

From the Department of Dermatology, Marselisborg Hospital, The Department of Internal Medicine, Aarhus County Hospital and the Institute of Medical Microbiology, University of Aarhus, Aarhus, Denmark.

TRANSFER FACTOR AS AN ADDITIONAL THERAPEUTIC AGENT IN MYCOSIS FUNGOIDES

By

H. ZACHARIAE, E. GRUNNET, J. ELLEGAARD &
K. THESTRUP-PEDERSEN

During recent years, transfer factor (TF) has been given to a number of patients with immunodeficiency diseases, such as Wiskott-Aldrich's syndrome (5) and chronic mucocutaneous candidiasis (6). Lately TF has also been used to intensify cell-mediated immunity in patients with relative immunological defects (1, 7). Although mycosis fungoides seems to be a T-cell lymphoma (9), a number of patients with this disease show a reduced ability to develop cellular immunity (8). It would, therefore, be reasonable to try TF in addition to other therapeutic measures in patients not responding to conventional treatment.

We report on the use of dialysable TF as an additional therapeutic agent in a patient with mycosis fungoides, who had not responded to nitrogen mustard, methotrexate or grenz rays alone.

CASE REPORT

A 64-year-old male was admitted to the Department of Dermatology in May 1973 because of: a 1½ year history of general itching; the appearance of scaly erythematous plaques localized to the sacral region and elbows; eczematous reac-

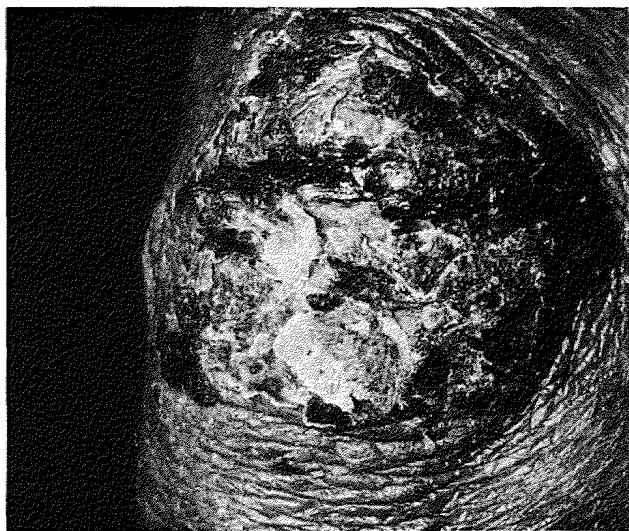


Fig. 1.

Ulcerated tumor on elbow prior to treatment.

tions of hands and feet; and a 2-month history of a more generalized erythroderma.

Prior to the onset of these signs and symptoms, the patient stated that he had been in excellent health, except for a period with lower back pain in 1946 and an abscess on the lung in 1927.

There was no history of previous skin diseases, no family history of allergy or skin diseases, and especially no family history of psoriasis.

Physical examination findings were essentially within normal limits, except for the skin which showed ulcerated, somewhat psoriasiform plaques and tumors located on the elbows (Fig. 1) and the gluteal area (Fig. 2), together with heavy keratotic infiltrations of palms (Fig. 3) and soles with many fissures (Fig. 4). The patient also showed a more generalized, but not too pronounced, scaly erythroderma.



Fig. 2.

Mycosis fungoides plaque in gluteal area prior to treatment. Note scaly erythroderma of adjacent skin.

A biopsy (Fig. 5 & 6) showed an infiltrate in the upper as well as in the lower dermis, consisting of a multiplicity of cell types and pleomorphism of histiocytes, together with atypical reticulum cells with large hyperchromatic nuclei and Pautrier's microabscesses in the epidermis.

A diagnosis of mycosis fungoides was made and treatment was started with topical nitrogen mustard (Fig. 7). The treatment lasted from May 21st till June 8th without effect on the tumors or infiltrations; the more generalized erythroderma responded to topical steroids. However, as the patient was severely disabled by the ulcerations of his hands and feet, methotrexate was given from June 28th till September 5th; in all 10 dosages of 5 mg four times once a week with 8 hour intervals. This treatment had no effect on the lesions.



Fig. 3.

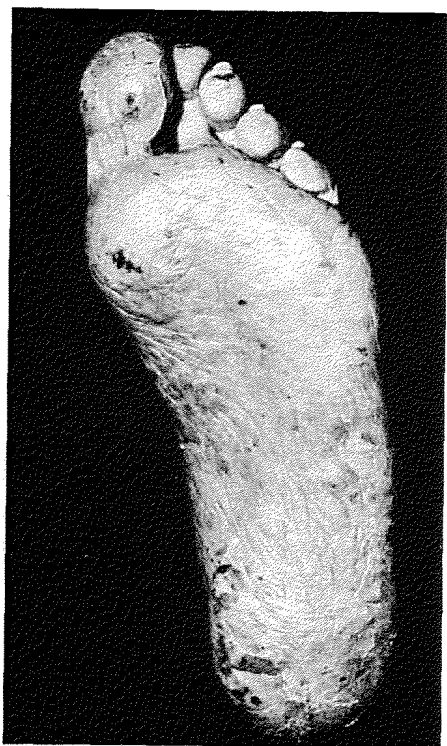
Keratotic erythematous and scaly infiltration of skin of palms prior to treatment.

It was therefore decided in September to start treatment with TF and at the same time give X-rays to the tumors in order to reduce tumor load. X-rays were given to tumors only; that is to mycosis fungoides lesions on elbows and the gluteal area. In all, the patient received 900 r (50 kV 1 mm Al) from October 3rd, 1973 to April 2nd, 1974. Grenz rays were given on three occasions to the hands and feet, but this treatment was discontinued because the patient had the impression that treatment aggravated the disease. Nitrogen mustard was also administered on three occasions during the period from December 1973 till May 1974.

TF was given intramuscularly six times in all, with approximately 1 month intervals, as it has been our experience that a TF-induced increase in delayed hypersensitivity lasts approximately 4 weeks (Fig. 8 & 9). As the patient seemed to go

Fig. 4.

Fissures and infiltration of skin on the soles of the feet prior to treatment.



into a total remission in May 1974 (Figs. 10 to 13), all treatment was discontinued. This remission has now lasted 11 months.

Transfer Factor

The donors of the leucocytes for the TF preparations were young, healthy male or female volunteers who exhibited positive reactions to skin testing with PPD.

An amount of 500 ml of venous blood was drawn into a glass containing 20,000 I.U. of phenol-free heparin. The

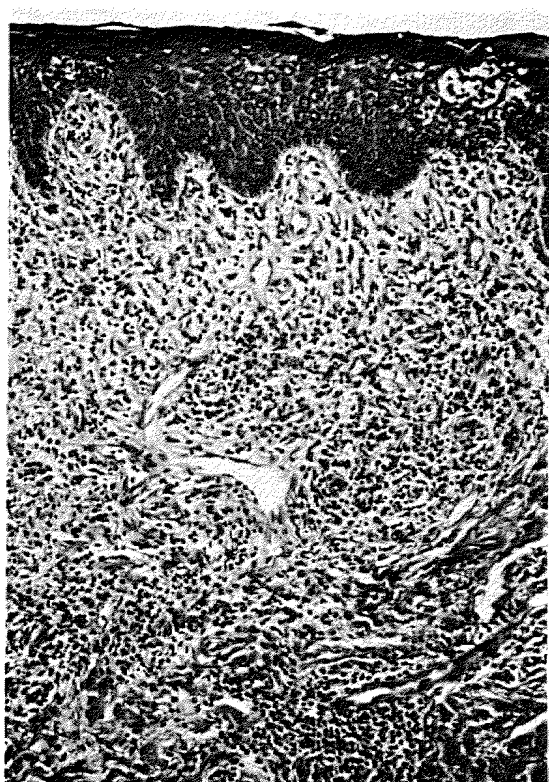


Fig. 5.

Photomicrograph of biopsy from mycosis fungoides plaque from elbow. Note Pautrier's microabscesses in the epidermis and the diffuse infiltrate in the upper dermis together with a more sharply demarcated patchy infiltrate in the lower dermis ($\times 100$).

blood was diluted 1:1 with tissue culture medium (TC-199 Wellcome) without serum. Separation of cells was done by the Isopaque-Ficoll method described by Böyum (2). Approximately 8×10^8 mononuclear cells were isolated from the blood. The leucocytes were washed twice in Hank's BSS, then

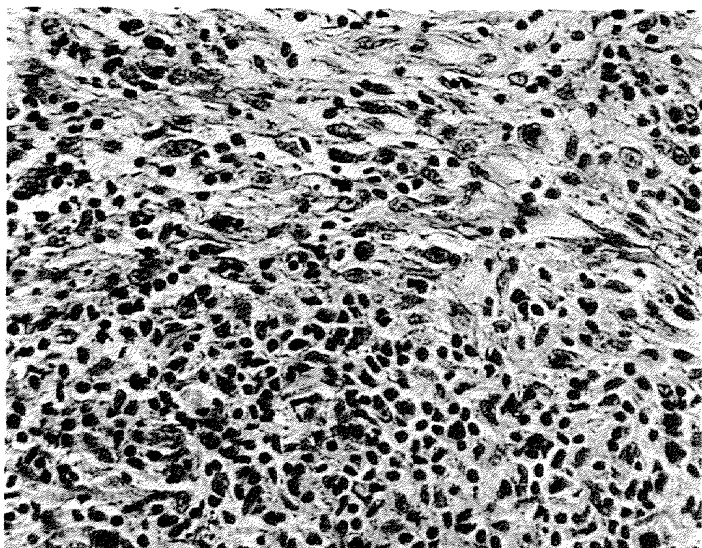


Fig. 6.

Photomicrograph of the dermal infiltrate of mycosis fungoides plaque from the elbow. Note the multiplicity of cell types. A number of mycosis fungoides cells can be seen, several having two nuclei ($\times 200$).

subjected to freezing and thawing 10 times, and to ultrasonification for 30 sec. The suspension was dialysed for 48 h against 200 volumes of distilled water in a dialyzing tube that permitted molecules of a molecular weight of up to 20,000 to pass. The dialysate was lyophilized, dissolved in 11–12 ml pyrogen-free, sterile water and finally passed through a $0.22\ \mu$ Millipore filter.

Laboratory Examinations

The percentage of T-lymphocytes in peripheral blood was measured by formation of E rosettes (10), and found to be only 18 per cent against 55–65 per cent in 12 controls. Serum IgE was $760\ \mu\text{g/l}$. Immunoelectrophoreses showed normal

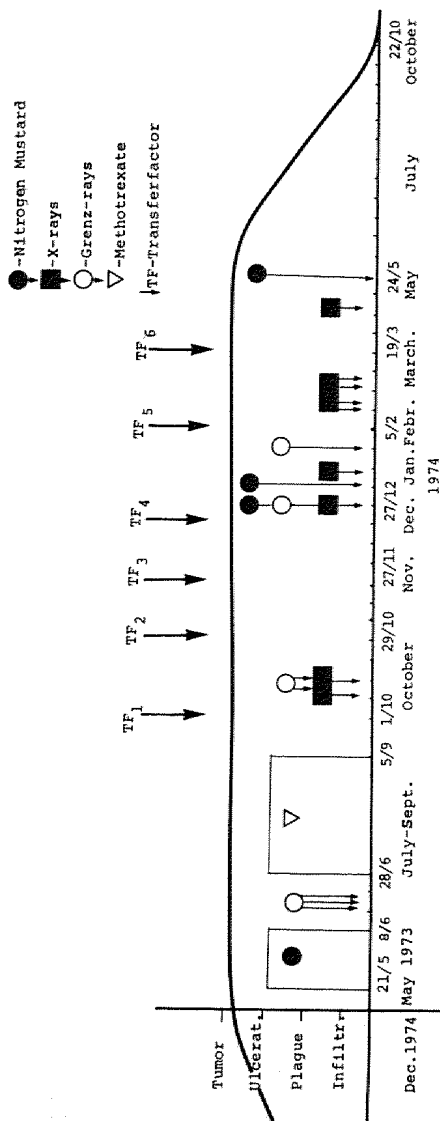


Fig. 7.
Clinical response to combined treatment.

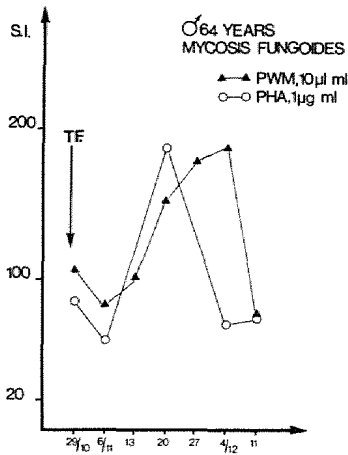


Fig. 8.

Stimulation indices to poke weed mitogen (PWM) and phytohaemagglutinin (PHA) following second injection of transfer factor (TF). Stimulation indices represent ratios between responses in counts of mitogen stimulated cultures to control cultures.

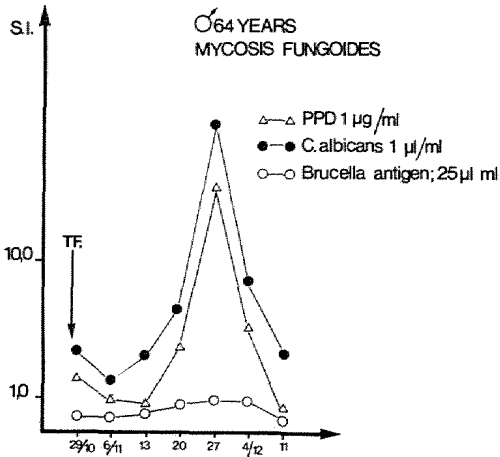


Fig. 9.

Stimulation indices in lymphocyte transformation tests to antigens indicated on figure. The figure shows response to the second injection of transfer factor (TF.)

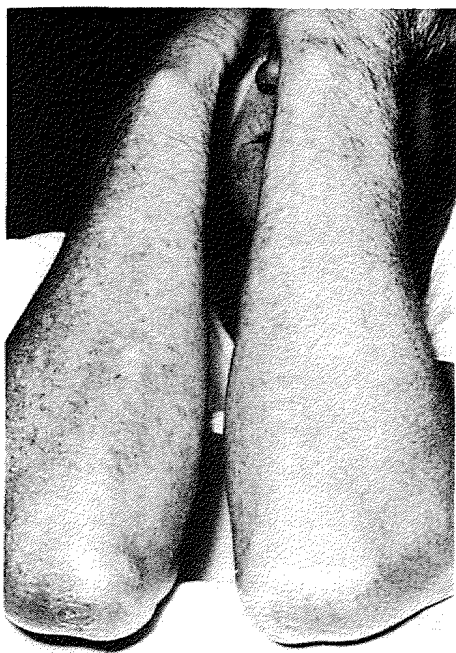


Fig. 10.
Elbows of patient
photographed on
October 22, 1974. Note
total absence of
infiltrate.

levels of IgG, IgA and IgM. Hemaglobin values varied from 12.7 g per cent to 14.6 g per cent, and sedimentation rates from 6 to 46 per h. Leucocyte and differential counts were normal.

The responses of peripheral blood lymphocytes to stimulation with phytohaemagglutinin (PHA) and poke weed mitogen (PWM) were followed from October 29th 1973, when the patient received his second injection of TF, until December 11th. Stimulation indices rose from low values to a peak four times higher (Fig. 6), and then returned to approximately the original values. In lymphocyte transformation tests with PPD and candida albicans performed during the same period, a similar stimulation of delayed hypersensitivity was demon-

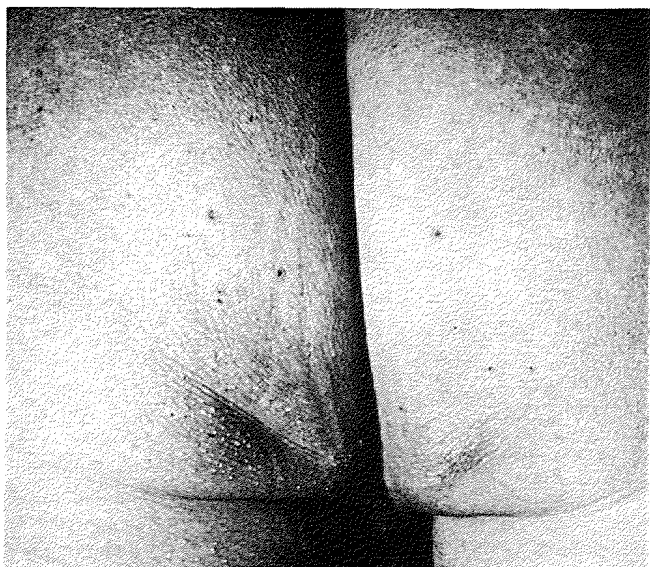


Fig. 11.

Nates photographed on October 22, 1974.

strated (Fig. 7). The highest values were obtained with PPD as antigen. There was no response to stimulation with brucella antigen either initially or after TF treatment.

COMMENTS

That immunity and malignancy are interrelated is a major discovery in medicine which has possible therapeutic aspects. The relative immunodeficiency of our patient with mycosis fungoides, showing a very low value of T-lymphocytes in peripheral blood together with a relatively poor *in vitro* response in the lymphocyte-transformation test, gives a basis for accepting that the induced remission in his disease has been partly due to treatment with TF. Although he received simultaneous treatment with X-rays, grenz rays and nitrogen mustard, this

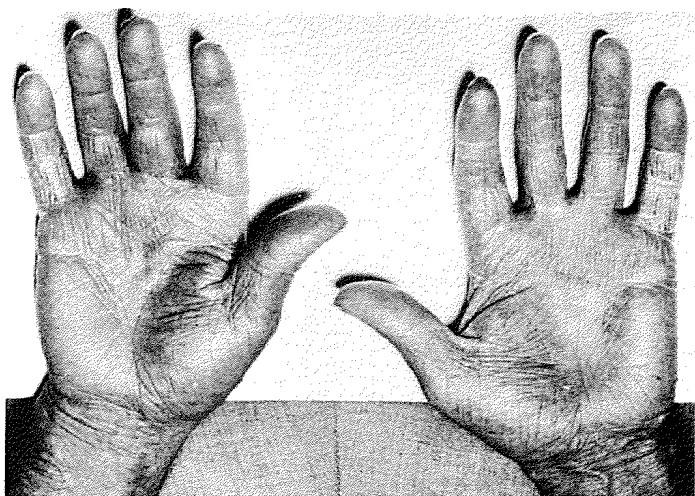


Fig. 12.

Palms of patient on October 22, 1974.

treatment alone did not seem to be enough to induce any remission. Moreover his hands and feet which are now also without lesions have never been treated with X-rays.

TF was originally introduced by Lawrence (4), and is still an experimental therapeutical agent. Its biochemical delineation has not yet been achieved. In our opinion, its use at present should be limited to patients whose health is severely compromised and who are unresponsive to conventional forms of treatment. However, TF may be applied, when an absolute or partial defect of delayed hypersensitivity exists. It is a general experience that TF does confer immunological reactivity on T-lymphocytes and increases *in vitro* responses to common mitogens as well as common antigens. Whether TF may be added to our list of therapeutic agents in mycosis fungoides remains to be seen. Functional abnormalities of the lymphocytes may be an important factor in this T-cell lymphoma.

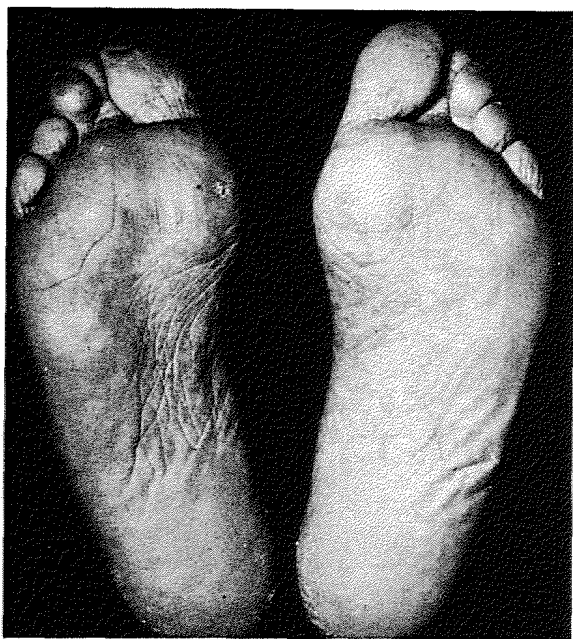


Fig. 13.

Soles of patient's feet on October 22, 1974.

REFERENCES

1. Bullock, W., Fields, J. P. & Brandriss, M. (1972): An evaluation of transfer factor as immunotherapy for patients with lepromatous leprosy. *New Engl. J. Med.* 287, 1053-1059.
2. Böyum, A. (1968): Separation of leucocytes from blood and bone marrow. *Scand. J. clin. Lab. Invest.* 21, Suppl. 97, p. 9.
3. Jersild, C., Platz, P., Thomasen, M., Hansen, G. S., Svejgaard, A., Dupont, B., Fog, T., Ciongoli, A. K. & Grob P. (1973): Transfer factor therapy in multiple sclerosis. *Lancet* ii, 1381-1382.
4. Lawrence, H. (1969): Transfer factor. *Advanc. Immunol.* 11, 195-266.
5. Levin, A., Spitler, I., Strites, D. et al. (1972): Wiskott-Aldrich Syndrome, a genetically cellular immunologic deficiency. *Proc. Nat. Acad. Sci. (Wash.)* 67, 821-828.
6. Schulkind, M., Adler, W., Altemeier, W. et al. (1972): Transfer factor in

the treatment of a case of chronic mucocutaneous candidiasis. *Cell Immunol.* 3, 606-615.

7. Thestrup-Pedersen, K., Thulin, H. & Zachariae, H. (1974): Transfer factor applied to intensify the cell-mediated immunological reactions against mycobacterium avium. *Acta allergol.* 29, 101-116.
8. Thulin, H. (1975): Immune response to primary immunization with brucella antigen. *Arch. Derm. Forsch.* 251, 311.
9. Winkelmann, R. (1974): Clinical studies of T-cell erythroderma in the Sezary syndrome. *Proc. Mayo Clin.* 49, 519-525.
10. Wybran, J. & Fudenberg, H. (1971): Rosette formation, a test of cellular immunity. *Trans. Soc. Amer. Phys. (Phila.)* 84, 239.

Author's address:

H. Zachariae
Dermatologisk Afdeling
Marselisborg Hospital
Aarhus
Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.