
Sneezing	DP	28	14	50	32	10	31
	P	31	10	32	32	9	28
Obstruction	DP	24	13	54	26	7	27
	P	24	10	42	30	11	37
Discharge	DP	32	11	32	31	7	23
	P	29	9	31	32	7	22
All symptoms	DP	33	9	27	33	1	3
	P	33	7	21	33	2	6

* The assessment was made in the 4 weeks following the completion of the weekly course. Since not all patients had all three symptoms present initially, the number of patients assessed for individual symptoms is less than the total. Also, the physician and the patient did not always agree on which symptoms were present.

Status during the monthly maintenance course

Exclusions. Sixteen patients (ten DP and six P) were excluded from the assessment of the maintenance course. Seven (three DP and four P) defaulted or left the country during the course, and six (five DP and one P) who had been admitted late completed the weekly course but did not complete their monthly maintenance course. Three (two DP and one P) were withdrawn, the P patient because, by mistake, the full course was not completed, and the two DP patients because moderately severe reactions occurred, which necessitated a return to weekly injections. These two patients have been included in the assessment of adverse reactions. Thus twenty-three DP and twenty-seven P patients were analysed for symptomatic improvement, but twenty-five DP patients were available for the analysis of adverse reactions.

Improvement in symptoms. Individual symptoms (sneezing, obstruction and discharge) showed consistent benefit to the DP patients (Fig. 1) as compared with the P patients throughout the period of maintenance injections, both in the diary and in the physician's assessment, but especially in obstruction and discharge as assessed by the

Table 3. Results of skin sensitivity tests and nasal challenge tests to DP pretrial, at end of weekly course and at 12 months after start

Test	Concentration of DP (%)	Assessment at the end of weekly course					Assessment at 12 months after start				
		DP			P		DP			P	
		No. with positive result pretrial	Improved* on retesting Total (%)	No. with positive result pretrial	Improved* on retesting Total (%)	No. with positive result pretrial	Improved* on retesting Total (%)	No. with positive result pretrial	Improved* on retesting Total (%)	No. with positive result pretrial	Improved* on retesting Total (%)
Skin	0.005	20	10	20	7	13	8	16	10		
	0.04	6	2	9	2	4	2	9	2		
	0.3	6	3	3	1	4	2	1	0		
	1.2	1	0	1	1	1	0	1	0		
Nasal challenge	0.005	4	3	10	5	3	2	7	6		
	0.04	10	6	12	6	7	3	10	4		
	0.3	19	1	11	1	12	2	10	1		
			30		36				32	41	

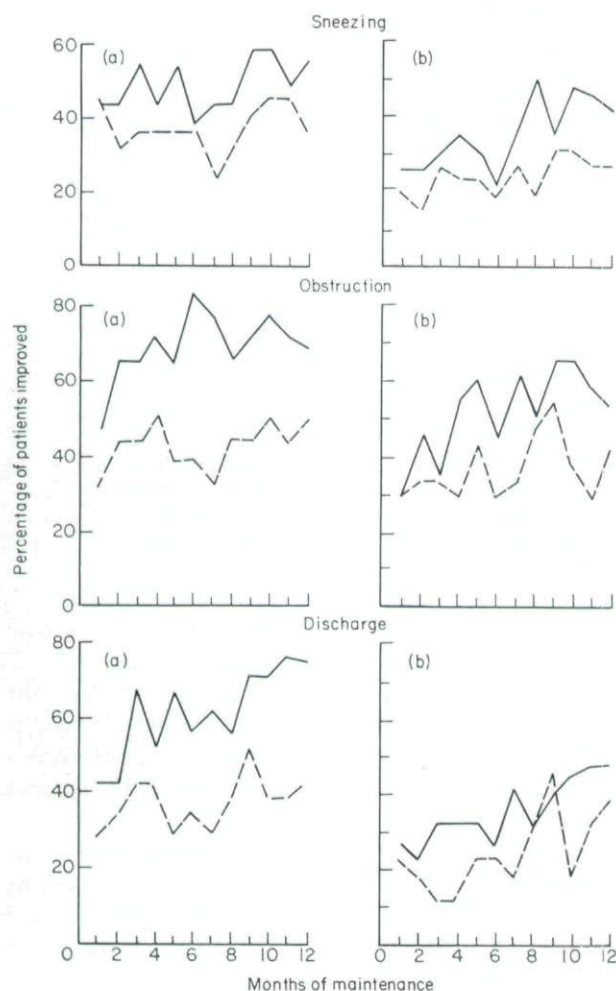


Fig. 1. Percentage of patients in whom individual symptoms were improved during the maintenance course, by patient's diary (a) and by physician's assessment (b). DP patients (—), P patients (---). For sneezing: (a) 55% of twenty-one DP patients and 36% of twenty-five P patients improved; (b) 41% of twenty-three DP patients and 27% of twenty-six P patients improved. For obstruction: (a) 69% of seventeen DP patients and 50% of eighteen P patients improved; (b) 53% of twenty DP patients and 42% of twenty-four P patients improved. For discharge: (a) 75% of twenty-one DP patients and 43% of twenty-three P patients improved; (b) 48% of twenty-one DP patients and 38% of twenty-six P patients improved. All comparisons at end of 12 months' maintenance.

patients. In the patients' assessment of discharge at the end of maintenance, improvement occurred in 32% more of the DP than the P patients.

When improvement in all the symptoms at the start was assessed (Fig. 2) (all three symptoms in twenty-nine, two of the three in seventeen and only one in four patients), the patient diaries showed progressive benefit to the DP series from 4 months onward, which was statistically significant at 12 months ($P = 0.02$). In contrast, the physician's assessment showed little difference between the two series at any time. An alternative assessment was the proportion of patients in whom all the symptoms present on admission were improved in *all* of the last 3 months. This was 43% of the DP and

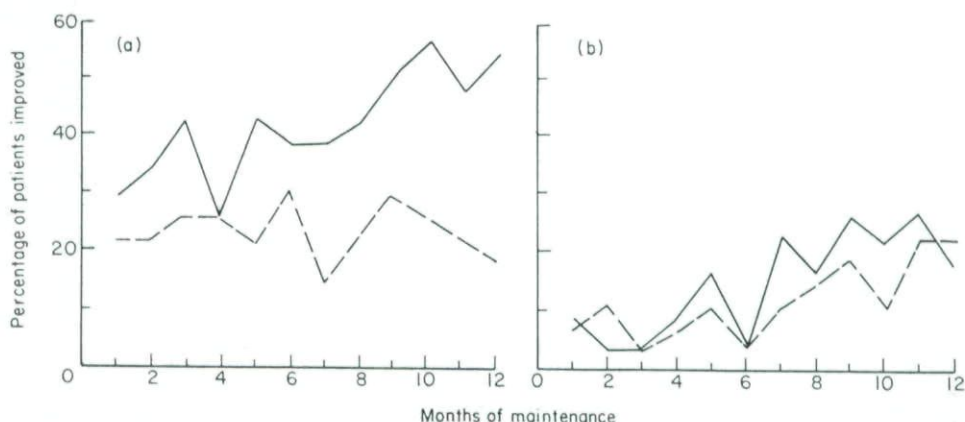


Fig. 2. Percentage of patients in whom all the symptoms present on admission were improved during the maintenance course, by patient's diary (a) and physician's assessment (b). DP patients (—), P patients (---). At the end of 12 months' maintenance: in (a), 55% of twenty-three DP patients and 19% of twenty-seven P patients improved; whilst in (b), 18% of twenty-three DP patients and 22% of twenty-seven P patients improved.

7% of the P series ($P = 0.01$) as assessed from the patient diaries. The corresponding proportions for the physician's assessment were 9% and 7% respectively.

The diaries were also analysed for the week preceding the patients' visit to the physician, to investigate whether the physician's assessments might reflect the symptoms recorded by the patient during that period rather than the whole month. However, the results of the analysis for that week were very similar to those for the whole month (data not tabulated).

Skin and nasal challenge tests. Skin and nasal challenge tests were repeated at the end of the weekly course and again 12 months after the start, that is, midway during the maintenance course (Table 3). There were only minor differences in the skin and nasal sensitivity of the DP and P series in the middle of the maintenance course, the position being very similar to that at the end of the weekly course.

Other investigations. The geometric mean of the specific serum IgE level on entry to the study was 2754 in twenty-three DP and 3631 in twenty-seven P patients. At the end of the weekly course of hyposensitization, the mean in the DP series was 2692, and 12 months after the start of hyposensitization had fallen to 2570 ($P = 0.05$). In the P series the corresponding mean values were 3715 and 3631. IgG antibodies to DP were present from the start in two DP and three P patients. They were doubtfully present in one further DP patient at the end of the weekly course, and had developed by the end of the monthly course in one P patient.

Changes in eosinophil counts were trivial in both series.

Adverse reactions

Weekly hyposensitization course. Adverse reactions were common, but mainly trivial. One or more occurred in 91% of the thirty-three DP patients, but in only 33% of the thirty-three P patients (Table 4). The average frequency of reactions was 9.2 per patient in the DP and 0.9 in the P series. These reactions are described below.

Cutaneous reactions. Localized reactions, that is erythema and swelling, with or without itching, occurred in 79% of the DP and 9% of the P series. They usually

Table 4. Adverse reactions during weekly course (thirty-three DP and thirty-three P patients)

Adverse reactions	Series			
	DP		P	
	No.	(%)	No.	(%)
Any	30	91	11	33
Cutaneous				
Localized	26	79	3	9
Generalized	2	6	1	3
Respiratory				
Rhinitis	3	9	2	6
Wheezing or asthma	2	6	2	6
Anaphylaxis	1	3	0	0
Other	3	9	3	9
Hyposensitization course prolonged	23	70	3	9

appeared immediately after the injection and subsided within 12–24 hours. Their average frequency was 8.3 per patient in the DP and 0.3 per patient in the P series. Generalized cutaneous reactions occurred in two DP patients and one P patient. One DP patient had a single episode; the other DP patient had two episodes of angioneurotic oedema affecting the face, and the P patient had rashes on two occasions.

Respiratory reactions. The symptoms of rhinitis were made worse in three (9%) of the DP and two (6%) of the P series on one occasion only, and those of asthma in two (6%) of the DP series (in one on six occasions and in the other associated with the anaphylactic shock reported below), and two (6%) of the P series (one on two occasions, the other on one occasion).

Other reactions. One DP patient had a short-lived anaphylactic shock, the injections were stopped for 7 weeks, but resumed at the patient's insistence without further incident.

Most patients experienced several types of reaction at different times during the weekly course. They caused delay in completing the course in 70% of the DP patients and in 9% of the P patients. The delay in 58% of the thirty-three DP and in all three P patients was less than 8 weeks. However, in four DP patients the delay lasted from 9 to 24 weeks. Adverse reactions did not prevent any patient reaching the maintenance dose of 1.0 ml of the highest concentration of extract.

Maintenance course. Adverse reactions occurred in 96% of the twenty-five DP and 11% of the twenty-seven P patients during the maintenance course. The frequency of adverse reactions was 7.2 per DP patient and 0.1 per P patient.

Cutaneous reactions. Localized cutaneous reactions were the most common and were present in 96% of the DP and 11% of the P patients with a frequency of 7.0 per DP patient and 0.1 per P patient. There were no generalized cutaneous reactions.

Respiratory reactions. In three DP patients the asthma became worse. In two this occurred on four occasions and resulted in the interruption of the maintenance

course, weekly hyposensitization with the strongest concentration being restarted. They then were able to return to the maintenance course uneventfully. The other patient had asthma only on one occasion.

Correlations with symptomatic improvement

It has been suggested that there might be a relationship between the symptomatic improvement and the degree of atopy (as shown by sensitivity to a number of antigens) and the fall in IgE level after hyposensitization. These factors were analysed but no correlations were found.

Discussion

The finding that improvement in the symptoms of rhinitis was absent during, and at the end of, the weekly course, and occurred only after prolonged hyposensitization, is in contrast with two other studies where early improvement was reported (Munro-Ashman *et al.*, 1971; Lees, 1974). However, in neither of these studies was detailed documentation presented of the individual symptoms of rhinitis or the degree of improvement, and the numbers of patients were small, twelve and ten respectively.

Most studies of the effect of hyposensitization with DP have examined the usefulness of this therapy in asthma, with or without rhinitis, and it seems that the response is not always the same for the two. Thus D'Souza *et al.* (1973) found improvement in the asthma symptoms at the end of a 12-week course of hyposensitization, but not in those of rhinitis, although nasal sensitivity was significantly reduced. This is in keeping with the suggestion of McAllen *et al.* (1970), that the reactivity thresholds of the lung and nasal tissues were different in the same patient. There has already been evidence from studies of hyposensitization for asthma that, in order to be effective, prolonged treatment of the kind used in the maintenance course in this study is required (Aas, 1971; Assem & McAllen, 1973). This was borne out in the present study for rhinitis so far as symptomatic improvement was concerned.

The assessment of overall clinical improvement, or of individual symptoms, may present difficulties. The patient's diary, while in general agreement with the physician's assessments, showed the greater improvement. When all the rhinitis symptoms were assessed together there was, however, a marked lack of agreement between the two: the patient's diary, unlike the physician's assessment, showing substantial benefit to the DP series over the whole period of maintenance. When the patient's diary was analysed for the week preceding the visit to the physician, on the assumption that the physician's assessment might only reflect the symptoms occurring in this period, the agreement between the two was no better, and the results from the diary for the week followed closely those for the whole month. The patient's diary, because it recorded symptoms day by day, is likely to be more reliable than the physician's assessment, because once a month he made a retrospective assessment for changes over the whole month.

Considering the more objective assessments of improvement in the present study there was no consistent change either in skin or nasal sensitivity at any stage.

D'Souza *et al.* (1973) found improved nasal tolerance, though no change in skin sensitivity. It is interesting that the prick test result which, before treatment, correlates closely and specifically with sensitivity to individual allergens, specific IgE and clinical provocations tests (Stenius *et al.*, 1971; Bryant, Burns & Lazarus, 1975), is not altered

by even prolonged hyposensitization. This lack of quantitative relationship has already been fully documented by McAllen *et al.* (1970), and thus there is little value in skin testing, or nasal challenge, as a means of assessing improvement.

Adverse reactions were much more common with the DP than with the placebo, and although they were by no means trivial, they were not so severe as to make unacceptable the concentration of the extract used in this study, which was twice that commercially available.

Because of the uncertainty of improvement, the difficulties of assessing whether it has been achieved, and the occurrence of adverse reactions, it is important to select, if possible, those patients who are most likely to benefit from this therapy.

It has been suggested that the patients with a single allergy to DP, as shown by a positive skin test to *D. pteronyssinus* only, are more likely to obtain benefit from hyposensitization with DP (Smith, 1971; Assem & McAllen, 1973; Choovoravech, 1974). Unfortunately, in the present study, there were only three such patients who completed the maintenance course, so this point could not be investigated. However, more information on this aspect would be of obvious value.

It has also been suggested that there are positive correlations between the severity of atopy before treatment (as measured by skin and nasal sensitivity), the specific IgE levels, the fall in IgE after hyposensitization, and the improvement in symptoms after hyposensitization (D'Souza *et al.*, 1973; Miller, 1971). No such correlations could be found in the present study, although the numbers were small, nor in the study of McAllen *et al.* (1970). In the present study there was a statistically significant, but trivial, fall in the IgE level in the patients in the DP series.

Even if patients likely to benefit can be identified with more certainty, the physician, when faced with individual patients, will have to decide whether the amount of benefit likely to be obtained warrants a course of over 30 injections over a period of approximately 18 months, and with the possibility of adverse reactions occurring, even though most of these are trivial. In clinical practice he will have to weigh the merits of hyposensitization, especially in view of its duration, against the claims of alternative treatments such as antihistamines, sodium cromoglycate or locally acting steroids.

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