

## A Study of Autoantibodies in Chronic Mycobacterial Infections<sup>1,2</sup>

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Infectious diseases are common in black South Africans, and tuberculosis (TB) is particularly prevalent. It has previously been reported that infections are associated with the induction of autoantibodies which, with the systemic manifestation of these common conditions, may lead to difficulties in differentiating them from the connective tissue diseases. To complicate matters further, controversy existed in previous reports regarding the prevalence of autoantibodies in mycobacterial infections. In fact, the association between autoimmunity and infection is currently being reassessed; recent reports have suggested that mycobacterial infection may play a role in the pathogenesis of autoimmune disorders (<sup>10, 15, 21, 27</sup>). This study was undertaken solely to discover the prevalence of certain autoantibodies in the chronic mycobacterial infections, TB and leprosy.

The prevalence of circulating rheumatoid factor (RF), antinuclear (ANA), anti-double-stranded DNA (dsDNA), and anti-extractable nuclear antigen (ENA) antibodies in the sera of black South African patients with pulmonary TB and leprosy infections was investigated.

### PATIENTS AND METHODS

**Patients.** Four groups of patients were included in the study. Table 1 summarizes

the demographic data. Group 1 comprised 41 consecutive black inpatients with leprosy from Westford Hospital, Pretoria. Applying the Ridley and Jopling classification (<sup>22</sup>), they comprised 18 patients with polar lepromatous, 10 with borderline lepromatous, 7 with borderline tuberculoid, 4 with borderline, and 2 with polar tuberculoid leprosy. Complications occurred in 6 patients; 5 had erythema nodosum leprosum, 1 had a reversal reaction. Most patients required treatment with clofazimine, dapsone or rifampin. No patient had any associated medical disease.

Forty-nine consecutive black pulmonary TB patients (Group 2) were studied. They had presented to the Hillbrow and Baragwanath Hospitals with a clinical history, physical examination, and radiological features compatible with pulmonary TB. All patients had *Mycobacterium tuberculosis* documented on sputum examination.

Group 3 comprised 73 black pulmonary TB inpatients receiving treatment at the Rietfontein Hospital, Johannesburg. In addition to having the clinical and radiological features of pulmonary TB, all of these patients had had bacteriological confirmation of *M. tuberculosis* in the sputum at the time of diagnosis. Sixty-five patients were being treated with isoniazid (INH) and other drugs; eight patients were not treated with INH.

In Group 4 (the control group), 100 healthy black blood donors from the Highveld Blood Transfusion Service, Johannesburg, were selected to provide an age distribution similar to the TB Groups 2 and 3.

A clinical history was obtained and each patient was examined for associated disease. Patients with clinical evidence of connective tissue diseases were to be excluded from the study; however, no patient demonstrated such features.

The clinical details of the patients are demonstrated in Table 1. The patient groups were reasonably matched for age and sex,

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TABLE 1. Clinical characteristics of the study population.

	Leprosy patients	Untreated TB patients	Treated TB patients	Controls
No. of patients	41	49	73	100
Male:female ratio	21:20	32:17	40:33	50:50
Mean age ( $\pm$ S.D.)	44.8 yrs $\pm$ 13.9	35.1 yrs $\pm$ 12.4	37.3 yrs $\pm$ 12.4	35.7 yrs $\pm$ 8.7
Mean disease duration ( $\pm$ S.D.)	12.6 yrs $\pm$ 12.4	1.9 mos $\pm$ 1.6	7 mos $\pm$ 7	—
Mean treatment duration ( $\pm$ S.D.)	12.6 yrs $\pm$ 12.4	—	3.6 mos $\pm$ 0.2	—

but the leprosy patients had mostly had protracted therapy. Informed consent was obtained from all of the patients participating in the study.

Rheumatoid factor (RF) was measured using both the RheumaTec® RF latex test (Labor Diagnostica, Federal Republic of Germany), which utilizes IgG-coated polystyrene beads, and the Rheuma-Wellcotest (Wellcome Reagents Ltd, United Kingdom).

**Antinuclear antibody (ANA) measurements.** ANA were measured by indirect immunofluorescence using as substrate 4- $\mu$ m-thick sections of rat kidney and liver as well as a HEP-2 cell line (Kalestad Laboratories, Federal Republic of Germany). Antibodies against dsDNA were measured by indirect immunofluorescence using *Crithidia luciliae* as substrate. Extractable nuclear antigen contains RNA and a protein with two different reactive components. Antibodies against these two reactive components, ribonuclear protein (RNP) and Smith (SM; named after a patient), were investigated by counterimmune electrophoresis using rabbit thymus powder as substrate; other autoantibodies, particularly prevalent in Sjögrens syndrome, anti-SSA (Ro) and anti-SSB (La), were assessed using an Ouchterlony double-immune gel-diffusion technique (Poly ENA commercial kit; Zeus Laboratories, Federal Republic of Germany), according to the manufacturer's instructions.

## RESULTS

**Rheumatoid factor.** The prevalence and titer of the RF measured, using the RheumaTec® RF latex test, were low in the population studied. In the leprosy group (41 patients) only one patient had a positive RF of 40 International Units (IU), and in the

treated TB group (73 patients) two patients had RF with titers of 80 IU and 160 IU, respectively. In the untreated TB group (49 patients) and the control group (100 patients), all patients were RF negative.

In addition, 43 serum samples (19 untreated TB patients and 24 treated TB patients) were randomly selected for comparative testing with the Rheuma-Wellcotest RF test. Using this technique, four of the untreated TB patients (21%) had a positive RF ranging from 1:20 to 1:40 compared with only one treated TB patient (4%) with a titer of 1:40. Because of the small sample population, this difference was not statistically significant (Yates  $\chi^2$  1.53;  $p$  = 0.23). However in the untreated TB patients, a comparison of the two detection systems (Rheuma-Wellcotest and RheumaTec® RF) for RF positivity suggested borderline statistical significance (Yates  $\chi^2$  2.51;  $p$  = 0.05).

**Antinuclear antibodies.** Table 2 shows that the prevalence of ANA in the leprosy group was 7.3% and although higher than in the control group (2%), it was not statistically significant. ANA positivity did not correlate with reactional states. In the TB patients, however, the treated patients did have a significantly increased ANA positivity (15.1%). It was noted that the eight treated patients who did not receive INH were all ANA negative. Conversely, 17% of the 65 patients treated with INH were ANA positive. Table 2 also shows the range of titers found. Although these were mostly low, they were as high as 1:640 in one of the treated patients. Although the speckled pattern was the one most frequently seen, there was no uniformity within the groups.

In TB patients ANA positivity was associated with treatment duration (mean duration of treatment of positives vs mean duration of treatment of ANA negatives  $p$  = 0.036), as well as being more significant

TABLE 2. ANA results (in black patients) with chronic mycobacterial infections compared with healthy controls.

	Leprosy patients	Untreated TB patients	Treated TB patients	Controls
No. of patients	41	49	73	100
ANA positive	3	3	11 <sup>a</sup>	2
Percentage positive	7.3%	6.1%	15.1%	2%
Titers	1:80	1:80	1:40–1:640	1:160–1:320
Patterns				
Speckled	3	1	8	2
Rim	0	0	0	0
Nucleolar	0	1	2 <sup>b</sup>	0
Homogenous	0	1	3 <sup>b</sup>	0

<sup>a</sup> Pearson  $\chi^2 = 10.863$ ;  $p = 0.0125$ .

<sup>b</sup> Of the treated TB patients, 9 had a single pattern and 2 had two simultaneous patterns (nucleolar and homogenous).

for those patients receiving INH therapy ( $p = 0.026$ ).

Of interest is the fact that none of the serum samples reacted against native DNA, SS-a, SS-b, RNP, or Sm antigens; nor did any of the patients with or without ANA show features of a connective tissue disease.

### DISCUSSION

Bonomo, *et al.* (<sup>5</sup>) were the first workers to describe autoantibodies in leprosy. Subsequently, the frequent occurrence of autoantibodies in patients with leprosy has been documented in a number of studies, and this work adds to the extensive literature on the subject. However, this is the first study dealing with the prevalence, pattern, and titers of autoantibodies in black South African patients. Moreover, in 1967 Bonomo, *et al.* (<sup>4</sup>) described a 42-year-old female with lupoid features who had positive RF, ANA and LE cell phenomenon, suggesting that a clinical overlap exists between leprosy and diseases with autoimmune phenomena, in particular systemic lupus erythematosus (SLE).

Discrepancy exists in the literature about the prevalence of RF in leprosy patients. Some investigators found up to 50% of leprosy patients RF positive (<sup>1</sup>), while others have failed to detect such autoantibodies (<sup>14</sup>).

A number of factors must be considered, including the type of assay utilized, genetic factors, study population, the type and severity of the disease, and the possible role of different treatment regimens. Unfortunately, since leprosy is an uncommon dis-

ease and the mean disease duration in this study was 12 years, we may have missed the immunological aberrations related to the patients' early disease and treatment.

Difficulty exists in assaying RF because the test has not been standardized. IgM RFs are multivalent antibodies and effective agglutinators of antigen-coated particles, such as bentonite or latex beads, which have been passively coated with human IgG. The cross-linking of these IgG-coated particles by IgM RF in serum produce a flocculation reaction. In addition technical problems have arisen, particularly in chronic infections where patients are hypergammaglobulinemic, because the IgG antigen with which RF reacts may crossreact or interfere with a specific detection system. Positivity may vary according to the size and characteristics of the particles used.

The Rheuma-Tec<sup>®</sup> RF latex test utilized in this study is an aqueous suspension of polystyrene particles coated with human gamma globulin. The positivity of the patients with mycobacterial infections who were tested was shown to be low. This is in contrast to the results obtained when using the Rheuma-Wellcotest system, where 21% of the untreated TB patients tested demonstrated a positive RF. The tests differ: in the Rheuma-Tec<sup>®</sup> RF test the patient serum is diluted in a physiological solution (saline 0.9%); the Rheuma-Wellcotest utilizes a glycine buffer as diluent.

When comparing the results of the two systems, the Rheuma-Wellcotest produced a higher positivity. Furthermore, the positivity of RF is dependent on the technique

TABLE 3. Rheumatoid factor (RF) in leprosy.<sup>a</sup>

Author(s) reference	Leprosy subtype	RA test	Percentage
Abe, <i>et al.</i> (1)	Lepromatous	Waller-Rose	60.4
		RA test (Hylands Laboratory)	28.0
		FII-LA	37.0
	Tuberculoid	Waller-Rose	53.0
		RA test	6.3
		FII-LA	28.0
Shwe (25)	Lepromatous	Latex agglutination	25.0
	Tuberculoid	(Hylands Lab.)	0.0
Dhople (8)	Lepromatous with arthritis	Latex (in-house) RA test	73.0
	Lepromatous without arthritis	Latex (in-house) RA test	32.0
Petchclai, <i>et al.</i> (18)	Lepromatous	Waller-Rose	13.8
		Latex (Hylands Lab.)	3.4
		Waller-Rose	5.2
	Tuberculoid	Latex (Hylands Lab.)	0.0
		Undefined	0.0
		Latex test (Sylvania)	35.0
Miller, <i>et al.</i> (14)	All types	Latex test (Behring)	18.7
Saha and Mittal (24)	Lepromatous		
Chavez-Legaspi, <i>et al.</i> (7)	Lepromatous		

<sup>a</sup> The table summarizes the findings of RF in different investigations with different methods.

used, as documented by other investigators and summarized in Table 3 (1, 8, 18). From the results obtained in this study, it appears that the Rheuma-Tec® RF system produces a low frequency of crossreactivity (false-positives) in chronic infections.

In addition, Reyes, *et al.* (20) demonstrated that RF positivity in TB patients was dependent upon disease severity. It may be possible that patients studied by other workers had more severe disease than those patients in the present study population.

Table 3 shows that the low prevalence of RF found in this study is similar to that of the tuberculoid patients in the study of Shwe (25), and of the whole group in the studies of Petchclai, *et al.* (18) and Miller, *et al.* (14). Petchclai, *et al.* (18) suggested that the low occurrence in their study could be due to an alteration in the immune response among the Thai subjects. Contradictory results have been obtained by Abe, *et al.* (1), Saha and Mittal (24), and Dhople (8) who studied the prevalence of RF during and after an acute lepra reaction in 39 patients. In Dhople's study, the patients were divided into two groups—those with acute lepra reaction with arthritis (11) and those with acute lepra reaction without arthritis (28) (8). He found that 73% of the patients in the first group (8 of 11 patients) had a positive RF during the acute attack compared with 32% (9 of 28) with positive RF in the second group (8). His conclusion was that RF may play a

role in the pathogenesis of arthritis and the rheumatological manifestations that patients with acute lepra reactions frequently experience. However, in contrast to Dhople's study, in the present study five patients had ENL, and none had a positive RF. In addition, our group contained a significant proportion of the lepromatous-type patients who did not demonstrate a high frequency of RF positivity.

From Table 4 it can be seen that there was also quite a wide variation in the reported occurrence of ANA in leprosy patients, ranging from absent or very low, as in the present study, up to the 28% reported by Masala, *et al.* (13). Shwe found ANA more common in the lepromatous patients (25), while in Masala's groups it was equally as common in the tuberculoid group (13). The low sensitivity of the ANA tests used in the present study is unlikely to be the reason for the low incidence. The tests have been used routinely in our lupus clinics, and over a number of years been found to be reliable.

In two separate studies of the presence of RF in TB patients (6, 12), a higher prevalence of RF positivity was demonstrated. Twenty-four percent of the untreated and 28.8% of the treated TB patients had a positive RF (6). Lindqvist, *et al.* (12) demonstrated in their study that RF was positive in 40% of patients, with titers ranging from 1:20 to 1:640. None of the untreated patients in the present study had RF, and it was present in only

TABLE 4. Incidence of ANA in leprosy in various studies.

Author(s) reference	Leprosy subtype	ANA test	Percentage
Wright ( <sup>28</sup> )	Lepromatous and tuberculoid	Indirect immunofluorescence with IgG conjugate	4.0
		As above but IgM conjugate	23.0
Shwe ( <sup>25</sup> )	Lepromatous Tuberculoid	Indirect immunofluorescence	17.9
			0.0
Petchelai, <i>et al.</i> ( <sup>18</sup> )	Lepromatous Tuberculoid	Tissue sections	0.0
			0.0
Masala, <i>et al.</i> ( <sup>13</sup> )	Lepromatous Tuberculoid	Indirect immunofluorescence	28.0
			28.0
Miller, <i>et al.</i> ( <sup>14</sup> )	All types	Tissue sections and HEP-2 cell line	16.0
Chavez-Legaspi, <i>et al.</i> ( <sup>7</sup> )	Lepromatous	HEP-2 cell line	3.1

2.8% of the treated TB group. As mentioned previously, the laboratory technique and possible genetic factors may account for this discrepancy.

ANA may be produced in the body as a response to a number of drugs; however, only a small proportion of patients who produce ANA as a result of drugs develop clinical SLE (<sup>2</sup>). In the present study, examination of all patients failed to demonstrate any clinical features of SLE. This is borne out by evidence from the Connective Tissue Disease Clinic at Hillbrow Hospital, Johannesburg, where, in our experience, only one equivocal case of drug-induced lupus was found out of a group of approximately 100 black SLE patients. Furthermore, one must remember that in the United States of America drug-induced lupus is a rare condition among blacks (<sup>9</sup>).

Among the untreated TB population only 6.1% had a positive ANA test compared with 17% of the treated TB group. However, none of the serum samples reacted against dsDNA, anti-Sm, anti-SSA, anti-SSB, or anti-RNP.

We found that the appearance of ANA correlated with treatment duration and not with disease duration, suggesting that ANA was induced mainly by antituberculous drugs, in particular INH. None of the patients treated with drugs other than INH had a positive ANA test. Titers were generally low, except for one patient whose ANA titer was 1:640. ANA was more prevalent in males than in females, this difference not being statistically significant but noteworthy, considering the predominance

of females suffering from SLE and drug-induced SLE.

The induction of ANA by antituberculous drugs was first described by Cannat and Seligmann (<sup>6</sup>). In their study the incidence of ANA in 125 untreated TB patients was compared to that of 75 treated TB patients. The prevalence of ANA was 4% in the untreated group and 20% in the treated group (<sup>6</sup>). These findings are similar to those of the present study. However, the authors did not comment on titers and did not analyze sex, age, and treatment duration in relation to the induction of ANA (<sup>6</sup>).

In a prospective study, Rothfield, *et al.* (<sup>23</sup>) also demonstrated the effects of treatment on ANA induction. Of 192 pulmonary TB cases, 4% were ANA positive before treatment and 21.6% developed ANA during treatment (<sup>23</sup>). The role of the duration of treatment was not analyzed.

Thewaini Ali (<sup>26</sup>) found only 4 out of 80 TB patients to have low titers of ANA. Lindqvist, *et al.* (<sup>12</sup>) found that 46% of 60 TB patients had a positive ANA. However, all of their patients were receiving TB treatment, and the study did not divide the patients into treated or untreated TB (<sup>12</sup>).

It was demonstrated by Price-Evans that INH and hydralazine were polymorphically metabolized in humans (<sup>19</sup>). Perry, *et al.* (<sup>16,17</sup>) and Alarcón-Segovia, *et al.* (<sup>2</sup>) have demonstrated that the presence of ANA is more prevalent in patients who phenotypically are slow acetylators. Alarcón-Segovia, *et al.* (<sup>2</sup>) analyzed the incidence of ANA in 184 treated TB patients. However, in contrast to our findings, their study showed a



higher prevalence of ANA in females <sup>(2)</sup>. In a different study, the same workers analyzed 153 TB patients receiving INH therapy <sup>(3)</sup>. Of this group of patients, 78 were slow and 75 rapid acetylators phenotypes; the overall ANA positivity was 20% <sup>(3)</sup>. In our current study, the patterns of acetylation in black South Africans were not analyzed, but it has been demonstrated previously that the prevalence of both slow and fast acetylator phenotypes is similar in black and white South Africans, with the exception of the Kgalagadi of the Sotho/Tswana tribe who have a low frequency of slow acetylation phenotype <sup>(11)</sup>. There were no Kgalagadi in the present study population.

### SUMMARY

Infections can cause autoantibody production. The purpose of this study was to determine the prevalence of autoantibodies in patients with chronic mycobacterial infections. Sera from 41 leprosy patients and from 49 untreated and 73 treated tuberculosis (TB) patients were tested for the presence of rheumatoid factor, antinuclear factor, and several other autoantibodies. The rheumatoid factor, measured by the RheumaTec RF latex test, was positive in 2.4% of the leprosy patients and 2.7% of the treated TB patients but absent in the untreated TB group. The titers ranged from 40 to 160 international units. Positivity was dependent upon the technique utilized, and existed in 21% of untreated TB group and 4% of the treated TB patients when using the Rheuma-Wellcotest technique. The antinuclear antibody was positive in 7.3% of the leprosy group, 6.1% of the untreated TB group, and 15% of the treated TB patients ( $p = 0.0125$ ). Antinuclear antibody positivity correlated with the duration of treatment of the TB patients ( $p = 0.025$ ). The antinuclear antibody titers were low and gave no specific pattern on staining. No patient had antibodies against native deoxyribonucleic acid, ribonuclear protein, Ro (SS-A) or La (SS-B) antigens.

Due to their low prevalence and frequency in these chronic infections, these autoantibodies should not lead to confusion in distinguishing these conditions from the connective tissue diseases.

### RESUMEN

Las infecciones pueden causar la producción de autoanticuerpos. El propósito de este estudio fue el determinar la prevalencia de autoanticuerpos en pacientes con infecciones micobacterianas crónicas. Los sueros de 41 pacientes con lepra, de 49 pacientes con tuberculosis (TB) no tratada y de 73 pacientes con tuberculosis tratada, se probaron para buscar la presencia de factor reumatoide, factor antinuclear, y otros autoanticuerpos. El factor reumatoide, medido con el reactivo RheumaTec RF fue positivo en el 2.4% de los pacientes con lepra y en el 2.7% de los pacientes con tuberculosis tratada pero fue negativo en los pacientes con TB no tratada. Los títulos variaron de 40 a 160 unidades internacionales. Con la técnica del Rheuma-Wellcotest, la positividad fue del 21% en el grupo TB no tratado y del 4% en los pacientes TB tratados. Los anticuerpos antinucleares fueron positivos en el 7.3% de los pacientes con lepra, en el 6.1% del grupo TB no tratado y en el 15% de los pacientes TB tratados ( $p = 0.0125$ ). La positividad de los anticuerpos antinucleares correlacionó con la duración del tratamiento de los pacientes con TB ( $p = 0.025$ ). Los títulos de anticuerpos antinucleares fueron bajos y no dieron un patrón específico de tinción. Ningún paciente tuvo anticuerpos contra DNA nativo, contra proteína ribonuclear ni contra los antígenos Ro (SS-A) o La (SS-B).

Debido a su baja prevalencia y frecuencia en estas infecciones crónicas, estos autoanticuerpos no afectan la diferenciación entre estas condiciones y las enfermedades del tejido conectivo.

### RÉSUMÉ

Des infections peuvent engendrer une production d'auto-anticorps. Le but de cette étude était de déterminer la prévalence d'auto-anticorps chez des patients avec des infections mycobactériennes chroniques. Les sérums de 41 patients lépreux, de 49 tuberculeux non traités, et de 73 tuberculeux (TB) traités ont été testés pour la fréquence de facteur rhumatoïde, facteur antinucléaire, et différents autres auto-anticorps. Le facteur rhumatoïde mesuré par le test au latex Theumatec RF, était positif chez 2,4% des malades de la lèpre, et 2,7% des tuberculeux traités, mais absent dans le groupe des tuberculeux non traités. Les titres variaient de 40 à 160 unités internationales. La positivité dépendait de la technique utilisée, et était présente chez 21% des tuberculeux traités quand la technique du Theuma-Wellcotest était utilisée. Le facteur antinucléaire était positif chez 7,3% des lépreux, 6,1% des patients TB non traités; et 15% des tuberculeux traités ( $p = 0,0125$ ). La positivité du facteur antinucléaire était liée à la durée du traitement des patients TB ( $p = 0,025$ ). Les titres du facteur antinucléaire étaient bas et ne donnaient aucune image spécifique à la coloration. Aucun patient ne présentait d'anticorps vis-à-vis de l'acide désoxyribonucléique naturel, la ribonucléoprotéide, les antigènes Ro (SS-A) ou La (SS-B). A cause de leurs

prévalence et fréquence basses dans ces infections chroniques, ces auto-anticorps ne devraient pas mener à confondre ces conditions des maladies du tissu conjonctif.

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