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Wiskott-Aldrich Syndrome, A Genetically Determined Cellular Immunologic Deficiency: Clinical and Laboratory Responses to Therapy with Transfer Factor*

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Abstract. Patients with diseases associated with defects in cellular immunity, such as the Wiskott-Aldrich syndrome, characteristically have severe recurrent infections and usually succumb to overwhelming infection at an early age.

This communication describes a patient with this syndrome, defective delayed hypersensitivity by skin tests and by *in vitro* lymphocyte response, who was treated with dialysate of peripheral blood leukocytes (transfer factor). After treatment, the clinical status of the patient improved dramatically, concomitant with the development of delayed hypersensitivity to antigens to which the donor was sensitive. *In vitro* tests after transfer indicated that the patient's lymphocytes, when stimulated by specific antigen, produced migration inhibitory factor without concomitant DNA synthesis. These observations dissociate skin test sensitivity and activity of migration inhibitory factor from *in vitro* blastogenesis. Further, the response to phytohemagglutinin remained diminished before and after therapy. While these findings represent only an individual case, the clinical results suggest that investigation of the use of transfer factor appears warranted in the therapy of Wiskott-Aldrich syndrome and other genetically-determined diseases associated with impaired cellular immunity.

The Wiskott-Aldrich syndrome is a sex-linked recessive disease characterized by recurrent pyogenic infections, eczema, and thrombocytopenia.[1,2] Patients with this syndrome have lymphopenia, lack delayed hypersensitivity as assayed by skin tests, and have defective lymphocyte blastogenesis *in vitro* in response to phytohemagglutinin and to specific antigens.[3] These patients also have a defective humoral antibody response to carbohydrate but not to protein antigens.[4] Most affected children die in infancy or early childhood.[5,6]

Immunologic reconstitution has been attempted in several patients by the administration of allogenic immune competent cells.[7–15] This procedure is hazardous because of the graft-versus-host reaction and is rarely therapeutically successful.[8,16]

Nonimmunogenic dialysates of peripheral blood leukocytes (transfer factor) from tuberculin-positive donors transfer skin test sensitivity to tuberculin-negative recipients. We felt that the administration of transfer factor might induce cellular immunity in patients with immune deficiency syndromes. Since

such transferred sensitivity would be directed against all of the antigens to which the immunologically normal donor was sensitive, the recipient would acquire the cellular components of immunity necessary to resist most infections, and the need for bone marrow transplantation might be eliminated. We also could assess whether skin test reactivity and *in vitro* lymphocyte responses to specific antigens were always concordant, that is, whether both are measures of "delayed hypersensitivity."

Case History. J. P. was born on March 12, 1960, of a 22-year-old primigravida after a normal term pregnancy and delivery. At the age of 9 months, he developed severe eczema; at 1 year pyoderma was treated with antibiotics; at 22 months a severe laryngotracheobronchitis required emergency tracheostomy; at 3 years he developed alopecia totalis (from which he recovered partially in 6–8 months) with a concurrent severe seborrhea resistant to all modes of therapy. During the first 9 years of life, he experienced chronic eczema, chronic draining bilateral otitis media, furunculosis, and 24 episodes of pneumonia documented by roentgenograms. He had persistent leukopenia (1900–5000 leukocytes/mm^3) and lymphopenia (455–2250/mm^3) without significant changes in white cell counts in response to infections. Despite persistent thrombocytopenia (30,000–90,000 cells/mm^3), several surgical procedures (including the tracheostomy and a herniorrhaphy) were tolerated without significant bleeding.

The patient has two normal siblings—one male aged 8, and one female aged 4 years. Several male members of the maternal family have malignancies, recurrent infections, and bleeding disorders; relatives of both sexes have asthma and thyroid dysfunction.

On initial examination, the child had normal height and weight for his age. He had patchy eczema, severe seborrhea, and several furuncles. The liver and spleen were enlarged. Liver and kidney function tests were normal; serum calcium, phosphorus, electrolytes, and fasting blood sugar were normal. Ivy bleeding time, Rumple-Leed test, prothrombin, partial thromboplastin time, platelet factor V, clot retraction, and fibrin split products were also normal.

Immunological Evaluation. The immunological defect was confined to defective cellular immunity and inability to recognize carbohydrate antigens; all other parameters of host resistance appeared normal.

Skin tests with Candida—Dermatophytin 0, 1:100 (Hollister-Stier); coccidiodin 1:100 and 1:10 (Cutter Laboratories); Mumps (Eli Lilly Company); Purified Protein Derivative from tubercle bacillus (PPD) intermediate and second strength (Merck, Sharpe and Dohme); Streptokinase-Streptodornase (Varidase) 1:5000 and 1:500 (Lederle Laboratories); Trichophytin (Dermatophytin) 1:30 (Hollister-Stier) were negative. The ability to undergo active sensitization to a potent skin-sensitizing agent was tested with 0.25 ml of a 1:1000 solution of dinitrochlorobenzene in acetone applied to the patient's arm. This procedure was repeated twice at 6-week intervals[17] prior to treatment with the transfer factor, and 6 weeks and 3 months after. The mother and the two siblings had normal skin test reactivity.

The humoral immune response to carbohydrate antigens was assessed by an attempt to hyperimmunize with blood-group specific substance B (Charles

Pfizer, Lot no. 88009) as a representative antigen. The patient's erythrocytes were blood group O. Before immunization the anti-B titer, determined by the saline room temperature method (Ortho Pharmaceuticals, Raritan, N.J.), was 1:16, and the anti-A titer was 1:8. Antigen (0.5 ml) was injected subcutaneously, and intradermally, in two different locations. This procedure was repeated in 2 days. After immunization with specific blood-group substance B, the anti-B titer did not change when assayed repeatedly over a 3-month period. Despite the lack of response to a carbohydrate antigen, normal responses to protein antigens were demonstrated by normal leukocidin titers[18] of anti-S of 1.3 μg/ml, anti-F of 1.6 μg/ml, and a negative Schick test.

The immune globulin concentration, as shown by radial immuno-diffusion,[19] were normal for the patient's age: IgG = 12.9 mg/ml (normal = 8–14 mg/ml); IgA = 1.34 mg/ml (normal = 1.0–1.8); IgM = 0.45 mg/ml (normal = 0.45–1.05); IgE was normal.[20]

The patient's granulocytes reduced nitroblue tetrazolium dye[21] and were able to ingest and kill *Escherichia coli*, *Serratia marcescans*, and *Staphylococcus aureus* normally.[22,23] Lysozyme concentration (Bacto-Lysozyme Tests, Difco Laboratories) was 13.2 μg/ml (normal = 5–20).

The leukopenia could not be attributed to circulating antibodies against leukocytes. No leukoagglutinins[24,25] were demonstrated in the patient's serum in tests against 10 normal group-O donors, and no lymphocyte-cytotoxic activity[26] was found against 2 normal group-O donors or against the patient's own lymphocytes. No antiplatelet antibodies[27] were found in tests against 10 normal platelet donors.

Salivary IgA and secretory components (as assayed by Ouchterlony plates with the appropriate monospecific antisera) were normal: antinuclear antibodies were not detected by indirect immunofluorescence; antithyroid antibodies (tested by thyroglobulin-sensitized sheep erythrocyte hemagglutination, Wellcome Research Laboratories, Beckenham, England) were not detected and C'3 levels (Agar diffusion, Hyland Laboratories) were found to be elevated.

Materials and Methods. Migration inhibitory factor was assayed by the technique of Rocklin *et al.*[28] Each supernatant was tested twice.

Lymphocyte blastogenesis in vitro: Lymphocyte stimulation was measured by a slight modification of the procedure described by Douglas *et al.*[29] Results are expressed as the ratio of the mean of triplicate experimental tubes, containing antigen or mitogen, to triplicate control cultures.

Transfer factor: Blood (450 ml) was drawn from a normal adult male volunteer selected because his skin tests were strongly reactive to Streptokinase-Streptodornase, PPD, candida, and mumps but not reactive to coccidioidin or trichophytin. These marked skin test reactions could be used to establish specificity of positive transfer.

The blood was drawn into 50-ml syringes containing sodium EDTA and 10% dextran (Macrodex 6%, Pharmacia Laboratories), mixed thoroughly, placed upright, and allowed to sediment for 2 hr. The plasma buffy-coat layer was collected, pooled, and centrifuged at 1000 rpm for 10 min at 4°C, to give a total volume of 1.6 ml of packed cells and a total cell count of 1500×10^6. The cells were resuspended in 4 ml of pyrogen-free saline and alternately frozen and thawed 10 times, using an acetone–dry ice mixture and a 37°C water bath. Magnesium and DNase (Worthington Biochemical) were added, and the mixture was incubated at 37°C for 30 min. The resultant cell lysate was dialyzed

against 500 ml of distilled water in the cold for 2 days, and redialyzed by the same procedure. The dialysate (transfer factor) was lyophilized and stored at −20°C until use, when it was dissolved in 2 ml of distilled water at room temperature and passed through a 0.45 μm Millipore filter.

1 ml of the transfer factor preparation, representing leukocyte extract obtained from 7.5×10^8 white cells, was injected subcutaneously into the deltoid area of the patient; another 0.1 ml was injected intradermally in the forearm to test for local transfer.

Results. Clinical status: The patient's repeated infections appeared to be caused by a defect in cellular immunity since other known defects in host resistance associated with recurrent infections were ruled out, e.g., abnormal granulocyte function, subnormal immunoglobulin levels, and complement deficiency. After therapy with transfer factor, the clinical condition of the child improved dramatically. There have been no new infections in the 5 months since the treatment. The seborrhea disappeared for the first time since the patient was 3 years old and new growth of hair was started. Eczema is now almost absent and the spleen is no longer palpable. The chronic otitis media has improved significantly and hearing has subsequently improved. The previously elevated serum C'3 levels (presumably due to chronic infection) have gradually returned to normal. Leukocyte and platelet counts have increased but are not yet normal.

Skin tests: The tests were performed 24 hr after administration of transfer factor and showed erythema to mumps, PPD, Streptokinase-Streptodornase, and trichophytin with no induration; however, there was no reaction to PPD at the site of local transfer. 10 days later, the patient showed stronger responses to mumps, PPD, and Streptokinase-Streptodornase. At 1, 3, and 5 months later, the skin tests were still positive (Table 1). Specificity of the transfer

TABLE 1. *Skin test results in donor and patient.*

			Result of Test*				
Antigen	Dose	Donor	24 hr	10 days	6 weeks	3 months	5 months
Candida	1:100	+	−	−	+	+	−
Coccidioidin	1:10	−	−	−	−	−	−
PPD	(2nd Strength)	+	−	+	+	+	+
Streptokinase-Streptodornase	40/10	+	−	+	−	+	+
Mumps		+	−	+	+	+	+
Trichophytin	1:30	−	−	n.d.	−	−	+
Dinitrochlorobenzene	1:1000	n.d.	n.d.	n.d.	−	−	n.d.

* (+), positive reaction; (−), negative reaction; n.d., not done (note that donor was never exposed to dinitrochlorobenzene). The patient had negative reactions to all antigens before treatment, including negative response to dinitrochlorobenzene after a complete series of sensitizing doses and a challenging dose.

factor was confirmed since the patient did not develop positive skin tests for antigens to which the donor had not been positive, e.g., coccidioidin and dinitrochlorobenzene.

***In vitro* lymphocyte response:** After transfer, when the patient's skin test was positive to PPD, the patient's cells produced migration inhibitory factor in response to this antigen (Fig. 1). Normal macrophages, cultured in supernatants obtained from a culture of the patient's cells with PPD, showed inhibition of

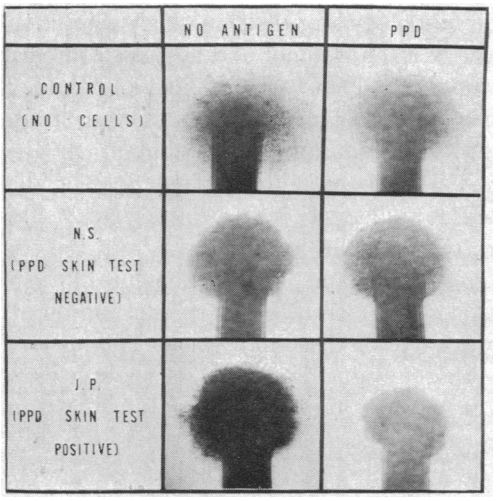

FIG. 1. Capillary migration in the patient after transfer factor administration and in a normal, tuberculin-negative, subject.

migration (planar area of migration was 63% of that in control chambers), whereas macrophages cultured in supernatants obtained from cells of a control subject who was tuberculin-negative were not inhibited (128% of control).

The patient's lymphocytes did not show increased DNA synthesis in response to PPD before treatment (when the skin tests were negative) or after (when the skin tests became positive); the cells of two controls (tuberculin-positive) showed the expected response (Table 2). The patient's lymphocyte response to culture with phytohemagglutinin was diminished before and after treatment, compared with that of the mother, siblings, and control subjects (Table 2).

Discussion. The poor prognosis of immune deficiency disease has led to attempts at immunologic reconstitution with bone marrow,[7-13] or thymic cells.[14,15] One patient with Wiskott-Aldrich syndrome, who had received a marrow transplant from a sibling compatible for the major transplantation antigens (the so-called histocompatibility or HLA antigens)[30] experienced a dramatic clinical improvement and remained well for at least 22 months thereafter.[31] However, only one of four siblings of any given patient would be HLA compatible on a statistical basis; the majority of patients would therefore, either not receive therapy or would be treated with HLA-incompatible cells. The transplantation of immunologically competent HLA-incompatible cells to

TABLE 2. *[^{14}C]Thymidine incorporation in vitro in response to PPD and Phytohemagglutinin.*

Antigen	Dose, μg	Before treatment*	After treatment 2 weeks	2 months	3 months
PPD†	10	1.2	0.9	1	n.d.
PPD	15	1.5	1	1	n.d.
PPD	50	n.d.	1	0.9	n.d.
Phytohemagglutinin‡	500	26, 8.6	n.d.	n.d.	14

* All data expressed as the ratio of (cpm experimental)/(cpm control) for triplicate determinations; n.d. = not determined.

† Normal range for PPD, 2.5–6.0, as determined in this laboratory.

‡ Normal range for phytohemagglutinin, 61–215, as determined on 25 different donors, including the mother and two normal siblings of the patient.

an immunologically deficient host carries the hazard of graft-versus-host reaction.[8,16] Even if donor and host are compatible by HLA and mixed lymphocyte culture techniques, the possibility of chronic low grade graft-versus-host reaction cannot be eliminated. Another serious limitation to this mode of therapy is the necessity for immunosuppression in an already compromised host. Further, even if the donor and recipient possess identical HLA antigens, as shown by mixed lymphocyte cultures, they may have different blood-group antigens; if so, red-cell aplasia can result from the production of isoagglutinins by donor cells reacting against formed elements of the host.[30]

In contrast, transfer of cellular immunity by means of leukocyte extracts carries none of these limitations. Transfer factor does not contain viable cells capable of producing a graft-versus-host reaction, it is not in itself immunogenic, and it contains no histocompatibility antigens.[32,33] Passive transfer of delayed hypersensitivity to specific antigens by dialysates of sensitive leukocytes (transfer factor), as measured by skin tests, was first demonstrated by Lawrence in 1955.[34] The active moiety is dialyzable, heat labile, resists freezing or treatment with DNase, RNase, or trypsin,[35] has a molecular weight under 10,000,[36] and contains adenine, guanine, cytosine, uracil, and ribose phosphate in polynucleotide material,[37,38] and perhaps small polypeptides.

Though the mechanism of action of transfer factor is unclear, it may act by virtue of its content of transfer, messenger, or ribosomal RNA, or it may be a nucleotide cofactor or derepressor. Despite its demonstrated potency, transfer factor has not previously been successfully utilized in the treatment of genetic diseases associated with defects in cellular immunity. Intact lymphocytes have been used successfully in the treatment of a child who, despite the presence of circulating antibody, had progressive disseminated vaccinia.[39] Immunologically competent cells have also been used successfully in the treatment of chronic mucocutaneous candidiasis.[40] Why treatment with intact cells can be successful is unknown; such successes may be caused by substances released by the transferred cells *in vivo*.

Since infections in the Wiskott-Aldrich syndrome are attributable primarily to the defective cellular immunity, it seemed reasonable to attempt therapy with transfer factor in our patient. The therapy was successful and clinical improvement was striking. The demonstrated changes are probably caused by improved host resistance resulting from the induction of effective cellular immunity to the antigens to which the immunologically competent donor was resistant. The transfer of cellular immunity was reflected by positive skin tests. The absence of infections might account for the reduction in spleen size and the observed increase in platelet and white cell counts. The improvement in the skin lesions is similar to that in patients with other types of immune disorders treated by other means. The return to normal of the previously elevated C'3 level was probably caused by cessation of infection (C'3 as well as many other proteins are elevated in acute and chronic infection).

The conversion of skin tests (concordant with the donor's reactivity) indicates that the transfer factor induces specific sensitization to antigens. The patient's inability to respond to dinitrochlorobenzene after transfer indicates that he

remained unable to undergo active sensitization. The ability of the patient's cells to produce migration inhibitory factor in response to PPD correlated with his skin test response to that antigen; however, there was no concurrent change in DNA synthesis by lymphocytes *in vitro*. We have previously demonstrated a similar correlation between skin test response and migration inhibitory factor production and discordance between the skin tests and DNA synthesis in the tobacco mosaic virus protein system.[41] Lawrence[32,33] reported that after transfer of delayed sensitivity to PPD to normal PPD-negative recipients the recipient's cells demonstrated increased blast transformation when incubated with the antigen. Our findings, however (in contrast to the prevailing concepts), indicate that *in vitro* response of the patient's lymphocytes to stimulation with specific antigen does not necessarily reflect presence or absence of delayed cutaneous hypersensitivity.

The *in vitro* response of our patient's lymphocytes with phytohemagglutinin was decreased both before and after the administration of transfer factor. There are numerous reports of decreased or absent cellular response to phytohemagglutinin in patients with many forms of immunologic deficiency diseases.[3,29,42-48] The relationship between clinical disorders such as the Wiskott-Aldrich syndrome and various aspects of lymphocyte response to mitogens *in vitro* remains unclear.

The case presented here is only an individual one, and further work will obviously be necessary to establish the general validity of the new principles proposed herein to Wiskott-Aldrich syndrome and other defects in cellular immunity. We conclude that therapy with transfer factor was a safe and effective mode of treatment in this patient and that further investigation of this therapeutic method appears warranted for the treatment of other immune deficiency diseases associated with impaired cellular immunity.

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Abbreviations: PPD, purified protein derivative from tubercle bacillus; HLA antigen, histocompatibility antigen

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