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Immune Deficit in Patients with Lepromatous Leprosy: Its Nature and Relation to Genetic Factors, Spectrum, and Duration of the Illness [1]

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Patients having lepromatous leprosy are almost invariably anergic to *M. leprae* and also sometimes unresponsive to other previously encountered antigens ([12]). They often suffer from generalized depression of cell-mediated immunity and show suppressed response towards many unrelated antigens such as tuberculin, picryl chloride, dinitrochlorobenzene, skin transplants and allogeneic lymphocytes ([6, 16]). This nonspecific deficit is not absolute but is relative and depends upon the dose and potency of a given antigen and also on the severity of the disease ([15]). Nevertheless, it may be restored with specific leprosy treatment ([9]). On the other hand, the specific unresponsiveness to *M. leprae* is long lasting and probably lifelong. It tends to persist in these patients even after their antigen loads are markedly reduced by chemotherapy ([4]). *In vitro* immune response studies, such as lymphocyte transformation and leukocyte migration inhibition tests with *M. leprae* have shown excellent correlation of the impairment of specific cellular immunity to *M. leprae* with the spectrum of the disease ([7]). Thus, it appears that as the disease progresses, the mycobacterial load increases and the cellular immune responses toward unrelated antigens are more and more depleted. The purpose of this presentation is to study the extent of the depression of cell-mediated immunity in relation to the disease spectrum, and in lepromatous leprosy (LL) in relation to the duration of the disease. Intrafamilial relation of specific unresponsiveness towards late lepromin reaction was also studied.

MATERIALS AND METHODS

Cell-mediated immunity in relation to the disease spectrum. Seventy-three patients having different forms of leprosy formed the basis of the present study. The diagnosis was supported by clinical examination, histopathologic and bacteriologic tests ([17]). Bacterial load was estimated according to the method described by Desikan ([3]). Classification of the leprosy type was delineated according to the scheme of Ridley and Jopling ([11]). The duration of illness was recorded. The following hypersensitivity determinations were per-

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TABLE 1. *Lepromin, tuberculin and DNCB response related to leprosy type.*

Histologic classification	No. of cases tested	Positive late lepromin reactivity (%)	Positive O.T. reactivity (%)[a]			Positive DNCB reactivity (%)[b]		
			10 T.U.	100 T.U.	500 T.U.	50 μg	400 μg	Unresponsive to both
TT	5	100	100	–	–	80	20	0
BT	9	56	100	–	–	55	44	0
BB	11	45	82	18	–	54	46	0
BL	28	14	71	14.5	14.5	32	64	4
LL	20	5	40	40	20	35	25	35

[a] If 10 units O.T. (old tuberculin) gave less than 6 mm response, the higher doses were used sequentially until a positive response of 6 mm or more induration was obtained ([15]).

[b] DNCB hypersensitivity reaction was considered positive if erythema and/or induration and/or vesiculation with or without bullae and ulceration appeared ([15]).

TABLE 2. *Relation of* M. leprae *tissue load to delayed-type hypersensitivity.*

Skin tests	No. positive related to number with indicated BI		
	0-2.0	2.1-4.0	4.1-6.0
Early lepromin	1/2[a]	0	0
Late lepromin	1/2[a]	0	0
Tuberculin[b]	2/2	9/11	14/17
DNCB[c]	1/2	5/11	6/17

[a] One borderline lepromatous patient.

[b] If less than 6 mm response to 10 units, then 100 unit challenge given.

[c] First challenge = 50 μg; if no response challenged with 400 μg.

TABLE 3. *Delayed-type hypersensitivity related to duration of illness.*

Response to	Duration of illness (years)			
	1-5	6-10	11-15	15+
All 3 antigens[a]	1/5	0	0	0
Any 2 antigens	1/5	6/9	1/15	3/7
Any 1 antigen	3/5	2/9	2/15	1/7
None	0	1/9	2/15	3/7[b]

[a] Lepromin (early), old tuberculin and dinitrochlorobenzene.

[b] Duration of illness was 21, 25, and 25 years, respectively.

formed: lepromin, tuberculin and dinitrochlorobenzene. Each patient was given intradermal injection of 0.1 ml armadillo-derived lepromin (World Health Organization). Early reaction was noted after 48 hours and late reaction was recorded after three weeks. These reactions were graded according to Beiguelman ([2]). Tuberculin response was studied by intradermal injection of graded dose of old tuberculin ([15]). Contact type delayed hypersensitivity was induced by 2,000 micrograms of dinitrochlorobenzene, which was subsequently followed by challenge of graded dose of the hapten ([15]). All patients received standard antileprosy chemotherapy.

Intrafamilial relation of late lepromin reactivity. The family pattern of Mitsuda reaction was studied in 13 leprosy affected families consisting of 13 couples and 22 offspring, none of the latter having any clinical evidence of childhood leprosy ([10]).

RESULTS

Table 1 depicts the depression of cell-mediated immunity as reflected by delayed-type hypersensitivity to the three test agents in correlation with the spectrum of leprosy. Mitsuda reactivity paralleled the disease spectrum. Only one of twenty (5%) LL cases exhibited late lepromin reactivity. Positive reaction was taken as a response of at least 3 mm in diameter. Impairment of delayed-type hypersensitivity toward the other unrelated antigens, e.g., tuberculin and dinitrochlorobenzene, was also recorded. The deficit was minimal in the tuberculoid cases and became pronounced towards the other end of the disease spectrum.

TABLE 4. *Mitsuda reaction in leprosy patients and their children.*

Parental couples			Offspring					
Mitsuda reactivity of either partner		No. of families studied	Mitsuda reactivity[a]/number of children 0	±	1+	2+	3+	No. of children studied
0 & 1+	one partner	3		2	3			5
0 & 2+	responsive	3	1		1	2		4
0 & 3+		1			1			1
Total number		7	1 (10%)	2 (20%)	5 (50%)	2 (20%)		10 (100%)
1+ & 1+	both	1				2	0	2
1+ & 2+	partners	2			2	1	1	4
1+ & 2+	responsive	3[b]			2		4	6
Total number		6			4 (33%)	3 (25%)	5 (42%)	11 (100%)

[a]0 = absent reaction; ± = perceptible reaction diameter < 3 mm; 1+ = conspicuous infiltration with 3-5 mm diameter; 2+ = reaction diameter > 5 mm; 3+ = reaction with ulceration.

[b]One couple was healthy, however the mother of the husband had lepromatous leprosy. Their two healthy sons were 15 and 17 years old and showed 3+ Mitsuda reaction.

Table 2 illustrates the progressive impairment of delayed-type hypersensitivity response with the LL group as their bacillary load increased. Table 3 shows the relation of delayed-type hypersensitivity response in the patients with lepromatous leprosy in relation to the duration of their illness. Twenty-three polar lepromatous and six borderline lepromatous cases were included. Their duration of illness varied from 1.5 to 25 years. The occurrence of total unresponsiveness towards lepromin (early reaction), tuberculin and dinitrochlorobenzene was more frequent as the duration of the illness increased. Thus, three of seven (43%) patients with a duration of illness of more than 15 years were unresponsive to all three antigens, while none responded to all three antigens. On the other hand, none of the five patients with a duration of illness of less than five years were anergic to all three antigens, and one patient (20%) responded to all three antigens. It was observed that anergy was pronounced only in those cases who had been suffering from the disease for more than seven to eight years.

Table 4 describes the pattern of late lepromin responsiveness in the families of leprosy patients. When both partners showed late lepromin reaction, their children were found to be more responsive to the Mitsuda test.

DISCUSSION

Delayed-type hypersensitivity response was tested in leprosy patients through the disease spectrum as defined by Ridley and Jopling ([11]). Patients having polar tuberculoid (TT) leprosy showed uniformly strong, late lepromin reactivity but this reactivity was variable in the borderline (BB) leprosy patients, while LL patients almost invariably showed negative reaction. This diversity of late lepromin reaction is clearly related to host resistance to the infection and is in conformity with the data of earlier workers ([7]). Also, very recently, Anders *et al* ([1]) showed that the lack of responsiveness to lepromin *in vitro* and *in vivo,* characteristic of lepromatous leprosy, was not altered by *erythema nodosum leprosum* or the presence of amyloidosis, though these conditions definitely impaired delayed-type cutaneous hypersensitivity towards PPD. Furthermore, a similar pattern of diversity of delayed hypersensitivity responses towards unrelated antigens,

e.g., tuberculin and dinitrochlorobenzene was also noticed over the spectrum of the disease. Thus, the disease spectrum reflected the ability of the host to mount his cell-mediated immunity towards specific as well as nonspecific antigens. This lends support to the spectral concept of the illness which is held by some to be unique to human leprosy ([8]). Moreover, it is evident from Table 2 that while the specific late lepromin reactivity was absent in some patients, nonspecific immune responses towards unrelated antigens still persisted in them.

Intrafamilial association of the degree of Mitsuda reactivity has been demonstrated previously among children of leprosy patients ([2]) and was confirmed by the present study. Thus, children born of couples with both partners showing negative Mitsuda reaction had more chance of being late lepromin response negative than those born of parents with both partners showing positive Mitsuda reaction (Table 4). This indicates the involvement of a genetic factor in the acquisition of positive late lepromin reactivity and associated resistance to lepromatous leprosy. Due to this initial poor specific immune status in individuals who are prone to develop lepromatous leprosy, they are unable to eliminate leprosy bacilli after they acquire them from the environment. Thus, *M. leprae* tend to grow intracellularly within the macrophages, and as the bacillary load increases there is frequent release of leprosy bacilli into the circulation leading to the formation of immune complexes and onset of *erythema nodosum leprosum* reaction ([12]). This tremendous bacillary load and immune complexes further throw these cases into a state of immunologic paresis, which is initially specific to *M. leprae* but becomes generalized with the progress of the disease (Tables 2, 3). Nevertheless, this immunologic impairment is yet partial and there is almost invariably some residual nonspecific cell-mediated immune response left behind, which could be provoked by the challenge of higher doses of antigens (Table 1). Moreover, it was discovered earlier that lepromatous patients, who are unresponsive to even a strong antigen such as dinitrochlorobenzene, can be sensitized to a key hole limpet hemocyanin, presumably a far stronger sensitizer than DNCB ([5]). Furthermore, this deficiency towards various unrelated antigens in lepromatous leprosy is not as marked as that found in primary immune deficiency diseases such as thymic aplasia. Thus, although there is progressive depletion of cell-mediated immunity with the ongoing progress of the lepromatous process, there is almost invariably some residual cell-mediated immunity which may provide adequate protection against viral and neoplastic diseases. This view is also parallel to the high incidence of Australia antigen in lepromatous patients without any occurrence of fulminant and fatal hepatitis ([13]), and also it is consistent with our earlier finding of the occurrence of *vaccinosum necrosum* without any incidence of generalized vaccinia following smallpox vaccination in such patients ([18]). The increased occurrence of malignant disease in leprosy patients ([19]) further supports the above concept. A similar interpretation was recently presented by Nath and associates ([9]) who found early T-cell binding their response to various mitogens to be profoundly depressed in untreated and partially treated bacilliferous lepromatous leprosy patients as compared to tuberculoid patients. On elimination of mycobacteria, as a result of chemotherapy, LL patients regained normal T cell number and functions. On the other hand, the specific response of lymphocytes to *M. leprae* did not alter with the mycobacterial load.

While the late lepromin unresponsiveness in lepromatous leprosy patients is most likely primary and not thymus-derived, the impairment of cellular immunity towards other unrelated antigens is due to the secondary effect of *M. leprae* antigens on thymus-derived T lymphocytes. This view is also supported by our recent study of human fetal thymus transplantation in LL patients ([14]). Although this immunologic manipulation readily showed early lepromin conversion and reverted tuberculin as well as streptokinase-streptodornase and dinitrochlorobenzene unresponsiveness, it was unable to produce late lepromin positivity.

SUMMARY

Cell-mediated immunity or hypersensitivity to *M. leprae* and other unrelated antigens, such as tuberculin and dinitrochlorobenzene, was studied in 73 leprosy patients of different histopathologic types. It was found that specific as well as nonspecific anergy intensified as the disease spectrum shifted from the tu-

berculoid toward the lepromatous immunologic pole. Within the lepromatous group, the impairment of cellular immunity became more pronounced as the bacillary load increased. It was found that the impairment of the cell-mediated immunity towards antigens other than *M. leprae* became more severe as the duration of the illness increased.

Late lepromin responsiveness, which is the hallmark of resistance of an individual to *M. leprae,* may be absent even before the onset of clinical illness. Its deficit seems to be primary and has a genetic predisposition.

RESUMEN

Se estudió la inmunidad celular o hipersensibilidad hacia el *M. leprae* y otros antígenos no relacionados (tuberculina y dinitroclorobenceno) en 73 pacientes con diferentes tipos histopatológicos de lepra. Se encontró que tanto la anérgia específica como la no específica se fueron intensificando conforme el espectro de la enfermedad se desplazó del extremo tuberculoide al lepromatoso. Dentro del grupo lepromatoso, las alteraciones en la inmunidad celular hacia otros antígenos distintos al *M. leprae* fueron más severas mientras la duración de la enfermedad fue más prolongada. La reactividad tardía a la lepromina, la cual se considera como evidencia de la resistencia de un individuo al *M. leprae,* puede estar ausente aún antes de la aparición de los síntomas clínicos de la enfermedad. Esta deficiencia en reactividad parece ser primaria y tener una predisposición genética.

RÉSUMÉ

Chez 73 malades souffrant de la lèpre, et atteints de différents types histopathologiques, on a étudié l'immunité cellulaire ou l'hypersensibilité à *M. leprae* et à d'autres antigènes non en relation avec *M. leprae,* telle que la tuberculine et le dinitrocholorobenzene. On a noté que l'anergie spécifique de même que l'anergie non spécifique, étaient intensifiées à mesure que le spectre de la maladie passait du pôle immunologique tuberculoïde au pôle lépromateux. Dans le groupe lépromateux, la détérioration de l'immunité cellulaire était plus prononcée à mesure que la charge bacillaire augmentait. On a également trouvé que la détérioration de l'immunité cellulaire vis à vis d'antigènes autres que *M. leprae* devenait d'autant plus grave que la durée de la maladie était plus longue.

La réactivité tardive à la lépromine, en fait le signe cardinal d'une résistance d'un individu à *M. leprae,* pouvait disparaître même avant l'apparition clinique de la maladie. Ce déficit semble être primitif, et dû à une prédisposition génétique.

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