Passive Transfer of Immunity into Leprosy Patients by Transfusion of Lymphocytes and by Transfusion of Lawrence's Transfer Factor¹

KUNAL SAHA, M. M. MITTAL, AND H. B. MAHESHWARI

G. B. Pant Hospital and Maulana Azad Medical College, Sir Ganga Ram Hospital and Lady Harding Medical College, New Dehli, India

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About 1,200 million viable lymphocytes from normal but lepromin- and tuberculin-positive human beings were transfused in four patients of lepromatous and one of tuberculoid leprosy three times at monthly intervals. Three patients of lepromatous leprosy suffered from erythema nodosum, whereas the other two developed severe reaction whenever put on the smallest dose of dapsone. In one patient of lepromatous leprosy, minimal improvement or none was observed, whereas in the remaining three cases of lepromatous and one of tuberculoid leprosy, clinical, bacteriological, as well as histological improvement occurred. Two of the five patients started to tolerate the dapsone during the period of study. The present study indicates that immunotherapy might have a definite role in the management of the disease especially in cases with erythema nodosum. Lawrence factor, prepared from leucocytes of normal donors, was transfused three times into four lepromatous leprosy patients who were intolerant to anti-leprosy drugs. The donors were healthy but were tuberculin and lepromin (Mitsuda) positive. The clinical, histological, bacteriological (morphological index), and immunological assessments of the patients were performed before and 5 months after starting the immunotherapy. In two patients conversion of Mitsuda reaction occurred, but there was no appreciable improvement in the clinical, histologic, and bacteriologic status of these patients.

Leprosy is an infectious disease associated with a generalized depression of delayed allergic responses. The depression is of greater severity in patients with lepromatous leprosy and less among tuberculoid patients (1, 19). A similar relationship between the loss of cellular immunity and the development of leprosy has also been observed in experimental animals. A disease resembling lepromatous leprosy has been produced in mice in which cell-mediated immunity has been suppressed by neonatal thymectomy and irradiation with 900 R (14). If the mice are first transplanted with lymphoid tissue from animals with normal cellular immune state, just after thymectomy and irradiation, and are then inoculated with *Mycobacterium leprae*, the resulting infection is much less severe (14). Furthermore, if, after the development of a lepromatous-type infection, the animals are made immunologically competent by the inoculation of syngeneic lymphoid cells from normal

mice the disease is converted into a condition resembling borderline leprosy (15). These observations stimulated us to study the role of homologous lymphoid transplantation obtained from normal human donors in five leprosy patients of various types. Further, it was suggested (4) that transfer factor might be adopted as a therapeutic immune reagent to convert lepromatous leprosy to the tuberculoid type. We have therefore also investigated the effect of transfusing Lawrence factor extracted from leucocytes obtained from normal donors into four lepromatous leprosy patients who were intolerant to anti-leprosy drugs.

MATERIALS AND METHODS

Lymphocytic transfusion in five leprosy patients. Five patients with leprosy of different type and severity were evaluated. Classification of leprosy type was based upon clinical history, physical examination, and skin biopsy (17). Erythema nodosum was classified according to Waters et al. (22). In each case the following tests were carried out: normal lymphocyte transfer (NLT) test (18), tuberculin sensitivity with graded doses of old tuberculin (1 to 1,000

¹ Send reprint requests to Dr. T. N. Harris, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd., Philadelphia, Pa. 19104.

tuberculin units), and induction of contact type sensitivity with 2,000 μg of dinitrochlorobenzene (DNCB) followed by challenge with graded doses of the hapten (50 to 400 μg) (19). In three patients (cases 2, 3, 5) of lepromatous leprosy, sensitivity to lepromin was also tested with 0.1 ml of Dharmendra lepromin. Then, every patient was transfused with an average of 400 million viable lymphocytes, separated from the peripheral blood of healthy but tuberculin- and lepromin-positive individuals, three times at monthly intervals. Thereafter, the patients were assessed clinically at 15-day intervals for 5 months after the first transfusion.

Each donor was tuberculin and lepromin (Mitsuda type) positive but did not exhibit any sensitivity to DNCB. Separation of lymphocytes was by the technique of Levine et al. (10), with final suspension of cells in 100 cc of normal saline. The viability of the lymphocytes was checked by the trypan blue test. NLT test and induction of delayed hypersensitivity with tuberculin and DNCB were done by the techniques of Saha and Mittal (19). Dharmendra lepromin, 0.1 ml, was injected on the flexor surface of the forearm, and induration was measured after 48 h (Fernandez type reaction) and 21 days (Wade-Mitsuda type reaction). An average diameter of firm induration (after 3 weeks of lepromin injection) of more than 3 mm was taken as a positive Mitsuda reaction. The skin tissue was fixed in 10% neutral formalin, embedded in paraffin, sectioned at 5 μm , and stained with hematoxylin and eosin. Special staining for the demonstration of acid-fast bacilli was by the Wade-Fite oil formaldehyde new fuchsin method (5). Each biopsy from lepromatous leprosy patients was assessed for morphologic index expressed as percentage, granuloma index as percentage, and logarithmic index of bacilli in biopsies, viable, as recommended by Ridley (16).

Transfusion of Lawrence transfer factor into four other lepromatous leprosy patients. Four patients of lepromatous leprosy were evaluated as described above. Classification of leprosy type was based upon clinical history, physical examination, and skin biopsy (17). Erythema nodosum leprosum (ENL) was classified according to Waters et al. (22). Each biopsy was assessed as described above. None of the four patients were able to tolerate dapsone at all. In each case the following skin tests were performed: lepromin test with Dharmendra antigen, tuberculin test with graded doses of old tuberculin (1, 5, and 10 tuberculin units), and DNCB contact sensitivity test with graded challenging doses of 50, 100, and 400 μg of the hapten after sensitizing them with 2,000 μg of hapten (19). The transfer factor was prepared from the leucocytes separated from 250 ml of blood taken from each donor. The donors were healthy, tuberculin and lepromin positive, and did not respond to 50- μg DNCB challenge without previous sensitization. Freezing and thawing as described by Lawrence (7) was employed to extract the transfer factor from the leucocytes. Each patient received transfer factor prepared from 250 ml of blood (containing an average of 400 million viable lymphocytes) three times, at

monthly intervals. Thereafter, the patients were assessed clinically at 15-day intervals for 5 months. The skin biopsies from the same sites were repeated 5 months after the first transfusion, and all the skin tests were carried out after 5 months.

To see the effect of the immunologic reconstitution therapy of the leprosy patients by lymphocytic transfusion upon humoral immunity, levels of serum immunoglobulins, complement (C3 and C4) and several autoantibodies were studied in these patients before and 5 months after the first transfusion of leucocytes. Single radial diffusion technique of Mancini et al. (11) was employed to estimate serum immunoglobulins (Ig G, A, M, and E and serum complement (C3 and C4). Some of these patients were taken from another, similar series of eight patients who received immunotherapy by lymphocytic transfusion, and which will be reported in a subsequent communication. IgE was estimated by the use of an IgE kit (Meloy Laboratories). C-reactive protein, rheumatoid factor, and anti-streptolysin titer were determined in the sera of these patients by standard methods before and 5 months after the first transfusion. Antinucleoprotein antibody was also determined, before and after immunotherapy, using a Hyland Laboratories latex agglutination kit. In addition, tests were performed to detect leucoisoagglutinins in the sera of these patients, as described by Dacie and Lewis (2).

RESULTS

Lymphocytic transfusion in five leprosy patients. Table 1 shows clinical, bacteriological, histological, and immunological features of the patients before lymphocytic transfusion. Patients with lepromatous leprosy suffered from ENL whereas the other two individuals developed severe reactions whenever put on even 1 mg of dapsone. All the patients were transfused with about 1,200 million viable lymphocytes in three divided doses at monthly intervals. In every patient the reaction appeared or increased in intensity after each transfusion and persisted for a period of 7 to 10 days (Table 2). It required no therapy in all the patients except case 3. The latter needed more than the usual doses of prednisolone after every transfusion for the suppression of this phase of reaction.

No improvement was observed in the clinical status of one patient of lepromatous leprosy (case 5). His attacks of erythema nodosum decreased neither in severity nor in frequency (Table 2). Definite clinical improvement was, however, observed in the other four patients (cases 1 to 4). In two of the patients (cases 3, 4) who suffered from erythema nodosum, the severity of erythema decreased progressively with every successive transfusion and both of them became free of it within the period of study. Patient 3 had taken 20 mg of prednisolone daily

TABLE 1. *Clinical, bacteriological, histological, and immunological features of leprosy patients before lymphocytic transfusions^a*

No.	Name	Age (years)	Duration of disease (years)	Type of leprosy					ENL	Immunological assessment				Remarks
				Clinical	Histo-logical	Gran-ulo-ma index (%)	Mor-pho-logical index (%)	LIB (viable)		NLT	Lepromin ^o	Tuberculin ^o	DNCB ^o	
1.	CL	18	8 to 12	Tuberculoid	BT				Absent	First peak positive		Positive with 10 U	Positive with 400 µg	Developed severe reaction ven with 1 mg of dapsone
2.	KL	25	10 to 12	Dimorphous	BL	20	47	1.47	Absent	Negative	Negative	Positive with 10 U	Positive with 400 µg	Developed severe reaction even with 1 mg of dapsone
3.	ND	50	25	Lepromatous	LL	20	47	2.97	++ +	Negative	Negative	Negative with 1,000 U	Negative with 400 µg	Took 20 mg of prednisolone daily for last 5 years
4.	GB	20	1.5	Lepromatous	LL	20	52	3.01	++	Negative		Positive with 100 U	Negative with 400 µg	
5.	P	28	8	Lepromatous	LL	50	53	4.42	++ + + +	Negative	Negative	Positive with 10 U	Negative with 400 µg	

^a LIB (viable), Logarithmic index of bacilli in biopsies (viable); BL, border line lepromatous; LL, lepromatous leprosy; BT, borderline tuberculoid.
^b Sensitivity tests.

TABLE 2. *Clinical and histological responses after immunotherapy by lymphocytic transfusions*

No.	Name	Initial assessment			Remarks during the period of study	Final assessment (5 months)		
		Histo-logical type ^a	Clinical			Histo-logical type ^a	Clinical	
			Type	Reaction			Type	Reaction
1.	CL	BT	Tuberculoid	Developed reaction even with 1 mg of dapsone	No treatment prior to therapy. Erythematous patches after every transfusion for 7 to 10 days; no therapy. Started to tolerate 10 mg of dapsone per week for 2 weeks prior to third biopsy without the development of reaction.	TT	Tuberculoid	Negative
2.	KL	BL	Dimorphous	Developed reaction even with 1 mg of dapsone	No treatment prior to transfusion. Erythematous lesions after each transfusion for 7 to 10 days. Fever after first transfusion, and lymphadenopathy after first and second transfusions. Started to tolerate 60 mg of dapsone per week 1 month before third biopsy without appearance of reaction.	BB	Dimorphous	Negative
3.	ND	LL	Lepromatous	ENL+++	Took 20 mg of prednisolone daily for suppression of erythema nodosum for last 5 years. Crops of painful, tender erythematous patches which persisted for 7 to 10 days, and arthralgia, after each transfusion, requiring prednisolone daily for 5 to 7 days after first three transfusions.	LL	Lepromatous	Negative
4.	GB	LL	Lepromatous	ENL++	No therapy before lymphocytic transfusions. Existing erythema nodosum patches red, tender, and swollen for 7 to 10 days after every transfusion, requiring no therapy. Fever after first two transfusions.	BL	Lepromatous	Negative
5.	P	LL	Lepromatous	ENL++++	No treatment before lymphocytic transfusions. After every transfusion erythematous patches became necrotic in addition to the development of arthritis, iridocyclitis, and neuritic symptoms. No therapy required.	LL	Lepromatous	ENL++++

^a BT, Borderline tuberculin; BL, borderline lepromatous; TT, tuberculoid; LL, lepromatous.

for the last 5 years for the suppression of erythema nodosum. It was possible to taper off the dose of prednisolone gradually in this patient, but he required higher than usual doses of prednisolone for the suppression of reaction appearing just after each transfusion (Table 2). The other two patients (cases 1, 2), who had developed severe reaction even with 1 mg of dapsone before immunotherapy, started to tolerate the drug after lymphocytic therapy. Case 1 started to tolerate the small doses of dapsone after the third transfusion and took 10 mg of dapsone per week for 2 weeks before the third biopsy. Case 2 also started to tolerate the drug after the second transfusion and took 60 mg of dapsone per week for 1 month before the third biopsy.

Lymphocytic transfusion in five leprosy patients. It has been possible to follow all the five patients for 8 more months and two patients (cases 2, 3) for 1.5 years. Of the three patients (cases 1, 4, and 5) who were followed for the 8 months, no improvement was observed in case 5 up to 7 months and thereafter his attacks of ENL decreased in severity. Case 4 started to tolerate dapsone gradually and took 150 mg of dapsone per week by the end of 8 months without appearance of a reaction. Case 1, who could tolerate 10 mg of dapsone per week at the end of study, tolerated 200 mg of dapsone per week by the end of 8 months. He also did not develop any reaction. Of the two patients (cases 2, 3) who had been followed for 1.5 years, case 2 has been taking 250 mg of dapsone per week for the last 7 months. He developed a severe reaction twice, one after 10 months and the other after 16 months. Both times he was relieved of these phases after further lymphocytic transfusions. Case 3 was not able to tolerate the drug even after 1.5 years. He developed four attacks of reaction during this period. The attacks appeared after 7, 10, 15, and 17 months, respectively. The first three occasions of the reaction persisted for 7 to 10 days and required no therapy. The last attack

persisted for 1 month without any improvement and was relieved with another lymphocytic transfusion. In these two patients, a test with lepromin was repeated after 18 months. Again the Fernandez type reaction was positive in case 2 and both Fernandez and Mitsuda reactions were negative in case 3.

Definite bacteriological and histological improvement was observed in four of the five patients in whom clinical improvement was also found (Tables 2 and 3). The response was most marked in two cases, one of tuberculoid leprosy (case 1) and the other of borderline lepromatous leprosy (case 2).

Repeat immunological assessment could be done only in three patients (Table 4, cases 2, 3, and 5) after lymphocytic transfusion. Testing with lepromin yielded Fernandez type of positive reaction only in one patient (case 2). NLT tests were repeated in two patients (case 3 and 5) and were negative in both. Tuberculin sensitivity tests were done in three patients and gave a positive reaction in all of them. Repeat contact sensitivity test with DNCB could be done in one patient (case 3) and was negative even with the challenge dose of 400 μ g. This patient was resensitized with 2,000 μ g of DNCB and a challenge dose of 400 μ g could not elicit the sensitivity again.

Transfusion of Lawrence transfer factor into four other lepromatous leprosy patients. Table 5 shows clinical, bacteriological, histological, and immunological features of the patients before immunotherapy. None of the patients were receiving any drug at the time of the study, and none of them was able to tolerate even 1 mg of dapsone. After each intravenous transfusion, the reaction increased (Table 6) in severity and persisted for a period of 3 to 5 days. No treatment was given during this phase of exaggerated reaction.

In two of the four patients (cases 6 and 7) there was improvement in the status of ENL (Table 6) which became evident only after the third transfusion. Apart from the improvement

TABLE 3. *Bacteriological and histological responses in four patients of lepromatous leprosy after lymphocytic transfusions*

Case no.	Name	Granuloma index (%)			Morphological index (%)			Logarithmic index of bacilli in biopsies (viable)		
		At start	After 3 months	After 5 months	At start	After 3 months	After 5 months	At start	After 3 months	After 5 months
2.	KL	20	20	10	47	22	3	1.47	0.64	1.0
3.	ND	20	20	10	47	29	15	2.97	2.78	1.67
4.	GB	20	20	10	52	21	11	3.01	2.64	1.54
5.	P	50	50	40	53	31	13	4.41	3.80	3.77

TABLE 4. Immunological status of various leprosy patients before and after lymphocytic transfusions^a

No.	Name	Assessment before therapy					Assessment after therapy				
		NLT	Lepromin reaction		Tuberculin test	DNCB sensitivity	NLT	Lepromin reaction		Tuberculin test	DNCB sensitivity
			F	M				F	M		
2.	KL	—	—	—	+	+	ND	+	—	+	ND
3.	ND	—	—	—	—*	—**	—	—	—	+	—***
5.	P	—	—	—	+	—	—	—	—	+	ND

^a —, Negative; +, positive; F, Fernandez type of reaction; M, Mitsuda type of reaction; *, negative even with 1,000 U of old tuberculin; **, challenged with 400 μ g of DNCB; ***, on exhibiting negative response to a challenge dose of 400 μ g the patient was resensitized with 2,000 μ g of DNCB and again exhibited negative sensitivity up to 400 μ g of DNCB. Tuberculin sensitivity test done with 10 U of old tuberculin.

TABLE 5. Clinical, bacteriological, histological, and immunological features of leprosy patients before transfusion of Lawrence transfer factor^a

No.	Name and sex	Age (years)	Duration of disease (years)	Type of leprosy					ENL	Immunological assessment (sensitivity to:) ^b		
				Clinical	Histological	Granuloma index (%)	Morphological index (%)	LIB (viable)		Lepromin (Mitsuda)	Tuberculin	DNCB
6.	J. (Male)	25	10	Lepromatous	LL	50	50	5.2	+++	Negative	+	+
7.	S.D. (Female)	45	25	Lepromatous	LL	55	57	4.5	++++	Negative	+	+
8.	S.J. (Female)	55	38	Lepromatous	LL/BL	60	43	5.43	++++	Negative	+	+
9.	M.H. (Male)	23	5	Lepromatous	BL	20	51	2.0	++	+	+	+

^a LIB, Logarithmic index of bacilli in biopsy (viable); LL, lepromatous leprosy; BL, borderline lepromatous; TU, tuberculin unit.

^b Tuberculin hypersensitivity was tested by graded doses of old tuberculin; DNCB contact sensitivity was tested by graded doses of DNCB. The minimum doses of old tuberculin and DNCB which could express these hypersensitivities in these patients have been given in parentheses.

of ENL in two cases, no appreciable clinical, histological, and bacteriological improvement was observed in any of the patients (Tables 6 and 7). However, there was considerable improvement in the status of cell-mediated immunity based upon testing with tuberculin, DNCB, and lepromin (Table 8). Of the four recipients of transfer factor, Mitsuda reaction became positive in two cases (cases 7 and 8); this was also shown by histological examination. Sensitivity to tuberculin and DNCB could be shown with lesser doses of the respective antigens than those doses required before the transfusion.

We have also been able to follow the four patients given transfer factor until the present (8 months after the first injection). After 7.5 months, one patient (no. 7) improved clinically to a great extent. Her ENL disappeared and her appetite increased considerably. But this improvement was short lasting. After being free

from lepra reaction only for 8 weeks, conditions again deteriorated to a great extent. She developed plus four ENL, high fever, and trophic ulcer on her foot. The clinical conditions of other three patients have not improved further than what was reported at the fifth month assessment.

Table 9 shows that this immunotherapy caused no appreciable change in the mean serum immunoglobulins and C3 and C4 levels, except for a 43% decrease of the average IgE concentration in the sera of these patients 5 months after the beginning of lymphocytic infusion. The changes observed in other immunoglobulin levels of the sera are within experimental variation of the single radial diffusion technique. The immunotherapy eliminated C-reactive protein in three out of four cases, whereas rheumatoid factor had disappeared in four out of five patients under similar condi-

tions. Leucoisoagglutinins appeared in the sera of three patients after immunotherapy, although they did not have this abnormality before the immunologic intervention. There was no alteration in the levels of anti-streptolysin titers of the sera of these patients after immunotherapy. Anti-nucleoprotein antibody was present in two patients before immunotherapy which persisted in them even after lymphocytic infusion.

DISCUSSION

Lymphocytic transfusion in five leprosy patients. The present study has shown that in

one patient of lepromatous leprosy minimal improvement or none was observed; in the remaining four cases, three lepromatous and one tuberculoid, clinical, bacteriological, as well as histological improvement occurred. Rees and Weddell (15) have also reported definite improvement in the clinical as well as histological picture of lepromatous leprosy in mice after the animals were made immunologically competent by the inoculation of syngeneic lymphoid cells from normal mice. The present study not only substantiates those observations but further suggests that the apparent features of the syngeneic mouse model can be extrapolated to the

TABLE 6. Clinical and histological responses after immunotherapy with transfer factor^a

No.	Name	Initial assessment			Remarks during the period of study	Assessment after 5 months		
		Histo- logical type	Clinical			Histo- logical type	Clinical	
			Type	Reac- tion (ENL)			Type	Reac- tion (ENL)
1.	J.	LL	Lepromatous	+++	No treatment prior to therapy. Existing erythematous patches red, tender, and swollen for 5 to 7 days after each injection. No therapy required.	LL	Lepromatous	++
2.	S.D.	LL	Lepromatous	++++	No treatment prior to therapy. Painful, tender erythematous patches for 7 to 10 days after each injection. Fever after every injection, and neuritic symptoms only after the first one.	LL	Lepromatous	+++
3.	S.J.	LL/BL	Lepromatous	++++	No treatment prior to therapy. For 6 to 10 days after each injection existing patches red, tender, and swollen, plus arthritis, iridocyclitis, and neuritic symptoms. No fever. No therapy required.	BL	Lepromatous	++++
4.	M.H.	BL	Lepromatous	++	After first two injections, crops of tender erythematous patches. Existing erythema nodosum patches reddened after every injection. No therapy required.	BL	Lepromatous	++

^a LL, Lepromatous leprosy; BL, borderline lepromatous.

TABLE 7. Bacteriological and histological responses in four patients of lepromatous leprosy after injection of transfer factor

Case no.	Name	Granuloma index(%)		Morphological index (%)		Lorarithmic index of bacilli in biopsy (viable)	
		At start	After 5 months	At start	After 5 months	At start	After 5 months
6.	J.	50	50	50	40	5.2	4.8
7.	S.D.	55	55	57	45	4.5	4.39
8.	S.J.	60	55	43	38	5.4	5.32
9.	M.H.	20	20	51	45	2.0	1.45

TABLE 8. *Immunological status of various leprosy patients before and after transfer factor therapy^a*

No.	Name	Assessment before therapy				Assessment after therapy			
		Lepromin reaction		Tuberculin test	DNCB contact sensitivity (μ g)	Lepromin		Tuberculin test	DNCB contact sensitivity (μ g)
		Fer	Mit			Fer	Mit		
6.	J.	—	—	+ (10)	+ (400)	—	—	+ (1)	+ (400)
7.	S.D.	—	—	+ (10)	+ (50)	+	+	+ (1)	+ (50)
8.	S.J.	—	—	+ (10)	+ (100)	+	+	+ (1)	+ (50)
9.	M.H.	+	+	+ (10)	+ (100)	+	+	+ (1)	+ (100)

^a Fer, Fernandez reaction; Mit, Mitsuda reaction; +, positive; —, negative. Tuberculin test and DNCB contact sensitivity were done by challenging with graded doses of the respective antigens. The patients were sensitized with DNCB (2,000 μ g) once before challenging with various doses of the hapten. They were not resensitized with DNCB after immunotherapy. The minimum doses which could express the positive tuberculin and DNCB sensitivity in these patients have been shown in the parentheses.

TABLE 9. *Effects of treatment by lymphocytic transfusion in lepromatous leprosy patients with ENL*

Classes of immunoproteins ^a	Serum concn of immunoproteins (mean values of seven recipients)		Statistical evaluation
	Before immunotherapy	After immunotherapy	
IgG	1,489 $\pm$ 104 mg/100 ml	1,683 $\pm$ 475 mg/100 ml	0.98
IgA	248 $\pm$ 53 mg/100 ml	260 $\pm$ 70 mg/100 ml	0.31
IgM	256 $\pm$ 82 mg/100 ml	259 $\pm$ 84 mg/100 ml	0.06
C3	186 $\pm$ 38 mg/100 ml	163 $\pm$ 20 mg/100 ml	1.51 ^b
C4	20 $\pm$ 6 mg/100 ml	23 $\pm$ 7 mg/100 ml	0.81
IgE ^c	6,685 IU/ml (< 700 to 9,600 IU/ml)	3,825 IU/ml (< 700 to 11,000 IU/ml)	

^a Average normal levels of IgG = 976 mg per 100 ml; IgA = 208 mg per 100 ml; IgM = 104 mg per 100 ml (Saha and Mittal, 1972). Mean normal serum levels of C3 and C4 are 160 mg per 100 ml, and 36 mg per 100 ml, respectively (Saha and Dutta, unpublished data).

^b $P < 0.1 > 0.2$.

^c IgE was estimated by direct method using Meloy direct IgE kit. In two cases, IgE concentration was below 700 IU/ml of serum before as well as after immunotherapy. Figures in parenthesis show the range of serum IgE levels. After lymphocytic transfusion, serum IgE levels decreased in 4, increased in 1, and remained unchanged in the remaining 2 patients. The mean level of serum IgE in normal Indians is 1,025 IU/ml; the mean level of serum IgE in leprosy patients is about five times higher than that of the normal mean value (22).

allogeneic system under study. Evidently the mechanisms involved can hardly be identical. Definite improvement in the severity and frequency of erythema nodosum was observed in two (cases 3 and 4) of the three patients with erythema nodosum. After each transfusion a reaction appeared in every patient. This persisted for a period of 7 to 10 days and required no therapy in all the patients except one (case 3), who needed higher than usual doses of prednisolone, which he was already receiving for the suppression of erythema nodosum. Reversal reaction has been reported in mice with fully developed lepromatous infection after syngeneic lymphoid transplantation from normal mice (15). Godal et al. (6) have recently demonstrated the essential role of lymphocytes from tuberculoid compared to lepromatous patients in inhibiting the multiplication of mycobacteria in vitro

within the macrophages. Therefore it can be speculated that lymphocytes of normal human beings who are tuberculin and lepromin positive, when transfused into leprosy patients, help the macrophages of the patients to lyse the bacteria by inhibiting the further multiplication of organisms, thus resulting in the gradual improvement of the disease. Another possibility could be considered. The donor, thymus-derived lymphocytes contained in the lymphocyte infusion could respond to the allogeneic recipient's histocompatibility determinants and in this process of reactivation, release soluble factors which could augment the humoral reactivity of the host's own lymphocytes. This 'allogeneic effect' has been described in experimental situations. The augmented reactivity is not antigen specific and lymphocytes from any allogeneic donor should suffice.

The histological and bacteriological improvements observed in cases 1 and 2 may also be due to D.D.S. therapy. But this possibility is remote because these patients started to take the drug only a few weeks before the third biopsy.

The lepromin test was repeated in all the three patients at the end of the study. It showed Fernandez type of positive reaction only in one patient (case 2). Paradisi et al. (13) have also observed positive Fernandez type lepromin reaction in four of 13 patients who had previously had a negative reaction to lepromin, after injection of leucocytes from lepromin-sensitive donors into lepromatous leprosy patients. In two patients, NLT tests were repeated. In both these patients, repeat NLT tests were negative. Sensitivity tests with tuberculin and DNCB in one patient (case 3), who prior to therapy exhibited negative sensitivity to both 1,000 U of old tuberculin and 400 μ g of DNCB, showed a positive response with 10 U of old tuberculin but a negative reaction to 400 μ g of DNCB. This patient was resensitized with 2,000 μ g of DNCB and again a negative reaction was observed with a challenge dose of 400 μ g. The latter finding suggests that even after immunotherapy there had not been any appreciable improvement in the status of cell-mediated immunity although there had been some clinical and histological improvement. The observation also explains the negative lepromin and NLT tests observed in two patients after immunotherapy, and is supported by the finding that after 10 years of continuous dapson therapy there was no reestablishment of paracortical area in the lymph nodes (Int. J. Lep., 38:443, 1970). Turk and Oort (21) have demonstrated that, after passive transfer of cells in an animal, the effector cells involved in the expression of a cell-mediated immune reaction are the host cells and not the passively transferred cells as had been assumed for long time. The finding that a patient (case 3) had exhibited a positive tuberculin response but could not express sensitivity to DNCB after the transfer of leucocytes from tuberculin-positive and DNCB-negative donors indicates that, in patients of leprosy, the expression component of cell-mediated immunity is intact, whereas the apparatus involved in memory formation is probably affected.

Transfusion of Lawrence transfer factor in four lepromatous leprosy patients. The role of the Lawrence transfer factor in transferring delayed hypersensitivity, and its use in the immunotherapy of immunological deficiency diseases, has been established (8, 9). Transfusion of immunologically competent lympho-

cytes in an immunological deficiency disease might lead to a graft-versus-host reaction; on the other hand there is no such danger in the immunotherapy with transfer factor. But the treatment with transfusion of viable lymphocytes has a definite advantage over treatment with transfer factor in that macrophage-lymphocyte interaction can take place, thus inhibiting the multiplication of the mycobacteria within the macrophages (6). This may explain the observed clinical, histological, and bacteriological improvements with the lymphocytic transfusion in the leprosy patients, in contrast to treatment with transfer factor. In the present series of the five leprosy patients who received lymphocytic transfusion, none developed graft-versus-host reaction, which shows that the cell-mediated immunity of these patients was not too depressed to reject these grafted cells. Therefore it seems that the immune therapy of leprosy patients with viable lymphocytes is not a dangerous procedure. The Mitsuda conversion reaction which was observed in the two patients (Table 8) who received transfer factor can be explained, in our opinion, by the direct effect of the massive and multiple doses of transfer factor, and to the individual status of the cellular immunity.

Increased levels of IgG, A, M, and E are frequently found in cases of lepromatous leprosy and erythema nodosum leprosum (23). The present study shows that the immunological reconstitution therapy of the leprosy patients had practically no effect on the serum immunoglobulin levels except serum IgE concentration, which was reduced by 43%. Also, the serum C3 level is reduced only by 12% after immunotherapy. This latter change is suggestive of shift of the spectrum of leprosy from lepromatous to tuberculoid end (23) and should be verified in further studies. Thus, these findings are in keeping with previous observations, which had shown no difference in the immunoglobulin levels in patients with or without ENL, although serum complement (C2 and C3) were found to be raised in patients with lepromatous leprosy. In this connection, it is worth mentioning that these patients before immunotherapy had been suffering from severe ENL which disappeared in most of them after immunotherapy (Table 2).

It is well established that C-reactive protein, rheumatoid factor, anti-nucleoprotein antibody, and high titers of anti-streptolysin O are often found in the sera of leprosy patients (20). After passive transfer of immunity into leprosy patients by lymphocyte infusion, some abnormal

immunoproteins (C-reactive protein and rheumatoid factor) could not be detected which were present before such immunological intervention; it did not remove other abnormal antibodies like anti-nucleoprotein antibody, nor did it lower the anti-streptolysin levels of the sera of these patients. The exact mechanism of these findings is difficult to understand at the present moment. Appearance of leucoisoagglutinins in the sera of three patients after immunotherapy supports the previous view that such antibody may appear after multiple transfusion of leucocytes (12).

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