

## Leprosy

### V. A Quantitative Comparison of Immune Globulins (IgG, IgM, and IgA) in the Sera of Patients with Pulmonary Tuberculosis and Patients with Leprosy<sup>1,2</sup>

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Using a semiquantitative immunoelectrophoretic method<sup>(6)</sup> for the relative quantitation of IgA and IgM immunoglobulins, we evaluated the immunoprotein changes in the sera of patients with leprosy<sup>(7)</sup> and patients with pulmonary tuberculosis<sup>(8)</sup>. In the latter study we showed an increase in concentration of IgA in the serum of the tuberculous patients. Using the Oudin quantitative method for the absolute determination of immunoglobulins, we have extended our studies and measured IgG, IgM, and IgA responses in the sera of patients with leprosy<sup>(9)</sup>. In this quantitative study, the immunoglobulin changes were found to have different patterns in the various types of leprosy. Since the pattern of immune response of patients with tuberculosis may be similar to the immune response of leprosy patients, we re-evaluated the immunoglobulins of our previously reported patients<sup>(8)</sup>.

#### MATERIALS AND METHODS

**Sera studied.** (a) Patients' sera were obtained from 46 patients with untreated pulmonary tuberculosis seen at the University Hospital, College of Medicine, Seoul National University, Seoul, Korea<sup>(8)</sup>. (b) Controls. Sera were obtained from 153 healthy subjects previously reported by us<sup>(9)</sup>.

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The diagnosis of tuberculosis was established by clinical findings, laboratory studies (culture, etc.), and chest x-ray examination. The patients were classified as to (a) extent of pulmonary tuberculosis, based on the criteria of the National Tuberculosis Association of the United States<sup>(2)</sup>, and (b) sex and age of the patients (Table 1). The serum of each patient was collected before any therapy was started and handled in the manner previously reported<sup>(6,7,8)</sup>.

The quantitation of each immune globulin (IgG, IgM; and IgA) was done as previously reported<sup>(9)</sup>. The values of immune globulin in the serum of patients with pulmonary tuberculosis were compared with the serum values of the control group and patients with various types of leprosy.

#### RESULTS

The values of the immune globulins in 46 cases of tuberculosis are shown in Table 2. The values of the immune globulins with respect to the extent of the pulmonary tuberculosis, i.e., far advanced (Adv.), moderately advanced (Mod.), and minimal (Min.) are summarized in Table 3. The findings with respect to the age of patients are seen in Table 4.

Tables 5-7 present a comparison of the serum globulin values of the control group with: (a) the serum values of patients with pulmonary tuberculosis (Table 5), (b) the serum values of the tuberculosis patients with respect to the extent of their pulmonary involvement (Table 6), and (c) the serum values of the same patients divided into three age groups (Table 7). The serum immunoglobulins of our previously

TABLE 1. Classification of patients with pulmonary tuberculosis.

Age (yrs.)	Sex		Extent of pulmonary disease			
	Male	Female	Adv.	Mod.	Min.	Total
<20	3	1	1	-1	2	4
20-39	26	4	8	11	11	30
>39	11	1	6	3	3	12
Total	40	6	15	15	16	46

Adv. = Far advanced.  
 Mod. = Moderately advanced.  
 Min. = Minimal.

TABLE 2. Values of immune globulins in sera of patients with pulmonary tuberculosis.

Immunoglobulins (mgm./100 ml. serum)	Mean	No.	S.D.	S.E.
IgG	2422	46	504	74
IgM	84	46	24	4
IgA	324	46	98	14

S.D. = Standard deviation.  
 S.E. = Standard error.

TABLE 3. Values of immune globulins in sera of patients with varying extents of pulmonary tuberculosis.

Immunoglobulins (mgm./100 ml. serum)	Extent	Mean	No.	±S.D.	±S.E.
IgG	Adv.	2583	15	517	134
	Mod.	2339	15	374	97
	Min.	2348	16	471	118
IgM	Adv.	93	15	29	8
	Mod.	85	15	25	7
	Min.	82	16	18	5
IgA	Adv.	361	15	104	27
	Mod.	314	15	75	19
	Min.	298	16	106	26

Adv. = Far advanced.  
 Mod. = Moderately advanced.  
 Min. = Minimal.

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TABLE 4. Serum values of immune globulins in tuberculosis patients of three age groups.

Immunoglobulins (mgm./100 ml. serum)	Age (yrs.)	Mean	No.	±S.D.	±S.E.
IgG	<20	2231	4	163	83
	20-39	2445	30	530	97
	>39	2427	12	535	155
IgM	<20	77	4	11	56
	20-39	89	30	27	5
	>39	75	12	16	5
IgA	<20	328	4	171	85
	20-39	328	30	93	17
	>39	311	12	90	26

reported leprosy cases (<sup>9</sup>) are compared with (a) sera of the tuberculous patients (Table 8) and (b) sera of the tuberculous patients subdivided according to the extent of pulmonary involvement (Table 9). The sera of the tuberculosis patients (subdivided as to extent of pulmonary involvement) are compared with serum immunoglobulins in: (a) the sera of lepromatous leprosy patients (L type, Table 10), (b) the sera of tuberculoid leprosy patients (T type, Table 11), and (c) the sera of indeterminate type leprosy patients (I type, Table 12).

#### DISCUSSION

As seen in Table 5, the serum IgG, IgM, and IgA concentrations of tuberculosis patients are significantly different from normal serum values. These results are not in agreement with those of other investigators

who reported an elevation in IgG globulins and no change in IgA and IgM (<sup>3</sup>). Our data show an elevation of IgG and IgA serum proteins ( $p < 0.01$ ) and a decrease in IgM ( $p < 0.01$ ).

Since tuberculosis is a chronic bacterial disease and is caused by an agent of the same bacterial genus (*Mycobacteria*) as leprosy, the significant elevation of IgG was expected, as IgG is increased in the sera of leprosy patients (<sup>9</sup>). The IgG findings in tuberculosis patients reaffirm the finding that gamma globulin increases in pulmonary tuberculosis sera as demonstrated by electrophoresis (<sup>1, 4, 5</sup>).

The increased concentration of IgA and the decrease of IgM denote a different immune response in patients with tuberculosis in comparison with the response in leprosy patients. The IgM was increased in the lepromatous leprosy patient (L type),

TABLE 5. Comparison of serum immune globulin values in a control group and patients with pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.
Control group	2035 ± 23	94 ± 2.0	267 ± 5
Tuberculosis patients	2422 ± 74 <sup>a</sup>	84 ± 4 <sup>a</sup>	324 ± 14 <sup>a</sup>

<sup>a</sup>  $p < 0.01$  when compared to values of control group.

TABLE 6. Comparison of serum immune globulin values in a control group and patients with varying extents of pulmonary tuberculosis.

Subjects	Immunoglobulin: (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Control group	2035 $\pm$ 23	94 $\pm$ 2	267 $\pm$ 5
Tuberculosis:			
Adv.	2583 $\pm$ 134 <sup>a</sup>	93 $\pm$ 8	361 $\pm$ 27 <sup>a</sup>
Mod.	2339 $\pm$ 97 <sup>a</sup>	85 $\pm$ 7	314 $\pm$ 19 <sup>b</sup>
Min.	2348 $\pm$ 118 <sup>a</sup>	82 $\pm$ 5 <sup>a</sup>	298 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to control values.<sup>b</sup> P < 0.05 when compared to control values.

TABLE 7. Comparison of serum immune globulin values in a control group and three age groups of patients with pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Control group	2035 $\pm$ 23	94 $\pm$ 2	267 $\pm$ 5
Tuberculosis:			
<20 years	2231 $\pm$ 82	77 $\pm$ 6 <sup>a</sup>	328 $\pm$ 85
20-39 years	2445 $\pm$ 97 <sup>a</sup>	87 $\pm$ 5	328 $\pm$ 17 <sup>a</sup>
>39	2427 $\pm$ 155 <sup>a</sup>	75 $\pm$ 5 <sup>a</sup>	311 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to control.

TABLE 8. Comparison of serum immune globulin values of patients with leprosy and patients with pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Leprosy	2498 $\pm$ 26	110 $\pm$ 3	274 $\pm$ 5
Tuberculosis	2422 $\pm$ 74	84 $\pm$ 4 <sup>a</sup>	324 $\pm$ 4 <sup>a</sup>

<sup>a</sup> P < 0.01 significance when compared to leprosy group.



and IgA was elevated in concentration in the tuberculoid leprosy patient (T type). Although the two diseases result from infections by agents of related bacterial families, they probably produce slightly different immune responses in patients. The two bacterial organisms most likely have chemical differences in their antigenic characteristics. In addition, their predilection for different tissues and the resulting tissue destruction, cause a varied immunologic response due to the various antigenic substances produced during the pathologic processes in the tissues.

If the patients are classified as to extent of their pulmonary tuberculosis (Table 6),

the serum immunoglobulin changes are more meaningful. IgG is significantly elevated in all three groups as compared with control values. The IgG elevation is highest ( $2583 \pm 134$  mgm.%) in the far advanced group. The minimal group shows significant elevations of IgG ( $2348 \pm 118$  mgm.%), as do the early forms of leprosy (indeterminate type,  $2306 \pm 77$  mgm.%). In addition the IgM and IgA are not elevated in the patients with minimal tuberculous disease (Table 6), and in patients with indeterminate leprosy (Table 12). IgM values appear normal in patients with far advanced tuberculosis, but significantly depressed in patients with minimal tuberculosis (Table

TABLE 9. Comparison of serum immune globulin values of patients with leprosy and patients with varying extents of pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Leprosy	2498 $\pm$ 26	110 $\pm$ 3	274 $\pm$ 5
Tuberculosis:			
Adv.	2583 $\pm$ 134	93 $\pm$ 7	361 $\pm$ 27 <sup>a</sup>
Mod.	2339 $\pm$ 97	85 $\pm$ 7 <sup>a</sup>	314 $\pm$ 19 <sup>b</sup>
Min.	2348 $\pm$ 118	82 $\pm$ 5 <sup>a</sup>	298 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to leprosy group.

<sup>b</sup> P < 0.05 significance when compared to control group.

TABLE 10. Comparison of serum immune globulin values in patients with L type leprosy and patients with varying extents of pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Leprosy	2598 $\pm$ 70	131 $\pm$ 6	261 $\pm$ 9
L Type			
Tuberculosis:			
Adv.	2583 $\pm$ 134	93 $\pm$ 8 <sup>a</sup>	361 $\pm$ 27 <sup>a</sup>
Mod.	2339 $\pm$ 97 <sup>b</sup>	85 $\pm$ 7 <sup>a</sup>	314 $\pm$ 19 <sup>b</sup>
Min.	2348 $\pm$ 118	82 $\pm$ 5 <sup>a</sup>	298 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to L type patients.

<sup>b</sup> P < 0.05 significance when compared to L type patients.

TABLE 11. Comparison of serum immune globulin values in patients with T type leprosy and patients with varying extents of pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Leprosy: T type	2410 $\pm$ 58	95 $\pm$ 3	286 $\pm$ 7
Tuberculosis:			
Adv.	2583 $\pm$ 134	93 $\pm$ 8	361 $\pm$ 27 <sup>a</sup>
Mod.	2339 $\pm$ 97	85 $\pm$ 7	314 $\pm$ 19
Min.	2348 $\pm$ 118	82 $\pm$ 5 <sup>a</sup>	298 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to T type patients.

TABLE 12. Comparison of serum immune globulin values in patients with I type leprosy and patients with varying extents of pulmonary tuberculosis.

Subjects	Immunoglobulins (mgm./100 ml. serum)		
	IgG	IgM	IgA
	Mean $\pm$ S.E.	Mean $\pm$ S.E.	Mean $\pm$ S.E.
Leprosy: I type	2306 $\pm$ 77	98 $\pm$ 4	274 $\pm$ 13
Tuberculosis:			
Adv.	2583 $\pm$ 134	93 $\pm$ 8	361 $\pm$ 27 <sup>a</sup>
Mod.	2339 $\pm$ 97	85 $\pm$ 7	314 $\pm$ 19
Min.	2348 $\pm$ 118	82 $\pm$ 5 <sup>a</sup>	298 $\pm$ 26

<sup>a</sup> P < 0.01 significance when compared to I type leprosy.

TABLE 13. Patterns of immunoglobulin changes.

	IgG	IgM	IgA
Tuberculosis	+	-	+
Leprosy			
(all patients)	+	+	0
L type	+	+	0
T type	+	0	+
I type	+	0	0

The symbols + and - indicate significant changes in immunoprotein concentration.  
The symbol 0 indicates no significant change.

6). The reverse is true of IgA; however, even the patients with moderately advanced tuberculosis show a significant elevation of IgA. The IgG and IgA serum elevations parallel the clinical severity of the pulmonary disease.

As seen in Table 7, the subdivision of the tuberculous patients by age groups confirms the findings set forth in Table 6. IgG and IgA values are elevated and IgM values are depressed. Since the number of tuberculosis patients is only 46 and the IgG and IgA means are elevated, we anticipate that, as the sample size is increased, the

standard error will decrease and the IgG in the group less than 20 years of age, and the IgA in groups under 20 years and more than 39 years of age will become statistically significant. There appears to be no remarkable difference in immunoglobulin levels by age group. This is in contrast to findings in leprosy sera. In lepromatous leprosy the IgG and IgM levels are increased in the younger age group, i.e., under 20 years of age.

When the immunoglobulin levels in leprosy and tuberculosis patients are compared (Table 8), the IgG levels are not found to be significantly different, but the IgM and IgA levels are very different ( $p < 0.01$ ). IgM is increased in L type leprosy and decreased in tuberculosis. IgA is not increased (above control values) in our leprosy patients (as a group, Tables 7, 8); however, the IgA is elevated in the T type leprosy patient (Tables 7, 11,  $286 \pm 7$  mgm.%;  $p < 0.01$  over control values). Yet that elevation is not as high as the IgA levels in the tuberculosis patients (Table 8). The pattern of immunoglobulin changes is found to be about the same when the tuberculosis patients are subdivided as to extent of their pulmonary tuberculosis (Table 9).

If the immunoglobulin changes in the tuberculosis patients (subdivided by extent of pulmonary involvement) are compared to immunoglobulin changes in the three types of leprosy (Table 10, L type; Table 11, T type; and Table 12, I type), the IgG values are found to be elevated in both diseases to approximately the same level. IgM values are most prominently elevated in L type leprosy; therefore, all three groups of tuberculosis patients (Table 10) show statistically significant depression of IgM values. Only the patients with minimal tuberculosis show significantly lowered IgM levels when compared with T and I types of leprosy (Tables 11, 12). The IgA elevation is much higher in the tuberculous patients than in the leprosy patients. The highest mean value of IgA in leprosy sera ( $286 \pm 7$  mgm.%, Table 11) is lower than the lowest mean value of IgA in the tuber-

culosis patients ( $298 \pm 26$  mgm.%).

The serum elevation of IgG and IgA immunoglobulins in tuberculosis patients was expected after the changes in leprosy serum were noted (<sup>9</sup>). The reason for the diminished level of IgM remains obscure. It appears that the pattern of immunoglobulin changes in tuberculosis sera is different from that in leprosy sera (Table 13).

### SUMMARY

Serum IgG and IgA levels of tuberculosis patients are significantly elevated, and IgM levels are significantly decreased. These changes are comparable to the immunoglobulin changes in the sera of patients with tuberculoid type leprosy, but are sufficiently different to show an IgG, IgM, and IgA serum pattern that is distinguishable from the serum pattern of leprosy patients.

### RESUMEN

Los niveles de IgG y de IgA en el suero de los enfermos de tuberculosis están significativamente elevados y los niveles de IgM están significativamente disminuidos. Estos cambios son comparables a los cambios de las inmunoglobulinas en el suero de los enfermos con lepra de tipo tuberculoides, pero son suficientemente diferentes para mostrar un padrón de IgG, IgM, e IgA en el suero que es diferenciable del suero de los enfermos de lepra.

### RÉSUMÉ

Chez les malades atteints de tuberculose, les niveaux des globulines IgG et IgA dans le sérum sont significativement augmentés, et le niveau des globulines IgM est significativement abaissé. Ces modifications sont comparables aux modifications des immunoglobulines dans le sérum de malades atteints du type tuberculoides de la lèpre, mais elles sont cependant suffisamment différentes que pour montrer un profil sérique des globulines IgG, IgM et IgA qui est discernable du profil sérique observé chez des malades de la lèpre.

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