Complement and Immunoglobulin Determinations in Leprosy and Lepra Reaction¹

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The immunology of leprosy is one of the most intriguing problems in disease proc-(5, 10, 16, 19, 20, 21, 22). The forms in esses which leprosy may occur vary. The most important form, lepromatous leprosy, is characterized by a negative reaction to the leprous material injected into the skin. The opposite is true in the relatively more benign tuberculoid form of the disease. Between these two are various transitional states, the most interesting being the dimorphous form, where lepromatous and tuberculoid reactions may be present at the same time. Additionally in lepromatous leprosy sudden changes in the general condition differing from the normal course of the disease may occur. This so-called lepra reaction has for many years been the main problem facing leprologists in the management of this disease.

The most characteristic symptom is the sudden appearance of an eruption of skin lesions of the erythema nodosum type in which there is an acute inflammation in the dermis and subcutis. This is usually accompanied by a high swinging pyrexia similar to that of a septic process. Joint swelling, neuritic pain, insomnia and malaise are symptoms which may occur. This reaction clinically has many aspects comparable with the appearance of the acute stage of lupus erythematosus. As in lupus erythematosus, erythrocyte sedimentation is rapid, but in contrast to that disorder leucocy-

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There are few reports dealing with the evaluation of complement and immunoglobulins in lepra reaction compared with their levels in other states of the disease (1, 2, 3, 4, 11, 13, 14, 23). The aim of this study was to ascertain whether differences exist in the various types of leprosy, and in addition to determine whether any changes occur after therapeutic suppression of the lepra reaction (6, 7, 17, 18). It was also desired to investigate whether patients who suffer from lepra reactions have serum levels which differ from those in patients in whom the reaction had never occurred.

It was hoped that these findings might shed some light on the nature of the lepra reaction, which is assumed to be an immunologic phenomenon. A number of smaller studies have shown trends of abnormal values in these states. Since many pathologic states of the patients may influence single results, a larger number of examinations during a two year period was evaluated. The results thus show any particular trend of the values to levels higher or lower than normal.

MATERIAL AND METHODS

Three hundred and fifty six sera of 130 leprosy patients were examined for complement (C') and immunoglobulins A, G and M, as noted in list below.

The reactional patients were divided into two groups, those in whom a reaction was present and those who were in remission. Both groups were compared with patients who never suffered from reactions, in order to demonstrate any differences existing during the remission of a reactional patient

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and any similarities to the patients with lepromatous leprosy in whom reactions had not occurred.

- 110 examinations in 79 patients with lepromatous leprosy
 - 7 examinations in 6 patients with tuberculoid leprosy
- 31 examinations in 17 patients with indeterminate leprosy
- 27 examinations in 11 patients with dimorphous leprosy
- 125 examinations in 14¹ patients with lepromatous leprosy while in reaction
- 56 examinations in 18¹ reactional lepromatous leprosy patients while in remission

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1In part from the same patients.

Two hundred and fifty sera from various dermatologic patients and 50 sera from healthy individuals served as controls. The sera from patients were taken at random and no characteristic pattern was found in the various dermatologic groups.

The method of examination used for complement was that cited by Kabat and Mayer (9), and the method for immunoglobulin that cited by Mancini *et al.* (12).

RESULTS

The complement levels in lepromatous and tuberculoid leprosy were similar, although the number of tuberculoid cases examined was too small to be of statistical significance. There was a tendency to low levels in the indeterminate form of the disease and to higher values in the dimorphous form (Table 1).

IgA levels showed a tendency to higher values in the tuberculoid type and in the indeterminate form (Table 2). IgG levels were slightly higher in the indeterminate form (Table 3). IgM levels did not deviate significantly from normal values (Table 4).

It was of interest to determine whether the amount of antigen produced in bacteriologically positive cases differed from that in bacteriologically negative cases. Sera of lepromatous leprosy patients with positive bacillary findings showed a tendency to lower complement levels than those of patients who were bacteriologically negative. The IgG levels were not significantly different, but IgA tended to be higher in cases without bacilli and IgM was higher in patients with positive bacteriological

	LEPROM	ATOUS Ses 45	TUBERCI Nr. of cas	JLOID ses 6		INDETER	MINATE ses 17		DIMOR P Nr. of cas	HOUS ses 11
Х	Nr. of EXAMINATIONS	PERCENTAGE		PERCENTAGE	X	Nr. of EXAMINATIONS	PERCENTAGE	X	Nr. Of	PERCENTAGE
row	29	26.4°/₀	2	28.6°/。		16	51.6%		4	14.8%
19-194	59	53.6%	3	42.8%		11	35.5%		12	44.A%
HOH	22	20.0°/₀	2	2 8. 6 %	Γ	4	12.9%		11	40.8%
TOTAL	110	100.0%	7	100.0%		31	100.0°/。		27	100.0%

TABLE 1. Complement levels in various types and forms of leprosy.

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	LEPROM	ATOUS ies 45	TUBERCI Nr. of cas	ULOID es 6		INDETERN Nr. of ca	MINATE Ses 17		DIMOR F Nr. of cas	PHOUS ies 11
X	Nr. of EXAMINATIONS	PERCENTAGE		PERCENTAGE	X	Nr. of EXAMINATIONS	PERCENTAGE	X	Nr. of EXAMINATIONS	PERCENTAGE
TOW	7	6.5°/₀	-	-		-	-		-	_
11-110	70	64 .2%	3	42.6 %		14	46.7 %		24	88.9 ^{0/} 9
HIGH	32	29.3 %	4	57.2%		16	53.3%		3	11.1%
TOTAL	109	100.0°/。	7	100.0°/a		` 30	100.0%		27	100.0°/。

TABLE 2. Immunoglobulin A levels in various types and forms of leprosy.

findings. This picture was altered when reactional lepromatous leprosy patients were examined (Table 5).

The serum of patients who were not treated with antireactional drugs during the lepra reaction showed a pattern of complement values similar to those in patients with lepromatous leprosy; half had normal values, a quarter high values and a quarter low values (Figs. 1, 2). Reactional type of patients examined while in remission and without antireactional therapy revealed a trend to lower values. Fortyfour per cent of the examinations were below normal, mainly as a shift from the group with normal values (Fig. 3). When these same groups were treated with steroids or with thalidomide, the trend illustrated in Figs. 4, 5, 6 was found.

The sera of patients in acute reaction

	LEPROM	ATOUS ses 45	TUBERC Nr. of ca	SULOID ses 6	INDETERM	VINATE ses 17	DIMOR P Nr. of Cas	HOUS ses 11	
	Nr. of EXAMINATIONS	PERCENTAGE		SPERCENTAGE	Nr. of EXAMINATIONS	PERCENTAGE	Nr. of EXAMINATIONS PERCENTAR		
NO1	12	11.0%	-	-	-	-	1	3.7%	
730-1670	66	60,6%	7	100 0%	19	63.3 [%]	23	85.2°/a	
H G H	31	28.4°/。	-	-	11	36.7%	3	11.1%	
TOTAL	109	100.0°/。	7	100.0°/a	30	100.0°/a	27	100.0°/a	

TABLE 3. Immunoglobulin G levels in various types and forms of leprosy.

	LEPROM Nr. of cas	ATOUS ses 45	TUBERCI	ULOID ses 6		INDETER	MINATE ses 17		DIMOR P Nr. of cas	HOUS ses 11
Z	NE OF	PERCENTAGE		PERCENTAGE	X	Nr. OF	PERCENTAGE	X	Nr. of	PERCENTAGE
LOW	10	9.7 °/₀	-	-		-	-		-	-
58-194	71	64.6°/s	6	85.7%		22	81.5%		24	92.3%
HGH	28	25.7°/。	1	14.3º/。		5	18.5%		2	7.7°/。
TOTAL	109	100.0°/。	7	100.0°/。		27	100.0°%		26	100.0°/s

TABLE 4. Immunoglobulin M levels in various types and forms of leprosy.

treated with steroids revealed higher than normal values in 65.4 per cent, and following thalidomide therapy were raised in 44.4 percent of the examinations. The low values seen in untreated patients (23.7%) were converted to normal or high values following antireactional therapy.

In reactional patients in remission the pattern changed considerably following thalidomide therapy. Two-thirds of the serologic values were within the normal range as a result of changes mainly of the lower values but also partly of the higher ones. No comparison of results with steroid therapy could be made, as no patient continued treatment with these drugs during remission of the lepra reaction.

Lepromatous leprosy patients with untreated lepra reactions have the same distribution of levels of complement as lepro-

	Cases in untr	reaction eated	Reactional cases without reaction untreated		Cases in reaction treated with steroids		Cases in reaction treated with thalidomide		Reactional cases without reaction treated with thalidomide	
	Nr of exam.	°/o	Nr. of exam	%	Nr. of exam	%	Nr. of exam	%	Nr. of exam.	%
LOW	6	23.1	11	44.0	-	-	4	5.6	7	22.6
40-60	13	50.0	9	36.0	9	34.6	36	50.0	20	64.5
HIGH	7	26.9	5	20.0	17	65.4	32	44.4	4	12.9
TOTAL	26	100.0	25	100.0	26	100.0	72	100.0	31	100.0

TABLE 5. Complement levels in lepromatous leprosy.



FIGURE 3





matous leprosy patients who never developed reactions. This might be due to the fact that the samples were taken during the first days of the reaction and there was not sufficient time for the body to react. However, when these reactional patients are in remission they have a much lower distribution of complement levels than lepromatous leprosy patients who never developed reactions. It may be that patients with a lower level of serum complement are more susceptible to reactions and that during reactions they have a compensatory rise in complement to levels found in lepromatous leprosy patients who never developed reactions.

Patients receiving steroid or thalidomide therapy have a higher distribution of complement levels than those not undergoing antireactional therapy. Patients still receiving thalidomide therapy, but recovering from their reaction, show a distribution of complement levels below that found in lepromatous leprosy patients who have never had reactions, but not as low as that in reactional patients who are not on antireactional therapy. It seems, therefore, that the effect of thalidomide is to cause a remission of the reactional state in which complement levels are moving toward levels found in nonreactional patients.

The immunosuppressive action of thalidomide in the human has so far been found to be specific only for patients in leprosy reaction $(^{6, 7, 17, 18})$. It has been demonstrated that ENL is an immunologic reaction in the skin caused by the deposition of immunocomplexes consisting of immunoglobulin (humoral antibody), soluble mycobacterial antigen and complement.

Immunoglobulin A (Table 6, Figs. 7-11). Sera of patients suffering from lepra reaction but not receiving therapy showed high values of IgA in 92.0 per cent of cases. When untreated and in remission 70.8 per cent showed higher than normal values. When treated with steroids or thalidomide

COMPLEMENT LEVELS

Reactional leprosy cases without reaction treated with thalidomide

2 cases	31	examinations	100.01
	4	high	12.91
	20	normal	64.51
	7	low	22.61



FIGURE 6

	Cases in reaction untreated		Reactional cases without reaction untreated		Cases in reaction treated with steroids		Cases in reaction treated with thalidomide		Reactional cases without reaction treated with thalidomide	
	Nr. of exam.	%	Nr. of exam.	%	Nr. of exam.	%	Nr. of exam.	%	Nr. of exam	%
LOW	-	-	-	-	-	-	-	-	-	-
80 350	2.	8.0	7	29.2	12	46.1	19	27.2	.14	45.2
HIGH	23	92.0	17	70.8	14	53,9	51	72.8	17	54.8
TOTAL	25	100.0	24	100.0	26	100.0	70	100.0	31	100.0

TABLE 6. Ig.A levels in lepromatous leprosy.

Ig. A. LEVELS In LEPROMATOUS LEPROSY PATIENTS WITH REACTION WITHOUT TREATMENT

9 cases 25 examinations 100.0 x 23 high 92.0 x 2 normal 8.0 x - low - Ig. A. LEVELS In REACTIONAL LEPROSY CASES WITHOUT REACTION UNTREATED

9 cases	24	examinations	100.0 %
	17	high	70.82
	7	normal	29.22
	-	low	-





there was a tendency to normalization of the values.

FIGURE 9

Sera of lepromatous leprosy patients in reaction showed 92 per cent high values before treatment, 53.9 per cent high values following steroids, and 72.8 per cent high values following thalidomide. High values were found in 54.8 per cent of reactional patients in whom the reaction subsided, but continued with thalidomide therapy, as compared with 70.8 per cent in untreated cases in reaction.

IgG (Table 7). There is a tendency to higher values of about 40 per cent IgG in patients with lepra reaction and in remission, which is higher than in lepromatous leprosy patients who never had reactions. But no significant difference of the values was found in the thalidomide-treated and nontreated groups, whether in reaction or not. The higher values tended to shift toward the normal range in the steroid treated group.

FIGURE 10

IgM (Table 8. Figs. 12-16). In sera from both groups of reactional patients normal IgM values were obtained; only 28.0 per cent and 16.7 per cent revealed values higher than normal. Following therapy with steroids and thalidomide the trend to higher values was present in both groups. Thus compared with changes of IgA levels, in which a tendency to normal values was observed, after therapy the opposite effect was noted.

DISCUSSION

Lepromatous leprosy patients in comparison with untreated reactional patients in

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Ig. A. LEVELS Ig. M. LEVELS In in LEPROMATOUS LEPROSY PATIENTS WITH LEPROMATOUS LEPROSY PATIENTS REACTION TREATED WITH THALIDOMIDE WITH REACTION WITHOUT TREATMENT 10 cases 70 examinations 100.0 x 9 cases 25 examinations 100.0 1 51 high 72.8 1 28.01 7 high 19 normal 27.2% 18 normal 72.01 - low - 1 o w -1000 1000



TABLE 7. Ig.G levels in lepromatous leprosy.

	Cases in untro	n reaction eated	Reactional cases without reaction untreated		Cases in treate ste	Cases in reaction treated with steroids		Cases in reaction treated with thalidomide		Reactional cases without reaction treated with thalidomide	
	Nr. of exam.	%	Nr. of exam.	%	Nr. of exam,	%	Nr. of exam.	%	Nr. of exam.	%	
LOW	1	3.8	2	8.4	-	-	-	-	-	-	
0/181-067	15	57.6	12	50.0	20	76.9	39	55.7	17	54 .8	
HIGH	10	38.6	10	41.6	6	23.1	31	44.3	14	45.2	
TOTAL	26	100.0	24	100.0	26	100.0	70	100.0	31	100.0	



	Cases i untr	n reaction reated	Reactional cases without reaction untreated		Cases in reaction treated with steroids		Cases in reaction treated with thalidomide		Reactional cases without reaction treated with thalidomide	
	Nr.of exam	°/o	Nr.o exam	°/o	Nr. of exam	°/o	Nr.of exam	°/o	Nr.of exam	%
LOW	-	-	-	-	-	-	-	-	-	-
50-200	18	72.0	20	83.3	14	53.9	35	50.0	20	66.7
HIGH	7	28.0	4	16.7	12	46.1	35	50.0	10	33.3
TOTAL	25	100,0	24	100,0	26	100.0	70	100.0	30	100.0

TABLE 8. Ig.M levels in lepromatous leprosy.

Ig.M. LEVELS in LEPROMATOUS LEPROSY PATIENTS WITH REACTION TREATED WITH THALIDOMIDE

0 cases	70	examinations	100.0 =
	35	high	50.0 =
	35	normal	50.0 I
	-	low	-

lg. M. LEVELS

REACTIONAL LEPROSY CASES WITHOUT REACTION TREATED WITH THALIDOMIDE

12 cases	30	examinations	100.0%
	10	high	33.32
	20	normal	66.7 z
	-	low	-



isonission are clinically similar. Complement in lepromatous reactional patients in remission is lower than in nonreactional patients. Individual patients, however, have been shown to have high levels of complement during attacks of lepra reaction. In remission resulting from thalidomide therapy the complement levels have been found to fall, often to normal levels.

It may be that the rise in complement in lepra reactions following therapy is a compensatory mechanism due to the massive fixation of complement components associated with the deposition of immunocomplexes in the tissues, or possibly that the complement is freed from the tissue and is circulating in the serum.

Immunoglobulins of the type IgA are produced mainly by plasma cells in the mucous membranes and the tissues lining the gastro-intestinal tract. Lepra reactions occur commonly during the first year of sulfone therapy. At this time there is massive destruction of mycobacteria and release of soluble mycobacterial antigens. In many cases the mucous membranes, especially of the nose, are a site of a high concentration of Mycobacterium leprae. Thus these tissues could receive strong antigenic stimulation at the time when patients are developing lepra reactions. This might explain the coincidental finding of higher levels of IgA in patients in reaction. Less high levels are found in such patients during treatment with thalidomide or steroids.

Patients with lepra reaction, and reactional patients in remission, tend to have higher levels of IgG and IgA than lepromatous leprosy patients who do not develop reactions. Patients in reaction have a higher level of IgM than reactional patients in remission.

However, higher levels of IgM are found in the serum of reactional patients on thalidomide than in those who had not received treatment. This differential effect of thalidomide on the immunoglobulin synthesis is difficult to explain but may indicate that thalidomide has an additional effect on the regulation of immunoglobulin synthesis.

SUMMARY

The determination of complement and immunoglobulins A, G and M revealed trends in patients with lepromatous leprosy different from those of patients who had never suffered from lepra reaction when compared with reactional patients. The values of complement tended to be lower in untreated reactional patients similar to those in acute systemic lupus erythematosus. Following therapy with steroids or thalidomide a shift to higher values of complement was observed.

A tendency to higher values of IgG, IgA and IgM was also present in reactional lepromatous patients, and especially significant in the case of IgA. The values of IgA dropped following therapy and those of IgM rose. No significant changes occurred in the IgG levels following therapy with thalidomide, but a drop could be found following steroid therapy.

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