Volume 68, Number 2, June 1997

LEPROSY REVIEW

Published Quarterly for Lepra: the British Leprosy Relief Association

ISSN 0305-7518

Leprosy Review

A journal contributing to the better understanding of leprosy and its control

LEPRA

Editorial Board

Editorial Office: LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England
Assistant Editor: Jennet Batten, 94 Church Road, Wheatley, Oxon OX33 1LZ, England

Leprosy Review is published by LEPRA with the main objective of contributing towards the better understanding of leprosy and its control. Original papers on all aspects of leprosy, including research, are welcomed. In addition, *Leprosy Review* seeks to publish information of educational value which is of direct benefit to the control of leprosy under field conditions, and hence to the individual patient. The Journal aims to interpret what is being done in other disciplines, particularly for field workers.

From time to time the Editorial Board invites special articles or editorials from experts in various parts of the world, and gives consideration to the production of a supplement or special number devoted to a particular subject or theme of major importance.

LEPRA
Registered Offices: Fairfax House, Causton Road, Colchester CO1 1PU

Lepr Rev (1997) **68,** 113

Editor's Choice

Clinicians treating mycobacterial diseases are all familiar with the anxiety that their treated patients may relapse with fresh disease. The apparent success of dapsone monotherapy in the 1950s was clouded by the presentation from the late 1960s onwards of relapse cases. The memories of these late relapses have made many leprologists feel cautious about the World Health Organization's Multi Drug Therapy (WHO–MDT) and not fully confident that six or twenty-four months treatment is adequate. This issue of *Leprosy Review* takes several different looks at the problem of relapse.

In an editorial Desikan (page 114) reviews the WHO data on relapse after MDT pointing out that in a large data set there has been very little evidence that the relapse after MDT is an important clinical problem. However the report from West Africa of a 20% relapse rate in patients with an initial Bacterial Index above 4 is worrying and emphasizes the importance of identifying patients who may be at greater risk of relapse and following these patients closely.

On page 131 Shetty *et al.* demonstrate that acid-fast bacilli can be cultured from peripheral nerve biopsies of patients who have completed a twenty-four month course of MDT. The culture technique used was very sensitive and involved using immunosuppressed mice. It is also important to note that there was no histopathological evidence of active disease. These data clearly demonstrate that bacilli can persist in the nerve, we do not know whether this is clinically important and how much late bacterial clearance occurs by immune mechanisms.

In this issue we are starting a case report section which we hope will encourage young clinicians to write up cases that have a particular clinical lesson. Two of our first case reports concern post-MDT treatment problems.

The role of peripheral nerve surgery in leprosy is a contentious topic. Bernardin and Thomas report on a new classification of nerve involvement at operation (page 147). I hope that this will stimulate surgical discussion and perhaps even a trial evaluating these criteria.

DIANA N. J. LOCKWOOD

Lepr Rev (1997) **68,** 114–116

Editorial

THE RISK OF RELAPSE AFTER MULTIDRUG THERAPY IN LEPROSY

The general concept of 'relapse' is the recurrence of a disease after cure. 'Cure' is again a concept which according to the patient or to the treating physician, means relief from the symptoms and the disappearance of the signs. A radical cure envisages, particularly in an infectious disease, a total elimination of the cause, namely the infecting agent. If the cause is totally removed, a recurrence of the disease could only be a reinfection, rather than a relapse. As such, a relapse invariably presumes persistence of the causative agent.

Earlier leprologists were reluctant to use the word 'cure' in leprosy and employed such words as 'quiescent' or 'arrested', not being sure of a total elimination of the causative agent. Today, with the advent of potent bacteriocidal drugs, we are emboldened to declare a case as cured. Even so, it is doubtful whether in highly-bacillated cases, total elimination is possible. It is estimated that there could be 10^{12} or 10^{13} bacilli in a lepromatous case of leprosy. Even if 99·999% of the germs are killed by the drug, the remaining 0·001% of the bacilli would still constitute a significant number. Added to this, there is the question of 'persister' bacilli which remain dormant in tissues into which drugs do not penetrate. The occurrence of drug-resistant or persistent bacilli could cause a relapse.

These are theoretical considerations. However, in practice it is not a significant problem. It is quoted that the relapse rate is well below 1% with WHO-multidrug therapy (WHO-MDT), which has a high degree of efficacy against multibacillary leprosy.[1] In a question survey organized by WHO,[4] data obtained from 30 centres from 17 countries showed an overall relapse rate of 0·51% or 2·3 per 100 patient years. Further data obtained from selected programmes, which maintain excellent information systems, showed that out of 20,141 patients observed during 1984–1992, there were only 67 cases of relapse. The relapse rate during different periods of follow-up being 0·07% in the first 3 years, 0·09% during 4–6 years, and 0·07% during 7–9 years. Probably the small number of bacilli remaining viable after potent chemotherapy are taken care of by the body's general immune system, preventing relapse of the disease.

While these data are encouraging, a recent publication by Jamet *et al.*[3] causes considerable concern. From a group of 35 multibacillary cases treated by WHO-MDT regimen for 2 years, 7 cases of relapse were found during a follow-up ranging from 27 to 84 months, giving a relapse rate of 20%. In an earlier publication from the same group of investigators,[2] obviously on the same group of patients, the relapse rate with WHO-MDT was only 2·9% during a follow-up period of 27 months. This indicated that relapses occur late, 5–7 years

 0305-7518/97/068114+03 $01.00

after stopping MDT. It was further found by this group that the relapse rate closely correlated with the bacterial load before and at the end of fixed duration MDT of 24 months.[3]

The observation of Jamet *et al.*[3] and the Marchaux Chemotherapy Study Group[2] needs careful consideration. The two factors which govern the observed rate of relapse are the high bacterial load in the patients and the long period of follow-up. This has to be considered against the recommendation of WHO[4] that, 'because the risk of relapse after completion of WHO-MDT regimens has been shown to be negligible, it is no longer necessary to continue routine annual surveillance of patients. The WHO recommendation is based on the low rate of relapse as assessed by their question survey. The data pertains to the group of multibacillary (MB) cases taken as a whole. The high rate of relapse reported by Jamet *et al.*[3] is among the highly-bacillated patients. Such patients no doubt form a very small proportion in the field, but if neglected could be a source of infection and possibly a source of drug-resistant strains. MB cases with initial high BI should be followed up with annual surveillance for a minimum period of 5–7 years.

This raises the question of skin smears in the field. The tendency in most national programmes is to diminish the importance of skin smears or drop them completely on the excuse of the poor standard of many of the field laboratories. Attempts must be made to improve the standard of field laboratories, rather than closing them down and avoiding doing skin smears. Fixed duration therapy is recommended today, and MB cases are released from treatment even if the skin smears are positive at the completion of 2 years of treatment. The findings of Jamet *et al.*[3] indicate that in cases of a bacillary index (BI) of 4·0 before MDT or a BI of 3·0 at the end of MDT, the risk of relapse is very high. Hence, monitoring the bacterial load in a patient by regular skin smears is essential. At the same time quality control on laboratory services should be maintained with regular monitoring by reference laboratories.

Short course chemotherapy is most welcome in a chronic disease like leprosy. The WHO-MDT regimen has proved its efficacy and fixed duration therapy is worth a trial. Further, the newer antileprosy drugs hold a great promise. It is hoped that even more potent drugs would be available in future which may make it possible to cure an MB case in 2–3 months. But it should not be forgotten that *Mycobacterium leprae* are notorious for remaining dormant in protected tissues for several years. Hence the need for follow-up and careful surveillance remains extremely relevant. The finding of Jamet *et al.*[3] that a clinically-cured case could relapse after 5–7 years, particularly if the patient is highly bacillated, is an important lesson for the field programme.

The WHO study[5] while ruling out the necessity to continue annual surveillance has suggested that patients should be taught to recognize early signs of relapse and report promptly for treatment. Relapse in lepromatous cases is first by bacterial increase and it is difficult for the patient to recognize skin changes. By the time they recognize skin changes and relapse, the bacterial load will have increased considerably with consequent problems. Thus MB cases with high initial BI should get special attention with regard to regular postMDT follow-up and bacterialogical assessment. This will not add greatly to the workload of the field programme because there will be only a small number of such cases.

References

[1] ALM Consensus Development Conference on Chemotherapy of Leprosy. Consensus development statement on chemotherapy of leprosy. *Int J Lepr*, 1992; **60:** 644–652.

[2] Marchoux Chemotherapy Study Group. Relapses in multibacillary leprosy patients after stopping treatment with rifampin-containing combined regimens. *Int J Lepr*, 1992; **60:** 525–535.
[3] Jamet P, Ji Baohony and the Marchoux Chemotherapy Study Group. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. *Int J Lepr*, 1995; **63:** 195–201.
[4] WHO Leprosy Unit. Risk of relapse in Leprosy. *WHO document WHO/CTD/LEP 94.1.*
[5] WHO, Action programme for elimination of leprosy. *Lep News*, 1994; **3:** 1–5.

Leprosy Histopathology Centre K. V. DESIKAN
Mahatma Gandhi Institute of Medical Sciences
Sevagram 442102
India

Lepr Rev (1997) **68,** 117–124

Detection of S-100 protein and anticeramide antibodies in leprosy patients by ELISA

R. NARAYAN*, P. K. MAHESHWARI†,
K. V. DESIKAN‡ & B. C. HARINATH*§
**Department of Biochemistry & J. B. Tropical Disease Research Centre, † Division of Skin and VD, Department of Medicine; and ‡ Leprosy Histopathology Centre, Mahatma Gandhi Institute of Medical Sciences, Sevagram-442 102, India*

Accepted 11 November 1996

Summary The status of assay for S-100 antigen protein and anticeramide antibodies in serum in understanding nerve damage in different forms of leprosy were evaluated by the enzyme immunoassay. Based on the clinical and smear examination, patients were classified as indeterminate (Ind), tuberculoid (TT), borderline tuberculoid (BT), borderline lepromatous (BL) and lepromatous (LL).

Antibody levels against ceramide were observed in sera of leprosy patients with 37·5% of Ind, 28% of TT, 66% BT, 78% BL and 62% LL patients positive as against 8% endemic normal sera. The mean OD ranged from 0·141 to 0·275 in different groups of leprosy. In contrast, S-100 was detected in 71·4% Ind, 88·8% TT, 76·4% BT, 100% BL and 95·8% LL, while 5% of ENL samples were positive for S-100 antigen. Mean S-100 levels in these different categories of patients were significantly higher Ind—0·45 ng/ml, TT—0·32 ng/ml, BT—0·23 ng/ml, BL—0·23 ng/ml, LL—0.19 ng/ml as compared to that of normal 0.07 ng/ml.

In general S-100 seems to be a more sensitive and reliable marker than anticeramide antibodies for nerve damage. Five out of 7 indeterminate cases show increased levels of S-100, showing an extent of nerve damage similar to that of TT and could be a useful marker for assessing nerve damage in indeterminate patients for better management.

Introduction

Leprosy is a granulamatous disease primarily affecting the peripheral nerves. Nerve damage has been observed with varying degrees of involvement in virtually all leprosy patients. The possible role of autoimmune mechanism in the nerve damage has been implicated.[1] Antibodies against nerve components have been detected in sera of leprosy patients by screening them against different preparations of nerve antigens.[2–6] Nerve tissue antigens like

Correspondence: § Director-Professor and Head, Department of Biochemistry & J. B. Tropical Disease Research Centre, MGIMS, Sevagram-442 102, India.

0305-7518/97/068117+08 $1.00

glycosphingolipids (ceramide, galactocerebroside, gangliosides and sulphatides) present in the nervous tissue are known to be immunogenic. Antibodies to total nerve lipids and galactocerebrosides have been demonstrated in the sera of leprosy patients.[7] Patients suffering from Gullian-Barré syndrome and systemic lupus erythromatosis with peripheral neuropathy have elevated levels of antiglycosphingolipids.[8] In an experimental study on Mangaby monkeys, antibodies to ceramide, galactocerebroside and gangliosides have been shown to be increased 15 months prior to clinical evidence of nerve damage.[9] In a more recent study Vemuri *et al.*[10] have detected antibodies to all categories of leprosy patients, with anticeramide antibodies showing higher titres.

A specific nerve tissue protein S-100 protein, (so called because of its solubility in 100% saturation with ammonium sulphate) has been demonstrated in normal nerves and nerve complexes by immunoperoxidase staining.[11] Employing the same technique the depletion of S-100 protein in dermal nerves of leprosy patients was shown, suggesting the usefulness of this technique in assessing the presence of nerve damage.[12–14] In the present study we have estimated levels of S-100 and levels of anticeramide antibodies in the sera of leprosy patients by ELISA.

Materials and methods

SUBJECTS

Blood samples were collected from untreated leprosy patients, attending the Skin and VD Outpatient Department of Kasturba Hospital, Sevagram. The patients were classified according to the Ridley–Jopling criteria as indeterminate (Ind), tuberculoid (TT), borderline tuberculoid (BT), borderline lepromatous (BL), lepromatous (LL) cases. Blood samples were also collected from healthy subjects living in this region to be used as negative controls. Sera were separated and stored at −70°C with 0.01% sodium azide as a preservative.

SERUM SAMPLES

A total of 92 serum samples belonging to different groups, namely, Ind (7), TT (18), BT (17), BL (6), LL (24) and EN (20) were analysed for the presence of S-100 protein.

In addition to the above sera, 68 serum samples of which Ind (1), TT (7), BT (12), BL (17), LL (26) and EN (5) were also screened for anticeramide antibodies. Hence, a total of 160 samples were screened for anticeramide antibodies.

ANTIGENS AND ANTIBODIES

S-100a protein (Sigma Chemical Company, USA) and rabbit anti-S-100 protein antibodies (Dako, Denmark) were provided by Lepra, UK. Ceramide (Centre for Biochemical Technology, New Delhi) and antihuman IgM horse radish peroxidase (HRPO) conjugate (Sigma Chemical Co. USA) and antirabbit IgG HRPO conjugate (Cappel, USA) were used in this study.

INHIBITION ELISA FOR DETERMINATION OF S-100 PROTEIN

For the detection of S-100 protein, each serum was saturated 50% with ammonium sulphate

and centrifuged. The supernatant was collected and added to EDTA at a final concentration of 1 mM, and then preincubated with 500 ng of rabbit anti-S-100 protein antibodies at 37°C for 30 min and then used for screening by ELISA.

Flat-bottomed PVC microtiʳre plates (Dynatech, USA) were sensitized with S-100 protein (0·1 μg/50 μl/well) in a 0·06 M carbonate buffer pH 9·6 (37°C for 2 hr). The wells were further blocked with 3% bovine serum albumin 100 μl/well in the same buffer (37°C for 2 hr) and washed 5 times with phosphate buffer saline (0·01 M pH 7·2) containing Tween 20 0·01% (PBS/T). Then 50 μl of preincubated reaction mixture of sera were added to the wells (as described above), and incubated at 37°C for 1 hr. After washing with PBS/T the wells were further incubated with optimally diluted (1 : 8000) antirabbit IgG HRPO conjugate at 37°C for 1 hr. Following, the final washing, the immune reaction was revealed by incubating with orthophenylene diamine (OPD) substrate consisting of 5 mg OPD, 5 ml citrate phosphate buffer pH 5·0, and 5 μl of 30% H_2O_2. The enzyme substrate reaction was then terminated by addition of 2N HCl 50 μl/well and the absorbance was read at 490 nm using ELISA reader (Dynatech, MR-250 USA). The optical density values were interpreted in a dose response curve to obtain S-100 protein level in ng/ml. The dose response curve was prepared by using varying concentrations (0·4 to 2·5 ng/ml) of S-100 protein in pooled normal serum.

DETECTION OF ANTICERAMIDE IgM ANTIBODY

Indirect ELISA was performed as described by Vemuri *et al.*[7] Briefly, PVC microtitre plates were coated with ceramide in methanol (2 μg/ml) overnight until completely evaporated and blocked with 3% BSA in phosphate buffered saline (PBS 0·01 M pH 7·2) at 37°C for 2 hr. After 2 washes with PBS, the plates were incubated with sera (1 : 100 in PBS/2·5% NRS) at 37° for 2 hr. After 3 washes with PBS the plate was incubated with antihuman IgM HRPO (1 : 2500) at 37°C for 2 hr. This was followed by 3 washes in PBS. The immune reaction was observed by incubating the wells with OPD substrate and the results evaluated after blocking the reaction using 2N HCl at 490 nm.

STATISTICAL ANALYSIS

Student's *t* test was used to compare the means of the results obtained in various groups of sera.

Results

The nerve marker S-100 protein content has been estimated in a total of 92 sera by inhibition ELISA. Figure 1 shows the calibration curve obtained using pooled normal serum quenched with standard S-100 protein (0·4 to 2·5 ng/ml). The mean S-100 protein levels as summarized in Figure 2 in different groups of leprosy sera ranged between 0·19 to 0·45 ng/ml compared to that of normal sera (0·07 ng/ml) and the difference was significant ($p < 0·005$).

Considering the mean ± SD of S-100 protein levels in normal group as threshold value for positive reaction 5 of 7 indeterminate cases, 16 of 18 TT cases, 13 of 17 BT cases, 6 of 6 BL cases and 23 of 24 LL cases showed the presence of S-100 protein (Figure 3).

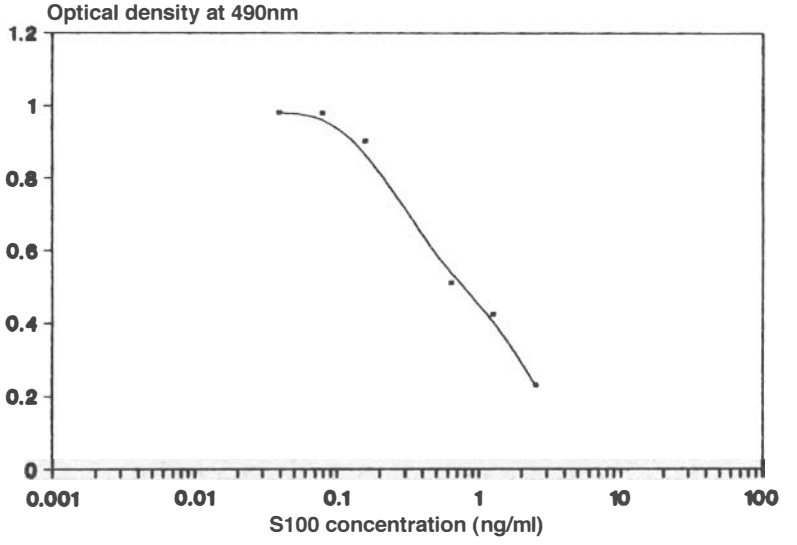

Figure 1. Calibration curve for S-100 using standard (S100a) concentration (0·4–2·5 ng/ml) by inhibition ELISA.

The results of analysis of sera samples for anticeramide IgM antibodies have been summarized in Figures 4 and 5. The mean OD values of anticeramide antibodies in different groups of leprosy sera varied between 0·141 and 0·275 compared with that of normal 0·063 and the difference was highly significant ($p < 0{\cdot}0005$).

By considering the mean ± 2 SD of optical density shown by normal sera as threshold

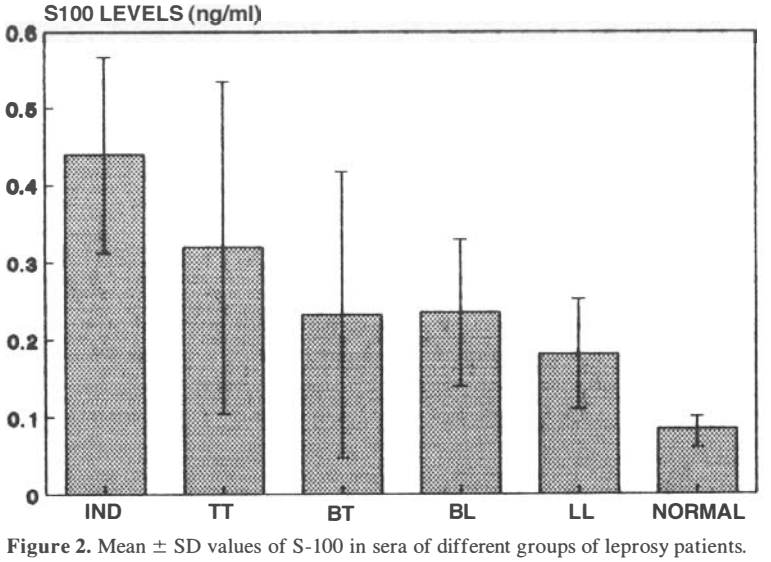

Figure 2. Mean ± SD values of S-100 in sera of different groups of leprosy patients.

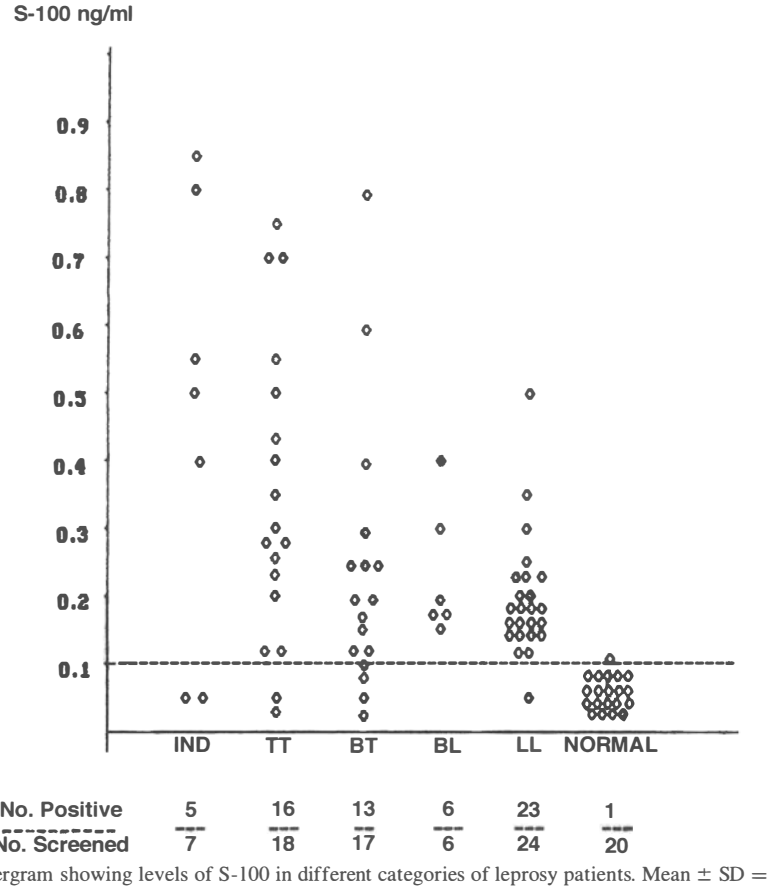

Figure 3. Scattergram showing levels of S-100 in different categories of leprosy patients. Mean ± SD = 0·1 ng/ml.

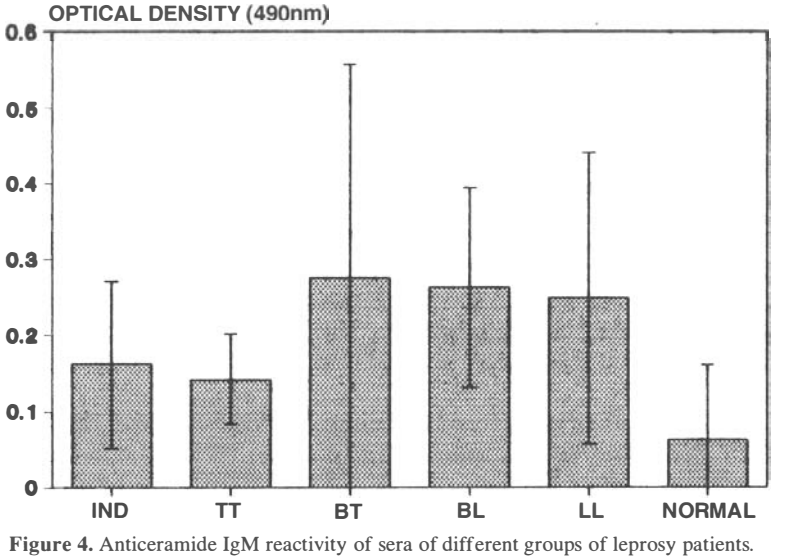

Figure 4. Anticeramide IgM reactivity of sera of different groups of leprosy patients.

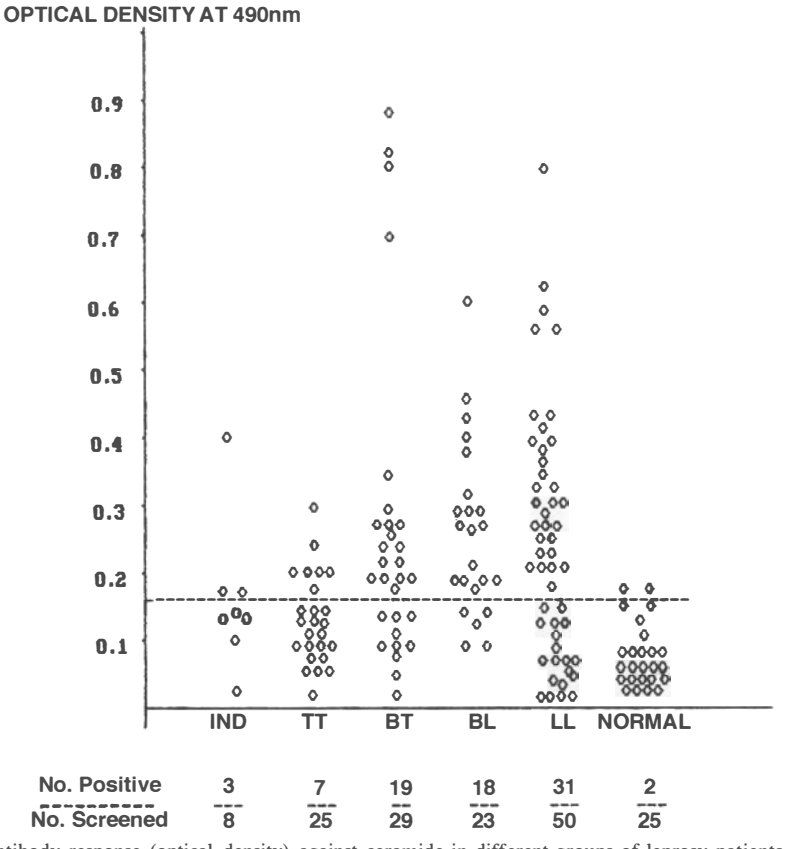

Figure 5. Antibody response (optical density) against ceramide in different groups of leprosy patients. Mean ± 2 SD = 0·162 of normal samples taken as cut off for positivity.

value for positive reaction, 3 of 8 indeterminate, 7 of 25 TT, 19 of 29 BT, 18 of 23 BL and 31 of 50 LL had detectable values of anticeramide antibodies.

Discussion

Leprosy being essentially a disease of the peripheral nerves, leads to nerve damage of varying extents in virtually all leprosy patients. Having no definite information on the exact cause of pathogenesis, the autoimmune response against nerve antigen is believed to be one of the possible events leading to nerve damage. The assay of S-100 protein as well as the anticeramide IgM antibody have been assessed as to how well they detect nerve damage in leprosy patients.

The results of the present study for anticeramide antibodies showed 37·5% indeterminate cases, 28% TT, 66% BT, 78% BL and 62% LL positive. The sera of borderline cases had higher levels of anticeramide antibodies (Mean ± 2 SD; OD 0·222 ± 0·220) compared to the levels in tuberculoid group ($p = <0{\cdot}15$). In a recent study anticeramide and antigalacto-cerebroside antibodies were found in sera of all categories of leprosy patients. Further,

anticeramide antibody titres were found to be higher compared to the titres of antigalactocerebroside antibodies.[10] Antigalactocerebroside antibodies have been shown to be a cause for demyelination.[15,16] Antibodies to galactocerebroside and to nerve tissue preparations containing galactocerebroside have been found in patients suffering from multiple sclerosis and other demyelinating diseases.[17,18] Antibodies against total nerve lipid were demonstrated in 50% TT, 36% BT, 50% BL and 42% LL as against galactocerebroside in 71% TT, 71% BT, 33% BL and 50% LL cases. This could be due to a secondary effect as a release of otherwise sequestered myelin lipids that are recognized by the immune system.[7] On immunoblotting, anti S-100 antibody and antiglial fibrillary acidic protein were found to react with antigen obtained from nerve sonicate.[5]

Analysis of the sera for S-100 antigen detection shows that while only 5% of normals had higher S-100 protein, as many as 87·5% of different groups of leprosy patients show higher levels (Figure 2). Since S-100 protein is shown to be specific to nerve tissue[19] higher circulating levels detected in a majority of leprosy patients, possibly indicate progressive destruction of peripheral nerves in these cases. In indeterminate groups 5 of 7 cases had higher levels of S-100 protein. It is possible that these 5 cases are suffering from silent neuritis, and hence had no history of extensive nerve involvement. Such cases could be rigorously followed for better management. High levels of S-100 protein were also observed in 83% of borderline cases, possibly as a result of reversal reaction, a common phenomenon seen in this group. S-100 is a calcium-binding protein believed to be specifically present in the nervous system. However, it has also been shown by immunoperoxidase staining, to be present in various carcinomas of neurogenic and nonneurogenic origin, and also in a limited number of normal cells. It has been speculated that the presence of S-100 in nonneural cells is due to the origin of these cell types from a common ancestor and migrate to different tissues during embryogenesis.[11] Depletion of S-100 protein in peripheral nerves in a tuberculoid granuloma, were studied by immunoperoxidase staining.[12,14] Further, Job *et al.*[13] also showed the usefulness of S-100 staining to aid in histopathological diagnosis of tuberculoid leprosy lesions, and concluded that S-100 staining is a useful marker.

Acknowledgments

This work was supported by JBTDR Research Scheme of MGIMS, Sevagram. The authors are grateful to Dr Sushila Nayar for her keen interest and encouragement. One of the authors (R. Narayan) is grateful to Dr Rama Mukherjee, NII, New Delhi for training and guidance in standardizing anticeramide IgM ELISA.

References

[1] Benjamins JA, Callahan RE, Runft D, Gerras G, Lefford MJ. Anti neural antibodies in leprosy sera further characterization of the antigens. *J Neuroimmunol*, 1989; **21:** 125–135.
[2] Wright DJM, Hirst RA, Waters MFR. Neural autoantibodies in leprosy. *Lepr Rev*, 1975; **46:** 157–169.
[3] Mshana RN, Harboe M, Stoner GM, Hughes RAC, Kadlubowski M, Belehu A. Immune responses to bovine neural antigens in leprosy patients I. Absence of antibodies to an isolated myelin protein. *Int J Lepr*, 1983; **51:** 33–40.
[4] Eustis Turf EP, Benjamins JA, Lefford MJ. Characterization of antineural antibodies in sera of leprosy patients. *J Neuroimmunol*, 1986; **10:** 313–330.
[5] Thomas BM, Mukherjee R. Antineural antibodies in sera of leprosy patients. *Clin Immunol Immunopathol*, 1990; **57:** 420–429.

[6] Rekha V Sahasrabudhe, Subhada R Dandekar, Damayanti H Shah, Subhada S Pandya, Ganapati R. Humoral response to nerve glycolipid antigen in sera of leprosy patients. *Int J Lepr*, 1992; **60:** 488–490.
[7] Nalini Vemuri, Rama Mukherjee. Immunoreactivity of nerve lipid antigens in leprosy. *J Clin Lab Anal*, 1991; **5:** 157–161.
[8] Zeballos RS, Rox RI, Cheresh DA, McPherson RA. Antiglycosphingolipid autoantibodies in rheumatologic disorders. *J Clin Lab Anal*, 1994; **8:** 378–384.
[9] Sang Nae Cho, Bobby J Gormus, Keyu Xu, Rudolf P Bohm, Jr., Gerald P Walsh, Wayne M Meyers, Joo Deuk Kim. Serologic responses to nerve antigens in sooty mangaby monkeys with experimental leprosy. *Int J Lepr*, 1993; **61:** 236–244.
[10] Vemuri N, Viera LM, Taneja KK, Gangal SV, Mukherjee R. Antisphingolipid antibodies in the sera of leprosy patients. *Lepr Rev*, 1996; **67:** 95–103.
[11] Harriette J Kahn, Alexander Marks, Heather Thom, Reuben Baumal. Role of antibody to S-100 protein in diagnostic pathology. *Am J Clin Path*, 1983; **79:** 341–347.
[12] Raul N Fleury, Carlos E Bacchi. S-100 protein and Immunoperoxidase technique as aid in histopathologic diagnosis of leprosy. *Int J Lepr*, 1987; **55:** 338–344.
[13] Charles K Job, Angelina T Deming, Robert C Hastings. Role of S100 protein as a marker for schwann cells in diagnosis of tuberculoid leprosy. *Int J Lepr*, 1990; **58:** 392–393.
[14] Navjeevan Singh, Arora VK, Ramam M, Tickoo SK, Bhatia A. An evaluation of the S-100 stain in the histological diagnosis of Tuberculoid leprosy and other granulomatous dermatosis. *Int J Lepr*, 1994; **62:** 263–267.
[15] Hruby S, Alvord EC, Seil FJ. Synthetic galactocerebrosides evoke myelination-inhibiting antibodies. *Science*, 1977; **195:** 173–175.
[16] Fry JM, Weissbarth S, Lehrer GM, Bornstein MB. Cerebroside antibody inhibits sulfatide synthesis and myelination and demyelinates in cord tissue culture. *Science*, 1974; **183:** 225–248.
[17] Lisak RP, Heinze RG, Falk GA, Kies MW. Search for antiencephalatogen antibodies in human demyelirative diseases. *Neurology*, 1968; **14:** 122–128.
[18] Ruutiainen J, Reunanen M, Frey H. Galactocerebroside antibodies in multiple sclerosis. *Acta Neurol Scand*, 1982; **65** (Suppl 90) 260–261.
[19] Moore BW. A soluble protein characteristic of the nervous system. *Biochem Biophys Res Commun*, 1965; **19:** 739–744.

Lepr Rev (1997) **68,** 125–130

Lymphostimulatory and delayed-type hypersensitivity responses to a candidate leprosy vaccine strain: *Mycobacterium habana*

N. B. SINGH, H. P. GUPTA, ANIL SRIVASTAVA, HEMA KANDPAL & U. M. L. SRIVASTAVA
Division of Microbiology, Central Drug Research Institute, Chattar Manzil Palace, P.B. No. 173, Lucknow-226 001, India

Accepted for publication 7 October 1996

Summary Lymphostimulatory and delayed-type hypersensitivity (DTH) immune responses to a candidate antileprosy vaccine *Mycobacterium habana* have been quantified in inbred AKR mice. *M. habana* vaccine in three physical states, live, heat-killed and γ-irradiated, was given intradermally to separate groups of mice and after 28 days these mice were given subcutaneous challenge with heat-killed *M. leprae* and heat-killed *M. habana* in the left hind footpad. Live BCG vaccine alone and in combination with γ-irradiated *M. habana* were also compared similarly. A sufficient degree of DTH response was generated in mice by *M. habana* vaccine in all physical forms against two challenge antigens (lepromin and habanin). The BCG combination with *M. habana* did not increase the DTH response indicating internal adjuvanticity endowed in *M. habana*. The active hypersensitivity of immunized mice was transferable to syngeneic mice by the transfer of sensitized cells from the donor to the recipient mice intravenously. *M. leprae*-infected Rhesus monkey PBMC have shown comparable stimulatory response with *M. habana* (sonicate), and *M. leprae* (sonicate) antigens. The possibility of developing *M. habana* as a candidate antileprosy vaccine is discussed.

Introduction

In mycobacterial diseases, protective immunity is mediated through bacterial kill and/or modulation of the immune response which is essentially cell mediated with two basic cell types: the T-lymphocytes and macrophages interacting through cytokines.[1,2] The basis of *in vivo* and *in vitro* tests is to examine and measure the nature of the responses of these cells to the immunogens. The most commonly employed test is the delayed type of hypersensitivity response in the skin elicited by an intradermal injection of the immunogen. The *in vitro* tests, measuring the T-cell immunity are lymphocyte proliferation test (LPT) and the leucocyte migration inhibition test (LMIT). LMIT measures the release of lymphokines from antigenically driven lymphocytes and LPT measures DNA synthesis in actively multiplying cells due to release of lymphostimulatory factor(s). The skin DTH response assesses the individuals ability to mobilize the immunocytes to the injection site of the antigen. The DTH response evaluated in the form of a footpad enlargement (FPE) after injection of

0305-7518/97/068125+06 $1.00

the antigen in animals is a way to monitor the test and to prove the indirect efficacy of antileprosy vaccines.[3,4]

One candidate antileprosy vaccine: *M. habana* (*M. simiae* serovar 1) protects mice against infectious challenge with *M. tuberculosis* $H_{37}Rv$, *M. leprae* and *M. ulcerans*.[5–9] *M. habana* generates a cell-mediated immune response (CMI) which recognizes *M. tuberculosis* and *M. leprae* antigens[10,11] and shares several immunodominant proteins with them.[12,13] *M. habana* combines the useful traits of these mycobacteria and may suitably be developed as a vaccine against leprosy.

In this report we present the data of comparative evaluation of *in vivo* DTH response generated by *M. habana* and other vaccine(s) in mice and successful transfer of the active immune hypersensitivity through sensitized cells in syngeneic mice. The *in vitro* lympho-stimulatory response of *M. leprae* sensitized monkey cells have also been studied against *M. habana* antigen(s).

Materials and methods

GROWTH AND PREPARATION OF IMMUNIZING ANTIGENS

Mycobacterium habana (*M. simiae* serovar-1, TMC 5135) was obtained from the TMC collection centre Saranac Lake, New York. The strain of BCG (Madras) was procured from the Tuberculosis Research Centre, Madras and freeze-dried preparations of armadillo derived *M. leprae* were obtained through Dr R. J. W. Rees of the National Institute for Medical Research Mill Hill, London. Mycobacteria other than *M. leprae* were maintained separately on Lowenstein-Jensen medium and their bulk growth was obtained in Sautons liquid medium. A live culture of BCG was used as vaccine, while *M. habana* vaccine was treated by γ-irradiation of the culture at 300 K rads from a ^{60}cobalt source. *M. habana* was also used in live and heat-killed states for immunization. Freeze-dried *M. leprae* preparations was reconstituted in normal saline at the required concentration.

CHALLENGE ANTIGENS

Integral habanin was prepared from mid-log culture of *M. habana* by standard procedures as applied for the preparation of integral lepromin (WHO protocol). The Mitsuda lepromin was obtained through Professor Noordeen, Chief Medical Officer, WHO, Geneva.

DOSE OF VACCINE AND ANTIGENS

Mice were immunized i/d with $6{\cdot}27 \times 10^8$ organisms ($63{\cdot}3\ \mu$g protein/animal) of *M. habana* in either live, heat-killed or γ-irradiated states while the dose of BCG and *M. leprae* were $6{\cdot}0 \times 10^5$ and $2{\cdot}0 \times 10^7$ bacilli per animal respectively (recommended optimal doses). The challenge dose of each antigen (habanin and lepromin) was 3×10^7 bacilli per footpad.

THE EXPERIMENTAL ANIMALS

Inbred AKR mice maintained in the Institute's animal house were used. The animals were kept on a pellet diet of Hindustan Lever Ltd, with water *ad libitum*. They were divided in groups on a similar weight basis. All vaccinations were done intradermally on the back and 28

days postvaccination the animals were challenged with eliciting antigens in the hind feet. The footpad thickness was measured prior and after challenge with a Schnelltäster (made in Germany) and corrected footpad enlargements (FPE) were calculated according to Shepard's method.[4]

ADOPTIVE TRANSFER OF IMMUNITY

Sensitized splenic cells from vaccinated mice were obtained by extirpation of the spleen and mincing and passing through a metal sieve. The method of Patel & Lefford[14] was followed with slight modifications. The viability of the cells was determined by staining with Trypan blue. 1×10^8 viable splenic cells obtained from actively sensitized (vaccinated) mice were given i/v to separate groups of syngeneic mice for passive sensitization. After 24 h these passively sensitized mice were given a S/C challenge in the hind footpad with homo and heterologous eliciting antigens and the FPE was measured as described earlier.

LYMPHOCYTE TRANSFORMATION TEST (LTT)

Peripheral blood mononuclear cells (PBMC) were separated from heparinized blood of normal (tuberculin and lepromin negative) and *M. leprae* infected Rhesus monkeys by density gradient centrifugation (Lymphoprep–Nyegard S.Co.OSLO, Norway). These cells were washed thrice and their viability was determined by staining with Trypan blue (93% viable). The cells were finally suspended at 2×10^6 cells/ml in RPMI-1640 supplemented with 10% foetal calf serum (GIBCO, Grand Island, New York, USA), glutamine and antibiotics (streptomycin 100 μg/ml, penicillin 100 units/ml and gentamycin 20 μg/ml). 100 μl of this suspension were dispensed in each well giving a concentration of 2×10^5 cells/well. The antigens used were *M. leprae* and *M. habana* sonicate (soluble fraction at 2·5, 5·0 and 10 μg/well and mitogen PHA-P (Sigma Chemical Co., USA) at 0·5, 1·0 and 2·0 μg/well. Control cultures received no mitogen/antigen. The cultures on day 4 were pulsed with 0·5 μ Ci of [^{3}H]-thymidine (specific activity of 18 mCi/u mole) obtained from Bhabha Radiation and Isotope Technology, Bombay, India. Harvesting of the cells was done on day 5 through a semiautomatic harvester (PHD cell harvester, Cambridge Technology Inc., Cambridge, Massachusetta, USA) using glass fibre filters (GF/C Whatman, England) and radioactivity was counted in a liquid Scintillation counter (LKB Finland) using a toluene based scintillation cocktail.

RESULTS

INDUCTION OF DTH RESPONSE BY DIFFERENT VACCINES

All the three preparations (live, heat killed, and γ-irradiated) of *M. habana* live, BCG, heat-killed *M. leprae* and live BCG+ γ-irradiated *M. habana* were tested for generation of DTH response against homologous and heterologous antigenic challenge. The data are presented in Figure 1. Average FPE with homologous antigen-habanin are 28·33 ± 7·53; 31·43 ± 6·90 and 31·66 ± 7·30 respectively in three types of vaccinated animals. With lepromin the FPE response of these groups of animals were 26·67 ± 5·15, 26·66 ± 8·16 and 28·33 ± 7·53 respectively. In animals vaccinated with live BCG heat killed *M. leprae* and live BCG+ r-irradiated *M. habana* the responses with habanin were 23·33 ± 5·16, 21·66 ± 4·08 and

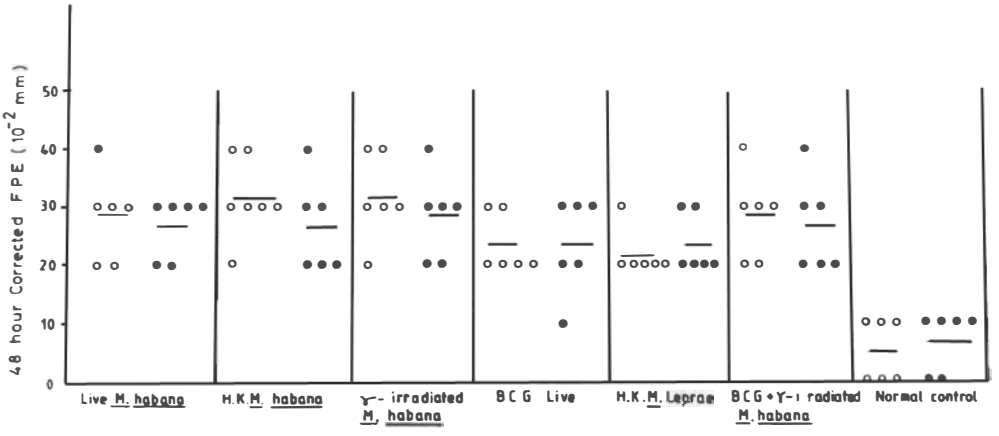

Figure 1. Forty-eight footpad enlargement in mice actively sensitized with different vaccines after challenge with habanin and lepromin. FPE in AKR mice ID route ($6{\cdot}27 \times 10^8$ bacilli); ○ → habanin; ● → lepromin.

$28{\cdot}33 \pm 7{\cdot}52$ and with lepromin the responses were $23{\cdot}33 \pm 8{\cdot}16$, $23{\cdot}33 \pm 5{\cdot}16$, $26{\cdot}66 \pm 8{\cdot}16$ respectively. It is apparent that both the sensitins have generated sufficient degree of DTH response in vaccinated animals than unvaccinated controls. The combined vaccination of animals with BCG + *M. habana* did not impart better DTH response than with either vaccine alone.

ADOPTIVE TRANSFER OF IMMUNITY THROUGH SENSITIZED CELLS

Sensitized splenic cells from mice vaccinated with γ-irradiated *M. habana*, heat-killed *M. habana* and heat-killed *M. leprae* were transferred intravenously to normal syngeneic mice. After 24 hours of passive sensitization these groups of animals were challenged with homologous and heterologous antigens. The individual animal data are presented in Figure 1. A considerably higher number of animals developed passive sensitization and had higher FPE values than the controls with both the sensitins (habanin/lepromin). Gamma irradiated *M. habana* group of passively sensitized animals had better response than other groups. The average FPE of respective groups was $23{\cdot}33 \pm 8{\cdot}16$, $20{\cdot}00 \pm 8{\cdot}94$ and $16{\cdot}66 \pm 8{\cdot}16$ with habanin challenge and $20{\cdot}00 \pm 8{\cdot}94$, $18{\cdot}7 \pm 8{\cdot}99$ and $20{\cdot}00 \pm 5{\cdot}77$ with lepromin challenge.

LYMPHOSTIMULATORY RESPONSE

It is evident that optimal dose PHA-P is 1 μg/ml since this dose has generated maximum response in normal as well as *M. leprae* sensitized monkeys. The other two doses of PHA-P (one less, other higher) have also responded well but less than the optimal dose of 1 μg/ml. The lymphostimulatory responses with leprosin and habanin have also indicated that 0·5 μg/ml dose of both the antigens are optimum. Habanin has generated the LP response closer to PHA-P where as homologous response with leprosin and habanin have also indicated that 0·5 μg/ml dose of both the antigens are optimum. Habanin has generated the LP response closer to PHA-P where as homologous response with leprosin is of a lower order.

Discussion

The delayed-type hypersensitivity response is one of the several parameters used to test the indirect efficacy of cell-mediated immunity (CMI) to candidate vaccines. The test is conducted by inoculating the vaccine strain intradermally in mice and challenging the vaccinated mice S/C in the footpad after 3–4 weeks with heat-killed *M. leprae*. The footpad enlargement (FPE) is measured after 24 and 48 hr of challenge. Sensitized PBMC either by production of disease and/or by artificial *in vitro* sensitization when allowed to react with the specific antigen(s) secrete lymphocyte stimulatory factor(s) which stimulate the sensitized cells to proliferate profusely. This cell division is measured in terms of DNA synthesis which increases many fold. This test is specific in recognizing the antigenic relatedness/similarity between species/strains.

M. habana (M. simiae) an atypical mycobacterium, has afforded protection against *M. leprae* and *M. tuberculosis* infectious challenges: in mice.[5–8] It generates strong cell-mediated immune responses, possesses several common and specific immunodominant protein epitopes with *M. leprae*, and *M. tuberculosis* and BCG.[10–13]

This study was undertaken to elucidate, if *M. habana* stimulates DTH responses in mice which could be recognized by *M. leprae* antigens and whether *M. habana* antigen(s) could produce lymphostimulatory response in PBMC(s) obtained from *M. leprae* sensitized Rhesus monkeys.

M. habana vaccine in all the physical states (i.e. live, heat-killed and γ-irradiated) was able to generate DTH response against the homologous antigen habanin and the heterologous antigen lepromin. The DTH responses stimulated by heat-killed and γ-irradiated *M. habana* were apparently better than that stimulated by live vaccine although there were no statistically significant differences. This finding correlates well with a similar findings with heat-killed *M. leprae* by Shepard *et al.*[16] This may possibly be due to exposure of other antigens normally at some inaccessible regions after gamma irradiation or heat treatment. The DTH response stimulated by live BCG was inferior to those stimulated by other vaccines, although a heat-killed preparation of BCG was not included. It has been proved beyond doubt by several investigators that killed BCG does not sensitize mice.[16] The combined vaccination with live BCG and γ-irradiated *M. habana* did not increase sensitization more than either vaccines alone, which may possibly be due to internal adjuvanticity in *M. habana*. In animals, heat-killed *M. leprae* in combination with BCG does not enhance sensitization,[17,18] although in contrast to this, BCG in combination with heat-killed *M. leprae* in man provides an adjuvant effect.[19,20] This property of *M. habana* and *M. leprae* seems to be similar in animals. Data for humans in respect of *M. habana* vaccine are not available at present, which is in progress. Heat-killed *M. leprae* was a poor sensitizer of mice than *M. habana* in our hands, whether tested against habanin or lepromin.

Like *M. leprae* (γ-irradiated), BCG and other candidate leprosy vaccines, *M. habana* also produces adoptive immunity which is transferable to syngeneic mice with actively sensitized cells.

M. habana antigen(s) have also stimulated strong lymphostimulatory responses, comparable to those stimulated by *M. leprae* antigen(s) in PBMC(s) from *M. leprae* sensitized Rhesus monkeys. This indicates sharing of common epitopes between these two mycobacteria.

Since *M. habana* possesses several immunogenic, it could be developed as a vaccine for the prophylaxis/immunotherapy of leprosy.

Acknowledgment

The authors are grateful to Dr V. P. Kamboj, Director and Dr G. P. Dutta, Head, Division of Microbiology, Central Drug Research Institute, Lucknow for their keen interest in the work. The technical help of Sri Horilal, and Sunil Chakraborty was appreciable and is duly acknowledged. The authors are thankful to the Biometery & Statistics Unit for analysis of the data.

References

[1] Nath I. Immunological aspects of human leprosy. *Lepr Ind*, 1983; **55:** 752–762.
[2] Bloom BR. Rationales for vaccine against leprosy. *Int J Lepr*, 1983; **51:** 505–509.
[3] Shepard CC, Van Landingham R, Walker LL. Searches among mycobacterial cultures for antileprosy vaccines. *Infect Immunity*, 1980; **29:** 1034–1039.
[4] Shepard CC, Minagawa F, Van Landingham R, Walker LL. Foot pad enlargement as a measure of induced immunity to *Mycobacterium leprae*. *Int J Lepr*, 1980; **48:** 371–381.
[5] Gupta HP, Singh NB, Mathur IS, Gupta SK. A new immunogenic strain *Mycobacterium habana* in experimental tuberculosis of mice. *Ind J Exp Biol*, 1979; **17:** 1190–1193.
[6] Singh NB, Srivastava A, Gupta HP, Sreevatsa, Desikan KV. Immunological potential of cutivable mycobacterial strain *M. habana* against leprosy bacillus in mouse foot pad. *Ind J Lepr*, 1985; **57:** 278–281.
[7] Gupta HP, Singh NB, Ashok Kumar. Containment of *Mycobacterium leprae* multiplication in foot pad of *M. habana* vaccinated animals. *Biological Memoirs*, 1987; **13:** 174–178.
[8] Singh NB, Lowe ACRE, Rees RJW, Colston MJ. Vaccination of mice against *M. leprae* infection. *Infect Immunity*, 1989; **57:** 653–655.
[9] Singh NB, Mathur IS, Gupta HP, Srivastava A. A novel immunogenic strain *Mycobacterium habana* against *M. ulcerans* (Buruli ulcer) infection in mice. *Curr Sci*, 1981; **50:** 994–996.
[10] Singh NB, Gupta HP, Mathur IS, Ashok Kumar, Chakraborty SK. Leukocyte migration inhibition response of *Mycobacterium habana* with sensitized animals and leprotic human cells. *Ind J Lepr*, 1985; **57:** 273–277.
[11] Singh NB, Srivastava A, Gupta HP, Ashok Kumar, Chaturvedi VK. Relative cross reactivity of habanin, lepromin and tuberculin in guineapigs sensitized with homologous and heterologous mycobacteria. *Ind J Lepr*, **60:** 407–412.
[12] Singh NB, Sinha S. Comparison of antigenic profile of a candidate vaccine strain *M. habana* with other mycobacteria by poly-acrylamide gel. *Curr Sci*, 1985, **54:** 568–569.
[13] Lamb FI, Singh NB, Colston MJ. The specific 18 kilo dalton antigen of *M. leprae* is present in *M. habana* and functions as heat shock protein. *J Immunol*, 1990; **144:** 1922–1925.
[14] Patel PJ, Lefford MJ. Specific and non-specific resistance in mice immunized with irradiated *M. leprae*. *Infect Immunity*, 1978; **20:** 692–697.
[15] Jeevan A, Bapat CV. Induction of delayed type hypersensitivity by ICRC antileprosy vaccine and the adoptive transfer of cell mediated immunity in mice. *Ind J Lepr*, 1984; **56:** 754.
[16] Shepard CC, Walker LL, Van Landingham R. Heat stability of *Mycobacterium leprae* immunogenicity. *Infect Immunity*, 1978; **22:** 87–93.
[17] Mehra V, Bloom BR. Induction of cell-mediated immunity to *Mycobacterium leprae* in guineapigs. *Infect Immunity*, 1979; **23:** 787–794.
[18] Shepard CC, Van Landingham R, Walker LL. Immunity to *Mycobacterium leprae* infections in mice stimulated by *M. leprae*, BCG and graft versus host reactions. *Infect Immunity*, 1976; **14:** 919–928.
[19] Convit J, Aranzazu N, Pinardi M, Ulrich M. Immunological changes observed in intermediate and leprosy patients and Mitsuda negative contacts after the inoculation of a mixture of *M. leprae* and BCG. *Clin Exp Immun*, 1979; **36:** 214–220.
[20] Convit J, Aranzazu N, Ulrich M, Pinardi ME, Reyes O, Alvarado J. Immunotherapy with a mixture of *M. leprae* and BCG in different forms of leprosy and in Mitsuda negative contacts. *Int J Lepr*, 1982; **50:** 415–424.

Lepr Rev (1997) **68,** 131–138

Higher incidence of viable *Mycobacterium leprae* within the nerve as compared to skin among multibacillary leprosy patients released from multidrug therapy

V. P. SHETTY, K. SUCHITRA,
M. W. UPLEKAR & N. H. ANTIA
The Foundation for Medical Research, 84-A, R. G. Thadani Marg, Worli, Bombay 400 018, India

Accepted for publication 2 December 1996

Summary As identified by a significant growth in the footpads of immunosuppressed mice, the incidence of viable bacteria in a group of 26 multibacillary (BL–LL) patients released from multidrug (MDT) treatment was found to be two times more in the nerves (46%) as compared to skin (23%). Evidently there was a positive correlation between the overall bacterial load and the incidence of viable organisms. Bacterial growth was also observed in two out of five cases where neither the skin nor the nerve homogenate had shown any presence of acid-fast bacilli. Histopathology of biopsies, skin as well as nerve, including those having viable bacteria did not show any features of active disease.

Introduction

It has been well documented that peripheral nerves harbour *Mycobacterium leprae* and its antigens in higher frequency both before and after treatment of leprosy.[1–6] Investigations to estimate the extent of the viable bacterial load in the peripheral nerve compared with skin, persisting after complete multidrug therapy, have not been carried out so far. The present study investigates the frequency and magnitude of the viable bacterial load in the skin and nerve biopsies obtained from multibacillary leprosy cases (BL–LL) released from multidrug therapy (MDT). The bacterial index (BI) and load/g wt of tissue assessed in the smear and tissue homogenates respectively were compared with their viability status obtained using the footpads of immunosuppressed mice. The histopathology of skin and nerve biopsies was studied with a view to identifying reliable and practical indicator/s if any, of disease activity, treatment success, and differences between skin and nerve tissues. The observations are presented and discussed.

Material and method

Twenty-six multibacillary cases (BL–LL) of leprosy, between 15 and 55 years of age were

0305-7518/97/068131+08

Table 1. Bacterial Index (BI), load/g wt and viability test results of skin and nerve of post MDT-MB cases

		SKIN		NERVE	
Sl. No.	Smear Ave BI(+)	Bact.load/g wt (×106)	No. of +ve takes Harvests	Bact. load/g wt (×106)	No. of +ve takes Harvests
1.	3·3	230	0/8	330	0/4
2.	2·6	62	1/3	2·2	4/4
3.	2·2	36	3/11	16	3/6
4.	0·16	50	0/5	13	0/5
5.	1	30	0/11	110	3/7
6.	4·25	250	0/3	35	1/4
7.	2·1	340	2/5	13	2/4
8.	1	40	0/5	40	1/6
9.	0	22	0/5	0	2/5
10.	0	29	4/6		6/7
11.	0	3·4	2/3	10	2/3
12.	0	0	6/12	0	4/12
13.	0	0	0/7	6	0/7
14.	0	8·6	0/8	14	0/8
15.	0	3·2	0/10	9·9	0/10
16.	0	0	0/6	0·6	0/5
17.	0	0	0/8	1·7	1/8
18.	0	3·9	0/5	6·5	0/8
19.	0	0·95	0/3	0·96	0/5
20.	0	0	0/5	1·6	0/4
21.	0	0	0/7	0	0/10
22.	0	1	0/7	2·1	0/8
23.	0	0·37	0/6	90·7	0/8
24.	0	0	0/7	0	1/3
25.	0	0	0/5	0	0/4
26.	0	0	0/6	0	0/8

+ve takes means *M. leprae* fold increase ≥ 10 fold

included in the study. All the patients had completed a minimum of 24 months of WHO-recommended MDT for multibacillary leprosy, namely 600 mg RFP and clofazimine (CLF) 300 mg once a month (supervised) 50 mg CLF and dapsone (DDS) 100 mg daily. One of the patients (No. 4) was on DDS monotherapy before starting on MDT and five others (Nos 1, 2, 19, 20 and 26, Table 1) had received, 32 to 42 months of MDT. The remaining 21 patients had received 24 months of MDT-MB. One of the patients (No. 7) had repeated episodes of ENL reaction and was given prednisolone during the reaction. Biopsies were obtained between 2 months and 6 months of release from treatment (RFT) to ensure that there was no circulating active drug components and to avoid any confusion with relapse or reinfection. All the patients were regular in their intake of prescribed treatment. Slit-skin smears from 6 sites were taken from all the patients and bacterial indices (BI) were recorded along with a detailed clinical examination and charting.

BIOPSY

Using local anaesthesia a deep incision skin biopsy from a site that showed highest BI or an earlobe biopsy were taken from cases who were smear negative and a biopsy of thickened

Table 2 Size of the inocula and the footpad harvest results of only the cases showing >10 fold growth

Case S. No.	Inocula size × 10^4	*Count/footpad x 10^4	
		with skin homogenate	with nerve homogenate
2	S = 5 N = 3	10, 35, 122	155, 56, 122, 48
3	S = 6 N = 2	74, 44, 21, 11 14, 63, 113, 14, 14, 50, 26	30, 17, 29, 20, 3, 6
5	S = 5 N = 2	26, 3, 8, 3, 4, 3 2, 8, 0, 3, 2	31, 56, 44, 45, 22, 25, 0
6	S = 7 N = 2	10, 2, 5,	35, 0, 0, 0, 3, 2
7	S = 2 N = 0·2	39, 26, 5, 8, 3,	8, 3, 2, 10
8	S = 4 N = 2	3, 5, 8, 5, 0	97, 2, 0, 0, 2, 2
9	S = 2 *N* = <1	5, 2, 0, 4, 3	59, 0, 3, 0, 0
10	S = 1 N = 1	0, 0, 0, 11 13, 7, 6	18, 108, 61, 21, 8, 17, 17
11	S = 1 N = 1	2, 11, 4, 6	2, 37, 3, 45
12	S = <1 N = <1	1, 20, 0, 3, 2 0, 2, 5, 3, 0, 0	0, 0, 8, 0, 2, 15, 2, 1, 0, 0
17	S = 1 N = 1	0, 0, 0, 3, 2 2, 1, 2, 1	2, 2, 79, 0, 0 3, 0, 0
24	S = <1 N = <1	0, 0, 0, 0, 0, 0, 0	0, 27, 2, 0, 0

* Counts rounded to the nearest whole number
0 = No. bacilli in > 100 folds

sural nerve were taken from all the cases after obtaining an informed consent. A part of each skin and nerve biopsies were fixed and processed for light microscopy and another part used for bacterial harvest. Nerve biopsies were stripped clean of all the epineural and perineural connective tissue before the homogenization was carried out using a Corning glass homogenizer. The bacterial load/g weight of tissue was determined using the standard protocol.[7] All the skin and nerve homogenates (26 each) regardless of their bacterial status were injected into the hind footpads of Swiss White mice, immunosuppressed using T200 × 5R protocol.[8] Inocula containing not more than 10^5 in 0·03 ml were injected into both the hind footpads of 8–12 mice within 24 h of collecting the biopsy. Footpad harvests were scheduled for the 12th month. However if any mice died or were sick after the 6th postinfection month, footpad harvests were carried out to record the counts. The fold increase per footpad were calculated from the number inoculated. Homogenization of the footpads was carried out using a 'OMNI' homogenizer that had a foam-reducing style generator, treatable volume of 3–5μl and a speed of 0–18,000 rpm (OMNI Cat No. 15005).

Results

BACTERIAL INDEX AND LOAD/GWT IN SKIN AND NERVES

Of the 26 MB cases included in this study only 8 were smear positive and all the smear positive cases had a pretreatment BI status of over 5+. In these smear positive cases the average bacterial index (BI) assessed by the slit-skin smears taken from 6 sites ranged between 0·16+ and 4·25+ (see Table 1) and bacterial load/g wt of biopsies, both skin and nerve were between 10^7 to 10^8. In 13 out of the 18 smear negative cases, *M. leprae* counts were obtained in the homogenates. In one case (1/13) only skin was positive, in three cases (3/13) only nerves were positive while in the remaining 9 cases (9/13) both skin and nerve homogenates were positive. In all except one nerve homogenate bacterial load/g wt were between 10^5 and 10^6. In one of the nerve homogenates the count was $9{\cdot}7 \times 10^7$/g wt. In the remaining 5 smear negative cases no detectable counts were obtained in the homogenates of either skin or nerve.

VIABILITY OF *M. LEPRAE* IN SKIN AND NERVE OF POST MDT–MB CASES.

Out of 26 postMDT–MB cases included in this study, 12 (46·2%) showed presence of a significant number of viable bacteria as evidenced by over 10-fold growth in the footpads of immunosuppressed mice, in skin and/or nerve biopsies (see Tables 1 and 2). In half of them positive takes were obtained with both skin and nerve while in the remaining half, only nerves were positive. On comparing the overall bacterial load with the viability test results (see Table 1), 6 of the 12 cases (50%) that showed positive takes were smear positive and they had a bacterial load per g wt more than 10^7. There were 4 positive takes (33·3%) in the lower BI group, i.e. 10^5 to 10^6 ML/g w. While one skin biopsy and two nerve biopsies derived from two patients, that showed positive takes in the footpad have had no detectable counts in the homogenates of the skin and nerve.

HISTOPATHOLOGY

Chronic granulomatous cellular infiltration was seen in all except 3 skin and 6 nerve samples. There was a considerable variation in the extent of cellular infiltrate. Some of the common features noted were: a, the higher the bacterial load the higher the cellular infiltrate; and b, foamy cells were normally seen as aggregates around the blood vessels and adnexa in the skin and around blood vessels in nerves (see Figure 1). What appeared to be a fresh influx of perivascularly located mild lymphocytic infiltrate were seen in 3 skin biopsies (Nos 13, 14 and 15) and 6 nerve biopsies (Nos 13, 14, 15, 19, 20 and 23).

Discussion

One of the main objectives of this study was to record the relative difference in the incidence of the viable bacteria in the contemporary skin and nerve biopsies obtained from multibacillary cases released from multidrug therapy (MB–MDT–RFT). Of the 26 MB–MDT–RFT cases studied 6 showed viable bacteria in both skin and nerve, and in another 6 cases viable bacteria were detected in the nerve only. Thus the incidence of viable bacteria in this group of MB–MDT–RFT cases was found to be two times more in the nerve compared with

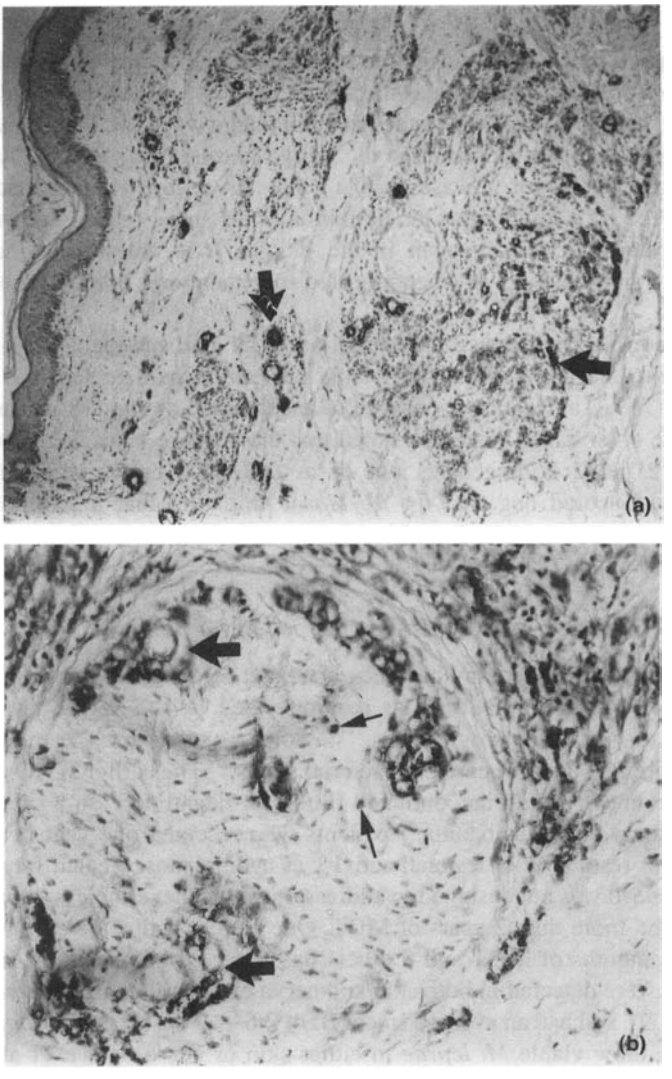

Figure 1(a). Part of the earlobe biopsy from patient S.No.7, where both skin and nerve were positive for viable *M. leprae.* Paraffin embedded section immunostained with *M. leprae* cross reactive anti BCG antibody in an indirect peroxidase assay. Note the presence of large aggregates of BCG positive foamy cells (arrow) along the dermis. Mag. ×100. **(b)** Part of the sural nerve T.S. from the above patient similarly stained. Note the presence of BCG positive foamy cell aggregates around the endoneurial blood vessels (big arrow) and Schwann cells (small arrow) on a background of dense collagen. Mag. ×120.

skin. This was despite the finding that in several cases, the skin showed a higher bacterial load/g wt compared with nerve (see Table 1). Apart from this difference between skin and nerve it is noteworthy that the present study also records a much higher incidence of viable bacteria in the skin, i.e. 23% as against 9%–10% documented by the THELEP study reported in the year 1987.[9]

BACTERIAL LOAD AND INCIDENCE OF VIABLE BACTERIA

The bacteriological index (BI) as assessed by the multiple smears is the most practical and commonly used tool for monitoring at the field level.[10–12] It must be noted that the smears scored negative in all the cases where the bacterial load/g wt was $< 10^6$. Smear positivity was recorded in 8 out of 26 cases included in the study (30·8%). Not surprisingly the skin biopsy homogenates were positive in 18 cases (68%) while nerve biopsy homogenates were positive in 20 cases (76·9%). This highlights the limitation of the smear techniques as the indicator of presence or absence of an organism in the biopsy. It is noteworthy that the detection sensitivity was improved by 37% when biopsied specimen were homogenized and scored for AFB.

A positive correlation between the overall bacterial load and incidence of viable bacteria was evident from the findings that the viable bacteria were detected in 6 out of 8 smear positive cases (75%), as against 6 positive takes obtained among 18 smear negative cases (33·3%). On the other hand, it must be noted that the positive takes were also obtained with one skin and 2 nerve homogenates out of a total of 5 cases, where both smear and homogenates had scored negative for *M. leprae* implying that a subminimal but viable load of bacteria were present in these biopsies.

DURATION OF TREATMENT AND INCIDENCE OF VIABLE *M. LEPRAE*

The duration of multidrug therapy has been a subject of debate.[13] For multibacillary cases, two years of fixed duration, 3 drugs as recommended by the WHO has been the policy adopted by several national programmes.[14,15] Some suggest that the treatment should be extended in relation to the pretreatment bacterial status.[16] The earlier WHO recommendation was that the treatment should be continued till smear negativity.[9] In a small clinical-based study it was shown that paucibacillary patients who received one year of MDT–PB fared better in terms of resolution of lesional activity as against those treated for 6 months.[17] The present study indeed was not designed to address this issue, nevertheless there were 6 patients who had received more than 2 years of MDT. One patient had received 24 months of DDS followed by 24 months of MDT and 5 others had received more than 32 months of MDT. Viable bacteria were detected in both skin and nerve of one of the patients who had received 32 months of MDT and had an average smear BI of 2·6 + at the time of biopsy. The remaining 5 cases did not show viable *M. leprae* in either skin or nerve. However absence of viable bacteria among these patients could not be attributed to the extended treatment alone, as there was also significant difference in their pretreatment BI. It is of relevance to mention that no viable bacteria were detected in a similar study carried out on contemporary skin and lymph node biopsies obtained from 11 LL cases, who had received 5 years of DDS monotherapy prior to 2 years of MDT.[18] All the patients included in this study had a comparable post-treatment BI of over 3+. However as pointed out by the authors, use of non immunosuppressed mice in their study might have restricted the sensitivity of test system. The THELEP study, on the other hand, using immunosuppressed mice records no difference in the degree of persisters in the skin biopsy, with treatment duration ranging from 3 months to 2 years and with different regimens.[9] These results in turn have led to the acceptance of persisters as unavoidable and of little significance.

A significant drop in prevalence and exceptionally low relapse rate are the two prominent justifications offered in favour of fixed-duration therapy. However events subsequent to

similar exceptions in the early years of dapsone monotherapy and the emergence of multidrug resistance despite short-course chemotherapy in tuberculosis warrants a cautious approach and careful monitoring of the long-term sustenance of MDT in multibacillary leprosy.

The presence of viable bacteria in 12 of the 26 MB cases (46%) that were released from a well-implemented regimen of WHO-MDT in the present study should be viewed with concern, for it indicates a very poor cure rate. This study, the first of its kind, also establishes that the incidence of viable bacteria in the peripheral nerve is twice as high as compared to skin. Since all the nerves included in this study were grossly involved, the prima-facie evidence[19] suggest that the penetration of the drugs into the endoneurial compartment or to the Schwann cell *per se* may have little to do with the higher incidence of viability. On the other hand, immunological seclusion of the peripheral nerve or a yet unknown micro-environment of the Schwann cell may be playing a role in promoting the bacterial survival.

Histopathology did not prove very useful except for the findings that all the biopsies that showed viable bacteria did not show evidence of active disease. This was partly due to the time of biopsy. Whether use of immunotherapy will have any beneficial effect in bringing down the 'viable' bacterial load from the peripheral nerve compartment remains to be seen. Results obtained in the present study make a strong case for such monitoring.

Acknowledgments

We gratefully acknowledge the help of Dr Satish Arolkar with the biopsies. Dr R. Ganpati, Director, BLP for referring some of the patients for this study. Mrs Jayalakshmi for typing the manuscript. This data was presented in part at the 14th International Leprosy Congress held at Orlando, 1993.

References

[1] Bhatt PV, Antia NH. Study of viability of *M. leprae* from multiple tissue biopsies of ten leprosy patients using the mouse foot pad technique. *Lepr Ind* 1976; **46**(2): 1–10.

[2] Antia NH, Pandya NJ. Qualitative histology and quantitative bacteriology in various tissues of 50 leprosy patients. *Lepr Rev.* 1976; **47**(3): 175–183.

[3] Antia NH, Kamala N. Persistence of *M. leprae* in peripheral nerve. *Ind. J. Med. Res.* 1983; **77**(4): 42–422.

[4] Barros U, Shetty VP, Antia NH. Demonstration of *M. leprae* antigen in nerves of tuberculoid leprosy. *Acta. Neuropathol.* (Berl). 1987; **73:** 387–392.

[5] Shetty VP, Suchitra K, Uplekar MW, Antia NH. Persistence of *M. leprae* in the peripheral nerve as compared to skin of multidrug treated leprosy patients. *Lepr. Rev.* 1992; **63:** 329–336.

[6] Shetty VP, Uplekar MW, Antia NH. Immuno-histochemical localization of mycobacterial antigens within the peripheral nerves of treated leprosy patients and their significance to nerve damage in leprosy. *Acta Neuropathol.* 1994; **88:** 300–306.

[7] WHO. Laboratory techniques for leprosy. 1987; CDS/LEP 86.4

[8] Colston MJ. Application of thymectomized irradiated mouse to the detection of persisting *M. leprae. Int. J. Lepr.* 1987; **55:** 859–863.

[9] THELEP Subcommittee on clinical trial of chemotherapy of leprosy. Scientific working group UNDP/World Bank WHO Special Programme for research and training in tropical diseases. Persisting *M. leprae* among THELEP trial patients in Bamako and Chingleput. *Lepr. Rev.* 1987; **58:** 325–327.

[10] Waters MRF, Rees RJW. Changes in the morphology of *M. leprae* in patients under treatment. *Int. J. Lepr.* 1962; **30:** 266–277.

[11] Ridley DS. Bacterial indices. In: *Leprosy in theory and practice.* Ed. Cochrane RG, Davey TF. Johnwright & Sons Ltd. Bristol. 1964; pp. 620–622.

[12] McRae DH, Shepard CC. Relationship between staining quality of *M. leprae* and infectivity for mice. *Infect. Immun.* 1971; **3:** 116–200.

[13] Ganpati R, Pai R, Gandevar KL, Tharessia XJ. For how long should a multibacillary leprosy patient be treated (?). *Ind. J. Lepr.* 1989; **61:** 467–471.
[14] NLEP overview. *Count down towards irradication of leprosy from India,* Ministry of Health and Family Welfare, New Delhi. (1987).
[15] NLEP (1994). *Guidelines for multidrug treatment in non endemic districts.* Leprosy division, Directorate General of health Services, Govt. of India, New Delhi.
[16] Katoch K, Natarajan M, Bagga A, Katoch VM. Clinical and bacteriological progress of highly bacillated BL–LL patients discontinuing treatment after different periods of MDT. *Int. J. Lepr.* 1991; **59(2):** 248–254.
[17] Katoch K, Ramanathan U, Natarajan M, Bagga AK, Bhatia AS, Saxena RK, Ramu G. Relapses in paucibacillary patients after treatment with three short-term regimen. *Int. J. Lepr.* 1989; **57:** 458–464.
[18] Sivaprasad N, Snehalatha S, Lobo D, Aschhoff M, Job CK. Viability of *M. leprae* in lepromatous patients after five years of dapsone, monotherapy supplemented with two years of multidrug therapy. 1995; **64:** 427. 433.
[19] Save MP, Shetty VP, Antia NH. Intracellular localization of dapsone and rifampicin in skin and nerve of multidrug treated leprosy patients. *Ind. J. Lepr.* 1995; **67**(3) 273–284.

Lepr Rev (1997) **68,** 139–146

Tuberculosis control is good for established leprosy programmes

ROSEMARY A. CROFT & RICHARD P. CROFT
The Leprosy Mission, Danish Bangladesh Leprosy Mission, PO Box 3, PO and District Nilphamari 5300, Bangladesh

Accepted for publication 11 November 1996

Summary Tuberculosis (TB) control was introduced into part of the Danish Bangladesh Leprosy Mission's large leprosy control programme in 1994. This was in line with the Government's policy of combining leprosy and TB control. We report our experience with integration. Leprosy case-finding has increased during the period, and staff satisfaction and morale has also risen despite the larger workload. We observed that the field work skills of leprosy workers was brought to bear in a very positive way on TB control. TB patients suffer considerable impoverishment as a result of their illness, paralleling the social dehabilitation often seen in leprosy sufferers. TB control is good for established leprosy programmes.

Introduction

Combining tuberculosis control with leprosy control has often been suggested as a way forward for vertical leprosy programmes to sustain their services in situations of falling prevalence.[1,2] In a recent article in the *British Medical Journal*, Lockwood & Saunderson[3] drew attention to the way that the traditional strengths of leprosy programmes—namely in case-holding and case-finding—can be successfully harnessed to TB control to the mutual benefit of both services. They were writing from the background of a successful programme at ALERT, Ethiopia where TB is a major health problem but leprosy prevalence has declined considerably. The prevalence of leprosy in now falling in many parts of the world, and the future of maintaining existing leprosy projects will be under discussion. The incidence and prevalence of TB remains high.

In the past TB programmes have been chronically underfunded—it was a curable disease not being cured! Recently renewed interest is being given partly because of the link TB has with AIDS. WHO declared TB a 'global emergency' in 1993.[4] TB treatment has been shown to be one of the most cost-effective health interventions available.[5]

Saunderson[6] has drawn attention to some of the similarities between leprosy and TB control, as summarized in the section below.

0305-7518/97/068139+08 $1.00

Similarities between TB and leprosy

Bacteriology—both acid-fast bacilli spread mainly by droplets from the respiratory tract and necessitating similar diagnostic microscopy facilities.

Treatment and case-finding—Case-finding mainly by encouraging self-reporting through dissemination of information. Case-holding a priority to prevent relapse and treatment failure.

Management and cohort reporting—both rely on the same principles.

Psychosocial/economic aspects. Disruption of patients' lives leading to dehabilitation caused by both diseases.

Advantages of combined programmes

There are disadvantages in running combined leprosy/TB programmes which benefit the control of both diseases. These are listed below.

A leprosy team and clinic infrastructure can be maintained even when leprosy prevalence falls to low levels.
The diagnosing and treatment of TB patients can be done without duplication of physical and manpower resources.
Staff skills and work methods developed in leprosy can be deployed to the advantage of another very needy group of people.
Integration reduces the stigma of leprosy.
Job security and satisfaction among staff increases.
Leprosy case-finding is maintained by continuing to disseminate information about both diseases.

In 1994 the Danish Bangladesh Leprosy Mission (DBLM), who are a large leprosy control programme in northern Bangladesh, adopted TB control into one part of its working area as a pilot programme. The experience has been very positive, and we share our findings as an encouragement to other programmes considering this kind of step.

PROGRAMME DETAILS

A joint TB/leprosy control programme has existed in Bangladesh since 1976, but in 1993 the Government of Bangladesh committed itself to an ambitious project of leprosy and TB control with financial support from the World Bank and technical support from WHO. The twin aims were:

> the elimination of leprosy as a public health problem by the year 2000, defined as a reduction in prevalence below 1 : 10,000; and
> to reduce the incidence of TB until it is no longer a public health problem by diagnosing and treating effectively as many sputum positive TB patients as possible. The immediate objectives in Bangladesh are to increase the cure rate of new sputum smear positive TB from less than 40% to 85% and to increase case detection from the present 10% to over 50% of the incidence.

In order to maximize resources, the Government signed a memorandum of understanding in

1994 with a consortium of leprosy control agencies, the Leprosy Co-ordinating Committee (LCC), of which DBLM is member. Under this memorandum, in return for agreeing to operate leprosy control services in defined districts, leprosy NGOs (Non-Government Organizations) receive multidrug therapy (MDT) supplies free from the Government. Further, leprosy NGOs were encouraged to take up TB control as well, and were offered free drugs to enable them to carry this out, providing the NGO undertook to follow Government guidelines for diagnosis and treatment.

DBLM decided in 1994 to begin a pilot TB control programme in one of its areas of operation with the aim of seeing how well the two disease control structures could sit together. Since its beginning the combined leprosy/TB control programme has mushroomed and is now an established part of DBLM.

Details of the leprosy control programme

DBLM is a large leprosy control project operating in four northern districts of Bangladesh, an area considered to have the highest prevalence of leprosy in the country (5/1000).[7] The area is divided into 3 'fields', and in one of them, the Thakurgaon field, the control programme has now been operating since 1978. MDT was introduced in 1984. The Thakurgaon field comprises the districts of Thakurgaon and Panchagar with an area of 3214 km^2 and a population of 1,723,000. It is supported by a small hospital of 16 beds in the district town of Thakurgaon (see Table 1).

The number of new leprosy cases found in this field has been increasing each year since the project began (see Figure 1) because of larger number of staff deployed in the area and intensified case-finding activities (planned before the introduction of the TB programme). Mass surveys indicate that the overall (absolute) prevalence rate is now falling as expected (1991: 10/1000, 1995: 3.7/1000). With the increased proportion of paucibacillary patients, abandonment of routine follow-up (surveillance) after release from treatment (RFT) for relapse/reaction and reduction in active case-finding, the leprosy workload of patient care in the area is actually decreasing. It was for these reasons, and because the authors were living in Thakurgaon at the time, this area was chosen to start the TB pilot project.

Details of the TB programme

TB is a major public health problem in Bangladesh. The prevalence rate is considered to be 2–3/1000 across the country (Dr Liisa Parkkali, personal communication), and our impression

Table 1. Statistical information relating to leprosy control in the Thakurgaon Field of DBLM in 1994 and 1995

	1994	1995
New leprosy patients detected	652 (MB* 148)	708 (MB 141)
Cases on treatment 31 December	808	600
Registered prevalence/10,000	4·69	3·48
Number of field staff	26	30
Number of peripheral clinics (mostly monthly)	22	21

* Multibacillary.

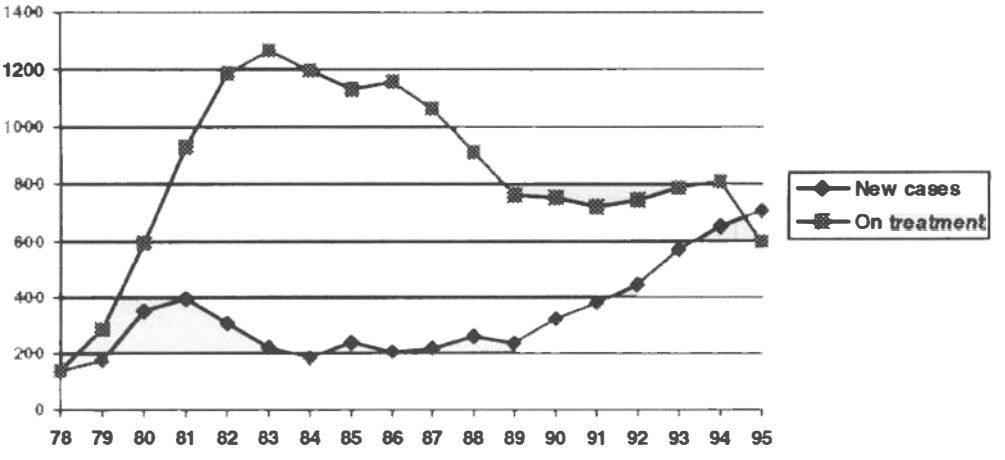

Figure 1. New leprosy case-finding and patients on treatment in DBLM Thakurgaon field, 1978–1995.

is that the level of TB in northern Bangladesh is of that order. Thus in the Thakurgaon project area there is a prevalence of roughly 4500 cases.

The TB programme was started in June 1994 following a short training course for the staff involved. Since then there has been a weekly diagnostic and treatment clinic at Thakurgaon Centre and monthly diagnostic clinics operating at another 4 peripheral clinics. After completing their initial intensive phase of treatment patients can collect their medicines monthly from their nearest leprosy (now leprosy/TB) clinic.

Diagnosis is by sputum examination, and treatment follows the Bangladesh national TB control programme's guidelines. All TB medicines are obtained quarterly from the Government. Since TB work has been started only one additional staff member has been added to the team to help with medicines and record keeping. She packets the TB intensive phase medicines into long cylindrical polythene bags, each day's drugs being sealed into a separate compartment using a candle flame to melt the plastic. The patients are then supplied with one month's medicines, conveniently packed into 28 separate days' supply, as an aid to compliance (the equivalent of MDT blister packs).

All new sputum positive patients receive an 8-month treatment regime consisting of 2 months' intensive phase of daily rifampicin, pyrazinamide, ethambutol and isoniazid followed by a 6-month course of isoniazid and thiacetazone.

Apart from clinic days most of the fieldworkers' time is spent on patient follow up. The Government TB control programme requires that every smear positive TB patient in the first 2–3 months of treatment takes his or her drugs in front of a health worker at least every other day to ensure complete and correct medicine intake. Ideally DOTS—Daily Observed Therapy, Short course—should be implemented to minimize the risk of patient non-compliance and the development of drug resistance. We found this to be operationally difficult with only 1 fieldworker per 60,000 population, so the DBLM field staff enlist the help of a responsible relative who agrees and signs that s/he will supervise the patient's medicine intake daily. Compliance is then checked at each weekly visit by the DBLM field worker. It is estimated that excepting clinic time, 60% of a TB/leprosy field workers' time is taken up with these TB follow up visits, done on a bicycle.

TB and leprosy case-finding activities

The case-finding activities have been fully integrated; the fieldworker going to a new area uses a flip chart and gives information to a group of villages about the signs and symptoms of leprosy and TB, telling them what to do if either are suspected. Each weekday night a slide presentation about leprosy and TB is shown in a different village, featuring a series of slides similar to the flip chart; these 'information programmes' are very popular and are often shown to a crowd of over 500.

In addition to mass information, field staff carry out contact surveys of both leprosy and TB cases. Mass surveys are also part of the leprosy case-finding activities, but this is being reduced steadily because of time constraints. Leprosy case-finding rests increasingly on voluntary self-reporting of cases and this is proving to be successful. In 1995 70% of new leprosy cases self-reported, and overall case-finding was higher than 1994.

Leprosy case-finding has not decreased but rather has increased since the addition of the TB programme (see Table 2). Ten leprosy patients have incidentally been found among people attending the TB clinics. The workers have 'leprosy eyes', and suspicious skin patches are sometimes spotted on exposed skin or as the shirt/blouse is lifted for chest auscultation. New leprosy patients have also been found when the fieldworker visits a new area for TB patient follow up. In one case, a fieldworker visited an area where he assumed there was no leprosy. After attending a TB patient in that area he sat with a group, showed his flip chart, and found 5 new cases of leprosy that day.

Unlike leprosy patients, it has usually not been difficult to motivate suspected TB sufferers to attend a clinic. People in Bangladesh are aware that TB is a potentially fatal disease, and it does not carry the stigma that leprosy does. TB clinics have been flooded with people suffering from chest symptoms wanting to have a sputum test simply as a result of mass information. The number of clinic days has purposely been kept low to limit the number of TB patients receiving treatment because of staffing constraints. It is anticipated that in the future more clinics will be offered to increase coverage of the area.

Stigma

The TB programme may help to decrease the stigma against leprosy. Each month over 1000 people visit the 'leprosy hospital' and 'leprosy clinics' for TB checks. There have been no problems in admitting sick patients to the 'leprosy hospital'.

Table 2. Statistical information relating to TB control in DBLM Thakurgaon Field 1994/1995

	1994 (Jun–Dec)	1995 (Jan–Jun)
New cases registered	196	279
Smear positive cases among new	158 (81%)	215 (77%)
Number of chest symptomatics screened	1555	4555
Outcome—completed treatment	151 (77%)	222 (79·8%)

Staff response

In many ways the addition of the TB project has increased the staff workload and it was anticipated that there would be some resistance. However this has not been the case and staff openly admit that this is because the TB project has brought perceived job security. The fieldworkers were not blind to the decreasing prevalence of leprosy with its obvious implications for their future. Many staff, (if not most), had or have relatives or neighbours with TB and were only too aware of the lack of affordable local treatment. The knowledge that their work is worthwhile in reducing death and suffering has of course increased their job satisfaction, and this has been expressed by many of them.

Before working with DBLM one author (RAC) was attached to a TB project running from a general mission hospital. The expertise that the leprosy fieldworkers have brought to the TB work, lacking in those fieldworkers from the general hospital, is very evident. This is especially true in the field of health education, information dissemination and in case holding. The longer-standing fieldworkers also bring to the work a knowledge of the area and the local community whose influence can be invaluable to persuade an infectious defaulting patient to take his medicines.

Financial implications

Financial implications for DBLM has been minimal since:

TB medicines have been given by the Government;
the necessary laboratory equipment and technicians were already in place.
the clinic infrastructure and staff were already in place. An extension has been added to one clinic facility because of the large number of people attending each week;
The hospital infrastructure and staff were in place. Approximately 2–3% patients require admission for complications, severe illness, drug reactions etc.; and
only one new member of staff has been added to the team specifically to look after the TB records and to help package medicines.

Socioeconomic impressions

Many TB patients are among the poorest of the poor. An experienced nurse at Thakurgaon hospital commented that the TB patients admitted were worse off than leprosy patients admitted to the same hospital. We conducted a small survey among 21 of our patients registered serially during one month, looking at expenditure and loss of income directly related to their illness before coming to clinic (see Figure 2). Out of the 21 patients interviewed, 11 had lost between Bangladesh Taka (BDT) 8000–40,000 (US$200–1000), mainly because of loss of income and drug costs. Such sums of money are a huge drain on poor families (average monthly family income in rural Bangladesh is BDT 2670 (US$65)[8]). Often the money is raised by selling livestock and/or land thus impoverishing the family for a long time to come. Eight patients suffered minimal loss (less than BDT 2000—US$50); 5 of these were able to continue working despite their illness. The mean period from onset of illness until diagnosis at our clinic was 16 months (range 0–60 months). A local synonym for TB is 'King's disease' as it is believed that only kings can afford the treatment and food needed to obtain cure!

Leprosy work has a long history of devoted help for humanitarian or religious reasons to

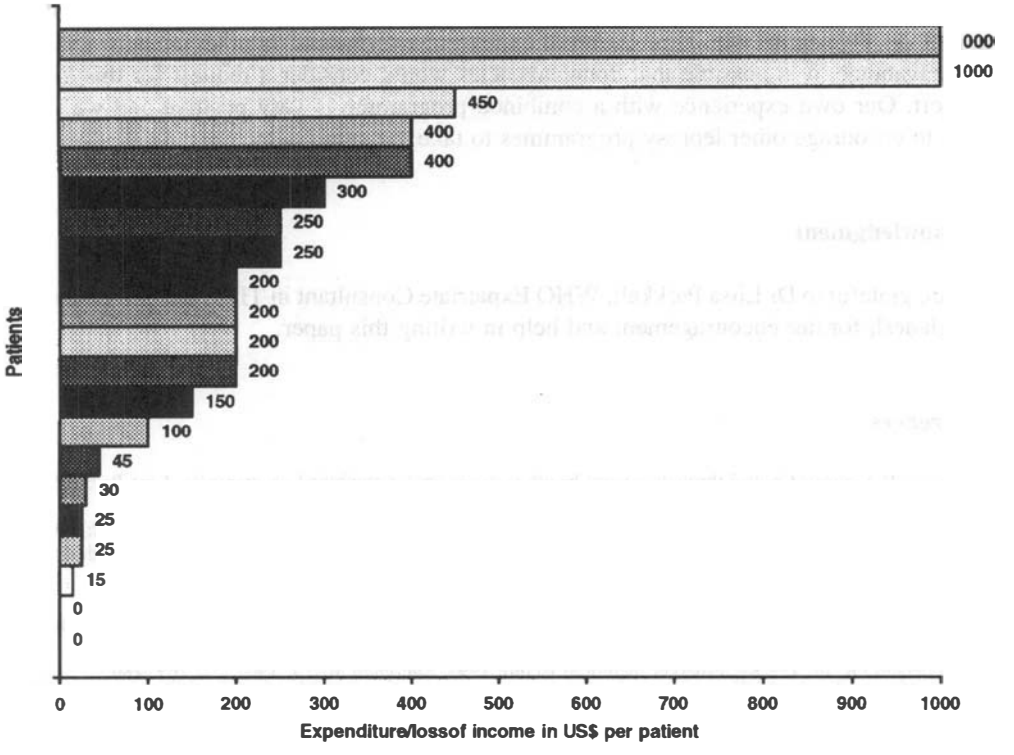

Figure 2. Total loss of income and expenditure related to TB in patients before registration at DBLM TB clinic.

those considered to be at the bottom of the social heap. TB sufferers in developing countries are also in desperate need. While in Bangladesh most do not suffer social stigmatization (only 8 out of 21 in the above study said that their neighbours now avoided their family for fear of catching the disease), in Africa stigma is growing because of the connection with AIDS.

Discussion

One aim of TB control work is to integrate treatment services into the general health sector, but this is practically very difficult in many developing countries. In the Kellersberger Memorial lecture of 1982, Dr Styblo said that 'in many developing countries TB has been so perfectly integrated that nobody cares about it'.[9] Integrating with another vertical programme, such as leprosy, has much to commend it. It is possible that leprosy control projects are better able to handle the new challenges of TB control than other types of health programme. It is also true that TB control programmes have much to learn from the longer and better established leprosy programmes.[3] As already stated, it has certainly been our impression that the leprosy workers brought their considerable field experience to bear very positively in the TB work. In our own programme, adding TB control did not bring the feared 'swamping' of leprosy work but in fact injected a new lease of life into it.

It is true that the Bangladesh situation is perhaps better than many, with the Government

encouraging NGO cooperation and bearing the major cost, that of drugs. This enabled DBLM to pick up TB control with a minimum of expense. Nevertheless, in other situations without this advantage, it is possible that donor agencies would consider a request for this kind of support. Our own experience with a combined programme is very positive and we would want to encourage other leprosy programmes to take the same step.

Acknowledgment

We are grateful to Dr Liisa Parkkali, WHO Expatriate Consultant in TB to the Government of Bangladesh for her encouragement and help in writing this paper.

References

[1] Feenstra P. Leprosy Control through general health services and/or combined programmes. *Lepr Rev*, 1993; **64:** 89–96.
[2] Feenstra P. Sustainability of Leprosy Control Services in low-endemic situations. *Int J Lepr*, 1994; **62:** 599–608.
[3] Lockwood DNJ, Saunderson PR. Harnessing the strengths of the leprosy programme to control tuberculosis. *BMJ*, 1995; **311:** 862–3.
[4] TB—a global emergency: WHO report on TB epidemic, WHO 1994.
[5] Murray C, Styblo K, Rouillon A. In *Health sector priorities review—tuberculosis*. Population, health and nutrition division, The World Bank, Washington DC, June 1991.
[6] Saunderson PR. In: The Kellesberger memorial lecture 1994, *Ethiopian Med J*, 1994; **32:** 269–280.
[7] Richardus JH, Croft RP. Estimating the size of the leprosy problem: the Bangladesh experience. *Lepr Rev*, 1995; **66:** 158–164.
[8] 1994 Statistical Yearbook of Bangladesh, Bangladesh Bureau of Statistics, August 1995.
[9] Styblo K. The Kellersberger Memorial lecture, 1982 *Ethiopian Med J*, 1993; **21:** 101 (quoted by Saunderson P, in: The Kellersberger Memorial lecture, 1994 *Ethiopian Med J*, 1994; **32:** 269–280).

Lepr Rev (1997) **68,** 147–154

Surgery for neuritis in leprosy: indications for and results of different types of procedures

RAYMOND BERNARDIN & BERMAN THOMAS
Hopital Cardinal Léger, Institut Fame Pereo, 160 Avenue Poupelard, Port-au-Prince, Haiti (W.I.)

Accepted for publication 26 November 1996

Summary From December 1988 to December 1992, 129 surgical procedures were performed on the peripheral nerves of 64 leprosy patients at the Hospital Cardinal Léger de l'Institut Fame Pereo for leprosy control in Haiti.

Sixty-four patients totalizing 129 nerves with sufficient clinical data form the basis of this study.

Based on the retrospective analysis of the operated cases, a new classification built on macroscopic findings of the involved nerves is presented. Five grades, according to the presenting aspects of these nerves, are set up as guides for different surgical procedures to be performed on the nerves: external decompression for the lesser grades I and II, intraneural neurolysis, interfascicular neurolysis for the higher grades III and IV, cleaning, and debridement for grade V. The final results are discussed. This new macroscopic grading done at surgery helps to minimize the aggressive procedures performed on nerve trunks, decrease the morbidity of surgical action on the nerve vascular structures, and consequently, preserves all possible sensory and motor functions of a nerve.

Introduction

All patients with leprosy present some form of nerve involvement at the skin level (hypoaesthesic or anesthesic lesion); it has even been described as some form of 'pure neuritic' leprosy without or before skin lesion, 'silent neurits' or 'quiet nerve paralysis' (QNP). However, most forms of nerve involvement are too often not recognized until the hands or feet are damaged.

Early detection and treatment of nerve trunk lesion in leprosy neuritis before permanent damage, loss of neural function, and subsequent disability, are the ultimate goals in dealing with neuritic leprosy. Once the nerve lesion is detected early, the physician, fieldworker, therapist, and all other personnel involved, hope that adequate and effective treatment is available in order to interrupt the downhill progression of the lesion, preserve the most valuable function of the nerve and, in so doing, protect the patient from a lifelong physical disability.

0305-7518/97/068147+08 $01.00

Table 1. Distribution of nerves according to the proposed macroscopic grading

GRADES		II	III	IV	V	Total nerves
Ulnar	40	19	10	6	3	78
Median	22	11	4	–	–	37
Common peroneal	9	2	3	–	–	14
Total grades	71	32	17	6	3	129

Materials and methods

From December 1988 to December 1992, 129 surgical procedures were performed on nerve trunks in both upper and lower limbs of 64 patients at the Hospital Cardinal Léger of the 'Institute Fame Pereo'.

Thirty-six males and 28 females were registered. The age difference between male and female was not significant. The youngest patient was 8 years; the oldest 65. Four patients were aged below 10 years; 28 were in their teens; 16 ranged between 20 and 30 years; seven, five and three were respectively within 40, 50 and 60 years. One patient was 65.

From a total of 129 nerves which were operated on, the ulnar nerve accounted for 78 cases, the median nerve for 37, the common peroneal nerve 14. Seventeen patients did not present their nerve involvement at once. Thirteen patients required two operations at different times; four, three operations.

Bacteriological studies from these patients showed at 52 (81·2%) were paucibacillary and 12 (18·8%) multibacillary. In our series polyneuritis was more frequent in paucibacillary

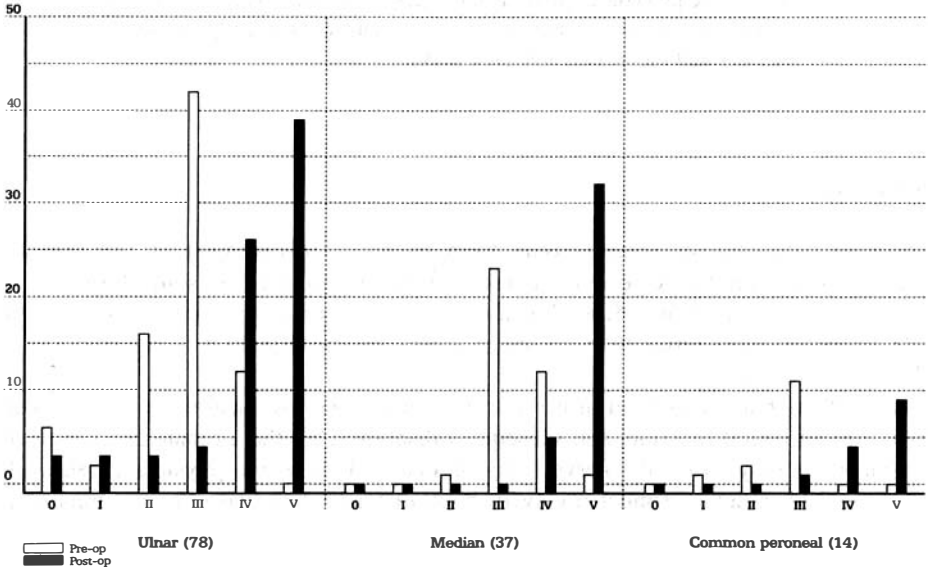

Figure 1. Pre- and postoperative motor assessment.

patients: 46 out of 52; also mononeuritis seemed to be more typical of multibacillary patients: 7 out of 12.

All these patients were evaluated for sites of tenderness along the nerve trunks, sweating of hands and feet, level of sensory as recorded on hands and feet charting, bone absorption of fingers and toes, status of finger joints motion, voluntary and manual testing of muscle strength in hands and feet, occupation, age and sex distribution. Prior to their diagnosis all the adult patients were involved in some profitable activities as farmers, housewives, street vendors and craftsmen. At the time of referral for orthopaedic evaluation the patients presented persistent and severe pain, severe paresthesia, sometimes muscle wasting and deformity. Detection of nerve involvement was based on the evaluation of voluntary muscle strength against resistance and sensory testing using Semmes-Weinsten monofilaments in order to assess the patient's touch-pressure recognition. A negative response to 4·56 (3·63 g) filament marking was considered as loss of protective sensation for the hand; and for the foot a negative response at 6·65 (4·48). Assessment of motor function consisted in voluntary testing of selected muscles for each nerve: abductor digiti minimi, flexor carpi ulnaris and first dorsal interosseous muscles for the ulnar nerve; opponens pollicis and abductor pollicis brevis for the median nerve; tibialis anterior and extensor muscles of the toes for the common peroneal nerve. The pre-operative evaluation for motor and sensory functions of the involved nerves was done from a few days to 4 weeks prior to surgery. We found for the ulnar nerve, in preoperative assessment, no case with normal sensation (grade V), five cases with diminished light touch (grade IV), 42 with diminished protective sensation (Grade III), 27 with loss of protective sensation (grade II) and four with only deep pressure sensation (grade I). In motor testing there was no case of normal function (grade V), 12 of grade IV, 42 of grade III, 16 of grade II, 2 of grade I and 6 of grade 0.

For the median nerve, preoperatively, we found no case of normal sensation (grade V), 6 of grade IV, 27 of grade III, 4 of grade II and no case of grade I or 0. Testing motor strength revealed one case of grade V, 12 of grade IV, 23 of III and one of II; there was no case of grade I or 0.

For the common peroneal nerve, 11 cases were of sensory grade III, 2 of grade II and one of grade I; for the motor function there was one case of grade I, 2 cases of grade II, 11 of grade III.

Functional deficit of a nerve can be the result of increased external pressure on the nerve trunk which from hypertrophy cannot accommodate its larger size within the fibro-osseous channels such as the cubital tunnel at the elbow, carpal tunnel at the wrist, retro-fibular tunnel at the knee. This hypertrophy represents one of main characteristic changes in leprosy neuritis.

The main indications for surgery were:

failure of medical treatment in controlling the patient's symptoms after at least 4 weeks of 30–40 mg of prednisone a day (17 patients);
complications from medical treatment such as gastritis, gastroduodenal ulceration, hypertension, psychotic disorders, toxicity (15 patients);
young age associated with severe symptoms (12 patients);
great severity of neural symptoms with excruciating pains (10 patients);
lack of compliance to the medical treatment (3 patients);
rapid deterioration of neural status (3 patients);
infectious process and immune deficiency (2 patients);
pregnancy (one patient); and
psychiatric disorder (one patient).

Fifteen patients who obtained improvement of their symptoms from prednisone had to stop their medical treatment because of complications. These patients' charts mentioned only improvement of their neural symptoms without real assessment of the nerves sensory and motor functions.

At surgery the trunks of different nerves presented various macroscopic aspects which allowed us to realize different types of surgical procedures according to these aspects. In the first type of nerve lesion, hypertrophy of the trunk was obvious. However the nerve appeared normal in spite of a yellowish or brownish discoloration due to impregnation by medication, in particular clofazimine. The perinerve appeared shiny, glistening and transparent. At gentle palpation the nerve was supple with a regular consistency and free of any induration. For this type of lesion we performed an external decompression in which the constrictive fibrous ligament structures compressing the nerve were opened and excised, creating more space to accommodate the hypertrophied nerve trunk. In doing this ligamentotomy we made sure we relieved all the surrounding compressing fibrous bands or ligaments according to the anatomical specificity of the nerve involved; for example, in the case of the ulnar nerve, all three levels of possible compression, at the medial intermuscular septum, in the cubital tunnel and distal to the tunnel at the aponeurosis of the flexor carpi ulnaris muscle, should be explored and decompressed as necessary. During the course of this procedure all the vascular channels penetrating or leaving the epineurium should be left intact; the nerve should not be subjected to undue displacement from its bed, nor put under tension or traction through the use of rubber bands, gauze strips (umbilical tapes) or any other materials, for fear of tearing the fragile blood vessels (arterioles and veinules) on the posterior aspect of the nerve trunk. This is one of the main reasons the anterior transposition of the ulnar nerve and epicondilectomy are not done systematically.

From 78 ulnar nerves operated on in our series only 3 anterior transpositions (3·8%) with epicondylectomy were performed.

In the second type of nerve trunk lesion, inflammation of the perinerve was evident; it lost its brilliance and shine; it looked pale and more or less opaque. There was an apparent state of vascular congestion. Some small areas of focal haemorrhage (probably as a result of trauma from rubbing and scratching) could also be noticed. Nevertheless the nerve was still supple, regular and without induration. At the opening of the nerve sheath, dissection of the bundles is quite easily performed because of little and rather loose interfascicular fibrosis formation and mild oedema of the axons. The primary purpose of this neurolysis is to decompress the inner structures of the nerve.

A more advanced macroscopic lesion showed thickening and irregularity of the epineurium along with its paleness and opacity. In addition they were short segments (1 to 5 mm) of induration. At epineurotomy an important intraneural fibrosis and numerous interfascicular connecting fibrous bands could be found. Dissection of the fascicles was still possible. But the axonal fibres were the site of important oedema. Some of the fibres presented small areas of necrosis (softening); there were also marked vascular congestion. For this advanced lesion a more aggressive surgery was used. It consisted in longitudinal opening of the epineurium, dissecting off its edges in order to create sufficient room for the axonal bundles. In the course of dissecting the epineurium, the penetrating vessels should be left intact by making step-ladder, discontinuous types of incisions, or placing the axial incision away from the main vascular channels.

The fourth type of lesion is represented by long segments of induration along the nerve trunk, which made very difficult all attempts of intraneural dissection. The sheath is very

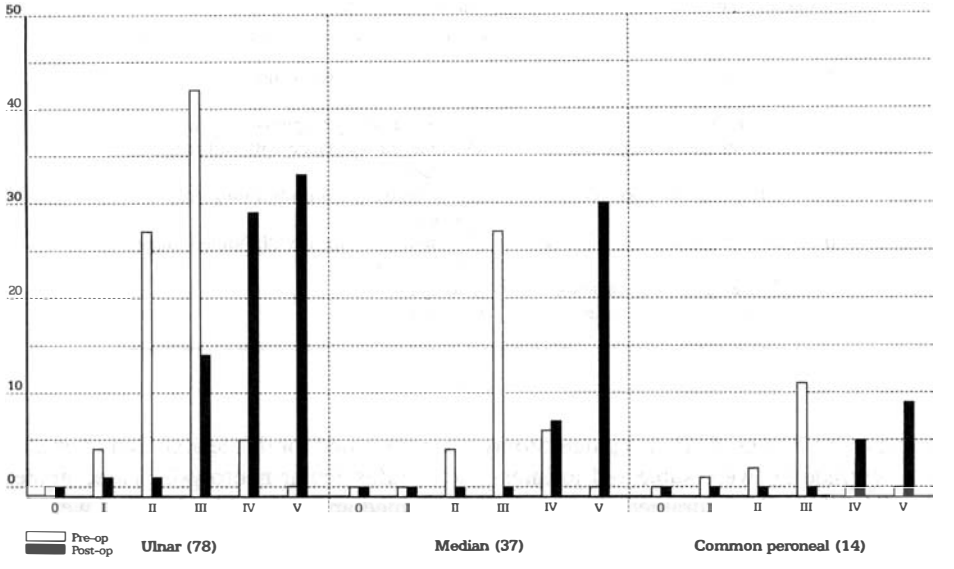

Figure 2. Pre-and postoperative sensory assessment.

thick, adherent, completely opaque and difficult to dissect off. In some areas the nerve trunk is transformed into a long hard cord by intense fibrosis. Softening of the axons and in some places, formation of small abscesses were seen as signs of advanced axonal necrosis. Surgery for this type of lesion was carried out inside the nerve fascicles, mainly the better preserved ones, following the same principles of vascular channels preservation. After opening the thick endoneurium, dissection reached some intact or partly intact axons which were freed from any persisting constriction.

The fifth type of lesion was represented by an abscess made of large areas of purulent collection along the nerve trunk. Sometimes the abscess had already burst through the skin (fistulization). There was also complete necrosis and liquefaction of the nerve around the site of the abscess. Surgery for this type V of lesion consisted essentially in cleaning the abscess which was washed out, drained and packed open. During a second procedure, 48–72 h or later if necessary, following daily dressing changes, the integuments could be repaired. At this time, fibrous ligaments causing compression on the nerve could be resected.

The macroscopic grading devised from operated cases serves as an indication of stage of lesions involving the nerve and its inner structures. The surgical procedures performed on various nerves were based on this grading for the following definite reasons:

To limit the surgery to strictly necessary action requiring decompression of the nerve and its axons.
To minimize, as much as possible, surgical trauma to the nerve structures, in particular to decrease the damage of the nerve vascular component to the minimum.
To reduce to the very minimum the postoperative morbidity to nerve functions.
To make the surgical act as simple as possible for the surgeon by providing him with some sound guidelines.

From the 78 ulnar nerves, at surgery 40 showed a grade I lesion and underwent a

Table 2. Grading parameters for sensory and motor testing

Sensory testing	Motor testing
V- 2. 83: normal sensation	V: normal strength against resistance
IV- 3. 61: diminished light touch	IV: reduced resistance with full range of motion
III- 4. 31: diminished protective sensation	III: no resistance with full range of motion
II- 4. 56: loss protective sensation	II: visible movement with limited range of motion
I- 6. 65: deep pressure sensation	I: flicker
0- complete loss of sensation	0: paralysis

decompression; 19 a grade II, an epineurotomy was performed for this lesion. Ten of grade III and six of grade IV were subjected to inter- and intrafascicular neurolysis. Three grade V lesions were cleaned and drained. From a total of 37 median nerves, 22 of grade I were only decompressed; 11 of grade II and four of grade III were operated on following the same principles of neurolysis. The common peroneal nerve accounted for 14 nerves from which nine were of grade I lesion, two of grade II and three of grade III. Only the last two groups underwent epineurotomy and neurolysis; the first one only a decompression.

At follow-up (24–53 months) results for the ulnar nerve showed a good improvement of the nerve functions: 33 nerves (from nil) regained a normal sensory function (grade 5), 29 lost minor sensation (grade 4) and five pre-operatively. Fourteen nerves persisted with diminished

Table 3. Pre and post-operative sensory and motor assessment (follow-up 13 to 53 months—mean 32·5)

Ulnar nerve (78)			Median nerve (37)			Common peroneal nerve (14)		
Pre	Grade	Post	Pre	Grade	Post	Pre	Grade	Post
	Sensory			Sensory			Sensory	
0	0	0	0	0	0	0	0	0
4	I	1	0	I	0	1	I	0
27	II	1	4	II	0	2	II	0
42	III	14	27	III	0	11	III	0
5	IV	29	6	IV	7	0	IV	5
0	V	33	0	V	30	0	V	9
	Motor			Motor			Motor	
6	0	3	0	0	0	0	0	0
2	I	3	0	I	0	1	I	0
16	II	3	1	II	0	2	II	0
42	III	4	23	III	0	11	III	1
12	IV	26	12	IV	5	0	IV	4
0	V	39	1	V	32	0	V	9

protective sensation (grade 3) from 42. Only two patients did not regain protective sensation against pressure from 27; and no case of complete loss of sensation from four preoperatively. For the motor function of the ulnar nerve-depending muscles, three cases remained paralysed (grade 0) and three with flicker motion (grade 1). Thirty-nine cases (from nil) regained normal strength on the tested muscles (grade V); 26 cases presented some reduced resistance (grade 4); and seven were found with very weak muscle strength (grade 3 and 2).

The median nerve, which totalled 37 cases, was found with preserved sensory function in all the cases: 30 presented a normal sensation (grade 5) and seven showed a diminished sensation to light touch (grade 4). Similarly strength of the tested muscles was normal in 32 cases (grade V); and five presented some mild weakness (grade 4) at voluntary muscles testing.

For the 14 common peroneal nerves, nine remained with normal sensation (grade V), and five with minor diminished sensation (grade 4). As far as motor function is concerned, nine cases presented at follow-up a normal resistance (grade 5), four minor loss of strength (grade 4) and one a grade III manifested by supple drop foot.

There were 7 minor (3·4%) complications which were controlled by adequate measures:

Three 'stitch' abscesses which responded to topic antibiotics.

Two upper arm haematomas; one required drainage for 3 days, while the other one reabsorbed spontaneously.

Two wound dehiscences; one needed secondary sutures in the upper arm, while the other one was controlled with taping (steri-strips). There was also a case of an ulnar abscess at the Guyon's canal which required, for control, a second operation 3 weeks after the first surgical intervention.

Discussion and conclusion

Setting up a clinical classification in leprosy neuritis that can serve as a guide for the precise surgical procedure to be performed, has been a challenge throughout the years. Surgery is used as a helpful tool in the armarium of means for relieving and controlling this microbacterial nerve involvement. The classification by Srinivasan of the affected nerves according to stages of 'involvement', 'damage', and 'destruction' is one that describes the severity of the peripheral nerve lesion. However, this classification does not help the surgeon much because the findings by palpation through the skin of an hypertrophied, thick, tender nerve does not indicate the actual condition of the nerve lesion. This is complicated by the fact that damage to a nerve can be established at once from the onset of neuritis at the time the patient is seen. Furthermore, it is not always quite predictable to state that a particular nerve has absolutely no chance to partially recover some of its function.

The ultimate goal is to diagnose the neuritic condition before irreversible, functional deficit occurs. For in the type of entrapment neuropathy found in leprosy, the anoxal damage is related to both the immunologic phenomena responsible for all the inflammatory modifications and pathological changes in the nerve and also the hemodynamic alteration in the vascular system of the nerve in term of compression of the arteriolar walls, with direct consequences of anoxal ischemia. The definite treatment should be applied before any irreversible changes or destruction reach the axons, and should achieve the following two goals:

decrease hypertension around and within the nerve; and

prevent ischemia.

Besides the specific antibacterial therapy, the immunosuppressive effect of certain drugs such as corticosteroid agents, the sedative and analgesic properties of thalidomid, and anti-inflammatory ones of clofazimine are used to relieve pain and control hypertrophic neuritis. The various success of these drugs is indisputable. However, the following limitations do exist:

They must be used from the very beginning of the neuritis before ischimia takes place.
Their use can be for prolonged periods of time and at very high doses (such as prednisolone for up to 6 months). At such doses (starting dose 40–60 mg per day) and side-effects (mental, endocrine, gastroduodenal) may very much limit their use.
Those drugs are usually used in association with rest and immobilization of the involves limb or limbs, sometimes for long periods of time (6–8 weeks or more). This immobilization may represent quite a handicap for the patient with multiple nerve involvement.
Their use does not guarantee success as far as the control of severe symptoms is concerned, nor prevent the downfall progression of the nerve lesion. Surgical decompression and neurolysis, properly and completely done (in particular, in the case of the ulnar nerve), have an immediate effect on relieving pain, decompressing the nerve at once, and relieving the compression of the axons and the vascular structures of the nerve. In doing so there is no need for immobilization; and both techniques serve as a sure, definite, and immediate way to prevent ischemia of the nerve and should be carried out:

Immediately, in cases of severe, acute, hyperalgic neuritis; mainly if the anti-inflammatory drugs cannot be used because of other medical conditions (such as infections, pregnancy, gastroduodenal ulcers, mental disorders, hypertension, diabetes) or if some of the drugs (Thalidomid in our case) are not available.
Surgery can be delayed in cases where these drugs and immobilization are used and the patient shows overt clinical improvement of his/her symptoms for 3 weeks at the most. If in this delay, there is no sign of improvement or even worsening in the nerve condition, in spite of the treatment, one should immediately consider surgery.
For such neuritis of less than 1-year duration with apparent sensory loss, muscle weakness, and paralysis (macroscopic lesions of grade III and IV) surgery can still be of value, allowing that intact axons, not yet touched by necrosis, especially the 'small, slower conducting fibres' which are more resistant to elevated pressure than the 'large, fast conducting fibres'[1] can be saved through internal decompression.
Even for long-term lesions, in particular for cases of insensitive feet with plantar ulcer, after healing the ulcer by successive, pressure-control casting or other means, the decompression surgery of the posterior tibial artery can offer some hope in preventing the recurrence of these ulcers by way of increasing vascularization of the plantar tissues and improve the proprioceptive function and neural feedback of those tissues.

References

[1] Hargens AR, Romine JS, Sipe JC, Evans KL, Mubarak SJ, Akeson WH. Peripheral nerve-conduction block by high muscle-compartment pressure. *J Bone Joint Surg* 61-A:2; March 1979, 192–200.
[2] Srinivasan H. Prevention of disabilities in patient with leprosy. A practical guide WHO Geneva 1993.

Lepr Rev (1997) **68,** 155–161

An investigation of attitudes, beliefs and behaviour of leprosy patients, family members and PHC workers towards multidrug therapy in Yangzhou and Dongtai Districts of China

CHEN XIANG-SHENG,* YE GAN-YUN,* JIANG CHENG,* LI WEN-ZHONG,* BIAN JINGUO,† WANG HOUZHENG‡ & CHEN WENHUA†

** Department for Leprosy Research, Institute of Dermatology, CAMS & PUMC, National Center for STD and Leprosy Control, 12 Jiangwangmiao Street, Nanjing 210042; †Yangzhou Institute of Dermatology, Yangzhou 225300; ‡Dongtai Institute of Dermatology, Dongtai 224200, China*

Accepted for publication 24 September 1996

Summary To improve the operational efficiency of multidrug therapy (MDT) implementation in rural areas, an investigation into the attitudes, beliefs and behaviour of leprosy patients and their family members as well as primary health care (PHC) workers towards MDT was carried out in Yangzhou and Dongtai Districts of China. A sample of 370 leprosy patients, 594 family members and 730 PHC workers was interviewed or investigated individually using questionnaires. The results showed that: 1, the presently used MDT is acceptable to a wide range of patients although a small number of patients have various problems in their treatment; 2, the patients' habit in daily drug administration, their awareness of the risk of default and confidence in MDT have a positive influence in increasing drug compliance; and 3, the supervision and encouragement of family members to patients' treatment which is associated with their knowledge on MDT is also beneficial to patients' drug compliance. However, only half of the PHC workers had a basic knowledge of MDT and a desire to participate in MDT implementation, a finding which clearly calls for urgent attention and improvement. In order to ensure the effective implementation of MDT, there is a need to educate leprosy patients and their family members as well as PHC workers to establish the patients' correct awareness of MDT, obtain the family support and motivate the PHC workers.

Introduction

The introduction of multidrug therapy (MDT) recommended by WHO has been a major advance in the treatment of leprosy because of its relatively short treatment course and a low rate of relapse.[1–4] Since MDT was implemented in Jiangsu Province in 1984, almost all the

0305-7518/97/680155+07 $1.00

newly-detected leprosy cases have been treated with these regimens on a domiciliary basis. In order to ensure the effectiveness of presently used MDT, it is important to have an insight into the social aspects associated with its operational implementation. In this paper, the results of a sociomedical investigation on MDT implementation among the leprosy patients and their family members, and primary health care (PHC) workers are reported.

Materials and methods

Yangzhou and Dongtai Districts are situated in the North of Jiangsu Province of China with a total of 21,534 accumulated cases of leprosy since 1949 and 1551 cases treated with 'loose' drugs of WHO–MDT (MB–MDT 1229 and PB–MDT 322) since 1984 were selected for the investigation. In these areas, the WHO regimens were usually delivered to patients' homes at monthly intervals by the designated leprosy field workers of the County Station for Skin Disease Control with monthly supervised intake of rifampicin 600 mg, clofazimine 300 mg, together with daily, unsupervised clofazimine 50 mg and dapsone 100 mg for MB patients; monthly supervised rifampicin 600 mg and daily, unsupervised dapsone 100 mg for PB patients. Some patients, however, collected their drugs and were supervised at skin clinics, and a small number of patients liked to be treated in secret and/or without supervision in order to avoid the social stigma from community to their families. A sample of 370 leprosy patients and 596 of their family members were selected randomly from these areas and interviewed individually using the questionnaires. The interview was conducted by the authors with the assistance of the leprosy field workers who were experienced in dealing with leprosy patients and their family members. Before the interview, the aims and purpose of the investigation were clearly explained to the interviewees. Also, a sample of 730 PHC workers, including 137 part-time leprosy workers (PLWs), 61 paramedical workers (PMWs), 76 township health workers (THWs), 343 village health workers (VHWs) and 113 managerial health workers (MHWs), were investigated using the questionnaires in the same areas.

Drug compliance was defined as taking more than 90% of the prescribed medications estimated through the intensive interview.

All data from the questionnaires were put into the computer to establish a database, and analysed using the computer software of EpiInf 5.0.

Results

There were 370 (279 male and 91 female) leprosy patients with an average age of 49·6 ± 12·9 years, including 257 cases (69·5%) on MB–MDT and 113 (30·5%) on PB–MDT, and 594 members with an average age of 43·0 ± 6·4 years from these patients' families who responded to the questionnaires.

Leprosy patients were questioned about their treatment behaviour and beliefs in an attempt to determine whether their behaviour and beliefs were associated with their drug compliance (Table 1). The daily drug administration at a fixed time, patients' awareness of the risk of drug default and their confidence in MDT had a statistically significant affect in increasing patients' drug compliance. However, whether treated in the usual way with monthly attendance and supervision, or secretly, the drug compliance rate was the same. When questioned on the biggest problem in their treatment, 24·3% of patients had problems

Table 1. Relationship between patients' treatment modes/beliefs to MDT and their drug compliance

Patients treatment modes/beliefs to MDT	Drug compliance		Total	χ^2-test
	Yes	No		
Being supervised				
Yes	256 (74·9)	86 (25·1)	342 (100·0)	0·19
No	22 (78·6)	6 (21·4)	28 (100·0)	NS*
Drug delivery				
Home delivery	136 (74·7)	46 (26·3)	182 (100·0)	3·24
Clinic collection	84 (71·2)	34 (28·8)	118 (100·0)	NS
Hospitalization	58 (82·9)	12 (17·1)	70 (100·0)	
Daily administration				
Fixed time	253 (78·1)	71 (21·9)	324 (100·0)	12·15
Indefinite time	25 (54·3)	21 (45·7)	46 (100·0)	HS
Secret treatment				
Yes	105 (77·2)	31 (22·8)	136 (100·0)	0·49
No	173 (73·9)	61 (26·1)	234 (100·0)	NS
Risk of drug default				
Awareness	246 (76·9)	74 (23·1)	320 (100·0)	3·84
Unawareness	32 (64·0)	18 (36·0)	50 (100·0)	SS
Confidence in MDT				
Yes	221 (78·6)	60 (21·4)	281 (100·0)	7·71
No	57 (64·0)	32 (36·0)	89 (100·0)	HS
Total	278 (75·1)	92 (24·9)	370 (100·0)	—

Numbers in parentheses are percentages. *NS: $p > 0{\cdot}05$; SS: $p < 0{\cdot}05$; HS: $p < 0{\cdot}01$.

and more MB–MDT patients (30·4%) had problems than PB–MDT patients (10·7%) ($\chi^2 = 16{\cdot}6$, $p < 0{\cdot}001$). Of 78 MB–MDT patients with problems, for about 50% had the biggest problem was skin discoloration due to clofazimine and for 25% the biggest problem was the length of treatment. However, the vast majority of both MB–MDT (99·6%) and PB–MDT (98·2%) patients could accept or tolerate the present regimen-duration of MDT (Table 2). Among the noncompliant patients, the common reasons contributing to the patients' noncompliance in these areas were their farming activities (70%) and frequent movement from place to place (10%).

As shown in Tables 3 and 4, only 20·2% of family members had a basic knowledge of MDT. Of those who had the knowledge, 60·8% supervised and encouraged their family patient's treatment at home, whereas 42·4% who did not have any knowledge of MDT did so ($\chi^2 = 13{\cdot}1$, $p < 0{\cdot}001$). On the other hand, the supervision and encouragement of family members, mainly from their parents and spouses, significantly increased drug compliance.

Out of 730 PHC workers, 41·0% had a basic knowledge of MDT, 41·0% had an involvement in MDT implementation before and 52·9% had a desire to participate in it in future. As shown in Table 5, VHWs were a group in which fewer workers had knowledge about MDT but more had a desire to participate in MDT implementation in future, as compared with the others except PLWs.

Discussion

It is clear that the introduction of multidrug therapy (MDT) recommended by WHO has

Table 2. Attitudes towards the biggest problem in MDT treatment and the acceptability of the present MDT course

Patients' attitudes	MDT Regimens		Total
	MDT–MB	MDT–PB	
The biggest problem			
No problem	179 (69·6)*	101 (89·4)	280 (75·7)
Long MDT course	21 (8·2)	4 (3·5)	25 (6·8)
Discoloration	38 (14·8)	0 (0·0)	38 (10·3)
Other side-effects	12 (4·7)	2 (1·8)	14 (3·7)
Others	7 (2·7)	6 (5·3)	13 (3·5)
	$\chi^2 = 26{\cdot}5,\ p < 0{\cdot}01$		
Present MDT course			
Acceptable	256 (99·6)	111 (98·2)	367 (99·2)
Unacceptable	1 (0·4)	2 (1·8)	3 (0·8)
	$\chi^2 = 1{\cdot}9,\ p > 0{\cdot}05$		
Total	257 (100·0)	113 (100·0)	370 (100·0)

* Numbers in parentheses are percentages.

offered an important opportunity to attain the global elimination of leprosy as a public health problem by the year 2000. However, for the effective implementation of MDT, it is not only the 'therapeutic factors', but also the 'patient factors' and 'service factors' which require consideration.[5] Moreover, the patient factors are often given priority for consideration.[6] This

Table 3. Family members' knowledge of MDT, different family relation and their behaviour to patients' treatment

	Supervising/encouraging patients' treatment		Total
	Yes	No	
MDT knowledge			
Yes	73 (60·8)*	47 (39·2)	120 (100·0)
No	201 (42·4)	273 (57·6)	474 (100·0)
	$\chi^2 = 13{\cdot}1,\ p < 0{\cdot}001$		
Family relation			
Parents	48 (60·0)	32 (40·0)	80 (100·0)
Spouses	130 (60·5)	85 (39·5)	215 (100·0)
Children	58 (34·3)	111 (65·7)	169 (100·0)
Siblings	38 (29·2)	92 (70·8)	130 (100·0)
	$\chi^2 = 48{\cdot}4,\ p < 0{\cdot}001$		
Total	274 (46·1)	320 (53·9)	594 (100·0)

* Numbers in parentheses are percentages.

Table 4. Family members' behaviour to patients' treatment and patients' drug compliance

	Drug compliance		
	Yes	No	Total
Supervising/encouraging patients' treatment			
Yes	239 (87·2)*	35 (12·8)	274 (100·0)
No	245 (76·6)	75 (23·4)	320 (100·0)
	$\chi^2 = 11{\cdot}6, \quad p < 0{\cdot}001$		
Total	484 (81·5)	110 (18·5)	594 (100·0)

* Numbers in parentheses are percentages.

investigation is designed to evaluate the attitudes, beliefs and behaviour of patients and their family members as well as medical workers towards MDT.

Although some patients collected their drugs and were supervised at skin clinics, and even a small number of patients were treated secretly and/or without supervision in order to avoid the social stigma from community to their families, their drug compliance fortunately was not decreased. The patients' drug administration at a fixed time, awareness of the risk of drug default and confidence in MDT had a significant affect on enhancing their drug compliance (Table 1).

As confirmed by this investigation, a very high proportion of MB patients agreed to take MDT in spite of the main problem of skin discoloration due to clofazimine (a constituent of MDT), and the MDT regimen-duration was acceptable to a vast majority of patients, since the benefits of MDT have been very well appreciated.[2] However, patients' behaviour in response to treatment is not only determined by their subjective desire, but influenced by some objective social and environmental factors such as agricultural activities and population migration.[6] As found in this study, 80% of the noncompliant patients believed that their noncompliance was due mainly to their farming activities and/or frequent movement from place to place. It is our experience that some patients in rural areas believe that their

Table 5. Attitudes, beliefs and behaviour of PHC workers towards MDT

Personnel	Number	Knowledge on MDT	Involvement in MDT	Desire to participate
PLWs	137	67 (48·9)*	81 (59·1)	81 (59·1)
PMWs	61	27 (44·3)	24 (39·3)	28 (45·9)
THWs	76	34 (44·7)	13 (17·1)	26 (34·2)
VHWs	343	121 (35·3)	150 (43·7)	199 (58·0)
MHWs	113	50 (44·2)	31 (27·4)	52 (46·0)
χ^2 test	—	$p > 0{\cdot}05$	$p < 0{\cdot}01$	$p < 0{\cdot}01$
Total	730	299 (41·0)	299 (41·0)	386 (52·9)

* Numbers in parentheses are percentages.

agricultural activities, especially the farming activities is more important than their regular MDT treatment.

Family has played an important role in leprosy control. Family members' knowledge about MDT and their relation to the patient within family determine their behaviour towards patient's treatment. Family members who have knowledge of MDT and a closer relation to patients tended to give more supervision and encourage the patients' treatment, which could significantly increase the patients' drug compliance.

The concept of the integration of leprosy case into general health care has been proven worthy to be recommended, based on the consideration that it will lead to much more efficient use of staff, transportation and financial resources.[8,9] At present, the leprosy control project in the investigated areas is mainly run as a semivertical control programme and is in a process of transition towards integration into primary health care. However, from the results of this investigation it must be pointed out that amongst the 730 PHC workers only 41·0% had a basic knowledge about MDT, 41·0% had been involved in MDT work before and only 52·9% had a desire to participate in MDT implementation in future, which meant that in terms of PHC workers the improvement of their knowledge and the motivation of their involvement in MDT should be a prerequisite for the integration of leprosy care.[3] Interestingly, amongst the PHC workers, VHWs were a group which had less knowledge about MDT but more desired to participate in MDT implementation, suggesting that VHWs may be the easier access to PHC workers for the integration.

Conclusion

The conclusion drawn from this investigation is that in order to ensure the effective implementation of MDT and its successful integration into primary health care, the greater emphasis must be given to health education. In addition, the supervision of MDT in farming activities, and the management of MDT must be strengthened. The revelation in this study that only half the PHC workers interviewed had a basic knowledge of MDT and a desire to participate in MDT implementation clearly calls for urgent attention.

Acknowledgments

This investigation was generously supported by the Ciba-Geigy Leprosy Fund. We wish to thank our leprosy field workers, PHC workers, leprosy patients and their family members who contributed to this investigation. We also thank Mrs Jin Yi for her secretarial help in data and manuscript preparation.

References

[1] WHO. Chemotherapy of leprosy for control programmes. Report of a WHO Study Group. Technical Report Series 675. World Health Organization, Geneva, 1982.
[2] Noordeen SK. Eliminating leprosy as a public health problem; why the optimism is justified. *Int J Lepr*, 1995; **63:** 559.
[3] Feenstra P. Needs and prospects for epidemiological tools in leprosy control. *Lepr Rev*, 1992; **63 (suppl):** 3s–10s.
[4] WHO. Risk of relapse in leprosy. WHO/CTD/LEP/94.1 The Leprosy Unit, Division of Control of Tropical Diseases, WHO, Geneva, Switzerland.

[5] Premkumar R and Dave SL. Impact of multidrug therapy on health personnel in their level of job satisfaction. *Indian J Lepr*, 1993; **65:** 429–438.
[6] Gilbody JS. Impact of MDT on the treatment and control of leprosy. *Int J Lepr*, 1991; **59:** 458–478.
[7] Hertroijs AR. A study of some factors affecting the attendance of patients in a leprosy control scheme. *Int J Lepr*, 1974; **42:** 419–438.
[8] Haydar, AH. Leprosy control in a primary health care programme in the Sudan. *Lepr Rev*, 1982; **53:** 175.
[9] Nkinda SJ. Leprosy and primary health care: Tanzania. *Lepr Rev*, 1982; **53:** 165–173.

Lepr Rev (1997) **68,** 162–166

CASE REPORT

Relapse in a borderline–tuberculoid case of leprosy 5 years after the release from rifampicin monotherapy

V. P. SHETTY & N. H. ANTIA
The Foundation for Medical Research, 84-A, R. G. Thadani Marg, Worli, Bombay 400 018, India

Accepted for publication 5 February 1997

Introduction

Paucibacillary cases of leprosy are now routinely being treated with two drugs, namely rifampicin (RFP) and diamino diphenyl sulphone (DDS). We report here a paucibacillary case of borderline–tuberculoid (BT) leprosy, who had taken a one-year course of daily RFP monotherapy, and relapsed as BT five years after the release from treatment. *Mycobacterium leprae* derived from this case was sensitive to both 0·01 g% DDS and 0·03 g% RFP.

Case report

A 67-year-old unmarried female was referred to us complaining of the reappearance and increase in size of an old patch on the dorsum of her left leg. The history goes as follows.

In the year 1981 she noticed a coin-sized patch on the dorsum of the left leg. In 1983 she was diagnosed as having leprosy, was smear negative and was put on DDS and RFP. She developed a severe allergy to dapsone and this was withdrawn within a week, and she was maintained on RFP alone. The patient continued with daily 600 mg RFP for one full year. She was fair skinned and was unwilling to take clofazimine as advised by the referring doctor. The patch subsided completely and the patient remained symptom free till 1989. In that year the patch reappeared, remained static till around 1992, and slowly increased in size thereafter. Upto April 1995 the patient only used a local antihistamine ointment.

On examination the old patch had increased three-fold in size, and was well defined, erythematous and anaesthetic. The left sural nerve was palpably thick and slightly tender. There was no other apparent patch or nerve involvement. Lepromin given at this stage was reading 4·9 mm at three weeks.

Investigations

The skin patch and the sural nerve were biopsied under local anaesthesia. Part of both skin and nerve were fixed in Formal Zenker and processed for histology. Other portions of the

 0305-7518/97/068162+05 $1.00

biopsies were homogenized for bacterial count and injected into the footpads of normal Swiss white (SW) mice. Tests for sensitivity to 0·01 g% DDS and 0·03 g% RFP were set up along with a control group of mice using the standard protocol.[1]

Part of the nerve biopsy was also fixed in glutaraldehyde and processed for electron microscopy.

Results

HISTOPATHOLOGY

Skin: The skin patch biopsy sections stained with Trichrome modified Fite Faracco (TRIFF) showed flattened retepegs and normal keratinization. In the superficial dermis and around the adnexa a moderate degree of loosely arranged oedematous infiltrate consisting of epitheloid cells and scattered lymphocytes was seen. One deep dermal nerve was replaced by epitheloid cells. No acid-fast bacilli were detected in the section.

Nerve: In the TRIFF-stained section, there were multiple fascicles and two of them were grossly infiltrated. The infiltrate was more organized, in which epitheloid cells were seen surrounded by a moderate number of lymphocytes in the endoneurium.

Araldite-embedded 1-μ thick section of nerve (TS) stained with toluidine blue showed six fascicles, of which three were partially involved. Active epitheloid type macrophages surrounded by lymphocytes, a few plasma cells and mast cells were seen in the endoneurium. The infiltrated area showed severe fibre dropout (see Figure 1).

Ultrathin sections stained with uranyl acetate and lead citrate were scanned using a transmission electron microscope. The presence of a fair number of bacteria, either singly or in small clusters were seen predominantly in the nonmyelinated fibre Schwann cells (Figure 2) in all the three involved fascicles. Both skin and nerve pathology were thus consistent with a borderline–tuberculoid type of lesion.

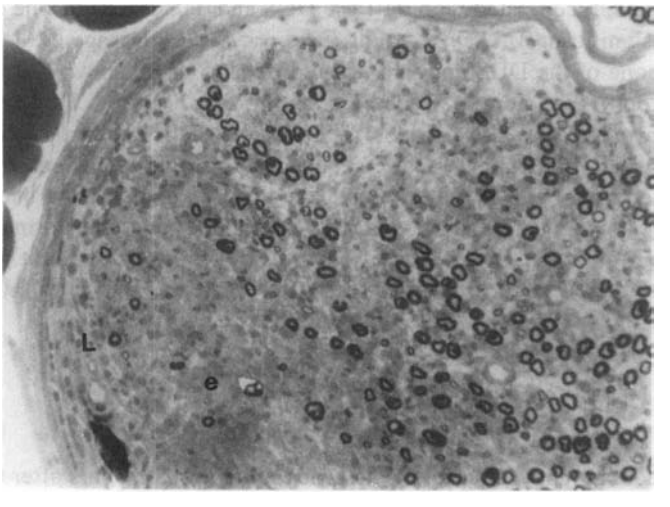

Figure 1. Part of one of the involved fascicles of the sural nerve in T.S. showing drop out of myelinated fibres in the infiltrated area. Note the presence of epitheloid cells (e) and lymphocytes (L) in the periphery of the lesion. Araldite embedded one-micron-thick section stained with toluidine blue ×120.

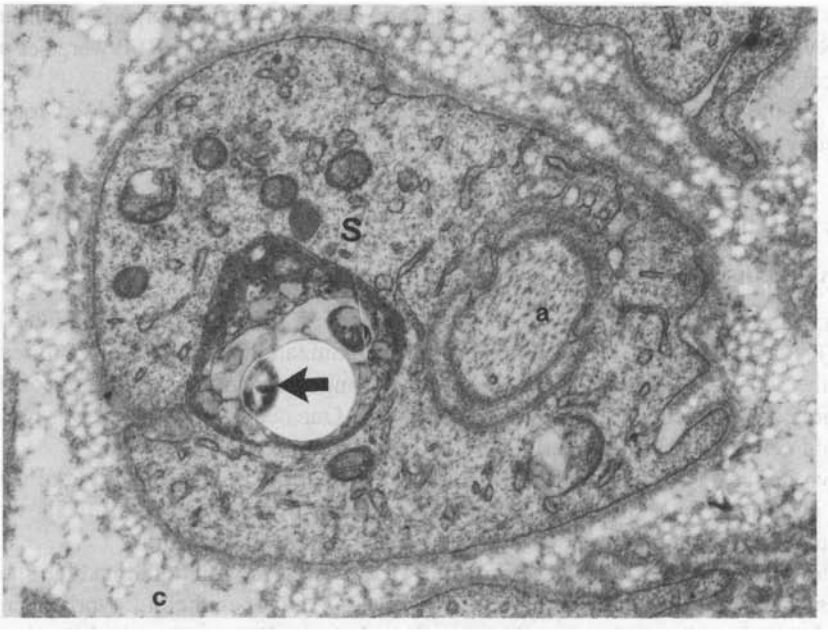

Figure 2. Part of the nerve shown in Figure 1 under the electron microscope. Note the presence of bacillus (→) within a phagosome in the Schwann-cell cytoplasm(s). a, axon; c, collagen; ×, 16,000.

Bacterial load in skin and nerve, viability and sensitivity to drugs

Skin biopsy homogenate showed no detectable *M. leprae* count in over 200 fields on a spot slide. Multiple harvests were carried out at 12 months after the footpad inoculation from both control (No Rx) and mice treated with 0·01 g% DDS and 0·03 g% RFP. The control group of mice showed a significant *M. leprae* count (take = 5/7 and average *M. leprae* count was 6×10^5), while none of the DDS and RFP treated mice (5 each) showed any count.

The nerve biopsy homogenate yielded a count of '1×10^6 g/wt'. However, it was noted that the bacteria were very weakly acid fast (stained with Ziehl Neelsen's cold method). Both skin and nerve biopsy homogenates were streaked onto Lowenstein Jensen media and soft agar plate, showed no growth in either, thus excluding any contaminant bacteria.

Nerve biopsy homogenate that was injected into the footpads of normal SW mice also showed *M. leprae* multiplication in all the six control mice (average count was 2×10^6) and none in the drug treated mice (5 each), proving to be sensitive to both 0·01 g% DDS and 0·03 g% RFP.

Discussion

This is a paucibacillary case of leprosy who probably relapsed 5 years after the release from RFP monotherapy and remained untreated for the following 5 years. It is noteworthy that the reactivation of the old skin lesion occurred 5 years after release from treatment, remained static for another 3 years and then increased in size. Histopathology of both skin patch and

involved sural nerve, obtained 7 years after the first sign of reactivation, confirmed borderline–tuberculoid leprosy.

The first question that arises is, could it be a case of reinfection? Circumstances of relapse in this case, that is the reactivation followed by increase in size of the old lesion and the patients very sedentary life style for the past 10 years are strongly in favour of relapse due to persisters and as such this may not be an isolated incidence.

Persistence of viable bacteria in this case could be attributed to the inappropriate treatment regimen, i.e. use of RFP monotherapy. This indicates that one year of 600 mg daily RFP failed to eliminate a bacterial load of approximately less than 10^6. Since *M. leprae* when tested were sensitive to RFP, it appears that the RFP failed to act on nondividing bacilli and it may be that the addition of a bacteriostatic drug such as DDS may also prove counterproductive.

It was interesting to note that even though the skin patch did not show any bacilli either in the histology or in the homogenate, a significant yield was obtained in the footpad of normal SW mice at the 12th month, albeit delayed and lower than the one obtained with the nerve homogenate, thus demonstrating that the skin lesion also harboured viable bacteria, either in a very small number or they were nonacid-fast.[2] The second explanation derives further support from the observation made on the nerve homogenate of this patient, where the bacilli were found to be very weakly acid fast, to the extent that we ourselves initially thought that they might be contaminant bacteria. However, lack of growth in the LJ slope and on soft agar plating, confirmation using electron microscopy of the presence of bacilli in the Schwann-cell cytoplasm, which remains a unique characteristic of *M. leprae*,[3] and the subsequent growth in the footpad of the mouse confirm all the characteristics of *M. leprae* and indicate that these were viable in both the skin and nerve lesions of this patient.

Another point that needs to be reiterated is that the clinical findings or even the histopathology of the skin would have led to a wrong conclusion of late reversal reaction.[4,5] Even though the time course favours relapse, in the absence of any demonstrable acid-fast organism very often such cases are considered for steroid therapy without the coverage of antileprosy treatment.[6] The mouse footpad results obtained in the present study is strongly in support of the view held by a few that when there is any evidence of deteriorating neural symptoms, it is very likely a case of relapse.[7] In the present case the sural nerve probably acted as a bacterial repository.

Treatment and progress: Following the biopsy the patient was put on ofloxacin—450 mg (BD) and rifampicin 450 mg (OD) for one month followed by RFP (OD) for 6 months. The response remains good up till now.

Acknowledgments

We thank Dr Swaran Arora of Tata Department of Plastic Surgery, J. J. Group of Hospitals, Bombay, for referring the patient, Dr Satish Arolkar for doing the biopsy and Ms Anju Dighe for technical assistance.

References

[1] World Health Organization, 1987, *Laboratory techniques for leprosy.*

[2] Barros U, Shetty VP, Antia NH. Demonstration of *M. leprae* antigen in nerves of tuberculoid leprosy. *Acta Neuropathol* 1987; **73:** 387–392.

[3] Antia NH. Leprosy—A disease of the Schwann cell. *Ind J Lepr* 1982; **54:** 593–604.
[4] Panikar V, Jesudasan K, Vijayakumaran P, Christian M. Relapse or late reversal reaction. *Int J Lepr* 1989; **57:** 526–528.
[5] Ramachandran R, Seshadri PS. Relapse or reversal reaction: The case for a therapeutic trial of steroids. *Lepr Rev* 1988; **59:** 271–272.
[6] Pfaltzgraff RE. Management of reactions in leprosy. *Int J Lepr* 1983; **57:** 103–109.
[7] Kesava Reddy P, Cherian A. Relapse in leprosy after multi drug therapy and its differential diagnosis with reversal reaction. *Ind J Lepr* 1991; **63(1):** 61–69.

Lepr Rev (1997) **68,** 167–172

CASE REPORT

Transepidermal elimination of lepromatous granuloma: a mechanism for mass transport of viable bacilli

M. NAMISATO*†, M. KAKUTA*†, K. KAWATSU‡, A. OBARA§, S. IZUMI‡ & H. OGAWA†
**National Hospital Tama-Zenshoen, Aoba-cho 4-1-1, Higashimurayama-shi, Tokyo 189, Japan;*
†Department of Dermatology, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo, Japan;
‡National Institute for Leprosy Research, Tokyo, Japan;
§Department of Dermatology, Kyoto University Hospital, Kyoto, Japan

Accepted for publication 7 October 1996

Summary A 35-year-old male with lepromatous leprosy showed significant progression of the disease on initial examination. Along with typical lepromatous skin lesions, many scar-forming lesions were present, mainly on his extremities. Some lesions showed erosive surfaces. From clinicopathological findings, these lesions were suspected to be due to the partial excretion of intradermal lepromatous granulomata by 'transepidermal elimination'. Increased local volume, which might be due mainly to rapidly growing lepromatous infiltration before chemotherapy, is suspected of triggering this phenomenon. There is no doubt that many fresh *Mycobacterium leprae* were included in these excretions. After the initiation of chemotherapy, no new scar-forming lesions were observed.

Introduction

The details of transmission of leprosy are not clear, but the main portals of exit for *Mycobacterium leprae* (*M. leprae*) are generally assumed to be the skin and nasal mucosa. It is well known that a large quantity of *M. leprae* can be secreted from the nasal mucosa of patients with the lepromatous type of leprosy (LL).[1] Although *M. leprae* are found in the epidermis and desquamating epithelium,[2] the amount of these bacilli is considered to be very small from an infectious point of view. LL patients have a larger number of bacilli deep in the dermis; however, without skin ulcers or breakdowns, it might be difficult to detect these bacilli in large quantity on skin surfaces.[3] We recently encountered scar-forming lesions on the limbs of an LL patient, and many fresh *M. leprae* were suspected of being excreted through these lesions. *M. leprae* can maintain prolonged viability under many different environmental conditions.[4] From an epidemiological perspective, we should pay particular

0305-7518/97/068167+06 $1.00

attention to skin lesions of leprosy patients, especially untreated active LL cases, and consider these lesions as one of the possible sources of infection.

Case report

The patient was a 35-year-old male of Japanese origin who was born and raised in Paraguay until the age of 29. No leprosy was reported in his family history.

He consulted a local hospital with many asymptomatic skin lesions that had persisted for about 1 year. On this initial examination, numerous pea-sized intradermal nodules, coexisting with slightly red papules, were noticed mainly on his extremities and buttocks. At the same time, disseminated scar-forming lesions were also noticed. Some of these had erosive surfaces. The biopsy specimens of the intradermal nodule and scar-forming lesion showed many rod-shaped bacilli on Fite's staining. Soon after the diagnosis of leprosy was established, 200 mg/day of minocycline was administered. Thereafter, the patient was referred and admitted to the National Hospital Tama-Zenshoen. When we first examined his condition, 2 weeks after the initial examination, he had massively infiltrated earlobes and swollen digits as well as many nodules and papules, but no sign of madarosis. Skin smears from these areas showed that the BI was 5~3+ and the MI was 10~5%. On his trunk, diffuse obscure erythematous lesions were noted with a BI of 2+~0. Histological findings of the papules and intradermal nodules disclosed typical lepromata. Based on all these findings, the patient was diagnosed with actively progressing LL.

Scar-forming lesions measuring 8~15 mm in diameter were seen mainly on the lateral aspects of the extremities, especially the distal extremities to the elbows or knees. Most lesions were composed of slightly red circular papules with atrophic hypopigmented central

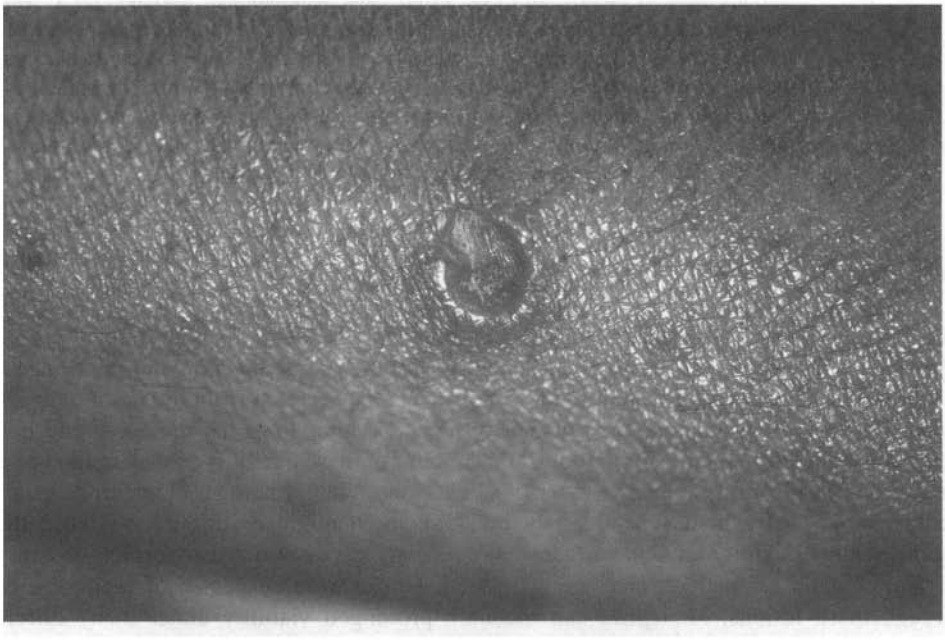

Figure 1. One of the umbilicated, scar-forming lesions on the lower leg.

portions causing umbilication (Figure 1). Some of these had small crusts on the surfaces, but there was no further erosion. About 1 year earlier, the patient had noticed numerous small masses under the skin surface where scars later developed. He said they had gradually moved superficially followed by ulceration of the central portion from which pus-like material discharged. He had experienced no symptoms, and did not find any purpura or bulla-like lesions on his extremities during the whole course of developing these lesions. He also added that he had scratched some of these lesions.

After he was admitted to our hospital, WHO-multidrug therapy (WHO-MDT)[5] for multibacillary leprosy was administered. Two months after the start of chemotherapy, he developed an apparent Type I leprosy reaction (reversal reaction), but it was well controlled by 30 mg/day of prednisolone.

The following month, some of the scars on his extremities were excised for cosmetic reasons. During a one-year follow-up period, no new scar-forming lesion presented, and the central area of each umbilication has become shallower. While continuing MDT, he has returned to society and is currently employed.

Histopathological findings of scar-forming lesions

The biopsy specimen taken at the initial examination and the samples taken 3 months after chemotherapy was started are compared. The observation of longitudinal sections of all these specimens showed one or two residual hair follicles at the slightly protruded marginal areas.

Figure 2 shows the histology of the specimen taken at the initial examination, including

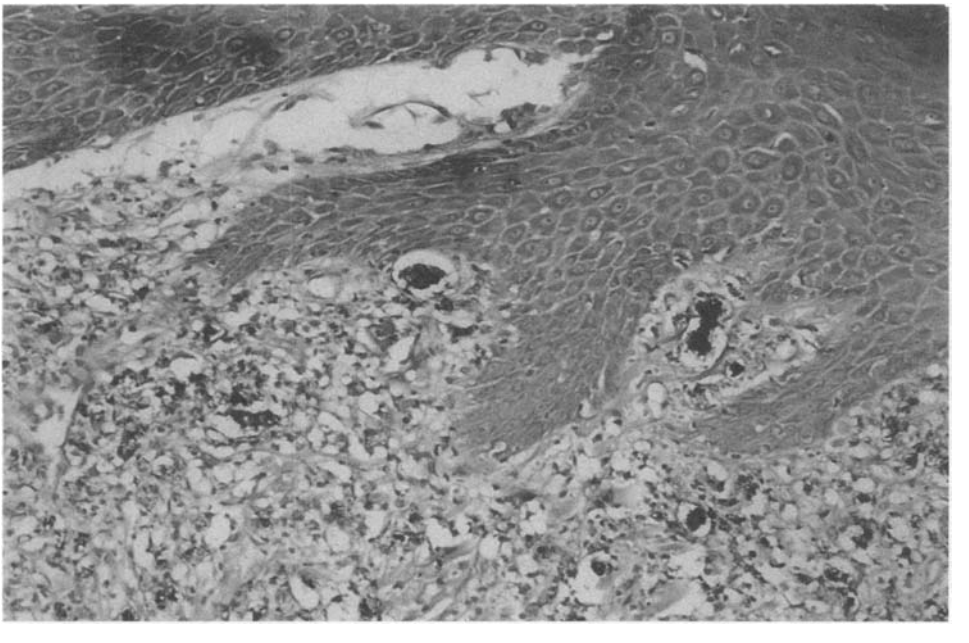

Figure 2. The histology of scar-forming lesion taken at the initial examination shows irregular acanthosis and invading tendency of the epithelium into the intradermal lepromatous granuloma which contains many rod-shaped acid-fast bacilli. (Fite's stain ×100.)

the marginal area (Fite's stain). The follicular and interfollicular epithelium showed irregular acanthosis and tended to invade the dermis in an effort to engulf the intradermal granuloma. Small parts of the granuloma were observed within the hyperplastic epithelium. The dermis was occupied by massive granuloma which consisted of characteristic foamy cells with many acid-fast bacilli (AFB). Most of these AFB were rod-shaped and some formed globi.

Figure 3 shows the histology of one of these lesions taken 3 months after the start of chemotherapy (hematoxylin–eosin stain). The structure of the hair follicle was apparent on each side of this specimen. Neither the epidermal hypertrophy nor the epidermal invasion into the dermis was seen anymore. Around the hair follicle, there was dense lymphocytic infiltration mixed with wasted (devitalized) leprous granuloma in which many granulated AFB were recognized by Fite's stain (not shown). At the flat central area of this specimen, the epidermis is atrophic, and the corium consists mainly of fibrous connective tissue.

Discussion

From the histopathological findings, some parts of intradermal lepromatous granuloma are suspected to have been expelled through the epidermis, and the follicular epithelium is thought to be strongly involved in this process. As a result, many fresh AFB must have been discharged.

Mehregan described the mechanism of eliminating intradermal materials in discussing the pathogenesis of elastosis perforans serpiginosa.[6] According to his description, the

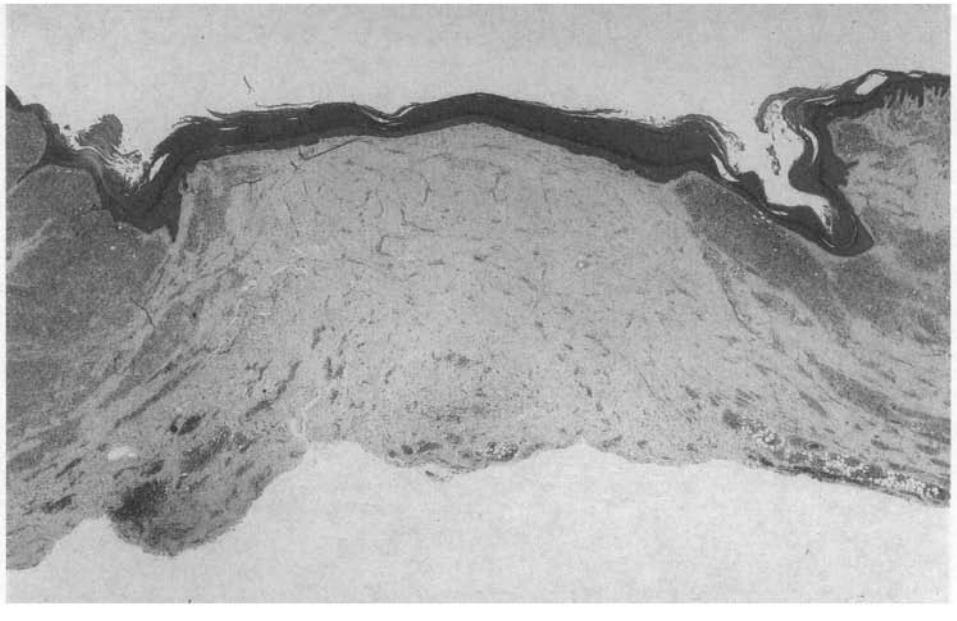

Figure 3. The histology of one of the scars taken at 3 months after chemotherapy shows a structure of hair follicle on each side of this specimen. Around the hair follicle, there is dense lymphocytic infiltration mixed with wasted leprous granuloma. (Hematoxylin-eosin stain ×10.)

phenomenon of 'transepidermal elimination (TEE)' seems to occur with non-irritating material. If the material to be eliminated is small, there is no significant derangement of the epithelium. On the other hand, if the material is composed of larger particles, varying degrees of pseudoepitheliomatous hyperplasia of the epidermis or follicular epithelium may occur in areas of contact with this material. Subsequently the hyperplastic epidermis may engulf the dermal material and eventual elimination may occur. Mehregan *et al.* added reactive perforating collagenosis (RPC) as another model of this phenomenon.[7] In our case, umbilicated clinical features and histologically apparent hypertrophic changes of follicular epithelium engulfing the intradermal granuloma were very similar to that of RPC. To our knowledge, there has been no report of TEE of lepromatous granuloma involving engulfment by hypertrophic follicular epithelium.

The granuloma of LL is unique in that it can stay for a long time without receiving any rejection from the host. Normally, thin fibrous stroma called free zone intervenes between intradermal lepromatous granuloma and epidermis, but hair follicles are tightly surrounded by the granuloma without free zone. In the case discussed, the scars were located mainly on the anterolateral aspect of the extremities and these areas contain many terminal hairs especially in male.

Bayoumi[8] observed the phenomenon of TEE using animal models and proved that follicular epithelium was more actively involved in this process. This case suggests that the terminal hair follicles which survived against invading lepromatous infiltration played a role in this phenomenon.

On his first visit, the patient's condition was highly progressive as shown by many rod-shaped AFB. So the lepromatous infiltration might have been rapidly increasing in size until chemotherapy was started. Meanwhile, it is well known that LL cases can manifest Type II leprosy reaction even before the commencement of chemotherapy. One of the characteristics of leprosy reactions, including Type II reaction, is acute oedematous infiltration which becomes apparent in each local lesion. Rapidly increasing local volume caused by these conditions may stimulate follicular epithelium and trigger subsequent phenomenon.

Based on the fact that we could not find any erosive lesion when we first examined the patient, two weeks of chemotherapy seemed to be able to suppress this phenomenon. After MDT was started, even during the period of reversal reaction, there was no erosion of these lesions.

We should also discuss the superficial trauma which is most likely to precipitate skin lesions of RPC.[7] Trivial traumas resulting from scratching the lesions might have contributed to this phenomenon to some extent.

Malak & Kurban[9] summarized the excretory function of the epidermis proposing the term 'catharsis'. They postulated that this mechanism could be observed in a variety of skin lesions and the close dermoepidermal interactions should have an important role in this mechanism. As one of the dermal factors which can influence this mechanism, they mentioned macrophages. Recently, there was a report about cutaneous leishmaniasis,[10] which showed transepidermal elimination of causative parasites (Leishmania amastigotes) in large quantity.

It is interesting that both of cutaneous leishmaniasis and leprosy are considered to be deeply related to the dysfunction of dermal macrophages.

Acknowledgment

We are grateful to Dr Y. Fujita of Yamato City Hospital for his significant contribution to the preparation of pathological specimens for this case.

References

[1] Pedley JC. The nasal mucus in leprosy. *Lepr Rev*, 1973; **44:** 33–35.
[2] Okada S, Kimura J, Nishiura M. *Mycobacterium leprae* found in epidermal cells by electron microscopy. *Int J Lepr*, 1978; **46:** 30–34.
[3] Pedley JC. Composit skin contact smears: a method of demonstrating non-emergence of *Mycobacterium leprae* from intact lepromatous skin. *Lepr Rev*, 1970; **41:** 31–43.
[4] Desikan KV, Sreevatsa. Extended studies on the viability of M.L. outside the human body. *Lepr Rev*, 1995; **66:** 287–295.
[5] WHO. Chemotherapy of leprosy for control programmes. *WHO Technical Report Series No. 675*, 1982.
[6] Mehregan AH. Elastosis perforans serpiginosa. *Arch Derm*, 1968; **97:** 381–393.
[7] Mehregan AH, Schwartz OD, Livingood CS. Reactive perforating collagenosis. *Arch Derm*, 1967; **96:** 277–282.
[8] Bayoumi AHM, Gaskell S, Marks R. Development of a model for transepidermal elimination. *Brit J Derm*, 1978; **99:** 611–620.
[9] Malak JA, Kurban AK. 'Catharsis': an excretory function of the epidermis. *Brit J Derm*, 1971; **84:** 516–522.
[10] Azadeh B, Abdulla F. Transepidermal elimination in cutaneous leishmaniasis. *Acta Derm Venereol* (*Stockh*), 1994; **75:** 159.

Lepr Rev (1997) **68,** 173–174

CASE REPORT

Ulnar abscess: 4 months after release from control with paucibacillary–multidrug therapy

ERIN JUSTUS DARIUS, ABRAHAM SELVASEKAR, MOZHI N. MANI & K. JESUDASAN
Schieffelin Leprosy Research & Training Centre, Karigiri, PO-632 106, North Arcot Ambedkar District, Tamil Nadu, India

Accepted for publication 16 December 1997

A 14-year-old girl was diagnosed as having borderline–tuberculoid leprosy. Paucibacillary multidrug (PB-MDT) was started and she completed treatment in 6 months. During the period after release from treatment (RFT) there were no complaints. Two years after (RFT) she was released from control (RFC). Four months after RFC she presented with swelling in the left hand above the elbow of 15-days duration.

There was a history of fever from the onset of swelling, and of pain at the site of swelling.

The swelling was situated on the medial side of the left arm 4 cm above the left elbow. There was no pulsation seen. On palpation the skin over the swelling was warmer compared with the surrounding skin. It was tender and the consistency soft. It was not fixed to the overlying skin or underlying structures, and movable more freely horizontally than vertically.

There was loss of sensation over the little finger and motor weakness of the abductor digiti minimi, apponens digiti minimi and flexor digiti minimi. A skin smear was negative. A diagnosis of ulnar nerve abscess was made and steroids were started, with prednisolone 30 mg once a day.

The patient improved within a week and the fever and pain reduced. Thirty milligrammes of steroids were given for 2 weeks, 20 mg for 2 weeks, 10 mg for 2 weeks, 5 mg for 4 weeks, and 5 mg on alternate days for 4 weeks. The nerve abscess responded well to steroids and at the end of the 14th week the swelling was less than 3 mm in size. Surgical intervention was thus not necessary, and motor power had also improved.

In this case because the abscess was treated initially with steroids the need for surgical intervention was prevented. Thus the use of steroids is a useful means to treat nerve abscesses and should be tried before surgical intervention.

Discussion

The cold abscess type of nerve lesions in leprosy are usually associated with neural or tuberculoid cases and is caused by liquefaction of the caseous nerve lesions. Lepra reactions are one of the main causes of abscess formation.

It is recognized that in BT and TT leprosy, caseation necrosis occurs in major nerve trunks

0305-7518/97/068173+02 $01·00

as well as on occasion in the skin.[1] It is probable that caseous necrosis occurring in leprosy is due to delayed-type hypersensitivity reaction and is directed to antigens of *Mycobacterium leprae* (1).

History and clinical presentation of the problem is more in favour of a localized nerve pathology probably a 'segmental necrotizing granulomatous neuritis'. There seems to be a predilection in the occurrence of ulnar nerve abscess in the right side,[1] 3–4 inches above the elbow joint.[1,2] In this case the swelling reduced to the size of a 3-mm nodule with steroid therapy. When the swelling had reduced, it was found to originate from the ulnar nerve. This implies that the pathology is from the ulnar nerve. The condition which commonly masquerades as nerve abscess in leprosy is semi-membraneous cysts.[3] The usefulness of steroid therapy in the treatment of leprosy nerve abscess is demonstrated in this case report.

Acknowledgment

We wish to thank Mr C. Lewis Kumar, Mr J. D. Raja Samuel, and Miss Helen Jothy for secretarial help.

References

[1] Chandi SM, Chacko CJG, Fritschi EP & Job CK. Segmental necrotizing granulomatous neuritis of leprosy. (SNGN) *Int. J. Lepr.* 1980; **48:** 41–47.
[2] Lowe John. Nerve abscess in leprosy. *Ind. Med. Gaz*, 1929; **64:** 24–25.
[3] Roy AT. A patient with semimembraneous cyst in leprosy simulating nerve abscess. *Lepr. Rev.* 1966. **37:** 45–46.

Lepr Rev (1997) **68,** 175–176

Obituaries

R. V. WARDEKAR, 1913–1996

Dr R. V. Wardekar, an eminent leprologist and Founder-director of Gandhi Memorial Leprosy passed away on 1 August 1996 at the age of 83.

Dr Wardekar was born in Pune on 27 October 1913. He had his earlier education in Pune and Baroda and took his medical degree (MBBS) in Bombay in 1940. Subsequently he took a postgraduate degree (MD) in pathology, also at Bombay University. Dr Wardekar was one of the very few qualified pathologists with an MD degree at that time. He taught pathology for a brief period in Grant Medical College, Bombay and then set up a private pathology laboratory.

Dr Wardekar had a very lucrative private practice and he could have had the material pleasures and luxuries in that metropolitian city; but he was made of a different mettle. The professional success and monetary gain did not give him any satisfaction. His values had become quite different, and so one fine morning he took a bold decision. He closed down the laboratory, sold off his car and all other belongings, and left for Wardha, where Gandhi had his 'Ashram' in Sevagram, and where he found mental peace. Gandhi's personal physician, Dr Sushila Nayar, had started a small rural hospital in Sevagram. Dr Wardekar took over the supervision of the hospital and also the health work in the surrounding villages. His great innovation was the system of health insurance—the villages paid the small insurance premium in kind with produce and in return had subsidized or free medical aid.

When Gandhi died, a memorial trust was formed and a part of the funds collected was set apart for leprosy relief work, because Gandhi had a great compassion for leprosy sufferers. (In fact when Dr Cochrane met him and told him about the need to help the leprosy cause, Gandhi is said to have remarked, 'You are trying to convert the converted'.) A committee was formed to take up leprosy work and Dr Wardekar was made the Secretary. This led to the establishment of the Gandhi Memorial Leprosy Foundation (GMLF) at Wardha in 1951.

At that time, leprosy work consisted of caring for the victims of leprosy in leprosaries or assylums on purely humanitairan grounds. Dr Wardekar decided to give a new trend to the work of GMLF. He planned to control leprosy by chemotherapy, with the newly-available drug, dapsone. He also used a public health approach with workers going into the community, spreading proper information about leprosy, detecting all cases and treating them, thereby removing the source of infection, was the strategy he adopted. I had the privilege of joining Dr Wardekar at that stage and working with the new strategy. At first this type of work was not accepted and was much opposed by existing workers but soon the rationale and results proved its worth. The Government of India accepted the method as the national policy for leprosy control. It is now the strategy followed all over the world, and the credit of initiating it goes to Dr Wardekar.

Dr Wardekar took a major role in the national leprosy control programme of the Government as consultant and guide. The Gandhi Memorial Leprosy Foundation grew to

0305-7518/97/068175+02 $1.00

have great prominence under his direction. The training of paramedical workers was first started at GMLF. Special importance was given to health education and methods of health education were demonstrated. In later years, social science research was established in GMLF.

With the death of Dr Wardekar, India has lost a pioneer in the fight against leprosy. He is survived by his wife, also a medical doctor, who was his constant companion, putting up with any personal inconvenience to help him in the great task.

K. V. DESIKAN

MICHAEL G. CORCOS, MRCS, LRCP, DTM&H
1919–1996

From his earliest days as a young medical officer working for the Colonial Service in Nigeria and Trinidad, my father was dissatisfied with the scientific dogma of the day, that ''Leprosy is caused by *Mycobacterium leprae*''. He saw that an uncritical acceptance of this assumption not only perpetuates fear of the disease and discrimination against sufferers, but effectively stifles scientific enquiry into its pathogenesis. His enjoining of the battle for a rational nomenclature of Hansen's Disease (to have done away forever with the stigmatizing ''lepr' prefix) was central to his search for the scientific truth about the cause of the condition. To him, these were not separate fields of endeavour. He was always aware of the clinical implications inherent in the usage of medical and scientific terminology, and he never flinched from seeking the truth and living it for the benefit of his patients. This sometimes aroused discomfort in less open-minded authorities and at times cost my father much in personal hardship.

Through his own research and reading, my father sought to understand some of the seeming paradoxes of Hansen's Disease. He once said that as a child he loved to lie on the grass, look down into it and imagine himself to be infinitesimally small. (He was not the first scientist to have carried out thought experiments like this. . . .). He thought that one way to explain the many otherwise paradoxical findings in Hansen's Disease would be to allow for Hansen's bacillus to harbour within it a DNA plasmid, capable of autonomous existence and pathogenicity.

His hypothesis was first published in 1982. Since then, research in the fields of molecular biology and genetics have borne out the existence and operation in nature of phenomena that he deduced through reading and contemplation. His work shows that arriving at scientific truth need not be an exclusive preserve of the 'experts'. My father worked without the advantages of a highly equipped laboratory, a team of technicians and thousands of dollars in research grants. As well as in *Leprosy Review*' he has had papers and correspondence published in *Transactions of the Royal Society of Tropical Medicine and Hygiene*, the *International Journal of Leprosy*, *The Lancet*, *New Scientist* and *The Star*. His writings will serve as a permanent reminder of that curiosity, originality, courage, discipline, respect, humility and humour that characterized his work as a clinician, his fellowship of the church and his relationship with his family.

I shall remember my father as a quiet, gentle and loving man who was passionate in the pursuit of truth, brilliant in his thinking with a delightful sense of the ironic, a man who puts others' wellbeing ahead of his own. The common theme was what C. S. Lewis called 'Grace'; a level of spiritual development, of relatedness to God, that few of us attain. We will all miss him.

C. D. CORCOS

Lepr Rev (1997) **68,** 177–180

Letters to the Editor

NEED FOR INTENSIVE LEPROSY CASE FINDING FOR THE ELIMINATION OF LEPROSY

Sir,

As a result of successful implementation of the multidrug therapy (MDT) programme, the registered prevalence rate (PR) of leprosy has shown more than a 70% decline under the National Leprosy Eradication Programme in India.[1] However, the new case detection rate (NCDR) has not shown a significant decline though several factors influence the interpretation of this rate. Similar observations are also made in urban situations like Bombay.[2] A marked fall in registered cases has led to complacency in case-finding activities in the leprosy control programmes. To study the true levels of occurrence of new cases during low endemicity, intensified active case detection was undertaken in a statistically drawn sample population in the Bombay Leprosy Project (BLP) field area in Bombay during 1989, and 1991 in the Wardha district in Maharashtra in 1991 by group survey methods. MDT was introduced in both these areas by 1982. The case-detection rates calculated after the group surveys were compared with case-detection rates reported by the leprosy control programmes.

The registered prevalence rate showed a steady decline in BLP from 17 per 10,000 population in 1982 to 9 per 10,000 population in 1989 and to 5 per 10,000 population in 1991. The registered prevalence rate in Wardha district also showed a steady decline from 120 per 10,000 population in 1982 to 13 per 10,000 population in 1991. However, the new case-detection rate was ranging between 4 and 5 in BLP area and 16 and 32 per 10,000 population in Wardha district. Intensified case-finding activities

Table 1. New case-detection rate

	Bombay 1989	Leprosy Project 1991	Wardha 1991
Intensive case finding			
Population examined	32,101	21,626	70,96
New cases detected	118	82	165
MB (smear + ve)	2	2	8
Total NCDR/10,000, population	37	38	60
NCDR of smear positive MB cases/10,000 population	0·6	0·9	1·1
Reported case-detection rate by the programme			
Total NCDR/10,000	6	3	21
NCDR of smear positive MB cases/10,000 population	0·1	0·2	0·2

showed that NCDR was significantly higher than reported figures including the multibacillary leprosy (smear positive) case-detection rate.

These findings indicate that intensive case-finding to identify hidden leprosy cases with special emphasis on smear positive cases should be attempted at regular intervals, even though the prevalence rate shows a marked decline, in order to reduce transmission of the disease and to reach a realistic level of prevalence before declaring disease elimination as a public health problem. It is suggested that in addition to the criteria laid down for elimination of leprosy, i.e. prevalence rate of less than 1 per 10,000, new case detection rate of less than 1 case per 100,000 population could be considered.

(This brief communication is prepared based on the paper presented at the 19th Biennial Conference of Indian Association of Leprologists, Pune 1995.)

Bombay Leprosy Project
Vidnyan Bhavan
11 VN Purav Marg
Sion-Chunabhatti
Mumbai 400 022, India

C. R. REVANKAR, M. S. ANTONY SAMY, K. L. GANDEWARR & GANAPATI

District Leprosy Unit
Wardha, Maharashtra
India

P. S. BHUSARI

References

[1] Peat M, Brolin L, Ganapati R, McDougall AC, Revankar CR & Watson JW. An Evaluation of the Contribution of the Swedish International Development Authority (SIDA) to Leprosy Control in India based on the Implementation of Multiple Drug Therapy (MDT) 1981–1983. *Ind J Lepr*, 1995; **67:** 447–465.

[2] Revankar CR, Pai RR, Girija D, Deshpande SS, Gandewar KL, Pai VV, Hiwase Nirmala & Ganapatti R. Epidemiological changes in an Urban Leprosy Control Project—15 years observations in Bombay. In Abstract book—14th International Leprosy Congress, Orlando, Florida, USA 1993.

AN ASSESSMENT OF PERFORMANCE 'CONTRACT LEPROSY WORKERS' IN A NATIONAL LEPROSY ERADICATION PROGRAMME

Sir,

To hasten multidrug therapy (MDT) coverage in 66 endemic districts with inadequate manpower in Northern India, the National Leprosy Eradication Programme (NLEP) authorities launched a novel scheme involving a category called 'contract leprosy workers', who were offered task-oriented training in leprosy to identify cases and deliver MDT.[1] The initial observations made after 4 to 5 days of task-oriented training to these untrained leprosy workers were reported earlier.[2,3]

To assess the performance of such minimally-trained leprosy workers with simple training methodology, Unnao MDT district in Uttar Pradesh was adopted by the Bombay Leprosy Project under the NLEP/WHO district consultancy services to MDT districts.

Forty contract leprosy workers were managing 40 sectors covering a population of approximately 120,000. Over a period of 18 months (1994–1995), these workers found 4770 suspected leprosy cases through house-to-house surveys. Of these 3138 (66%) were confirmed as leprosy cases (MB : 806; PB : 2332). They were also involved in delivering MDT.

These findings indicate that 4-to 5-days task-oriented training for this category of workers is quite adequate in intensifying leprosy elimination activities, and thereby strengthening the existing programme.

Bombay Leprosy Project
11, V.N. Purav Marg
Chunabhatti, Sion Bombay-400022
India

C. R. REVANKAR, V. V. PAI & R. GANAPATI

District Leprosy Unit
Unnao,
Utter Pradesh
India

D. N. PATHAK

References

[1] DGHS. *Annual Meeting of the Voluntary Organizations involved in National Leprosy Eradication.* Programme and State Leprosy Officers, New Delhi, 16–18 November 1993.
[2] Revankar CR, Pai VV, Naik SS, Acharekar MY & Ganapati R. Task oriented short term training to contract leprosy workers in a National Leprosy Eradication Programme. Letter to the Editor, *Lepr Rev*, 1995; **66:** 78–79.
[3] Pai VV, Niak SS, Revankar CR, Ganapati R. Task oriented training to contract leprosy workers in Arunachal Pradesh. *BLP Wall Journal* 1995; **5**.

INDIVIDUAL GOALS AND TRAINING IN LEPROSY: NEED FOR REVISION OF CURRENT STRATEGY

Sir,

I read with great interest Dr A. C. McDougall's apt editorial, ''Training in leprosy—does the current strategy need revision?'' (*Lepr Rev*, 1995, **66:** 88–95). I would however like to stress an aspect which was apparently under-emphasized by the author, i.e. the harmonization of individual goals of leprosy workers with organizational goals as far as leprosy training is concerned.

In a study related to job satisfaction amongst laboratory technicians in six leprosy projects in Nigeria[1], the major reasons for poor job satisfaction compared to that obtained by leprosy control supervisors and doctors, were, in order of frequency: lack of 'recognition'; slow career advancement; and inadequate overseas training. The study revealed that (further) training was of relatively low priority for this group of workers. My experience with other categories of leprosy workers trained over the past 6 years at the National Tuberculosis and Leprosy Training Centre, Nigeria, suggests that the feelings expressed by the leprosy technicians are shared by other groups of leprosy workers.

Most leprosy workers in developing countries apparently seek training mainly to achieve personal goals of 'recognition', (e.g. good credentials, promotion, improved status and financial remuneration), a well-defined and viable career path as well as an opportunity for a dream trip abroad! For as long as opportunities are not created for the realization of some of these personal goals, altruistic organizational goals are unlikely to receive the commitment they warrant no matter how well the leprosy training curriculum has been designed and/or revised.

The following measures may facilitate the realization of the goals of leprosy training in Nigeria:

development of a well-defined and viable path for graduates of the leprosy supervisor's course by, for example, making their certificates tenable for promotion in the Nigerian public service;
provision of incentives like financial rewards and travel fellowships to outstanding leprosy workers in every state of the Federation on a regular basis; and
adoption of a holistic view of training as provided for by the concept of Human Resources Development (HRD)[2]. HRD has been defined as 'organizational learning experiences in a definite time period to

increase the possibility of improving job performance and growth'. Growth is further defined as being both personal and organizational. This may entail (further) training of leprosy workers in areas in which they can positively contribute to leprosy control services and at the same time be ''recognized'' for such contributions, e.g. community empowerment strategies[3].

Acknowledgment

I sincerely thank Dr Pieter Degeling of the School of Health Services Management, University of New South Wales, Australia, for encouraging me to submit this letter.

References

[1] Awofeso N. Inventory of skin smear examination practices in sic leprosy control programmes in Nigeria. *Lepr Rev*, 1993, **64:** 150–156.
[2] Cocioppe R, Warren-Lanford P, Bell L. Trends in human resources development and training. *Asia-Pacific J of Human Resources Managagement*, May 1990, 55–77.
[3] Srinivassan H. Deformities and disabilities—the unfinished agenda in leprosy work. *Lepr Rev* (Editorial), 1995, **66:** 193–200.

NIYI AWOFESO

261 Dickinson House
The Prince Henry Hospital
Little Bay
NSW 2036
Australia

Lepr Rev (1997) **68,** 181–183

Teaching Materials and Services

International course on rehabilitation and prevention of impairment & disability in leprosy, Nepal

From 28 October to 18 November 1996 we conducted the first International Course on Rehabilitation & POID in leprosy at our Green Pastures Training Centre in Pokhara. Twenty experienced professionals from six countries contributed to the course as teachers and facilitators. The contributions made by NSL and the Gastmann-Wichers Stichting to enable respectively Dr Margreet Hogeweg and Dr Wim Brandsma to be teachers on the course, is gratefully acknowledged. The sixteen participants from Nepal and India represented no less than nine nationalities. Their professions varied from medical doctors to social scientists and rehabilitation workers. The multidisciplinary nature of the participant group fulfilled an important aim of the course. As one participant said during the closing ceremony: 'One of the main things I learned during this course is that rehabilitation is team work!'

The curriculum was based on the concepts of the International Classification of Impairments, Disabilities and Handicaps, published by the WHO in 1980. Following an overview of relevant anatomy and (patho)physiology, the course addressed treatment and prevention of impairments, prevention of disabilities and handicaps (the social consequences of impairment or disability), and rehabilitation of people with disability or handicap. This included teaching and practice on nerve function assessment, impairment grading, eye, hand and foot examination, disability assessment, psychological assessment and socioeconomic assessment. Recording, reporting and monitoring and evaluation of POID activities was also covered, using the ILEP guidelines. The teaching programme aimed at knowledge as well as skill acquisition. Half of the available time (56 hours) was therefore spent in practical sessions in the Training Centre, Green Pastures Hospital or Socio-Economic Services Programme.

Throughout the course the participants worked in multidisciplinary groups on a plan for an RPOID programme for their own area of work. These assignments, together with the results of a written exam formed the basis of the course examination. Feedback from participants and facilitators was very positive, indicating that the course met a real need in training in the field of rehabilitation. It was therefore decided to run the RPOID course again in 1997.

Venue: the Green Pastures Training Centre in Pokhara, Nepal
Tentative dates: 10 November–12 December 1997 (5 weeks)
Expected course fees (including board & lodging and field trip): NRs 27,500 (~$500)
Target group: Doctors, physiotherapists, occupational therapists, social workers, managers of RPOID programmes, and senior hospital staff and senior leprosy control staff responsible for RPOID activities. Experience in leprosy work will be an advantage, but is not essential.
Teaching/learning methods: Lectures, group discussion, group assignments, individual assignments, practical work in small groups, problem-based learning, self study, presentations, and simulation exercises. The course is in English.
Further information: The Training Officer, GPTC, P.O. Box 28, Pokhara 33701, Nepal. Tel: 977 61 20342. Fax 977 61 20430; and e-mail: lp@inf.wlink.comp.np.

Appropriate Health Resources and Technologies Action Group (AHRTAG)

The Appropriate Health Resources and Technologies Action Group (AHRTAG) is an international development agency established in 1977 to promote primary health care (PHC) in developing countries.

PHC aims to make health care accessible to everyone. Strategies for PHC include preventative care, community participation, intersectoral co-operation and an equitable distribution of resources.

AHRTAG actively contributes to the PHC effort to improve local health care by:

facilitating the exchange of information and experience by international government and non-government organizations working in health and development;
publishing practical manuals, international newsletters, bibliographics and resource lists;
disseminating such information through its extensive international network of collaborators and partner organizations; and
contributing to local institutional development through technical support and training.

AHRTAG has special interests in AIDS, disability and community-based rehabilitation, diarrhoeal diseases, acute respiratory infections, urban health, primary health care management, and training and health education. It provides a consultancy service to international and nongovernment organizations on information systems and resource centre development

Resource Centre publications

AHRTAG's Resource Centre produces a series of resource lists and directories which are available free or at low cost, including:

Directory of Primary Health Care Resources in and for the Middle East—listing of resources in Arabic and/or adapted for use in the Middle East;
Primary Health Care in Developing Countries—a guide to resources and information in the UK; and
Primary Health Care Courses Directory—long and short courses relating to PHC in the UK.

AHRTAG has also produced a compendium of 'Free and low cost international newsletters and recommended journals on subscription in English. Further enquiries: AHRTAG, Farringdon Point, 29–35 Farringdon Road, London EC1M 3JB, UK. Tel: 44 171 242 0606. Fax: 44 171 242 0041.

Teaching Aids at Low Cost (UK), TALC

TALC continues to produce and distribute a wide range of teaching and learning materials at low cost. The 1977 catalogue (27 pages) contains information on books, slides and accessories, videos and flannelgraphs, mostly intended for use in developing countries and the tropics. The main headings include: medicine; women's health/obstetrics; community health; nutrition and child growth; AIDS education and communication; child health, health care services/management; education and communication; disability, appropriate technology, child-to-child publications, health and pharmacy libraries.

To people working in leprosy, the section on disability given below may be particularly relevant:

Alternative Limb Making: AHRTAG—The manufacture and fitting of low-cost below the knee prostheses. Details of innovative products. Provides technical information and advice. £2.75.
Disabled Village Children: D. Werner—A guide for community health workers, rehabilitation workers and families. A very comprehensive book. English, £9.80 or Spanish, £7.50.
Essential Action to Minimise Disability in Leprosy Patients: J. M. Watson—Written for general medical staff who treat a few leprosy patients. £1.00.
Essentials of Leprosy: J. M. H. Pearson—4th edition. 48 pages which review briefly epidemiology, clinical features, diagnosis, complications, treatment, rehabilitation and control of leprosy. Free.

Hearing and Communication Disorders: S. Wirz & S. Winyard—An invaluable book for community based rehabilitation workers and their trainers. £4.00.
How to Make Simple Disability Aids: AHRTAG—Many illustrations. Minimum text. A revision for Simple Aids for Daily Living. £2.50.
Personal Transport for Disabled People: AHRTAG—Designs from all over the world to encourage the local manufacture of wheelchairs, trolleys and tricycles. £2.00.
Techniques for the Care of Leprosy Patients: J Harris—A 30 page workbook with checklists of 30 important tasks relating to patient care. Free.
We Can Play and Move: AHRTAG—From parent to expert, this book will help disabled children learn to move by playing with others. Well illustrated. £2.50.

Further information and catalogue: TALC, P.O. Box 49, St Albans, Herts AL1 5TX, UK. Tel: 44 1727 853869. Fax: 44 1727 846852.

Recent advances in leprosy, K. K. Koticha, Bombay, India

In October 1990, Dr Koticha's 'Concise Text' on leprosy was published in Bombay and received a wide circulation. It was certainly concise, but also extremely comprehensive and informative, including a formidable collection of no less than 961 references on all aspects of this disease. Now Dr Koticha has produced another publication (paperback, 272 pages), as a Supplement to the original, carrying 582 references spanning the years 1990–1996. These are accompanied in each case by a summary and comments, with expert help from the following; Dr K. Prabhakaran, Carville, USA; Dr U. Sengupta, JALMA, India; Dr V. M. Katoch, JALMA, India; Dr C. K. Job, St Thomas' Hospital and Leprosy Centre, India; Dr B. K. Girdhar, JALMA, India; Dr R. C. Hastings, Carville, USA; and Dr M. D. Gupta, CJIL Field Unit, Avadi, India. This is a tour de force which deserves wide distribution not only in India but elsewhere.

Price: Rs 275 in India, Nepal and Bangladesh only. Elsewhere US$15.00 or UK £10.00, or equivalent, inclusive of packing and postage. Further enquiries: Dr K. K. Koticha, 901 Nand Park, Lokmanya Nagar, 11, Thane-West, India 400 606.

Centre for International Child Health; Teaching Programme 1997–98

This Centre in London offers a number of research degrees and attachments, including MSc in Community Disability Studies (12 months), Diploma Course for Teachers and Planners of Community-Based Rehabilitation in Developing Countries (9 months), short courses for health workers intending to work overseas and management skills for project leaders in developing countries. The CICH resource centre is open between 10 am and 4 pm Monday to Friday and visitors are welcome. Apart from a collection of teaching and learning material on country and subject matters, computerized information is also available on community-based rehabilitation. The entire range of materials produced by Teaching Aids at Low Cost (TALC) can be studied. *Further information*: Continuing Education Office, Institute of Child Health, 30 Guildford Street, London WC1N 1EH. Telephone and Fax: +44 171 829 8692. Email; cont.edu@ich.ucl.ac.uk.

Lepr Rev (1997) **68,** 184–192

News and Notes

Health care for women in India

Under the heading 'India's women get poor deal on health care, says World Bank' the following appeared in the *British Medical Journal*, 1996; **312:** 1627–8:

Girls and women in India below the age of 30 have higher death rates from illness than men in the same age group, says a new report by the World Bank. The report says that the poor health status of women in India is a major cause of India's female deficient sex ratio—927 females for 1000 males in 1991.

Overall loss of healthy life from non-fatal illnesses and pathological conditions is also higher for women than for men, according to the report. It says that cultural factors, gender bias, and inadequate health care are all contributing to women's poor health.

According to the report, women in India experience more episodes of illness than men and are less likely to receive medical treatment before the illness is well advanced. Communicable diseases, maternal and perinatal conditions, and malnutrition account for 68% of death or disabilities among Indian girls and women.

Community-based studies in the country have shown that a high proportion of women receive no treatment at all for their illnesses and that among those who do the most common treatment methods entail self care, home remedies, or traditional medicine.

'Women's relatively low status and the risks associated with reproduction exacerbate what is already an unfavourable overall health situation,' the report says. It says that excess female mortality up to the age of 30 is a 'symptom of bias against females'.

Although there are wide disparities in female morbidity and mortality among different Indian states and between rural and urban areas, the worst affected are the so-called northern belt states of Bihar, Madhya Pradesh, Rajasthan, and Uttar Pradesh.

Drawing on national surveys, hospital records, and community-based studies, the report says that 80% of India's maternal deaths—estimated at 437 per 100,000 live births—result from anaemia, haemorrhage, eclampsia, obstructed labour, infection, or abortion. Although there are big differences in the urban and rural situations, the report estimates that only a quarter of all deliveries take place in health centres.

Anaemia is widespread among Indian women and affects between 50% and 90% of pregnant women. The govenment's anaemia prophylaxis programme, which provides iron and folic acid tablets to pregnant women, is crippled by problems ranging from erratic supply to 'poor and questionable' quality of tablets.

The report says that a lack of staff and facilities is pushing women towards illegal and unsafe abortions (estimated to be at least twice as many as the 600,000 legal abortions each year). Many existing facilities in the rural sector lack qualified specialists, operating theatres, or blood transfusion equipment.

Non-governmental organizations working on women's issues agree that government initiatives to improve women's health need to be strengthened significantly. They say that India's poor and vulnerable are suffering from inadequate government spending on public health, coupled with a growing private health sector.

'Existing government programmes are indeed making a difference, but a lot more can and needs to be done,' says Rebeca Robboy, an external affairs officer for South Asia at the World Bank. The report recommends that the government should expand initiatives to increase adolescent girls' knowledge of health and nutrition.—GANAPATI MUDUR, *Science Writer, New Delhi*

Developing a vaccine for tuberculosis

The following is extracted from an editorial published in the *British Medical Journal*, 1996; **312:** 1495 by Adam S. Malin, Department of Clinical Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT and Dougals B. Young, Department of Medical Microbiology, Imperial College School of Medicine at St Mary's Hospital, London W2 1PG:

Tuberculosis is a disease of superlatives. *Myobacterium tuberculosis* causes more deaths annually than any other infectious agent. Globally, it is one of the major pathogens associated with HIV disease. The tuberculosis vaccine, BCG, has been given to more people than any other vaccine. However, although this vaccine confers clear benefit against disseminated childhood tuberculosis, its efficacy against adult pulmonary disease has varied widely in different clinical trials. Curiously, protection induced by BCG seems to improve with increasing distance from the equator. In a large randomized controlled trial in Madras, southern India, and a large observation study in Malawi, BCG was no better than saline. It would be good to do better.

The reasons for the failure of BCG in adults remain unclear. Indeed, immunity to tuberculosis is poorly understood both at a cellular and molecular level. It is possible that the ability of BCG to protect against initial infection may wane with time. Alternatively, BCG may be unable to prevent the establishment of dormant infection, so giving the potential for reactivation later in adult life. An ideal tuberculosis vaccine would be given at birth as a non-living subunit formulation (with a view to safety and quality control) and would confer lifelong protection. Possible alternative profiles for new vaccines include a 'booster' vaccine that could be given to young adults (a high risk age group), 'transmission blocking' vaccine that would decrease positively in sputum smears, and an 'immunomodulating' or therapeutic vaccine that could be used as an adjunct to shorten current treatment protocols.

In March 1995, at a meeting in Madrid organized by the World Health Organization's global programme for vaccines, groups from the public and private sectors met to discuss a global coordinated programme for developing vaccines. Recent progress in mycobacterial genetics has uncovered exciting new strategies for generating candidate vaccines. Scientists are beginning to understand the molecular basis of attenuation of BCG and other avirulent strains of tuberculosis. This raises the possibility of designing new live vaccines, either by inactivating key genes in *M. tuberculosis* or by adding new genes to BCG. For example, BCG has been constructed to express cytokines designed to enhance its immunogenicity. Another approach is based on developing a subunit vaccine. Vaccination with secreted antigens isolated from *M. tuberculosis* cultures has been shown to confer significant protection against challenge in experimental models.

Alternatively, genes encoding appropriate antigens can be delivered using suitable expression systems or vectors for immunisation. Promising results have been achieved by vaccination with nucleic acid or 'naked DNA', and a range of bacterial or viral vectors is also under consideration. With information from the tuberculosis genome project, currently under way at the Sanger Centre in Cambridgeshire, it is possible to consider screening all the genes of *M. tuberculosis* for vaccine efficacy rather than relying on selection of particular proteins from laboratory cultures.

Formidable problems are likely in moving a vaccine from the laboratory into clinical trials. Protection in animal models cannot be taken as a measure of protection in humans. Seventy years of experience with BCG have shown the difficulty of evaluating a vaccine against tuberculosis. There is clearly a need to identify a short term surrogate marker of potential efficacy. The current Mantoux or Heaf tests based on skin test hypersensitivity do not reflect protection. Attempts are being made to develop new skin tests based on improved antigen preparations or using in vitro assays to assess

protective, cell-mediated immune responses. In the longer term, an ideal trial would involve vaccinating neonates and testing for protection against disease in young adults. However, initial shorter term trials of any new vaccine will probably focus on attempts to boost responses in high risk groups who may already have been exposed to infection or BCG vaccination.

Hansenologia Internationalis: leprosy journal in Portuguese from Brasil

Readers in other parts of the world may not be familiar with this excellent twice-yearly publication from *Instituto Lauro de Souza Lima*, Caixa Postal 62, 17001–970, Bauru, SP, Brasil, edited by Professor Diltor V. A. Opromolla. Although mainly in Portuguese, an English abstract is usually printed with each article. Manuscripts may be submitted in Portuguese, English, Spanish, French or Italian. The latest received (December 1995) includes an interesting editorial by the Editor on the role of nongovernmental organizations in leprosy control in Brasil and an extensive article by Marcos Virmond, Division of Research and Training at the above Institute, on 'Leprosy as a Low Prevalence Disease'. The issue ends with a valuable review of recent publications with summaries in Portuguese and English. This Journal is normally distributed on subscription.

Clinical tuberculosis, Crofton, Horne & Miller, TALC (UK)

This Book is sponsored by the International Union against Tuberculosis and Lung Disease and by TALC. A low cost edition for developing countries has been financially supported by the World Health Organization and other bodies. It is written primarily as a practical guide for busy nonspecialist doctors working in areas with few resources. The language is simple, and there is an extensive glossary. The Book can therefore be useful to health (medical) assistants and senior nurses with a limited knowledge of English. It can also serve as a helpful reference for younger doctors in developed countries who now have less experience of tuberculosis.

The Book covers diagnosis and treatment of all types of tuberculosis, pulmonary and nonpulmonary, both in adults and children. It deals fully with the effects of HIV infection on the disease and describes the essential elements of a National Tuberculosis Control Programme. There are many line drawings and flow charts as aids to training, learning and clinical practice. 'Stories' about individual patients highlight practical points.

The three authors have had many years experience of dealing with tuberculosis and of teaching both undergraduates and postgraduates. They have advised in many countries in Asia, Africa and South America. The final text incorporates constructive comments on an earlier draft by experienced consultants from the IUATLD, WHO and consultants working in several countries in Asia, Africa and the Pacific. The Book therefore represents much collective wisdom.

Recent information from TALC indicates that over 46,000 copies of this Book have been distributed in the 11 languages in which the book originally appeared; these include Chinese, French, Spanish, Portuguese, Thai, Vietnamese, Farsi (Iranian) and Mongolian. A Russian edition has recently been completed, as also Arabic; an Italian one should appear soon and funds are being sought for Urdu and Croatian editions. The level of interest and demand has thus exceeded all expectations and appears to be increasing. The price in developed countries is £10.99, but for most of those mentioned above it is £3.00 per copy. For those with absolutely no access to foreign currency, a free copy may be available, on application to TALC, P.O. Box 49, St Albans, Herts AL1 4AX, United Kingdom.

Minding your health abroad (MASTA)

MASTA, The London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (Tel: 0891 224100), offers information and a wide range of products and equipment for health

protection for people travelling abroad, including the tropics. This includes mosquito repellents, broad spectrum UVA and UVB protection for the skin, anti-malarials, water purifiers, and pumps, mosquito nets for beds and cots. The Blood Care Foundation provides fully screened and tested blood to travellers in countries where this is not readily available. Sterile medical equipment packs, with needles, syringes, dressings etc. are also included.

Global Tuberculosis Programme & Global Programme on Vaccines: statement of BCG revaccination for the prevention of tuberculosis

The following is reproduced from *Weekly Epidemiological Record* (1975) **70,** 229–30:

The Bacillus Calmette-Guerin (BCG) vaccine is derived from a live, attenuated strain of *Myobacterium bovis*. It has been used for the prevention of tuberculosis in humans since 1921 and approximately 3000 million doses have been administered. BCG is the most widely used vaccine in the world; in 172 countries where BCG immunization is given, 85% of infants received BCG in 1993, with average coverage ranging from 62% in Africa to 92% in South-East Asia and the Western Pacific.

The use of BCG vaccine has been controversial for decades, largely owing to disparate results from clinical trials evaluating its efficacy and the debate surrounding these differences. BCG vaccine is routinely administered in developing countries, whereas its usage has been discontinued or has diminished in many industrial countries of Western Europe and North America. There are different policies regarding the use of BCG in different countries and regions of the world, with different vaccine preparations. Where BCG is used, the vaccine is most commonly administered at birth or in the first year of life. In some countries, BCG revaccination is given to children at school entry, and in some regions, especially Eastern Europe, multiple revaccinations have been administered throughout childhood and adolescence. This document is intended to clarify WHO recommendations on BCG revaccination, based on currently available scientific evidence.

Efficacy of BCG vaccines

From 1927 to 1968, 21 controlled clinical trials of the efficacy of BCG vaccines were initiated in 10 countries, of which 19 were completed and evaluated. The protective benefit was found to be extremely variable, ranging from 0% to 80% with different vaccines in different settings. In the most recent and largest trial, performed in Chingleput, India with over 200,000 participants, the results were disappointing, as BCG showed no protective effect. Of 7 trials which reported on survival, the protective effect against death ranged from 7% to 88%, although in most studies there were few deaths. In trials which reported specific morbidity, protection against meningitis or miliary tuberculosis in children ranged from 46% to 100%.

In the past decade, there have been 14 case-control studies in 12 countries, comparing cases of tuberculosis to selected controls by BCG vaccination status. Efficacy has ranged from 2% to 83%, and against meningitis or miliary tuberculosis in children, 58% to 100%. Evaluation of household contacts of known cases of tuberculosis has also shown protective efficacy of 53% of 74% in those contacts who received BCG vaccine.

BCG vaccine does not appear to prevent primary infection with *M. tuberculosis* nor does it prevent an appreciable number of infectious pulmonary cases, and therefore does not significantly decrease transmission of tuberculosis within a community. Taken together with the variable efficacy noted above, BCG vaccination has a relatively low impact on the global control of tuberculosis.

[1] Earlier recommendations concerning BCG and HIV infection remain unchanged (see No. 40, 1987, pp. 297–299)

Tuberculin skin testing and BCG revaccination

Use of BCG vaccine results in conversion of tuberculin skin tests in most recipients; the duration of this hypersensitivity is variable, and the size of induration wanes with time. In some programmes, negative tuberculin skin tests have been used as indicators for the need to revaccinate with BCG. However, there is poor correlation between skin test conversion rates or size of induration and protective immunity, and there is no evidence that waning of post-BCG vaccination tuberculin sensitivity is associated with waning protective immunity. Once an individual has been vaccinated, there is no reliable way to distinguish tuberculin reactions due to BCG from those caused by natural infection. The risk of administering BCG vaccine to persons with positive tuberculin reactions due to either prior BCG vaccination or natural infection is minimal. Numerous studies have shown that direct vaccination, i.e. BCG vaccination without prior tuberculin testing, is safe and acceptable to populations being vaccinated.

Efficacy of repeated BCG vaccination

There is no definite evidence that repeated BCG vaccination confers additional protection against tuberculosis. In Hungary, where systematic BCG revaccination was utilized from 1959 to 1970, incidence of tuberculosis declined significantly in the following decade. However, there was no comparative control group and other factors may have been responsible. In a retrospective analysis in Poland from 1965 to 1977, persons with tuberculin skin tests <5 mm who were not revaccinated, compared with a group who were revaccinated, had a higher incidence of tuberculosis in the ensuing 12 years. The number of incident cases were few, and the groups were not randomized and may not have been comparable. In Chile, where BCG revaccination is given at ages 6 and 14 years, there was no difference in the percentage of young adults with 1, 2 or 3 BCG scars between patients with tuberculosis and controls, suggesting no benefit from repeated vaccination. There are as yet no reports of prospective, comparative clinical trials which have assessed the efficacy of BCG revaccination.

Although BCG vaccine is relatively inexpensive, the administration of BCG vaccines after the first year of life or giving repeated vaccinations may incur significant additional cost and is probably not cost-effective. However, the cost-effectiveness of BCG vaccine is difficult to study owing to the variability in vaccine efficacy, BCG preparations, vaccination schedules, and incidence of tuberculosis in different countries.

Recommendations

Based on the above information, the following recommendations reiterate and update previous WHO statements on the use of initial BCG vaccination and revaccination. Since BCG vaccination has variable efficacy, it should be considered an adjunct to national tuberculosis programmes. Rapid case detection and effective treatment remain the highest priorities for the control of tuberculosis in all countries.

1 In countries where the prevalence and incidence of tuberculosis are high, BCG vaccination should be given to infants as soon after birth as possible, and in any case, within the first year of life.
2 Where tuberculin skin testing is used to make decisions on BCG revaccination, the practice should be discontinued.
3 For persons who have received BCG vaccination, repeat vaccination is not recommended, as scientific evidence does not support this practice. Multiple revaccinations are not indicated in any person.

• A list of references is available on request from the Global Tuberculosis Programme, WHO, 1211 Geneva 27, Switzerland.

Report of 5th Independent Evaluation of the National Leprosy Eradication Programme (NLEP) India, June 1995

The National Leprosy Eradication Programme (NLEP) of India was subjected to a joint Government of India/WHO Independent Evaluation by teams with national and outside expert leprologists, health administrators, planners and communicators as members from 5–14 June 1995. The teams visited 13 states and 29 districts after interacting with authorities at national level. The Report (48 pages) describes the terms of reference, observations and activities of the teams in considerable detail. The main recommendations were as follows:

Political commitment

The political commitment displayed by the Government of India towards the leprosy eradication programme was greatly in evidence and has to be sustained till the goal of leprosy elimination is achieved. However, such commitment was not in evidence in several states where the leprosy programme is considered as the programme of the Government of India. This has to be changed early by interaction with the highest political administrative functionaries in the states.

Plan of action for leprosy elimination

None of the States visited had developed or implemented plans of action towards leprosy elimination based on the national plan which envisages attainment of the goal of leprosy elimination by reducing the leprosy prevalence rate to <1 case/10,000 population by 2000 AD. The Government of India should provide technical guidance to the states/UTs to develop their plans for leprosy elimination within a time frame as well as additional financial support as required. The states be encouraged to take initiatives on their own to achieve prevalence reduction and be considered for financial support towards such ad hoc activities.

The elimination goal calls for intensification of coordination efforts and setting up of intermediate targets to ensure steady progress towards elimination in each State specially the large ones. Such efforts would ungrade the political will and administrative support to the States besides promoting healthy competition for early attainment of the goal of leprosy elimination.

Strengthening of national & state programme headquarters

The staff position of several state leprosy programme headquarters require greater and quicker attention to improve the supervision and monitoring capabilities.

MDT coverage

Geographic coverage: While the Government of India has sanctioned MDT extension to all the 217 uncovered nonendemic districts in the country releasing funds and supplying vehicles during 1994–95, all the nonendemic districts, except in Maharashtra, are in the preparatory phase. Urgent review with the highest functionaries in the States/UTs to expedite the accessibility of MDT to all these districts is essential to accelerate the goal of leprosy elimination.

Sixty-six endemic districts in the states did not have adequate vertical infrastructure affecting the progress of MDT. The Government of India had released funds during 1994–95 to recruit additional leprosy infrastructure required to cover these districts on a contractual basis. However, none of the districts in Bihar had reported recruiting the staff due to administrative and procedural delays. A few districts in Uttar Pradesh also have to recruit the staff. The states have to be persuaded by the highest functionaries in the Government of India for ensuring full infrastructure.

Coverage of registered cases: MDT coverage of registered cases by and large was reported to be very high in all the states and districts visited. According to Government of India reports, 13 per cent of the leprosy cases were still on dapsone monotherapy at the end of March 1995. The primary health centres in nonendemic districts, except in Maharashtra, have to be assigned a more active role in the leprosy programme. It should be clarified that MLTUs are expected to provide MDT with active support from PHC systems in the implementation of leprosy programme activities.

Poor communication, low population density, high vacancy position of staff and special features of the communities make accessibility of MDT difficult in some areas in the endemic districts. Special flexible innovations should be considered for achieving higher accessibility of MDT to such difficult areas and the states encouraged and guided to initiate flexible, innovative ad hoc activities to accelerate the MDT coverage in such areas.

Fixed duration treatment, though adopted by the programme at national level, has yet to replace the longer duration MDT in some districts, especially to MB cases.

Antileprosy drugs

While it is gratifying to note that there was no shortage of antileprosy drugs during the year 1994–95 some excess stock of dapsone in a few districts some of which had become time-barred should be written off as per instructions for their disposal from the centre. Uninterrupted stocks of MDT drugs be ensured to last at least for 3 months in LCUs/ULCs and for 6 months in a district.

Filling up staff vacancy and orientation

Urgent action should be taken by some of the states to fill the large number of vacancies of different categories of staff.

A large proportion of vertical leprosy staff in some states like Bihar, especially medical officers are functioning under the programme without training, making then ineffective supervisors and motivators. Printed guidelines on MDT in non-endemic districts emphasizing the involvement of PHC staff should be disseminated in adequate numbers to all concerned defining the tasks to be assigned to different categories vis-a-vis MLTUs.

Supervision and monitoring of programme performance

Supervision and monitoring of the programme activities at grassroots level was one of the weak links in some districts visited and requires urgent improvement by identifying poor supervisors and making them answerable for their unsatisfactory performance.

Critical and rapid analysis of data generated and compiled from reports and feedback with suitable comments/clarifications to the reporting districts would help in taking timely corrective steps and careful preparation of future reports.

Periodic review of the progress of NLEP by the Health Secretary in the States/UTs especially those with unsatisfactory progress with all the concerned including district level officers should be undertaken to identify the problems and take correctives without delay.

Updating estimated leprosy cases

While the national figures were being updated annually since 1993, it was not done regularly by several districts. Guidelines on updating the figures should be shared with the districts so that they could start estimating prevalence annually, contributing to realistic estimates at the national level.

IEC activities

IEC activities should be intensified without delay to all the nonendemic district before MDT or at least

along with MDT introduction to increase community awareness which was found to be low in nonendemic districts.

Health education activities should be continued/strengthened in the endemic districts, in view of the low levels of community awareness observed in some of them till the goal of leprosy elimination is attained.

Resource mobilization

While the Government of India has been very active in the mobilization of resources and in providing the states additional funds from its own resources and from outside sources, some of the states remain passive recipients to this support without active involvement in decision-making.

Antileprosy Week, Health Education Activities, Bombay Leprosy Project

Antileprosy Week Observation, 30 January–5 February 1997, culminated in Dr V. V. Pai, the Deputy Director, being applauded for his work in the field of leprosy and assisting the National Leprosy Eradication Programme by Brihanmumbai Municipal Corporation. Listed below are the weeks activities:

Place	Activity		Audience (No.)	Resource person & subject
Thakkar Bappa Colony, Chembur	Slide show	Slum women	(45)	Mr S. S. Deshpande—Leprosy signs and symptoms
Thakkar Bappa Colony Chembur	Slide show	Slum Adults	(35)	Leprosy Signs and Symptoms
Chhatrapati Shivaji Terminus, Mumbai—Suburban Central Railway Hall	Exhibition	Railway commuters, staff, doctors and nurses	(20,000)	'Leprosy awareness' with posters, hand-outs, etc.
RRE Society ALH Wadala, Mumbai	Case demonstration	Postgraduate medical students		Dr R. Ganapati, Dr V. V. Pai
Shastrinagar Municipal Dispensary, Dharavi Mumbai—17	Training and Exhibition	Community health volunteers, health post workers and OPD patients	(CHV, 35; health post workers, 15; OPD patients, 100)	Dr Mahendra Singh, Asst Director of Health Services (Lep), Mumbai. Mr S. S. Deshpande, Mrs R. R. Pai Training on Leprosy 'How to detect leprosy'
Foundation for Medical Research, Worli Manbai—400 018	'Laboratory aspects of leprosy diagnosis. Monitoring and Cure'	Dermatologists	(21 Dermatologists and PG students; 18 other laboratory personnel)	Dr R. Ganapati Dr W. Upalekar Dr Geeta Rane Dr V. P. Shetty Mrs Kamal Sethna Dr V. V. Pai
Lecture Hall, Chetna College. Bandra	Exhibition	NSS students	(500 college students and staff)	On leprosy—with posters and handouts etc.

XV International Leprosy Congress, Beijing, China, September 1998

Basic concept and framework:

The XV International Leprosy Congress in Beijing, to be held in September 1998, may be termed a '*Centennial Congress*.' signifying the end of the first century of modern leprosy control. This century was initiated by the first Congress in Berlin in 1897 and, hopefully, will achieve the 'Elimination of leprosy as a public health problem.' This achievement will signal the start of the second century of our modern fight against the disease which should culminate in the total eradication of the disease and its consequences. Eradication means elimination of not only the disease itself but, also, of all the adverse effects of the disease, including the social problems faced by 'people affected by leprosy.'

Therefore, the Congress is being organized under the heading of '*Working Toward a World Without Leprosy*,' not just hoping but actually intending to achieve that final goal sometime during the next century.

The Congress will deal with leprosy and its problems from a holistic point of view, and try to come up with some practical, appropriate solutions in a closely-integrated manner.

The whole programme of the Congress, including keynote speeches, open panel discussions, workshops, question-an-answer sessions in plenary, oral presentations of individual papers in separate sessions as well as poster presentations and other exhibits, have been planned with this approach in mind.

The date of the Contress of six working days is currently fixed as from *Monday 7 September to Saturday 12 September 1998*. The venue will be the *Beijing International Convention Centre* with accommodation at the adjacent Continental Grand Hotel. Both are located well within the city on the 4th Ring Road of Beijing, less than half an hour from the airport by direct highway link, and about 20 minutes by car from Tian An Men Square, the centre of the city.

The Congress is being arranged quite differently from previous Congresses. Four main changes are proposed: 1, no more pre-Congress workshops; 2, much less time for oral presentations of individual papers; 3, much more provision for poster presentations; 4, much more time to be spent in plenary sessions. There will be short teaching sessions on 10–12 subjects on three or four evenings. The plan reflects the four main characteristics of the XVth Congress which are: '*Integrated*,' '*Action Oriented*,' '*Interactive*,' and '*Participant Friendly*.'

The *first official announcement of the Congress*, a one-page flier with dates, venue, and a broad outline, will be set out *later this year* without details such as daily programmes, which will appear only in the *second/final announcement* scheduled to be published in *October 1997*.

In addition to the daily programmes, we have discussed some other relevant matters as follows: The expected number of *Participants*, 800–1000 overseas plus 300 Chinese. The *Registration fee*, US$250 or less. *Accommodation cost*, with more than 10% annual inflation, the cost of living is increasing rapidly, but we are hoping to settle on US$100 with twin bedroom for two persons per day. *Language*, English only with Chinese translation as required. *Schedule* of events related to the preparation of the Congress: Joint consultation with Chinese Organizing Committee in September 1996. Second Organizing Committee meeting in April/May 1997 to decide the details of the programme, selection of people for key roles, sucy as keynote speakers, moderators and members of open panels and workshops, teachers for short-course sessions, etc. Closing of Abstract submission, end of March 1998, Third Congress Organizing Committee Meeting, June 1998.

Leprosy Review posters: Prevention of disability

The A3 poster enclosed with this issue of *Leprosy Review* is the fourth in a series of four covering important areas of management and research in leprosy and is distributed free to subscribers to the Journal. Additional copies are available from Lepra, Colchester, UK. Further posters are also being planned. 'A questionnaire on the posters is to be published in the September issue so that the choice of topic and other aspects can be guided by you the reader. So please do let us know what you think.'

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Dr Diana Lockwood, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of LEPRA. Manuscripts should be typewritten, in double spacing, on one side of A4 (297 × 210 mm) paper, with wide margins (4 cm all round). Contributors must send three complete copies of the text, tables and figures. On a separate sheet give the title, short title, name and postal address of the author, together with the name of the institution where the work was done. Abbreviations of titles of journals should follow the list of journals indexed in *Index Medicus*. References to books should include the editor(s), publisher and place of publication. Once manuscripts have been accepted a copy on disk that matches the hard copies exactly would be very much appreciated.

Units and Abbreviations. The Journal recognizes the adoption of the Système International d'Unitès (SI Units) proposed in *Units, Symbols and Abbreviations* (1972) published by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Abbreviations should be used for unwieldy names, and only when they occur frequently.

Proofs are submitted to authors for immediate return by air.

Copyright/Offprints. Authors submitting a manuscript do so on the understanding that if it is accepted for publication, copyright in the paper for the United States of America shall be assigned to LEPRA. Offprints may be ordered and a price list/order form is sent to authors with their proofs. LEPRA will not put any limitation on the personal freedom of the author to use material contained in the paper in other works which may be published in North America.

* * *

Leprosy Review is published quarterly (Mar., June, Sept., Dec.) by LEPRA. 1997: Volume 68, 4 issues; £30, or £7.50 per copy, inclusive of postage and packing (UK and abroad). Subscription orders or enquiries should be sent to (LEPRA), Fairfax House, Causton Road, Colchester CO1 1PU, England. At its own discretion, LEPRA will continue, and also expand, its policy of sending free issues of this journal to people in various parts of the world; this will include doctors working directly with leprosy who cannot afford the above subscription, or obtain foreign currency, together with selected libraries covering tropical medicine.

Typeset and printed in Great Britain by Alden, Oxford, Didcot and Northampton.

CONTENTS