Therapeutic Use of Transfer Factor *

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Abstract. Transfer Factor (TF) was produced by ultrafiltration of repeatedly frozen and thawed, pooled buffy coats of healthy blood donors. One unit of TF Zürich was defined as the cell extract originating from 1 - \(2 \times 10^3\) leucocytes. In collaboration with physicians and immunologists, 409 units TF have been given to 45 patients. Besides local pain and occasional fever no side effects were observed. Immune conversions and beneficial clinical effects were seen in 11 and 10 patients, respectively, out of 12 patients with chronic candidiasis. Immune conversion was also observed in patients with multiple sclerosis, while the clinical effects cannot yet be judged. The series also included patients with subacute sclerosing panencephalitis, HBAg-positive disorders, various immunodeficiency diseases, malignant melanoma and miscellaneous tumours. Immune conversion occurred only occasionally and the clinical effect was either non-existent or not judgeable. In the discussion the results of other investigators using TF therapy are included.

Key words: Transfer factor - production, - physio-chemical properties, - therapy: chronic candidiasis, subacute sclerosing panencephalitis, multiple sclerosis, HBAg positive-periarteritis, malignant melanoma

Introduction. Studies of human immunodeficiency diseases and animal experiments have led to the concept that cell mediated immunity (CMI) is of great importance (a) for resistance to viral and fungal pathogens, facultatively intracellular bacteria and other intracellular microorganisms, (b) in autoimmune processes and (c) for the rejection of transplanted or of neoplastic tissues (1-10). It has been postulated that only viable lymphocytes (T-cells) are capable of transferring CMI from one individual to another (11-13). The requirement for whole living cells was challenged in 1949 by Lawrence (14), who claimed that, in man, a cell-free dialysable extract of leucocytes was also able to transmit CMI and that this might, at least theoretically, be helpful in correcting cellular immunodeficiency states. The active principle was termed Transfer Factor (TF) (reviewed in 15). Since then many investigators have found evidence for successful transfer by demonstrating conversion of various parameters thought to give information on CMI from negative to positive after TF injections (16-23). TF preparations thus seem to contain one or most likely several biologically active substances. Their nature, structure and mode of action have not been clearly elucidated so far, but the following physico-chemical parameters are characteristic: TF activity is associated with molecules with molecular weights below 10,000 to 30,000. It is resistant to DNase, RNAse and trypsin, but is destroyed by pronase. There is evidence, that TF activity might reside in a complex of a small polypeptide and an oligonucleotide (15, 24, 25). However, at present no reliable in vitro tests are available to measure TF activity or activities directly; therefore no accurate analyses can be made.

Since 1969 TF has been used therapeutically in patients whose diseases were thought to be at least partly due to defective function of CMI. The purpose of this paper is to report on results of clinical trials obtained with a TF preparation produced in our laboratory, TF Zürich(TFz), and to give a short review on the findings of other investigators.

Materials and Methods

Preparation of TFz: TFz was produced according to a method modified from that originally described by Lawrence (26) (for details see ref. 27). Heparinised blood (400 ml/donor) collected in plastic bags (FENWAL) was centrifuged at 4,000 g for 5 minutes. The buffy coat was removed by careful compression of the bag. Buffy coats of 10–20 donors were pooled (= one batch), resuspended in an equal amount of 0.9 % saline, and slowly frozen at -20°C and quickly thawed in a water bath at 37°C ten times. This material was ultrafiltered either in a SARTORIUS ultrafiltration cell (membrane SM 121/36) or in an AMICON ultrafiltration cell (membrane PM 10), allowing only the passage of molecules with molecular weights below 10,000 daltons. [A functional control

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of the filters was performed with solutions of cytochrome C (mol. weight 13,000). The ultrafiltrate was again filtered through a MILLIPORE membrane (pore size 0.3μ), immediately placed in ampoules and lyophilised. For injections the lyophilised material was redissolved in sterile distilled water and injected subcutaneously as a hypertonic solution (800-1200 m osm). One unit of TF was defined as the dialysed and lyophilised extract of 1-2 x 10^9 leucocytes.

**Source of TF and further testing:** For the first trials in 1970 and 1971 only individuals who showed a strong delayed skin reaction towards candidin, PPD, varidase and mumps antigen served as leucocyte donors. Later the leucocytes were usually taken from unselected blood bank donors, since it was shown that 20-70% of healthy Swiss individuals had positive skin reactions when tested with each of the above antigens singly (comparable data are mentioned by Griscelli (23) for a French collective). Only blood which was negative for Hepatitis B Antigen (HBAg) and Hepatitis B Antibodies (HBAb) as measured by radioimmunoassay (RIA) was processed, except for one patient with a HBAg positive periarthritis in: in that case TF was produced from HBAb positive donors. Microbiological tests were performed with samples taken at each stage of TF production. Infected batches were discarded. 8 out of 62 batches (containing 80 units TF) displayed a weak pyrogenic activity as measured by the current rabbit test. They were used for therapy without any unusual clinical or laboratory side effects in the recipients.

**Patients selection and schedule of treatment:** The choice of patients and the procedure of treatment was decided in close collaboration with the patients' physicians, to whom TF was sent by air mail in the lyophylised state on dry ice. Uniform instructions and protocols were used. Usually 1 unit of TF (test dose) was given subcutaneously in small portions within 6-8 hours (day 1), followed on day 3 by a therapeutic dose (1 unit/10-20 kilo- grams body weight). According to the outcome of follow up tests on day 4 or 5 (skin test conversion or not) or to the clinical course (beneficial or stationary) the same or increased therapeutic doses were given at 1-4 weekly intervals.

**Follow up tests:** At least one, but often all of the following tests (depending on the disease) were performed before and at various stages during and after TF treatment. They were made either at the place of treatment (Table 1) or in our laboratory: a) Skin tests with candidin 1:1,000 eventually 1: 100 (Holister Stear), varidase [streptokinase 4 units, streptodornase 1 unit (LEDERLE LABORATORIES)], mumps skin test antigen (ELY LILLY), PPD 1:1,000 eventually 1:100 (BERNA), trichophytin 1:1,000 (INSTITUT MÉRIEUX), coccidioidin 1:100 (CUTTER LABORATORIES). The skin tests were performed and interpreted according to the recommendation of the World Health Organisation (28). b) DNA synthesis in lymphocytes was estimated by measuring thymidine uptake after stimulation of the recipients' peripheral lymphocytes with candidin, PPD, measles antigen (in Multiple Sclerosis -MS- patients) as well as with phytohaemagglutinin (PHA) according to current techniques (29). c) An indirect or direct method for (guinea pig) macrophage or (human) leucocyte migration (51) inhibition test (MII) was performed after stimulation with Candida or (in the case of MS) with measles antigen (36, 37). In a few instances the mixed lymphocyte reaction (MLC) between the patient's lymphocytes and various test lymphocytes were tested. An immune conversion was thought to have occurred when at least one of the formerly negative respectively pathological tests for (anti-a) became positive, respectively normal after TF. The immunoglobulins (Ig) G, A and M, as well as S; (a measurable metabolic product of the third complement component) were measured repeatedly. Although in many instances changes were noted, no reproducible trend emerged. Therefore, the respective results will not be further discussed (for details see ref. 21, 27).

**Results**

Despite a well standardised technique (starting from approximatively equal leucocyte numbers), the final properties of TF - at least according to the parameters tested - varied greatly from batch to batch. Thus osmolarities of comparable TF-solutions ranged from 330 to 650 m osm; absorptions at 280 nm gave values from 0.04 to 0.12, absorptions at 260 nm ranged from 0.19 to 0.39, and the ratio 260/280 varied from 2.6 to 5.0. Chromatography of TF (15 batches have been tested), using SEPHADEX G-10 usually revealed 8 peaks, but with varying heights and ratios (more details are given in 27).

Tables 1 and 2 give data on the outcome of TF therapy. Beginning in 1971, a total of 409 units of TF have been given so far to 45 patients. The respective diseases and the outcome of therapy are described below.

A. Chronic candidiasis. Chronic candidiasis is often combined with other disorders, such as agranulocytosis, malignant diseases, extensive skin lesions, endocrinopathies and primary or secondary immunodeficiency states. Many different clinical forms can be distinguished (33-41). Our group of 12 patients showed various clinical features (granulomatous, mucosal or scaling types, involvement of various organs) but all displayed some sort of immune defects (Table 2). All patients had suffered from their disease for months to years before TF was started and had been treated at least partly unsuccesfully with most of the accepted drugs including one of the following: Amphotericin B, Clo-trimazole, 5-fluorocytosine and carbimazon. At the time when treatment was started, TF was the only major therapy given with the exception of patient D.V. 108 units were given to 12 patients. Clinical improvement, at least transitory, occurred in 10 patients (Table 2). In 11 out of 12 patients formerly negative skin tests with Candidin became at least transiently positive. In 7 patients skin test conversion with other antigens occurred (PPD 3 x, varidase 2 x, mumps 1 x, trychophytin 2 x), while in 2 individuals formerly positive skin tests became negative. In 3 patients a negative lymphocyte stimulation with Candidin became positive; 2 of them also showed conversion of the NIF test (in-
Table 1. Therapeutic trials with transfer factor (TF) between November 1971 and December 1973

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients Treated</th>
<th>Total Units TF Given</th>
<th>Skin Test Conversion per Patient Tested</th>
<th>Conversion of in vitro Test for CMI per Patient Tested</th>
<th>Clinical Effect</th>
<th>Collaborators/Place of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Candidiasis</td>
<td>12</td>
<td>108</td>
<td>10/12</td>
<td>3/12</td>
<td>10</td>
<td>Rubinstein/Bern, Hitzig, Zürich+</td>
</tr>
<tr>
<td>Subacute Sclerosing Panencephalitis</td>
<td>9</td>
<td>125</td>
<td>0/9</td>
<td>1/9</td>
<td>-</td>
<td>Kääckel/Krech/Ter Meulen, Göttingen</td>
</tr>
<tr>
<td>Chronic aggressive Hepatitis</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>Alagille/Verdrenne, Paris</td>
</tr>
<tr>
<td>HBsAg positive Periarteriitis</td>
<td>1</td>
<td>7</td>
<td>1/1</td>
<td>0</td>
<td>-</td>
<td>Rudolf/Madalinski/Miescher, Geneva</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>5</td>
<td>45</td>
<td>not tested</td>
<td>5/5</td>
<td>-</td>
<td>Jersild/Dupont/Platz/Fog,++ Copenhagen</td>
</tr>
<tr>
<td>Myeloradiculoencephalitis</td>
<td>2</td>
<td>6</td>
<td>not tested</td>
<td>not tested</td>
<td>-</td>
<td>Waldvogel, Geneva</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>2</td>
<td>6</td>
<td>1/2</td>
<td>1/2</td>
<td>1</td>
<td>Vierucci, Florence</td>
</tr>
<tr>
<td>Wiscott Aldrich Syndrome</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>Hitzig, Zürich+</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>Hitzig, Zürich+</td>
</tr>
<tr>
<td>Systemic Lupus erythematosus</td>
<td>1</td>
<td>2</td>
<td>1/1</td>
<td>0</td>
<td>-</td>
<td>Herwig, Chur</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>5</td>
<td>71</td>
<td>2/5</td>
<td>0/3</td>
<td>-</td>
<td>Ott, Zürich Bläker, Hamburg</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>Wüthrich, Zürich</td>
</tr>
<tr>
<td>Rectum Carcinoma</td>
<td>1</td>
<td>4</td>
<td>1/1</td>
<td>1/1</td>
<td>-</td>
<td>De Créé/Vermaegen,Marksem (Belgium)</td>
</tr>
<tr>
<td>Lymphoepithelioma</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>1/1</td>
<td>-</td>
<td>Wagenknecht, Geneva</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>409</td>
<td>17/31</td>
<td>12/27</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

+ = First observations on some patients are given in 21,65.
++ = Preliminary note in 103.
+++ = MIF and/or lyc stimulation with specific antigens and PHA and/or MLC.
+ = Dead
Table 2. Transfer factor therapy in patients with chronic candidiasis syndromes. Immune parameters and clinical status before and after treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Candidiasis</th>
<th>Time of Treatment</th>
<th>Tested before TF (1st line) and after TF (2nd line)</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Organs</td>
<td>Total of TF Units</td>
<td>Lymphocyte Stimulation with PHA</td>
<td>Skin test with Candidin</td>
</tr>
<tr>
<td>Year of birth</td>
<td>Involved</td>
<td>Given</td>
<td>from (1st line) to (2nd line)</td>
<td></td>
</tr>
<tr>
<td>B.S. Female</td>
<td>Mouth</td>
<td>5</td>
<td>November 1971</td>
<td>Reduced</td>
</tr>
<tr>
<td>1969</td>
<td>Esophagus (Granulomatous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.V. Female</td>
<td>Skin (Perianal)</td>
<td>April 1973</td>
<td>February 1973</td>
<td>Normal</td>
</tr>
<tr>
<td>1968</td>
<td>Mouth</td>
<td>6</td>
<td>May 1973</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Nails (Squamous, Granulomatous)</td>
<td>June 1973</td>
<td>Normal</td>
<td>nd</td>
</tr>
<tr>
<td>B.G. Male</td>
<td>Mouth (Perianal)</td>
<td>October 1972</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>1964</td>
<td>(Granulomatous/8 Squamous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z.A. Female</td>
<td>Mouth</td>
<td>15</td>
<td>September 1972</td>
<td>Normal</td>
</tr>
<tr>
<td>1953</td>
<td>Perioral Nails (Granulomatous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.T. Female</td>
<td>Mouth</td>
<td>7</td>
<td>October 1973</td>
<td>Normal</td>
</tr>
<tr>
<td>1961</td>
<td>Skin (Face) (Granulomatous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.H. Male</td>
<td>Mouth</td>
<td>22</td>
<td>August 1971</td>
<td>Reduced</td>
</tr>
<tr>
<td>1955</td>
<td>Skin (Granulomatous/Squamous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Esophagus Lungs</td>
<td>December 1973</td>
<td>Reduced</td>
<td>+</td>
</tr>
<tr>
<td>F.M. Female</td>
<td>Vagina</td>
<td>9</td>
<td>April 1973</td>
<td>Normal</td>
</tr>
<tr>
<td>1942</td>
<td>(Squamous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V.M. Female</td>
<td>Mouth</td>
<td>4</td>
<td>July 1973</td>
<td>Normal</td>
</tr>
<tr>
<td>1921</td>
<td>Skin (perioral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.G. Male</td>
<td>Mouth</td>
<td>12</td>
<td>August 1973</td>
<td>Reduced</td>
</tr>
<tr>
<td>1964</td>
<td>Nails Conjunctiva (Granulomatous/Squamous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lungs</td>
<td>October 1972</td>
<td>Reduced</td>
<td>nd</td>
</tr>
</tbody>
</table>

Legend:
- Reduced: Reduced cell counts
- Normal: Normal cell counts
- +: Positive skin test
- -: Negative skin test
- nd: Not done
- (+): Positive skin test with positive Candidin
- (-): Negative skin test with negative Candidin
- (?): Questionable clinical status
- Improved: Improvement noted
- Severe: Severe condition
- Moderate: Moderate condition
- Unchanged: No change noted
- Cured: Cured condition
- Relapse: Relapse noted
Table 2, continued

<table>
<thead>
<tr>
<th>Patient</th>
<th>Candidiasis</th>
<th>Total Time of Treatment from (1st line)</th>
<th>Time of Treatment to (2nd line)</th>
<th>Tested before TF (1st line) and after TF (2nd line)</th>
<th>Lymphocyte Stimulation with</th>
<th>Skin test with</th>
<th>Candida</th>
<th>Smears/Cultures</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.M. ††</td>
<td>Skin</td>
<td>May 1971</td>
<td></td>
<td>Normal + - - - +</td>
<td>PHA</td>
<td>Candidin</td>
<td>Candidin</td>
<td>-</td>
<td>Severe</td>
</tr>
<tr>
<td>Male</td>
<td>Ears</td>
<td>January 1974</td>
<td></td>
<td>Normal + - - - nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved (Relapse Feb. 1974)</td>
</tr>
<tr>
<td>1967</td>
<td>Nails 13</td>
<td>(Granulomatous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.S. † †</td>
<td>Mouth</td>
<td>October 1973</td>
<td></td>
<td>Normal + - - - (+)</td>
<td>PHA</td>
<td>Candidin</td>
<td>Candidin</td>
<td>-</td>
<td>Severe</td>
</tr>
<tr>
<td>Female</td>
<td>Skin 4</td>
<td>(Granulomatous)</td>
<td></td>
<td>Normal + - - - nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unchanged</td>
</tr>
<tr>
<td>1967</td>
<td>Intestine</td>
<td>January 1974</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lungs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F.S. † †</td>
<td>Mouth</td>
<td>April 1973</td>
<td></td>
<td>Normal + - - - (+)</td>
<td>PHA</td>
<td>Candidin</td>
<td>Candidin</td>
<td>-</td>
<td>Severe</td>
</tr>
<tr>
<td>Male</td>
<td>Skin 3</td>
<td>(Granulomatous)</td>
<td></td>
<td>Normal + - - - nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved (up to Feb. 74)</td>
</tr>
<tr>
<td>1954</td>
<td>Morbus Addison Hypoparathyroidism</td>
<td>April 1973</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† = Status at the time of writing this paper.
†† = First observations on these patients are given in 21 and 65.

direct method). In most patients, in whom clinical improvement was observed, immune conversion also occurred, with the exception of patient Z.A. There was no characteristic clinical form of candidiasis and no specific type of immunodeficiency which responded better to TF therapy than others. The following case history is representative of many others: The first symptoms of this now 5 year-old girl (patient B.S. in Table 2) started at the age of 11 months with mucocutaneous candidiasis, high fever and recurrent diarrhea. For the next 1.5 years the girl was always hospitalised, with the exception of 2 short intervals, the severity of the candidiasis necessitating feeding by a nasal tube during most of the time. Skin tests were all negative, PHA stimulation was slightly depressed and the patient's lymphocytes reacted poorly in the MLC test. The first injections of TF₂ (2 units) were followed by a dramatic clinical improvement. Skin tests to Candida, mumps and varidase became positive and the patient's lymphocytes showed normal MLC reactions as well as normal PHA stimulation. At first mild relapses of the disease occurred, but disappeared each time after further TF₂ injections (4x2 units at 1-3 month intervals); the periods of clinical remissions and restored immune parameters (which were transiently positive at the beginning) lasting longer after each further treatment. Repeated transiently clinical improvement and conversion of immunological tests in association with TF injections were also noted in patients T.T., B.G., B.H., P.M. and P.G. (Table 2).

B. Subacute Sclerosing Panencephalitis (SSPE). SSPE is without exception a fatal disease in children and young adults (42-46). Although defects of CMI are not a typical feature in such patients, TF was tried because it is thought that a chronic infection with a measles (like) virus might be involved. Large doses (a total of 125 units, average 14 units per patient) were repeatedly given to 9 patients with SSPE over periods of 1-4 months. No obvious clinical effects were observed and, with one exception, no immune conversion occurred (skin tests usually are similar to those of normal individuals; out of the series of 7 skin test antigens usually 1-3 give positive results. After TF the pattern of positive skin tests remained unchanged.) In the only patient with reduced PHA stimulation, a normal thymidine uptake was measured after TF.

C. Multiple Sclerosis (MS). Patients with MS have been treated with TF because they show signs of an immunological imbalance, such as increase of antibody titres to measles and other paramyxoviruses and diminished CMI towards these antigens as measured by the leucocyte migration inhibition test (47-51). In all 5 patients so far treated with small doses of TF, CMI against measles antigens became positive (103). In those patients in whom the conversion was transitory, CMI could be reestablished after further TF-injections. The number of surface immunoglobulin positive cells, spontaneous rosette forming cells as well as the PHA stimulation were normal in these patients prior to TF and remained so thereafter.
D. Ataxia telangiectasia (AT). AT is an autosomal recessive disease characterised by progressive cerebellar ataxia, oculoctaneous telangiectasia, recurrent sinopulmonary infections and various immunological defects (62, 53). Two siblings with this disease (6 and 11 year-old) were treated with TF. In one child formerly negative skin tests with Candidin became transiently positive, and there was a transitory increase in the capacity of lymphocytes to be stimulated by antigen. Severe chronic pulmonary infections subsided or became less prominent for many months. Both children became positive for HBs while under treatment, but only the one child with conversion of CMI pressure tension site occurred. Fever appeared 1-24 hours after application of TF to 6-12x10^5 patients, lasting from a few hours to 1-2 days. In a few patients extensive skin test reactions occurred when tested with the mentioned antigens 24-48 hours after TF injections.

Discussion

The following discussion will also include results of others in order to give an overall impression on the outcome of TF therapy. However, great caution has to be applied when doing this, since TF-preparations used varied in quantity and quality from one group of investigators to another (it also varied between our own batches): Some investigators used only positive skin test reactions from individuals suspected individuals as leucocyte donors (coccidioidomycosis (55), lepromin positive donors for lepra (56), etc.), many others took pooled leucocytes from untested healthy blood bank donors. For some melanoma patients leucocytes were taken from individuals deliberately presensitised with corresponding tumours or from family contacts (57,58;ibid.). The separation of leucocyte rich fractions from total human blood also varied in many details (various anticoagulants, FENWAL bags, glass tubes, with or without washings, etc.). Disruption of cells was either achieved by freezing and thawing, by sonication (59) or by a combination of the two procedures (20). The mixture was then treated with DNase and magnesium sulphate by most investigators (except by 20,57 and us). Many investigators dialysed the disrupted cell mixture, except some groups (60-62; ibid.) who used ultrafiltration systems. A great variation also emerges when comparing the schedules of treatment and the quantities of TF used per patient: Thus a unit of TF corresponded to the extract of e.g. 4x10^8 leucocytes according to some investigators (62, 76), to 1-2x10^9 cells according to others (63; ibid.), or to 1 ml of packed leucocytes as described by Oettgen (64). - TF originating from 8x10^6 leucocytes suffices to transfer long lasting skin reactivity to healthy volunteers (15). - While the results of some investigators were based upon one single injection (e.g. 1 unit -65-), others have applied TF repeatedly and in high doses (64).

Despite these variations, the following preliminary conclusions emerge: Until the end of 1973 TF treatments of 233 patients have been published (Table 3). The most successfully treated disease group is chronic candidiasis (20, 21, 23, 65, 66). In almost 80% of 37 patients thus far described, at least one CMI parameter converted during therapy. In about half of the cases beneficial clinical effects have also been reported. Beneficial effects have frequently been transitory, but the clinical improvement could often, at least as far as has been attempted, be sustained by repeated injections of TF (21, 73; ibid.). In many instances, only a combination of TF together with antimycotics and/or iron gave satisfactory results, while each of the mentioned therapies alone had only little ef-
Table 3. Results of TF therapy, documented 1970-1973

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients treated</th>
<th>Immune conversion</th>
<th>At least transitory beneficial clinical effect</th>
<th>Authors (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Candidiasis</td>
<td>36</td>
<td>27</td>
<td>19</td>
<td>Bläker (21) - Griscelli (23) - Grob (ibid) - Hitzig (65) - Hobbs (89) - Kirkpatrick (35, 69) - Pabst (73) - Rich (70, 71) - Rocklin (66) - Schulkind (19, 68) - Swanson (67) - Valdimarsson (20)</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>Graybill (55)</td>
</tr>
<tr>
<td>Lepromatous Lepra</td>
<td>26**</td>
<td>6</td>
<td>0</td>
<td>Bullock (56) - De Bonaparte (81) - Lim (80)</td>
</tr>
<tr>
<td>Tuberculosis, Mycobacteriosis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Graybill (54) - Whitcomb (75)</td>
</tr>
<tr>
<td>Subacute Sclerosing Panencephalitis</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>Grob (ibid) - Vandvik (83)</td>
</tr>
<tr>
<td>HBAg-positive Disease</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>Grob (ibid)</td>
</tr>
<tr>
<td>Interstitial Pneumonia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Dupree (76)</td>
</tr>
<tr>
<td>Wiscott Aldrich Syndrome</td>
<td>22</td>
<td>12</td>
<td>11</td>
<td>Ammann (90) - Ballow (91) - Griscelli (23) - Grob (ibid) - Hitzig (65) - Hobbs (89) - Levin (86) - Spitler (63, 87) - Wybran (88)</td>
</tr>
<tr>
<td>Ataxia teleangiectasia</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>Griscelli (23) - Grob (ibid)</td>
</tr>
<tr>
<td>Severe Combined Immune Deficiency</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>Ammann (90) - Griscelli (23) - Grob (ibid) - Hitzig (65)</td>
</tr>
<tr>
<td>Thymic A-, Hypoplasia</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>Ammann (90) - Lawlor (92) - Wara (93) - Wybran (88)</td>
</tr>
<tr>
<td>Hypo-, Dysgammaglobulinemia</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>Griscelli (23) - Levin (72) - Wara (93)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>26</td>
<td>9</td>
<td>8</td>
<td>Brandes (57) - Grob (ibid) - Morse (97) - Spitler (58)</td>
</tr>
<tr>
<td>Breast Carcinoma</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>Oettgen (64)</td>
</tr>
<tr>
<td>Nasopharyngeal Carcinoma</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>Goldenberg (99)</td>
</tr>
<tr>
<td>Sarcoma, Alveolar and Osteogenic</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>Levin (79) - Lo Buglio (61) - Neidhardt (98)</td>
</tr>
<tr>
<td>Miscellaneous Tumours</td>
<td>56</td>
<td>5</td>
<td>17</td>
<td>Lo Buglio (61) - Morse (97) - Thompson (77, 78)</td>
</tr>
<tr>
<td>**Total</td>
<td>233</td>
<td>113</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

† = Of skin tests or/and in vitro test for CMI.

** = Treated with white blood cells.
fect (19, 21, 35, 58, 65, 73, 74). All other trials with TF concerning chronic diseases of established or suspected microbiological aetiology are difficult to evaluate at the present time, since only a few patients have been treated with each given disorder. Successful treatments have been reported in a few patients with progressive primary tuberculosis (75), miliary tuberculosis, mycobacteriosis (54), interstitial pneumonia (76) and coccidioidomycosis (55). Immune conversion to lepromin could be obtained in 6 of 9 patients with lepromatous lepra (4 received TF, 5 received lymphocytes), but there was no beneficial clinical effect (flare-up reactions of skin lesions occurred -56-). - However, Lim reported on successful treatments after injection of white blood cells (80). - Rarely immune conversion, at least as far as could be tested (since these patients usually have normal CMI reactions), and - except in 1 patient treated by Vandvik (89) - no proven clinical effects have been observed in patients with SSPE, despite large doses of TF.

Of the primary immune deficiency diseases, Wiskott Aldrich Syndrome is the most accepted indication for TF treatment: About half of the patients showed at least transient immune conversion and clinically beneficial effects, which were limited in most instances to a decrease in severity and frequency of recurrent infections, but which can also include ameliorations of eczema and bleeding. Similar results have been obtained in patients with Ataxia telangiectasia, but only a limited number of patients have so far been treated. At least transient improvements have been obtained in some patients with other combined immunodeficiency diseases.

Concerning malignancies, TF has most frequently been tried in patients with melanoma. Immune conversion could be observed in about one third of the patients, and longer lasting periods of disease inactivity seem to have been induced in a few instances. However, since melanoma is known to have a very variable natural course, these results have to be interpreted with great caution. TF therapy has also been tried in many patients with various other tumours. But the number of patients with a given type of tumour is either too small and/or the details given in the respective reports too scarce to allow any conclusions at the present time.

Side effects: Besides local pain at the injection site and occasional fever, more serious complications have been reported to occur after TF, such as nephrotic syndrome (1 patient) (100), haemolytic anaemia (1) (101), polyclonal gammopathy (1) (84), and malignancies (2) (100). However, the causal relationship of these disorders to the therapy has in no instances been clearly established.

Conclusions

The original rationale of TF therapy was to transfer CMI from sensitised healthy individuals to patients in whom CMI was defective in the hope of obtaining beneficial clinical effects. At the present time, it is established that in many patients formerly negative cellular immune reactivities can become measurable after TF injections. (It is still a matter of controversy whether such conversions are due to a specific transfer principle in TF preparations resulting in specific CMI in formerly non-sensitised recipients, and/or if they are due to other, non-specific mechanisms, e.g. by amplifying pre-existing but not measurable CMI.)

Clinically, TF seems to be an effective therapeutic agent for at least some but not all disorders associated with defective CMI. However, with the data available an accurate evaluation is difficult since many of the diseases in question are characterised by great clinical and immunological variabilities and by unpredictable disease courses; also their aetiologies and pathogeneses are poorly understood and might be multifactorial. Besides the postulated transfer capacity of TF in respect of CMI, other mechanisms might play a role, such as liberation of interferon (102). (TF does not only contain products of immunocytes, but also from other cell types). Despite these critical remarks, the promising results so far obtained with TF justify further trials.

Addendum

We are indebted to the following physicians and immunologists who participated in this study:

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Full reports with detailed information on the patients mentioned in this paper will be published separately by some of the investigators listed above.

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