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Editorial

THE SERODIAGNOSIS OF LEPROSY

At the 44th World Health Assembly a statement was approved committing WHO to the elimination of leprosy as a public health problem by the year 2000. The main strategy to achieve this goal is likely to be through detection and effective treatment of cases of leprosy with multidrug therapy,[1] though BCG vaccination may also make an important contribution to the decline in leprosy incidence in some settings.[2] The first priority for national leprosy control programmes must be to ensure that currently identified cases are properly treated as this is likely to reduce rapidly their infectiousness to others.[3] Until this is achieved there is little to be gained by extending case-finding activities. In many countries it will be necessary to strengthen leprosy control activities substantially to ensure an adequate coverage of diagnostic and treatment facilities. In general, the earlier cases are diagnosed and treated the less chance they have to pass on the infection to others. Clinical examination by trained workers provides a reliable and efficient method of diagnosis for the majority of patients who present to medical facilities with suspect lesions. There is considerable uncertainty, however, in the clinical diagnosis of early lesions and improved diagnostic methods for such patients are required. Furthermore, in the right circumstances, it may be very useful to have a diagnostic method that identifies 'cases' before they have any symptoms of disease, as early treatment of this group would reduce the chance of deformities and lower the risk of disease in the community by eliminating them as a source of transmission. Research on serodiagnostic methods has sought to identify markers that may facilitate the diagnosis of cases with few or no clinical symptoms.

Of the potential serological tests which have been developed, the one that has raised most interest, that has been well standardized between laboratories, and has been best evaluated epidemiologically is that based on the detection of antibodies to phenolic glycolipid I (PGL-I). This is a highly specific antigen of *Mycobacterium leprae* characterized by Brennan *et al.* in the early 1980s.[4–6] Enzyme-linked immunosorbent assays (ELISA) have been developed to detect antibodies that react with the native antigen or with neoconjugates containing the carbohydrate component towards which the antibody response is directed.[7] Most of the epidemiological studies that have been reported have been cross-sectional, variously comparing antibody levels among multibacillary patients, paucibacillary patients, contacts of such patients and healthy individuals from leprosy endemic and nonendemic areas. The findings in a selection of these studies are summarized in Table 1. Various criteria have been used to define the cut-off criterion for a 'positive' test and this accounts for some of the variability in the results shown for different studies.

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Table 1. Cross-sectional studies of the prevalence of antibodies to PGL-I among leprosy patients, household contacts of leprosy patients and other groups

Authors (place)	Percent with antibodies to PGL-I (no. studied)			
	Multibacillary patients	Paucibacillary patients	Household contacts	Controls [sources]
Menzel *et al.*[17] (Ethiopia)	—	—	43 (54 MB)* 21 (39 PB)	33 (99) [non-hshd]
Gonzalez-Abreau *et al.*[18] (Cuba)	100 (23)	—	—	5 (185) [blood bank]
Burgess *et al.*[19] (Malawi)	100 (7)	75 (95)	—	20 (85) [Europeans]
Mwatha *et al.*[20] (India)	96 (26)	—	—	11 (18) [endemic]
Petchclai *et al.*[21] (Thailand)	84 (38)	17 (24)	17 (6 MB)	4 (54) [blood donors]
Agis *et al.*[22] (West Indies)	100 (14)	32 (40)	13 (109)	4 (51) [blood donors]
Dhandayuthapani *et al.*[23] (India)	100 (40)	63 (19)	—	0 (35) [endemic]
Desforges *et al.*[24] (Melanesia)	100 (13)	21 (14)	14 (309)	4 (104) [non-endemic]
Izumi *et al.*[8] (Japan)	72 (69)	1 (86)	7 (70)	5 (428) [non-contact]
Soebono *et al.*[25] (Indonesia)	98 (41)	57 (44)	—	8 (49) [blood donors]
Krishnamurthy *et al.*[9] (India)	40 (10)	13 (122)	15 (~400)	13 (~4000) [endemic]
Lefford *et al.*[16] (Ethiopia)	84 (51)	47 (38)	—	0? (57) [non-endemic]

* MB, contacts of multibacillary cases. PB, contacts of paucibacillary cases.

A reasonably consistent finding has been that a high proportion of patients with multibacillary disease have elevated antibody titres to PGL-I. Not all of the studies summarized in Table 1 have excluded treated patients and this is likely to be the reason for the lower levels of antibodies in some of them (e.g. Refs 8 and 9) as antibody levels have been found to correlate with bacillary load and decline with therapy.[10,11] In general, in excess of 90% of untreated multibacillary patients have positive serology. Among paucibacillary patients the findings are more variable between studies, but in all of them a substantial proportion of such patients, often in excess of 40–50%, have not been found to have elevated antibody levels. In some studies household contacts have been found to have higher antibody levels than controls, but in others marked differences have not been reported. The proportion of healthy individuals from leprosy-endemic areas with PGL-I antibodies varies from 0% in one study to 33% in another, but, in general, the proportion with antibodies is around 5–10%.

The results from the cross-sectional studies suggest that PGL-I antibodies provide a sensitive test for multibacillary leprosy, but the test is much less useful for the detection of paucibacillary cases. The findings offer little encouragement for the notion that screening sera from healthy individuals in leprosy-endemic areas to detect 'pre-clinical' cases is likely to be a very useful strategy in most leprosy control programmes. The annual incidence of leprosy in endemic areas may be 1/1000 or less. In such circumstances a test with very high specificity is required. Even with a test which had a specificity of 95%, if only 1/1000 of those screened really had leprosy, there would be 50 times as many false positives as true positives in detecting cases.

To assess more rigorously the usefulness of PGL-I antibody levels in predicting who will develop clinical disease it is necessary to conduct studies in which individuals are followed prospectively for signs of leprosy after sera have been collected from apparently healthy individuals. Because in most populations the incidence of leprosy is relatively low, such studies must be large and few have been conducted. Bagshawe *et al.*[12] measured

antibody levels to PGL-I in 877 persons in a village in Papua New Guinea in a highly endemic area and found no association between antibody levels and the risk of leprosy among the 16 cases that developed over a 2-year period. This study is difficult to interpret, however, as even patients with prevalent leprosy did not have elevated PGL-I antibody levels. Douglas *et al.*,[13] in a study of household contacts in the Philippines, found over a 2-year period that leprosy developed in 3 of 36 contacts with elevated PGL-I antibody levels but only in 1 of 285 of those without elevated levels. Chanteau *et al.*[14] followed 724 household contacts on Tahiti Island for 2 years after assaying antibodies to PGL-I—3 cases of paucibacillary leprosy developed among the 631 contacts with negative serology and 1 multibacillary case developed among the 93 contacts with positive serology.

The largest prospective study yet conducted has recently been reported by Ulrich *et al.*[15] Serum was collected from contacts of leprosy patients as they were entered into the leprosy vaccine trial that is being conducted in Venezuela and PGL-I antibody levels were assayed for about 13,000 contacts. In a subset of 9545 individuals, on whose sera the same antibody assay method was used, 20 cases of leprosy developed in the following 4 years. A strong association was found between the antibody level and the risk of leprosy. Those with high antibody levels were at over a 10-fold increased risk of leprosy compared to those in the lowest category and there was a gradient in risk with antibody level. However, a striking finding was that most of the 20 cases occurred in those who had not had elevated antibody levels. Although 2 cases of multibacillary leprosy were detected among the 10 contacts with the highest antibodies to PGL-I, it was necessary to screen over 9500 sera to identify these 10 persons. Thus it seems from this study that screening populations for elevated PGL-I antibody levels in leprosy control programmes would be unlikely to be a useful way of detecting persons at high risk of developing leprosy, even if the necessary infrastructure for performing the tests were available at an acceptable cost.

Serological testing for PGL-I antibodies may be of some limited value in diagnosis for those who present to a medical facility with symptoms or signs of leprosy.[16] In a proportion of such persons it may not be possible to make a firm clinical diagnosis of leprosy or not leprosy. In this group of 'suspect' cases serological testing may be of value. A positive serological test would increase the probability of leprosy being the correct diagnosis (especially if the level of antibodies was high), though the diagnostic value of a negative test would not be great as a high substantial proportion of paucibacillary cases do not have elevated PGL-I antibody levels.

Other serodiagnostic markers for leprosy have been less well studied than has PGL-I and it is to be hoped that tests which are more sensitive and specific will be developed. At the present time, however, it appears that the contribution that serodiagnostic methods can make over normal diagnostic procedures is rather limited.

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