Acta Dermatovener (Stockholm) Suppl. 92: 121–127, 1980

EXPERIMENTAL TREATMENT IN ATOPIC DERMATITIS: IMMUNOLOGICAL BACKGROUND AND PRELIMINARY RESULTS

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Abstract. Experimental treatment in atopic dermatitis was undertaken with transfer factor, hyposensitization, or topical sodium chromoglycate. Both transfer factor and hyposensitization in open trials produced some clinical benefit. In both cases all patients could be controlled with medium strength topical steroids during therapy. In the latter case consumption of topical steroid was measured and found to decrease. Improvement generally followed a decrease in serum IgE after an initial rise. No significant changes in T-lymphocytes or serum IgE were observed during transfer factor therapy. Topically applied sodium chromoglycate 10% in white soft paraffin in a double-blind trial was no better than the placebo.

Key words: Hyposensitization; Transfer factor; Topical sodium cromoglycate

Management of severe atopic dermatitis (AD) is a great challenge to dermatology. As stated by Rajka (13) almost every conceivable internal remedy, which has been used anywhere in the world for recalcitrant skin diseases has been tried in AD, but only a few drugs have stood the test of time. The data we wish to present here are, as stated in the title, both experimental and preliminary. They do not seem to solve the overall problems of treatment in AD, but may, however, add somewhat to our understanding of it. We report here on three trials, one with Transfer Factor (TF), one with hyposensitization (HS), and one with topical sodium chromoglycate (SCG).

TRANSFER FACTOR

Patients with severe AD have in general a pronounced increase of IgE in their serum (4, 8). They also often show signs of a decrease in cell-mediated immune reactivity, such as decreased skin reactivity, low numbers of circulating T-lymphocytes in peripheral blood, a decrease of PHA reactivity of lymphocytes, and immunosuppressive factors in serum (3, 11, 15). Also, it has recently been shown that atopics seem to have an impaired monocyte function (9). Most of these findings fit well within the framework of Szentivanyi's beta adrenergic theory of the atopic abnormality (15).

The lack of immunological balance may be a major factor in the occurrence of atopic symptoms. The decrease in cell-mediated immune reactivity and its possible significance for the occurrence of symptoms has led to the use of immune-stimulation therapy in patients with atopic dermatitis. Our own results with TF (10) in mycosis fungoides, where patients during therapy showed an increase in the number of circulating T-lymphocytes and a decrease in serum IgE, together with two promising case reports from 1975 (1, 14), where TF improved clinical symptoms in AD, led us to try this therapeutical approach in 3 adult patients. All 3 had decreased numbers of T-lymphocytes in peripheral blood, no release of migration inhibitory factor (MIF) after PPD-stimulation, immunosuppressive factors for DNA synthesis in serum, and high levels of IgE.

The effect of TF was evaluated clinically and *in vitro*. There was an improvement in the patients' disease in that there were no admissions during the treatment period of 1½ years, compared with tree, two and one admission during the preceding 1½ years. Also, during the last 12 months of treatment, none of the patients had secondary bacterial infections, and their use of topical steroids could be limited to a medium-strength preparation (Locoid®). It should be pointed out, however, that none of the patients ceased to have clinically pronounced AD. Fig. 1 gives an indication of the number of T-lymphocytes in blood. The number was low from the beginning, but continued to be so throughout the treatment. In general, the variations observed were similar to the variations found in healthy donors. Fig. 2 shows the patients' *in vitro* reactivity to PPD in a leukocyte migration test. Most of the migration indices were

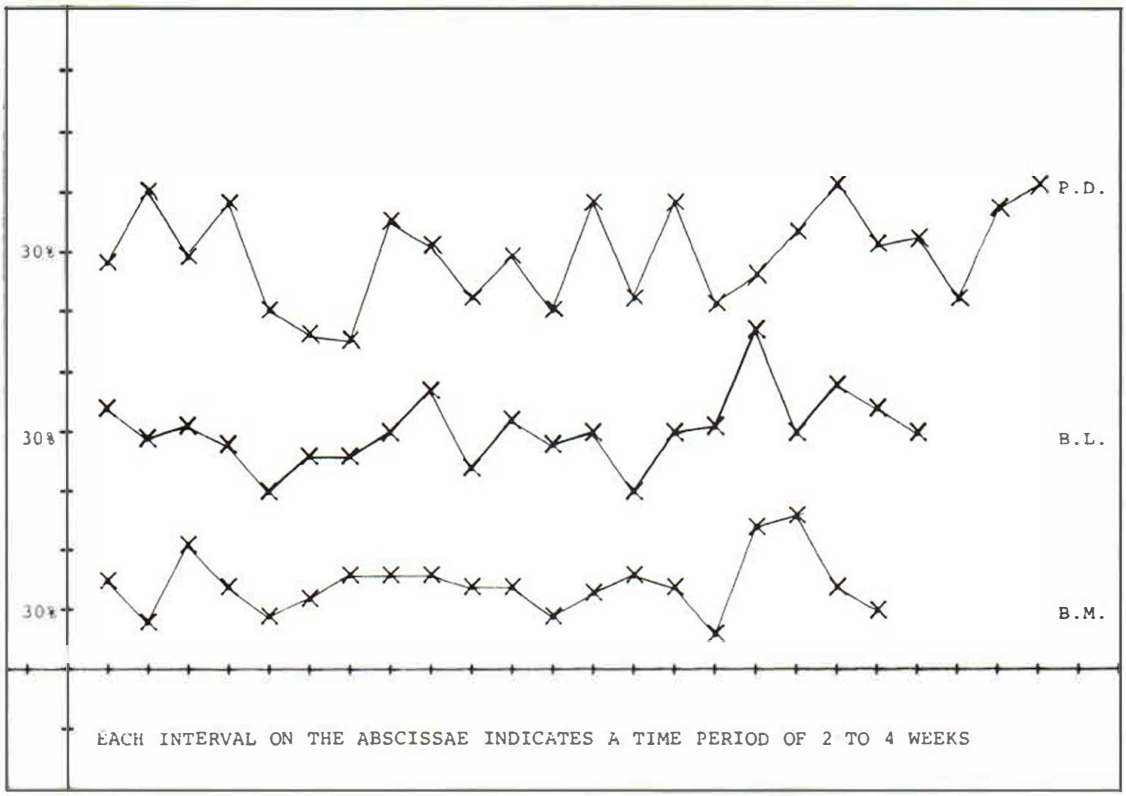

Fig. 1. E-rosette forming lymphocytes in patients with atopic dermatitis during treatment with transfer factor.

found in the upper part of the normal range, indicating only slight inhibition. It should be noted, however, that low values appeared early during treatment. This could be an effect of TF.

Immunosuppressive factors in serum were sought by adding patient's serum to lymphocyte cultures from two healthy donors and stimulating the lymphocytes with PHA. In one patient we found immunosuppressive factors during the first 6 months of treatment (Fig. 3). In another patient immunosuppressive factors were found on one occasion early during treatment.

Fig. 4 shows the variation in IgE levels in the patients' sera. Again we found variations, but none related to treatment.

The only double-blind trial so far (7) did not show

Table 1. *Clinical response following hyposensitization together with responses in serum IgE*

Pat. no.	Age/sex	Length of treatment (months)	IgE (units)			Clinical response
			Before	Highest	Latest	
1	32/F	24	3 680	4 480	2 490	Improved
2	32/F	24	6 370	7 500	3 540	Improved
3	58/F	20	11 300	22 900	3 970	Improved
4	23/M	18	4 418	9 450	6 570	Improved
5	31/F	22	2 550	7 200	2 730	Slightly improved
6	45/F	26	1 790	3 110	2 930	Slightly improved
7	33/F	24	1 580	1 860	1 510	Slightly improved
8	25/F	30	4 930	5 010	4 890	Unchanged
9	33/M	15	4 261	10 400	6 540	Worse

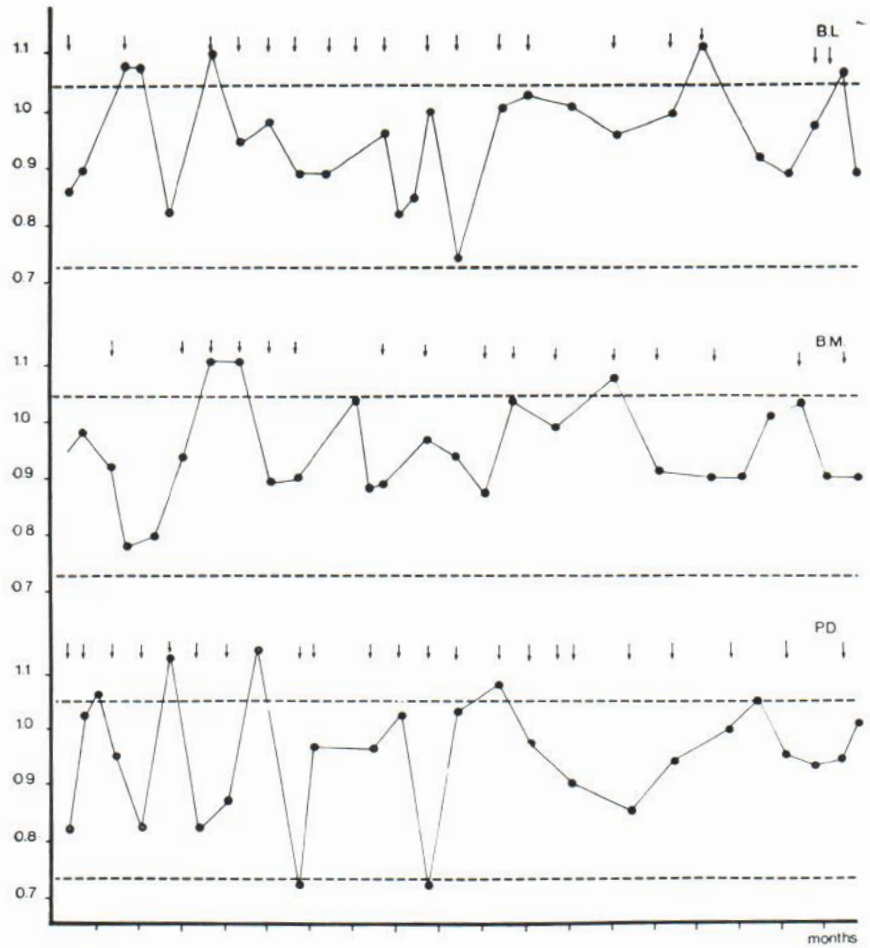

Fig. 2. Variations in cellular immunity to PPD as determined in vitro by the leukocyte migration test. The results are expressed as ratios between the migration areas in cultures with AB serum and PPD, and with AB serum alone. The range for normal persons is indicated as the average migration index (0.88)$\pm 2 \times$ S.D. Arrows indicate the times of transfer factor injections.

any beneficial clinical effect. We have recently started a double-blind trial of TF in 12 adult patients with AD. The dosage is higher than used by others and increased in comparison with our first open study. The dosage being 2 units, equivalent to extracts from 1×10^9 leukocytes every other week. The patients will be treated for 1 year. Among our initial laboratory findings, which included studies on subpopulations of T-lymphocytes in altogether 16 patients, we found a slight reduction of T-lymphocytes with F_c-receptors for IgG (Fig. 5), whereas the subpopulation with receptors for IgM was found to be slightly increased (Fig. 6). Findings during therapy are not yet available.

Table II. *Urinary histamine per 24 hours in 7 atopics prior to and following 6 months of hyposensitization*

	Urinary histamine (μg/24 h)	
	Before	After
4	37	
4	37	37
6	156	63
7	75	60
8	34	118
9	47	120
10	28	69
11	51	28
Average$\pm$S.D.	61$\pm$45	71$\pm$36

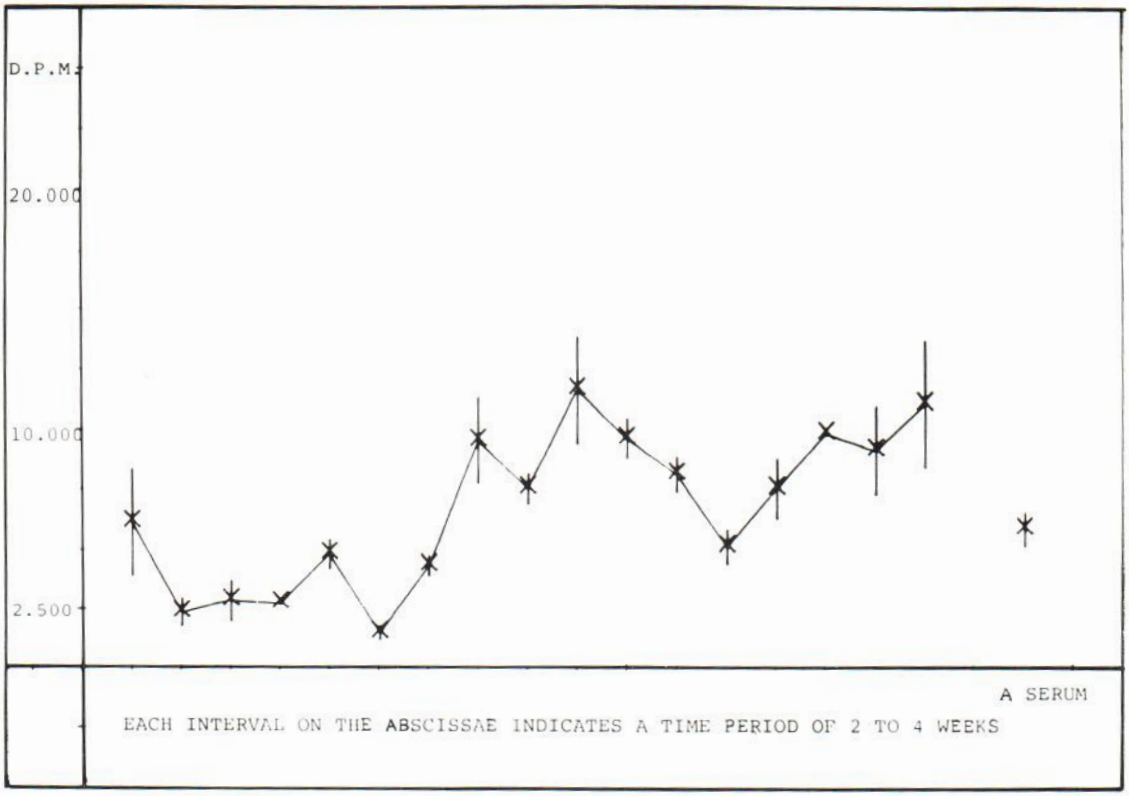

Fig. 3. PHA reactivity of lymphocytes from one normal donor after addition of 10% serum, measured by sub-optimal PHA concentrations in cultures.

SPECIFIC THERAPY

How hyposensitization works in respiratory atopics is not fully understood, but it is a common finding that following an initial increase in serum IgE, this parameter later decreases (2, 5, 13). The concept of an effect of blocking antigens which act against reagins (IgE) is still attractive to many allergologists, while others suggest that hyposensitization acts rather by a stimulation of specific suppressor T-lymphocytes (5).

Table III. *Average consumption of Locoid® cream during hyposensitization, in 6-month periods*

	Period no.			
	1	2	3	4
No. of patients	9	9	9	7
Consumption (g)	355	205	95	103

Due to conflicting data on the results of hyposensitization (13) in AD, we felt it reasonable to restudy this approach in patients with severe disease, using an allergen which is constantly found in the sensitized patients' environment.

Nine patients sensitive to housedust mites were hyposensitized. Injections were given in increasing dosages with intervals increased from 1 to 8 weeks. All patients were allowed to use a medium-strength topical steroid (Locoid®) according to their needs. The cream or ointment was delivered by us and the amounts used were measured.

Four of 9 patients improved (Table I), 3 patients showd slight improvement, one was unchanged, while one patient—the patient treated for the shortest period—was found worse. Most (but not all) patients followed the pattern of an increase in serum IgE, followed by a decrease. Urinary histamine (Table II) was studied in 7 patients (12) and was found unchanged following 6 months of treatment and generally to be within normal values. One

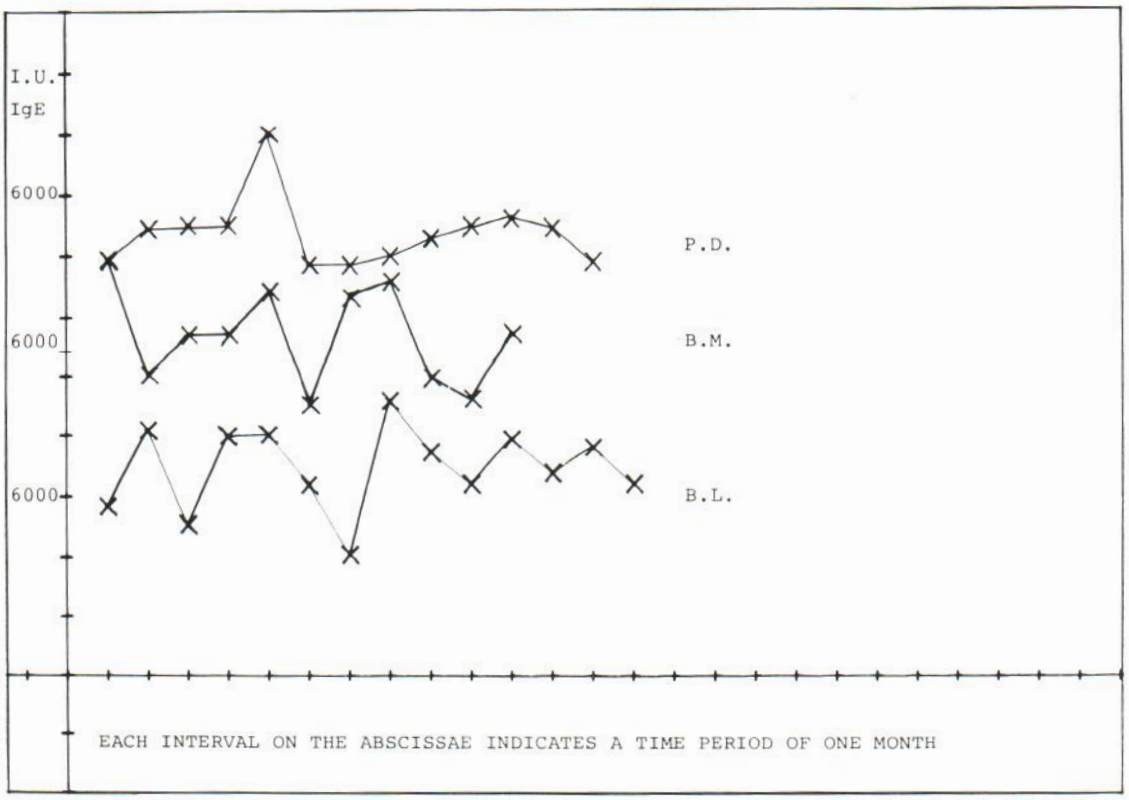

Fig. 4. IgE in serum during transfer factor treatment in patients with atopic dermatitis.

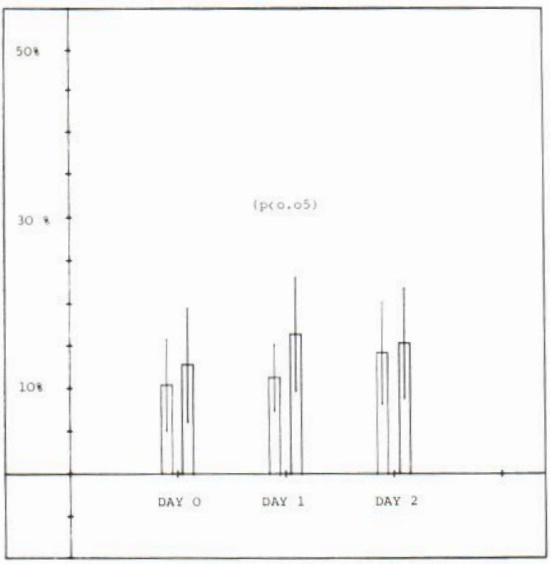

Fig. 5. Tγ-lymphocytes in peripheral blood from patients with atopic dermatitis and from normal donors.

parameter, however, indicated a more general improvement; the consumption of topical steroids (Table III) was reduced during treatment. It is our present opinion that it is worthwhile to proceed with investigations into the effect of hyposensitization in severe AD. This is especially so because we have today better allergen extracts and better tools with which to monitor the immunological status of the patients.

SODIUM CHROMOGLYCATE

Sodium chromoglycate (SCG) was first introduced as a prophylactic agent in the long-term management of asthma. The most important mode of action is believed to be related to its ability to inhibit mast cell degranulation and mediator release. The beneficial clinical effect found in allergic asthma,

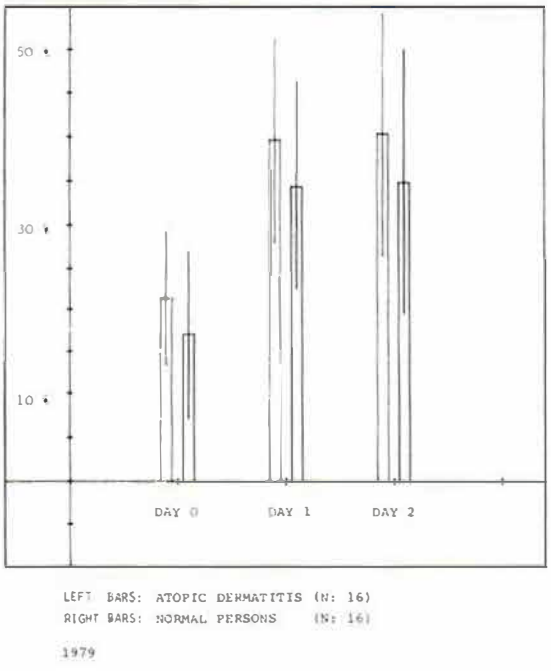

Fig. 6. Tμ-lymphocytes in peripheral blood from patients with atopic dermatitis and from normal donors.

allergic rhinitis, and allergic conjunctivitis has suggested a trial also in AD, in spite of the different target organ and the less well known pathogenesis. A preliminary double-blind trial was carried out by Haider (5) and suggested an effect. We have reported (17) on another, more recent trial on topically applied SCG.

A total of 35 children with AD, aged 2½–15 years were entered into the study. Almost all patients were using a topical steroid at the time of trial entry. 17 were on a double-blind basis allocated the active preparation 10% SCG in soft white paraffin, while 18 received placebo. The ointment was applied twice daily.

The clinical evaluation consisted of assessments of redness, dryness, lichenification, cracking, hyperkeratoses, excoriation and scaling graded from 0 to 3. Diary cards included the patient's or parents' evaluation of itch, sleep, and severity of condition.

Analyses of diary cards, weekly score totals, and of assessments, revealed only a single significant difference favouring the active preparation: fewer excoriations were found on the lower limbs at week 1. Nine patients in the placebo group and 7 in the SCG-treated group dropped out of the study before completion, the chief reason being worsening of the skin symptoms.

It was our conclusion, that in contrast to the work of Haider, we were not successful in controlling our patients with topically applied SCG, and in our hands the active drug was no better than the placebo. The lack of effect could have been due to a too low dosage, poor penetration into the skin, or a lack of pharmacological effect on main pathogenic mechanisms.

COMMENTS

In conclusion, none of our three experimental trials has given us the answer to the problem of management of the patient with severe AD. We do feel, however, that none of the three approaches should be discarded at present. We find it necessary to continue to study attempts at IgE regulation in atopic dermatitis as well as trials with new pharmacological agents.

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DISCUSSION

Bonifazi (Bari). Q: Did those patients who improved with house dust, hyposensitization also have respiratory allergy? I would also like to know your opinion about the possible prophylactic significance of this type of treatment in children with AD having a family history of respiratory allergy with housedust antibodies—that is, that we are afraid will develop into respiratory allergy.

A: Respiratory allergy was not a major problem in these patients, but two of them had it. The major problem was extensive and very severe skin disease and we chose this group because we had an antigen which would be in the patients' environment all year round and was scarcely related to the seasons. About the future use in children, our allergens are better made today and many of the studies which were undertaken by dermatologists previously were done for too short a period, I would believe. I think one should use the experiments of the allergologists and proceed for up to three years before making an evaluation of the patients.

Vickers (Liverpool). Q: Do you think the reason why the chromoglycate is not effective in most of the trials is that we are not using it for long enough and it may be that we should go on for 2 to 3 months before abandoning what would be such an attractive drug locally?

A: We used it for 6 weeks and I can assure you that the patients and the parents found that that was at least 3 weeks too long. It would not have been possible to continue further.