FAILURE OF TRANSFER FACTOR THERAPY IN
ATOPIC DERMATITIS

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Abstract. A controlled clinical study was conducted on 6 patients with atopic dermatitis to assess the efficacy of transfer factor. After the code was broken the 3 patients treated with placebo preparation were treated with transfer factor for a further period of 10 weeks. No definite therapeutic effects could be demonstrated. The immunological in vivo and in vitro tests failed to reveal any effects except for a change to positive in the tuberculin skin test in those patients who had previously been skin test negative. The treatment had to be discontinued in one patient due to a suspected allergic reaction against transfer factor.

Key words: Hypersensitivity, delayed

During recent years Transfer Factor (TF) has been used as a therapeutic and immunorestorant agent in patients with immunodeficiency diseases such as Wiskott-Aldrich's syndrome (13), and chronic candidiasis (2). Patients with atopic dermatitis (AD) have both in vivo and in vitro signs of depressed cell-mediated immunity (7, 15) and immunological disturbances still remain when the eczema is almost healed, indicating that there may be a basic primary abnormality in the immune system (8). They also often have increased serum levels of IgE and it has been demonstrated in rats (16) that a defective suppressor function of the T lymphocytes may cause increased IgE production. As TF has been reported to restore depressed cell-mediated immunity in immunodeficiency diseases, it might be of interest to study the immunological and clinical effects of TF therapy in patients with AD.

MATERIAL AND METHODS

Patient selection
Four women and 2 men were enrolled in the study. All patients were over 18 years old and suffered from severe atopic dermatitis. None of the patients had severe asthma or rhinitis. During the periods of investigation the patients used hydrocortisone creams locally, antihistamine tablets when they suffered from severe pruritus, and antibiotics when they had secondary infection of the skin.

Transfer Factor preparation
The preparation of TF was performed essentially as described by Basten et al. (2) and will be reported in detail elsewhere. Briefly, buffy coats from normal blood donors, all tested and found negative for HB,Ag (Hepatitis B surface antigen) by radioimmunoassay, were pooled and the mononuclear leukocytes purified by centrifugation over a Ficoll-hypaque gradient (Lymphoprep, Nyegaard, Norway) (5). The cells were frozen and thawed ten times in distilled water and ultrafiltered in a Sartorius system (SM 1625 apparatus; SM 12136 membranes). After passing through a 0.22 μm Millipore filter the ultrafiltrate was ammoniated, lyophilized and stored at -20°C until used. The content in each ampoule, one unit of TF, corresponds to 5 x 10⁸ E-rosetting lymphocytes (7-8 x 10⁶ leukocytes). The peptide content was estimated by using fluorescamine (19) (Fluram; Roche, Basle, Switzerland) with bovine insulin (Sigma, St. Louis, USA) as a standard. The ability of TF to augment the response to pokeweed mitogen (PWM) and PPD was tested in the lymphocyte transformation test (LTT) using lymphocytes from healthy adults.

Transfer Factor therapy
One unit of TF dissolved in 4 ml saline solution was given i.m. once a week for 10 weeks. The first part of the study (January-April 1977) was performed as a double-blind investigation in which 3 patients were given TF and 3 patients injections of saline solution. The second part (September-December 1977) was done as an open study where the patients who previously had received placebo were treated with TF.

Clinical evaluation
Clinical evaluations were performed before, during and after the periods of treatment. The extent of active dermatitis (percentage of total body surface), pruritus and secondary infections were recorded. Photographs of involved skin areas were taken before and after the test periods.

Immunological evaluation
Test for immunological evaluation were performed before and after the periods of treatment. Intracutaneous (i.c.) tests were carried out with 0.1 ml PPD-tuberculin 2 T.U. (Statens seruminstitut, Copenhagen, Denmark). 0.1 ml
### Table I. Results of TF and placebo treatment in patients with atopic dermatitis

<table>
<thead>
<tr>
<th>Activity of the dermatitis</th>
<th>Treatment</th>
<th>Patient</th>
<th>IgE/S U/ml</th>
<th>Tuberculin skin test</th>
<th>LTT with PPD (ratios)</th>
<th>T-cells in peripheral blood x 10⁹/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First test period</td>
<td>TF</td>
<td>LE before ++ 7 400</td>
<td>Neg</td>
<td>1.3</td>
<td>1.0</td>
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<tr>
<td></td>
<td></td>
<td>LE after ++ 4 500</td>
<td>Pos</td>
<td>1.9</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SL before + 9 300</td>
<td>Pos</td>
<td>3.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SL after + 11 500</td>
<td>Pos</td>
<td>13.3</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KH before ++ 9 000</td>
<td>Neg</td>
<td>1.6</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KH after ++ 11 900</td>
<td>Pos</td>
<td>2.2</td>
<td>1.4</td>
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<tr>
<td></td>
<td></td>
<td>Placebo UK before + 600</td>
<td>Neg</td>
<td>2.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo UK after ++ 1 100</td>
<td>Neg</td>
<td>–</td>
<td>1.1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Placebo UM before ++ 11 500</td>
<td>Pos</td>
<td>4.9</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>Placebo UM after ++ 4 100</td>
<td>Pos</td>
<td>4.1</td>
<td>0.9</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Placebo KM before ++ 5 800</td>
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<td>7.8</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo KM after + 3 100</td>
<td>Neg</td>
<td>3.5</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second test period</td>
<td>TF</td>
<td>UK before ++ 810</td>
<td>Pos</td>
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<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK after ++</td>
<td>(11x10 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UM before ++ 6 200</td>
<td>See under Results</td>
<td>4.8</td>
<td>1.0</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>UM after ++</td>
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</tr>
<tr>
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<td></td>
<td>KM before + 2 600</td>
<td>Pos</td>
<td>5.3</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>KM after +</td>
<td>(10x10 mm)</td>
<td></td>
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</tbody>
</table>

**Controls (9)**

- **Candida albicans** diluted 1/1000 (Vitrum, Stockholm, Sweden), 0.1 ml trichophyton vaccine (Sächsisches Serumwerk KG, Dresden, DDR) and 0.1 ml TF solution. The tests were read after 30 min and 72 hours.

  *Lymphocyte transformation tests were performed as described previously* (7). The following mitogens and antigens were used: PHA 1 µg/10⁶ cells/ml, ConA 50 µg/10⁶ cells/ml, PPD 1 µg/10⁶ cells/ml and herpes simplex antigen diluted 1/20. E-binding (T) rosette assays were performed as described previously (8) and the absolute numbers of T lymphocytes in peripheral blood were calculated after leukocyte and differential counting. Serum levels of IgE were determined by the PRIST method (commercial method, Pharmacia, Uppsala, Sweden).

**RESULTS**

The TF-batches used had a mean OD 260/OD 280 value of 2.46 (range 2.19–2.64) and the estimated peptide content varied between 16 and 38 mg/unit.

In the LTT, TF augmented the response to PWM and PPD in a dose-dependent manner with a decline at TF concentrations above and below the concentration giving maximum response.

The results of the therapy are given in Table I. No definite therapeutic effect of the TF treatment could be demonstrated in any of the patients. One of the patients (L. E.), who exhibited a marked tendency to secondary infections of the skin, demonstrated no such infections during the period of TF treatment. He experienced less pruritus but, although subjectively improved, the extent of the eczema was not reduced objectively. Another patient (U. M.) had an exacerbation of the eczema during the TF therapy and at the end of the therapy the skin tests were difficult to evaluate as the patient had developed erythrodermic skin.

In the immunological tests we found that the 4 patients who had previously been tuberculin skin
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After the 5th injection because of a highly suspicious immediate hypersensitivity reaction against TF. To our knowledge, no such side effects have been reported previously. The risk of allergic reactions from TF has been said to be minimal, as TF consists of very low-molecular products (<10,000 Daltons) and is considered to be non-antigenic in man and animals (9). The TF batch used for this patient was subjected to gel filtration on Sephadex G-100 to determine whether high molecular weight aggregates had been formed during lyophilization. No material with an estimated molecular weight above 5000 Daltons was found.

However, patients with atopy have a strong tendency to acquire reagin-mediated hypersensitivity and few patients with atopy have been treated with TF. Thus there may be a risk for hypersensitivity reactions against TF in this category of patients. In this investigation we were not able to confirm the promising results of TF therapy previously reported (1, 14). There may be many reasons to account for this.

It is unknown whether the depressed cell-mediated immunity in AD is primary or secondary. If the disturbances are secondary to the eczema, no clinical effects of TF therapy would be expected. Even if the disturbances in the immunity are primary, we still do not know where in the immune system the primary defect is located. Thus it is uncertain whether a drug, such as TF, can correct these immunological disturbances.

There are no good methods for testing the activity of TF for desired immunological effects. Thus different batches may have different activities and indeed both stimulative (3, 11) and suppressive (4, 12) activities have been found in chromatographic fractions of TF, using in vitro methods.

Another difficulty, due to the lack of methods to quantitate TF activity, is the schedule of treatment, i.e., the dose and the intervals between the injections. This may be very important, as many mechanisms in the immune system show a dose-response in regard to activating factors with a decline at concentrations above and below the concentration giving maximum response, e.g., high- and low-dose tolerance and mitogen responsiveness (10). This is also the case for the in vitro activity of TF in our experience. Therefore we believe that a true clinical evaluation of TF as a therapeutic agent can be accomplished only with a purified and clearly characterized substance.

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